PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

CALQUENCE 100 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg acalabrutinib.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule

Size 1 hard gelatine capsule with a yellow body and blue cap, marked in black ink with ‘ACA 100 mg’

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CALQUENCE is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

CALQUENCE is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL).

4.2. Posology and method of administration

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

Posology

MCL

The recommended dose of CALQUENCE for the treatment of MCL is 100 mg (1 capsule) twice daily.

CLL

The recommended dose of CALQUENCE for the treatment of CLL is 100 mg (1 capsule) twice daily, either as monotherapy or in combination with obinutuzumab. Refer to the obinutuzumab prescribing information for recommended obinutuzumab dosing information. (For details of the combination regimen, see section 5.1). Doses should be separated by approximately 12 hours.

Treatment with CALQUENCE should continue until disease progression or unacceptable toxicity.

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 capsules of CALQUENCE should not be taken to make up for a missed dose.

Dose Adjustment

Adverse Reactions

Recommended dose modifications of CALQUENCE for Grade ≥ 3 adverse reactions are provided in Table 1.

Table 1. Recommended Dose Adjustments for Adverse Reactions*

Adverse Reaction Occurrence	**Dose Modification** (Starting dose = 100 mg twice daily)
1st and 2nd	Restart at 100 mg twice daily
3rd	Restart at 100 mg daily
4th	Discontinue CALQUENCE

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

Table 2. Use with CYP3A Inhibitors or Inducers and Gastric Acid Reducing Agents

	Co-administered Drug	**Recommended CALQUENCE Use**
CYP3A Inhibitors	Strong CYP3A inhibitors	Consider alternative therapies to strong CYP3A inhibitors. Monitor patients closely for adverse reactions if taking strong CYP3A inhibitors.
CYP3A Inducers	Strong CYP3A inducers	Consider alternative therapies to strong CYP3A inducers. If these inducers cannot be avoided, increase CALQUENCE dose to 200mg twice daily.
Gastric Acid Reducing Agents	Proton Pump Inhibitors	Avoid concomitant use.
	H2-Receptor Antagonists	Take CALQUENCE 2 hours before taking a H2-receptor antagonist.
	Antacids	Separate dosing by at least 2 hours.

Method of Administration

CALQUENCE should be swallowed whole with water at approximately the same time each day.

CALQUENCE can be taken with or without food. The capsule should not be chewed, dissolved, or opened.

Special patient population

Elderly (≥ 65 years)

No dose adjustment is necessary based on age (see section 5.2).

Renal Impairment

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 5.2).

Hepatic Impairment

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 5.2).

Severe Cardiac Disease

Patients with severe cardiovascular disease were excluded from CALQUENCE clinical studies.

Paediatric and adolescents

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

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4.Special warnings and precautions for use Haemorrhage

Serious haemorrhagic events, including fatal events, have occurred in patients with haematologic malignancies (n=1040) treated with CALQUENCE monotherapy. Major haemorrhage (Grade 3 or higher bleeding events, serious, or any central nervous system events) occurred in 3.6% of patients, with fatalities occurring in 0.1% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in 46% of patients with haematological malignancies.

The mechanism for the bleeding events is not well understood. Patients receiving antithrombotic agents may be at increased risk of haemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary.

Consider the benefit-risk of withholding CALQUENCE for at least 3 days pre- and post-surgery.

Infections

Serious infections (bacterial, viral or fungal), including fatal events have occurred in patients with haematologic malignancies (n=1040) treated with CALQUENCE monotherapy. Grade 3 or higher infections occurred in 18% of these patients. The most frequently

reported Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation, aspergillosis, and progressive multifocal leukoencephalopathy (PML) have occurred. Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia (21%), anaemia (10%) and thrombocytopenia (7%) based on laboratory measurements, occurred in patients with haematologic malignancies (n=1040) treated with CALQUENCE monotherapy. Monitor complete blood counts as medically appropriate.

Second Primary Malignancies

Second primary malignancies, including non-skin cancers, occurred in 12% of patients with haematologic malignancies (n=1040) treated with CALQUENCE monotherapy. The most frequent second primary malignancy was skin cancer, which occurred in 7% of patients.

Monitor patients for the appearance of skin cancers.

Atrial Fibrillation

In patients with haematologic malignancies (n=1040) treated with CALQUENCE monotherapy, Grade 3 atrial fibrillation/flutter occurred in 1% of patients, and Grade 1 or 2 in

3% 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.

4.5. Interaction with other medicines and other forms of interaction 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 3.7-fold and 5.1-fold in healthy subjects (N=17), respectively.

When accounting for both acalabrutinib and its active metabolite, ACP-5862, physiologically based pharmacokinetic (PBPK) simulations with strong, moderate, and weak CYP3A inhibitors show no meaningful change in total AUC of active components. Consider alternative therapies that do not strongly inhibit CYP3A activity. Patients taking strong CYP3A inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole) with CALQUENCE should be monitored more closely for adverse reactions.

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.

When accounting for both acalabrutinib and its active metabolite, ACP-5862, PBPK simulations with strong CYP3A inducers showed a 21-51% decrease in total AUC of active components. Simulations with a moderate CYP3A inducer (efavirenz) showed a 25% decrease in total AUC of active components.

Consider alternative therapies to strong inducers of CYP3A activity (e.g., phenytoin, rifampin, carbamazepine). Avoid St. John’s wort which may unpredictably decrease acalabrutinib plasma concentrations. If a strong CYP3A inducer cannot be avoided, increase
the CALQUENCE dose to 200 mg twice daily.

Gastric Acid Reducing Medications

Acalabrutinib solubility decreases with increasing pH. Co-administration of acalabrutinib with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy subjects. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days), decreased acalabrutinib AUC by 43%.

If treatment with an acid reducing agent is required, consider using an antacid (e.g., calcium carbonate), or an H2-receptor antagonist (e.g., ranitidine or famotidine). For use with antacids,

separate dosing by at least 2 hours. For H2-receptor antagonists, take CALQUENCE 2 hours before taking the H2-receptor antagonist.
Due to the long-lasting effect of proton pump inhibitors, separation of doses with proton pump inhibitors may not eliminate the interaction with CALQUENCE.

Active substances whose plasma concentrations may be altered by CALQUENCE
CYP3A Substrates
Based on in vitro data and PBPK modelling, no interaction with CYP substrates is expected at the clinically relevant concentrations (see section 5.2).
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 5.2).
ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1 (see section 5.2).

Effect of food on acalabrutinib
In healthy subjects, administration of a single 75 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 73% and T_{max} was delayed 1-2 hours.

4.6. Fertility, pregnancy and lactation

Pregnancy
CALQUENCE should not be used during pregnancy and women of childbearing potential should be advised to avoid becoming pregnant while receiving CALQUENCE. Administration of acalabrutinib to pregnant rabbits at exposures 4-times the human AUC at the recommended dose was associated with reduced foetal growth (see section 5.3). Dystocia was observed in a rat study involving dosing animals from implantation throughout gestation, parturition and lactation at exposures > 2.3-times the human AUC at the recommended dose (see section 5.3).

Breastfeeding
It is not known whether acalabrutinib is excreted in human milk. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Breastfeeding mothers should not breastfeed during treatment with CALQUENCE and for 2 days 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 5.3).

4.7. Effects on ability to drive and use machines

CALQUENCE has no or negligible influence on the ability to drive and use machines. However, during treatment with acalabrutinib fatigue and dizziness have been reported and patients who experience these symptoms should observe caution when driving or using machines.

4.8. Undesirable effects

a) Summary of the safety profile

The overall safety profile of acalabrutinib is based on pooled data from 1040 patients with haematologic malignancies receiving acalabrutinib monotherapy.

The most common (≥ 20%) adverse drug reactions (ADRs) of any grade reported in patients receiving acalabrutinib were infection, headache, diarrhoea, bruising, musculoskeletal pain, nausea, fatigue, and rash.

The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were infection (17.6%), neutropenia (14.2%), and anaemia (7.8%).Dose reductions due to adverse events were reported in 4.2% of patients. Discontinuation due to adverse events were reported in 9.3% of the patients. The median dose intensity was 98.7%.

b) Tabulated list of adverse reactions

The following adverse drug reactions (ADRs) have been identified in clinical studies with patients receiving CALQUENCE monotherapy as treatment for haematological malignancies. The median duration of acalabrutinib monotherapy treatment across the
pooled dataset was 24.6 months. 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 3. Adverse drug reactions* of Patients with Haematological Malignancies treated with acalabrutinib monotherapy (n=1040)

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (all CTCAE grades)	Frequency of CTCAE Grade ≥ 3†
Blood and lymphatic system disorders	Leukopenia†	Very common (16.2%)	14%
	Neutropenia	Very common (15.7%)	14%
	Anemia	Very common (13.8%)	8%
	Thrombocytopenia	Common (8.9%)	4.8%
Cardiac disorders	Atrial Fibrillation/Flutter†	Common (4.4%)	1.3%
Nervous system disorders	Headache	Very common (37.8%)	1.1%
	Dizziness	Very common (13.4%)	0.2%
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common (7%)	0.3%
Gastrointestinal disorders	Diarrhoea	Very common (36.7%)	2.6%
	Nausea	Very common (21.7%)	1.2%
	Constipation	Very common (14.5%)	0.1%
	Abdominal pain†	Very common (12.5%)	1%
	Vomiting	Very common (13.3%)	0.9%
General disorders and administration site conditions	Fatigue	Very common (21.3%)	2%
	Asthenia	Common (5.3%)	0.8%
Metabolism and nutrition disorders	Tumour Lysis Syndrome±	Uncommon (0.5%)	0.4%
Musculoskeletal and connective tissue disorders	Arthralgia	Very common (19.1%)	0.7%
	Musculoskeletal Pain†	Very common (33.1%)	1.5%
Infections and Infestations	Infection†	Very common (66.7%)	18%
Neoplasms benign, malignant and unspecified	Second Primary Malignancy†	Very common (12.2%)	4.1%
	SPM excluding non-melanoma skin†	Common (6.5%)	3.8%
	Non-Melanoma Skin Malignancy†	Common (6.6%)	0.5%

Skin and subcutaneous tissue disorders	Bruising†	Very common (34.1%)	-
	Rash†	Very common (20.3%)	0.6%
Vascular disorders	Hemorrhage/Hematoma†	Very common (12.6%)	1.8%
*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. †Includes multiple ADR term ‡One case of drug-induced Tumour Lysis Syndrome was observed in acalabrutinib arm in the ASCEND Study			

Table 4. Treatment-emergent haematological laboratory abnormalities for acalabrutinib monotherapy (n=1040)

MedDRA SOC	**MedDRA Term**	**CIOMS descriptor/ Overall Frequency (all CTCAE Grades)**	**Frequency of CTCAE Grade 3-4**
Investigations (findings based on test results presented as CTCAE grade shifts)	Absolute neutrophil count decreased	Very common (41.8%)	20.7%
	Haemoglobin decreased	Very common (42.6%)	10.1%
	Platelets decreased	Very common (31.1%)	6.9%

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

Special populations

Elderly

Of the 1040 patients in clinical trials of CALQUENCE monotherapy, 41% were greater than 65 years of age and less than 75 years of age and 22% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, 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 (IC50 ≤ 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).

Pharmacodynamic effects

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 and safety in patients MCL

The safety and efficacy of CALQUENCE in MCL were evaluated in an open-label, multi-centre, single-arm Phase 2 study (ACE-LY-004) of 124 previously treated patients. All patients received CALQUENCE 100 mg orally twice daily until disease progression or unacceptable toxicity. The trial did not include patients who received prior treatment with BTK inhibitors. The primary endpoint was investigator-assessed overall response rate (ORR) per the Lugano classification for non-Hodgkin's lymphoma (NHL). Duration of Response (DoR) was an additional outcome measure. Efficacy results are presented in Table 5.

The median age was 68 (range 42 to 90) years, 79.8% were male and 74.2% were Caucasian. At 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 transplant. The most common prior regimens were CHOP-based (51.6%) and ARA-C (33.9%). At baseline, 37.1% of patients had at least one tumour with a longest diameter ≥ 5 cm, 72.6% had extra nodal involvement including 50.8% with bone marrow involvement. The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 43.5% and high in 16.9% of patients.

Table 5. Overall Response Rate and Duration of Response in (ACE-LY-004) Patients with MCL

	Investigator Assessed N=124	**Independent Review Committee (IRC) Assessed N=124**
	n (%) (95% CI[*])	**n (%) (95% CI[*])**
Overall Response Rate (ORR)		
Overall Response Rate	100 (80.6%) (72.6, 87.2)	99 (79.8%) (71.7, 86.5)
Complete Response	49 (39.5%) (30.9, 48.7)	49 (39.5%) (30.9, 48.7)
Partial Response	51 (41.1%) (32.4, 50.3)	50 (40.3%) (31.6, 49.5)
Stable Disease	11 (8.9%) (4.5, 15.3)	9 (7.3%) (3.4, 13.3)
Progressive Disease	10 (8.1%) (3.9, 14.3)	11 (8.9%) (4.9, 15.3)
Non-Evaluable[†]	3 (2.4%) (0.5, 6.9)	5 (4.0%) (1.3, 9.2)
Duration of Response (DoR)		
Median (months)	NR (13.5, NR)	NR (14.8, NR)
Landmark DOR		
12 months estimate (%) (95% CI)	72.1 (61.6, 80.2)	72.3 (61.9, 80.2)
18 months estimate (%) (95% CI)	63.3 (49.4, 74.3)	56.0 (38.2, 70.6)

CI=Confidence Interval; NR = Not Reached

[*]95% exact binomial confidence interval.

[†]Includes subjects without any adequate post-baseline disease assessment.

Based on investigator assessment, 92% of responders achieved a response by cycle 2, with a median time to documented response of 1.9 months. The median DoR had not been reached at 15.2 months median follow-up from treatment initiation. Seventy two percent (72%) of patients had an ongoing response at 12 months per Kaplan-Meier estimate. The ORR was consistent across all pre-specified subgroups including age, performance status, disease stage, and number of prior therapies.

CLL

Patients with Previously Untreated CLL

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. 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 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. Table 6 summarizes the baseline demographics and disease characteristics of the study population.

Table 6. Baseline Patient Characteristics in (ELEVATE-TN) Patients with Previously Untreated CLL

Characteristic	**CALQUENCE plus obinutuzumab N=179**	**CALQUENCE Monotherapy N=179**	**Obinutuzumab plus Chlorambucil N=177**
Age, years; median (range)	70 (41-88)	70 (44-87)	71 (46-91)
Male; %	62	62	59.9

Caucasian; %	91.6	95	93.2
ECOG performance status 0-1; %	94.4	92.2	94.4
Median time from diagnosis (months)	30.5	24.4	30.7
Bulky disease with nodes ≥ 5 cm; %	25.7	38	31.1
Cytogenetics/FISH Category; %			
17p deletion	9.5	8.9	9
11q deletion	17.3	17.3	18.6
TP53 mutation	11.7	10.6	11.9
Unmutated IGHV	57.5	66.5	65.5
Complex karyotype (≥ 3 abnormalities)	16.2	17.3	18.1
Rai stage; %			
0	1.7	0	0.6
I	30.2	26.8	28.2
II	20.1	24.6	27.1
III	26.8	27.9	22.6
IV	21.2	20.7	21.5

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 criteriawith 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 7. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 7. Efficacy Results in (ELEVATE-TN) Patients with CLL

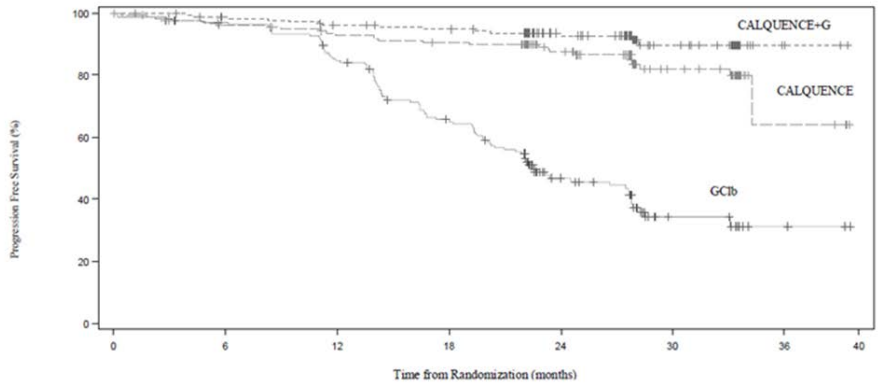
	CALQUENCE plus obinutuzumab N=179	**CALQUENCE Monotherapy N=179**	**Obinutuzumab plus Chlorambucil N=177**
Progression-Free Survival*			
Number of events (%)	14 (7.8%)	26 (14.5%)	93 (52.5%)
PD, n (%)	9 (5%)	20 (11.2%)	82 (46.3%)
Death events (%)	5 (2.8%)	6 (3.4%)	11 (6.2%)
Median (95% CI), months	NR	NR (34.2, NR)	22.6 (20.2, 27.6)
HR† (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
P-value	< 0.0001	< 0.0001	-
24 months estimate, % (95% CI)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
Overall Response Rate* (CR + CRi + nPR + PR)			
ORR, n (%) (95% CI)	168 (93.9) (89.3, 96.5)	153 (85.5) (79.6, 89.9)	139 (78.5) (71.9, 83.9)
P-value	< 0.0001	0.0763	-
CR, n (%)	23 (12.8)	1 (0.6)	8 (4.5)
CRi, n (%)	1 (0.6)	0	0
nPR, n (%)	1 (0.6%)	2 (1.1%)	3 (1.7%)
PR, n (%)	143 (79.9)	150 (83.8)	128 (72.3)
PRL, n (%)	0	2 (1.1)	0
SD, n (%)	4 (2.2)	8 (4.5)	15 (8.5)
PD, n (%)	0	3 (1.7)	0
Non-evaluable, n (%)	0	1 (0.6)	8 (4.5)
Unknown, n (%)	6 (3.4)	12 (6.7)	12 (6.8)

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; PRL=PR with lymphocytosis; SD=stable disease; PD=progressive disease

*Per IRC assessment

†Based on stratified Cox-Proportional-Hazards model

Figure 1. Kaplan-Meier Curve of IRC-Assessed PFS in (ELEVATE-TN) Patients with CLL (ITT Population)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39
CALQUENCE	179	166	161	157	153	150	148	147	103	94	43	40	4	3
CALQUENCE+G	179	176	170	168	163	160	159	155	109	104	46	41	4	2
GCIb	177	162	157	151	136	113	102	86	46	41	13	13	3	2

PFS results for CALQUENCE with or without obinutuzumab were consistent across subgroups, including high risk features. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation, and unmutated IGHV), the PFS HRs of CALQUENCE with or without obinutuzumab versus obinutuzumab plus chlorambucil was 0.08 [95% CI (0.04, 0.15)] and 0.13 [95% CI (0.08, 0.21)], respectively.

Patients with CLL who received at least one prior therapy

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. 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/m2) on Day 1 of each 28-day cycle for up to 6 cycles
  - Bendamustine 70 mg/m2 (Day 1 and 2 of each 28-day cycle) in combination with rituximab (375 mg/m2/500 mg/m2) 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.

Table 8 summarizes the baseline demographics and disease characteristics of the study population.

Table 8. Baseline Patient Characteristics in (ASCEND) Patients with CLL

Characteristic	**CALQUENCE monotherapy N=155**	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Age, years; median (range)	68 (32-89)	67 (34-90)
Male; %	69.7	64.5
Caucasian; %	93.5	91.0
ECOG performance status; %		
0	37.4	35.5
1	50.3	51.0
2	12.3	13.5
Median time from diagnosis (months)	85.3	79.0
Bulky disease with nodes ≥ 5 cm; %	49.0	48.4
Median number of prior CLL therapies (range)	1 (1-8)	2 (1-10)
Number of Prior CLL Therapies; %		
1	52.9	43.2
2	25.8	29.7
3	11.0	15.5
≥ 4	10.3	11.6
Cytogenetics/FISH Category; %		
17p deletion	18.1	13.5
11q deletion	25.2	28.4
TP53 mutation	25.2	21.9
Unmutated IGHV	76.1	80.6
Complex karyotype (≥3 abnormalities)	32.3	29.7

Rai Stage; %		
0	1.3	2.6
I	25.2	20.6
II	31.6	34.8
III	13.5	11.6
IV	28.4	29.7

The primary endpoint was PFS as assessed by IRC IWCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 16.1 months, PFS indicated a 69% statistically significant reduction in the risk of death or progression for patients in the CALQUENCE Arm. 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 investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab arm. Efficacy results are presented in Table 9. The Kaplan-Meier curve for PFS is shown in Figure 2.

Table 9. Efficacy Results in (ASCEND) Patients with CLL

	CALQUENCE monotherapy N=155	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Progression-Free Survival*		
Number of events (%)	27 (17.4)	68 (43.9)
PD, n (%)	19 (12.3)	59 (38.1)
Death events (%)	8 (5.2)	9 (5.8)
Median (95% CI), months	NR	16.5 (14.0, 17.1)
HR† (95% CI)	0.31 (0.20, 0.49)	
P-value	< 0.0001	
15 months estimate, % (95% CI)	82.6 (75.0, 88.1)	54.9 (45.4, 63.5)
Overall Response Rate* (CR + CRi + nPR + PR)		
ORR, n (%) (95% CI)	126 (81.3) (74.4, 86.6)	117 (75.5) (68.1, 81.6)
P-value	0.2248	-
CR, n (%)	0	2 (1.3)
PR, n (%)	126 (81.3)	115 (74.2)

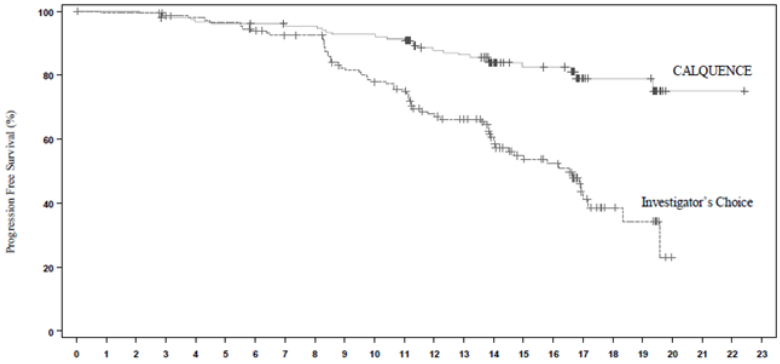
PRL, n (%)	11 (7.1)	3 (1.9)
SD, n (%)	9 (5.8)	12 (7.7)
PD, n (%)	2 (1.3)	1 (0.6)
Unknown, n (%)	7 (4.5)	22 (14.2)
Duration of Response (DoR)		
Median (95% CI), months	NR	13.6 (11.9, NR)

CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; PR=partial response; PRL=PR with lymphocytosis; SD=stable disease; PD=progressive disease

*Per IRC assessment

†Based on stratified Cox-Proportional-Hazards model

Figure 2. Kaplan-Meier Curve of IRC-Assessed PFS in (ASCEND) Patients with CLL (ITT Population)



Number of patients at risk

Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
CALQUENCE	155	153	153	149	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
Investigator's Choice	155	150	150	146	144	142	136	130	129	112	105	101	82	77	56	44	39	18	10	8	0			

PFS results for CALQUENCE were consistent across subgroups, including high risk features. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation, and unmutated IGHV), the PFS HR was 0.27 [95% CI (0.17, 0.44)].

5.2. Pharmacokinetic properties

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 does not differ significantly in patients with different B-cell malignancies. At the recommended dose of 100 mg twice daily in patients with B-cell malignancies (including MCL and CLL), the geometric mean steady state daily area under the plasma drug concentration over time curve (AUC24h) and maximumplasma concentration (C_{max}) of acalabrutinib were 1893

ng•h/mL and 466 ng/mL, respectively, and for ACP-5862 were 4091 ng•h/mL and 420 ng/mL, respectively.

Absorption

The median time to peak plasma concentrations (T_{max}) was 0.75 hours, and 1.0 hour for ACP-5862. The absolute bioavailability of CALQUENCE was 25%.

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.

Biotransformation/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.

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.

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.

Acalabrutinib may inhibit intestinal BCRP substrates (see section 4.5), while ACP-5862 may inhibit MATE1 (see Section 4.5) at clinically relevant concentrations. Acalabrutinib does not inhibit MATE1, while ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

Elimination

Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life ($t_{1/2}$) of acalabrutinib was 0.9 (range: 0.6 to 2.8) hours. The median $t_{1/2}$ of the active metabolite, ACP-5862, was 6.9 hours (range: 2.7 to 9.1) hours.

The mean apparent oral clearance (CL/F) was 70 L/hr for acalabrutinib and 13 L/hr for ACP-5862, with similar PK between patients and healthy subjects based on population PK analysis.

Following administration of a single 100 mg radiolabelled [14C]-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.

Pharmacokinetics in Special Populations

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 433 patients with mild renal impairment (eGFR between 60 and 89 mL/min/1.73m^2 as estimated by MDRD), 110 patients with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73m^2) relative to 204 patients 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 4.2).

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=651) hepatic function (total bilirubin and AST within ULN).

5.3. Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

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.

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 (2.5-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.

Reproductive toxicology

No effects on fertility were observed in male or female rats at exposures 10 or 9 times the human AUC exposure at the recommendeddose, 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). Acalabrutinib produced no maternal toxicity and no evidence of teratogenicity or foetal development, growth, or survival at doses of 50 mg/kg/day (approximately equivalent to the human AUC exposure at the recommended dose). 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule Content: microcrystalline cellulose, colloidal silicon dioxide, partially pregelatinized starch (maize), magnesium stearate (E572), andsodium starch glycolate (Type A).

Capsule Shell: gelatine, titanium dioxide (E171), yellow iron oxide (E172), and FD&C Blue 2 (Indigotine/Indigo carmine) (E132).

Printing Ink: Shellac, black iron oxide (E172), propylene glycol (E1520), ammonium hydroxide.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

36 months.

Store at or below 30 ^{O}C

6.4. Special precautions for storage

This medicine does not require any special storage conditions.

6.5. Nature and contents of container

Aluminium/Aluminium blisters. Cartons of 7 x 8 or 10 x 6 capsules.

Not all pack size may be marketed.

6.6. Special precautions for disposal and other handling

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets)

7. HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West,

Bryanston, Johannesburg

2191, South Africa

8. REGISTRATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION29

29 March 2022

10. DATE OF REVISION OF THE TEXT

AstraZeneca Logo

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