AUSTRALIAN PRODUCT INFORMATION

CALQUENCE®
acalabrutinib (as maleate monohydrate) tablets

1 NAME OF THE MEDICINE

acalabrutinib maleate monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains acalabrutinib maleate monohydrate equivalent to 100 mg of acalabrutinib.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

The CALQUENCE 100 mg film-coated tablet is an orange, 7.5 x 13 mm, oval, biconvex tablet, debossed with 'ACA 100' on one side and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Mantle cell lymphoma (MCL)

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

CALQUENCE in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous haematopoietic stem cell transplantation.

Chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (SLL)

CALQUENCE as monotherapy is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least one prior therapy.

CALQUENCE as monotherapy or in combination with obinutuzumab is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). For details of the combination regimens, see Section 5.1 Pharmacodynamic properties / Clinical trials.

CALQUENCE in combination with venetoclax with or without obinutuzumab is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). For details of the combination regimens, see Section 5.1 Pharmacodynamic properties / Clinical trials.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Recommended dosage (18 years and above)

Mantle cell lymphoma (MCL)

The recommended dose of CALQUENCE in monotherapy or in combination with other medicines is 100 mg (1 tablet) twice daily. For the combination regimens, refer to the Product Information of each of the medicines for dosing information. For details of the combination regimens, see Section 5.1 Pharmacodynamic properties / Clinical trials.

Chronic lymphocytic leukaemia (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 Product Information of each of the combination medicines for recommended dosing information (for details of the combination regimens, see Section 5.1 Pharmacodynamic properties / Clinical trials).

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 with or without obinutuzumab should continue until disease progression, unacceptable toxicity or completion of 14 cycles of treatment (each cycle is 28 days).

Missed dose

If a patient misses a dose of CALQUENCE by more than 3 hours, they should 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 adjustments

Adverse reactions

Recommended dose modifications for adverse reactions are provided in Table 1 (for patients receiving CALQUENCE monotherapy, and CALQUENCE in combination with obinutuzumab or in combination with venetoclax with or without obinutuzumab) and Table 2 (for patients receiving CALQUENCE in combination with bendamustine and rituximab). Refer to the Product Information of each medicine used in combination with CALQUENCE for additional information regarding management of toxicities.

Table 1 Recommended dose modifications for adverse reactions [a]

Event	**Adverse reaction occurrence**	**Dose modification** *(Starting dose = 100 mg twice daily)*
Grade 3 or greater non-haematological toxicities, Grade 3 thrombocytopenia with significant bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and second	Temporarily interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline (recovery) level, CALQUENCE therapy may be resumed at 100 mg twice daily.
	Third	Temporarily interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level (recovery), CALQUENCE therapy may be resumed at 100 mg daily.
	Fourth	Discontinue CALQUENCE.

[a] 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 [a] in patients receiving CALQUENCE in combination with bendamustine and rituximab

Adverse reaction	Bendamustine dose modification [b]	CALQUENCE dose modification
Neutropenia	If Grade 3 or Grade 4 neutropenia: 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 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 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 dose 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 haematological Grade 4 [c] 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 worse non-haematological toxicities	Interrupt bendamustine. Once toxicity has resolved to Grade 1 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, CALQUENCE may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd adverse reaction occurrence). Discontinue CALQUENCE at 3rd adverse reaction occurrence.

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

[b] For any toxicities not listed in this table refer to the bendamustine local product information.

[c] 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.

Dose adjustments for use with CYP3A inhibitors or inducers

Recommended dose adjustments are described in Table 3 below (see also Section 4.5 Interactions with other medicines and other forms of interactions).

Table 3 Use with CYP3A inhibitors or inducers

	Co-administered medicines	Recommended CALQUENCE use
CYP3A inhibitor	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE.
	Moderate CYP3A inhibitor	Reduce CALQUENCE dose to 100 mg once daily.
CYP3A inducer	Strong CYP3A inducer	Avoid concomitant use.

Special patient populations

Renal impairment

No dose adjustment is recommended in patients with mild to moderate renal impairment (estimated Glomerular Filtration Rate (eGFR) ≥30 mL/min/1.73 m^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 <29 mL/min/1.73 m^2) or end-stage renal disease have not been studied (see Section 5.2 Pharmacokinetic properties).

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 Pharmacokinetic properties).

Severe cardiac disease

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

Elderly patients

No dose adjustment is necessary based on age (see Section 5.2 Pharmacokinetic properties).

Paediatric patients

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

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 tablet should not be chewed, crushed, dissolved, or divided.

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemorrhage

Serious haemorrhagic events, including fatal events, have occurred in the combined safety database of 1478 patients with haematological malignancies treated with CALQUENCE monotherapy. Major haemorrhage (Grade 3 or higher bleeding events, serious, or any central nervous system events) occurred in 5.5% of patients, with fatalities occurring in 0.1% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in 46.1% of patients with haematological malignancies.

The mechanism for the bleeding events is not well understood. Use of antithrombotic agents concomitantly with CALQUENCE may increase the risk of haemorrhage. In CALQUENCE clinical trials, 3% of patients taking CALQUENCE without antithrombotic agents experienced major haemorrhage. The addition of antithrombotic agents increased the percentage to 4.3%. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infection

Serious infections (bacterial, viral or fungal), including fatal events have occurred in the combined safety database of 1478 patients with haematological malignancies treated with CALQUENCE monotherapy.

Grade 3 or higher infections occurred in 26.4% 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. Serious and/or fatal COVID-19 infection has occurred, particularly when CALQUENCE is used in combination with venetoclax with, or without, obinutuzumab. Appropriate monitoring and prophylaxis, as indicated, together with careful patient selection taking into account the risk of infection, are essential to optimise the benefit-risk profile of CALQUENCE.

Consider prophylaxis for opportunistic infections in line with standard of care. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Cytopenias

In the combined safety database of 1478 patients with haematological malignancies, patients treated with CALQUENCE monotherapy commonly experienced Grade 3 or higher cytopenias, including neutropenia (17.5%), anaemia (9.5%) and thrombocytopenia (6.2%). Monitor complete blood counts as medically appropriate during treatment.

Second primary malignancies

Second primary malignancies, including non-skin cancers, occurred in 17.6% of patients with haematological malignancies treated with CALQUENCE monotherapy in the combined safety database of 1478 patients. The most frequent second primary malignancy was skin cancer, which occurred in 9.9% of patients. Monitor patients for the appearance of skin cancers. Advise protection from sun exposure.

Cardiac arrhythmias including atrial fibrillation and flutter

Serious cardiac arrhythmias have occurred in patients treated with CALQUENCE. In the combined safety database of 1478 patients with haematological malignancies treated with CALQUENCE monotherapy, atrial fibrillation and atrial flutter of any grade occurred in 7.4% of patients and Grade 3 or higher occurred in 2.3% of patients. Monitor for symptoms of cardiac arrhythmia, including atrial fibrillation and atrial flutter, (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) and obtain an ECG as appropriate.

Hepatotoxicity, including drug-induced liver injury

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.

Use in the elderly

Of the 1478 patients in clinical trials of CALQUENCE monotherapy, 42% were ≥65 years of age and less than 75 years of age, and 20.6% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with CYP3A inhibitors and inducers

The clinical impact and prevention or management of interactions with CYP3A inhibitors or inducers are provided below in Table 4. See also Section 4.2 Dose and method of administration and Section 5.2 Pharmacokinetic properties.

Table 4 Interactions with other medicines – CYP3A inhibitors and inducers

Strong CYP3A inhibitors	
Clinical impact	Co-administration of CALQUENCE with a strong CYP3A inhibitor (e.g. itraconazole) increased acalabrutinib plasma concentrations. Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or management	Avoid co-administration of strong CYP3A inhibitors with CALQUENCE. Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE
Moderate CYP3A inhibitors	
Clinical impact	Co-administration of CALQUENCE with a moderate CYP3A inhibitor (e.g. diltiazem, erythromycin, fluconazole) may increase acalabrutinib plasma concentrations. Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or management	When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.
Strong CYP3A inducers	
Clinical impact	Co-administration of CALQUENCE with a strong CYP3A inducer (e.g. rifampin) decreased acalabrutinib plasma concentrations Decreased acalabrutinib concentrations may reduce CALQUENCE activity.
Prevention or management	Avoid co-administration of strong CYP3A inducers with CALQUENCE.

Effects of acalabrutinib and its active metabolite, ACP-5862, on CYP450 and UGT enzymes

In vitro data indicate no relevant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A2 or UGT2B7 by acalabrutinib or ACP-5862 at therapeutic concentrations. Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4; ACP-5862 weakly induces CYP3A4.

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.

ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1.

In vitro, acalabrutinib and 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. 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.

Effect of food on acalabrutinib

In healthy subjects, administration of a single 100 mg dose of acalabrutinib tablet 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.

Gastric acid-reducing medications

Acalabrutinib tablets can be co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy – Category C

No clinical data are available, but based on findings in animals (see below), CALQUENCE can cause fetal harm and dystocia if administered during pregnancy. Test for pregnancy prior to initiating treatment with CALQUENCE, and advise patients of the potential risk to a fetus. Patients who could become pregnant should use highly effective contraception (such as condoms) during treatment with acalabrutinib and for one week following the last dose.

In an embryofetal study in pregnant rabbits, decreased fetal body weight and delayed skeletal ossification were observed at exposure levels that produced maternal toxicity, which were 2.4 times greater than the clinical exposure (based on AUC) at the recommended dose.

No effects on embryofetal development and survival were observed in one study in pregnant rats, at exposures approximately 9 times greater than the clinical exposure (based on AUC) at the recommended dose. In another study in pregnant rats, underdeveloped renal papilla was observed in F1 generation offspring at doses resulting in maternal exposures approximately 5 times greater than the clinical exposure (based on AUC) at the recommended dose. In two rat reproductive studies, dystocia (prolonged/difficult labour) and mortality of offspring were observed at exposures >2.3 times greater than the clinical exposure (based on AUC) at the recommended dose. The presence of acalabrutinib and its active metabolite were confirmed in foetal rat plasma. Acalabrutinib and its active metabolite were present in the milk of lactating rats.

Use in lactation

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from CALQUENCE, advise patients not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

CALQUENCE monotherapy

Across 11 studies, 1478 patients with haematological malignancies have received CALQUENCE as monotherapy at the recommended dose (100 mg twice daily; approximately every 12 hours). The median and mean duration of treatment was 38 months. The most commonly reported (≥ 20%) adverse drug reactions of any grade were infection, diarrhoea, headache, musculoskeletal pain, bruising, cough, arthralgia, fatigue, nausea, leukopenia (mostly neutropenia) and rash. The most commonly reported (≥ 5%) Grade 3 or worse adverse drug reactions were infection, leukopenia, neutropenia, anaemia, second primary malignancy, and thrombocytopenia. Dose reductions due to adverse events were reported in 5.9% of patients (most frequently due to hepatitis B reactivation, sepsis, or diarrhoea). Discontinuation due to adverse events were reported in 14.6% of patients (most frequently due to pneumonia, thrombocytopenia, or diarrhoea).

CALQUENCE in combination regimens

The safety profile of acalabrutinib when used in combination with other therapies is described specifically for each combination regimen under the relevant clinical trial heading below.

Clinical trials experience

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data from clinical trials in mantle cell lymphoma (MCL)

ECHO (acalabrutinib+BR in previously untreated MCL not eligible for transplant)

The safety of CALQUENCE in combination with bendamustine and rituximab was evaluated in 297 patients with previously untreated MCL in ECHO (see Section 5.1 Pharmacodynamic properties / *Clinical trials*). The trial enrolled patients at least 65 years of age with no intention for transplant, with total bilirubin ≤ 1.5 × ULN, AST or ALT ≤ 2.5 × ULN, and estimated creatinine clearance of > 50 mL/min.

The median duration of treatment with CALQUENCE was 28.6 (range: 0.1 to 80) months. A total of 171 (58%) patients were treated with CALQUENCE for > 24 months and 122 (41%) patients were treated for >36 months.

Serious adverse reactions occurred in 69% of patients who received CALQUENCE. Serious adverse reactions reported in ≥ 2% of patients were COVID-19 (20%), pneumonia (9%), second primary malignancy (7%), pyrexia (5.7%), rash (3.4%), febrile neutropenia (3.4%), atrial fibrillation (3.0%), sepsis (2.7%) and anaemia (2.4%).

Fatal adverse reactions that occurred within 30 days of the last study treatment were reported in 12% of patients who received CALQUENCE plus BR including COVID-19 (6%), pneumonia (1.0%), second primary malignancy (0.7%), sepsis (0.3%), and pneumonitis (0.3%).

Dose interruption, reduction, and discontinuation due to any adverse reaction were reported in 74%, 10% and 43% of patients, respectively. Adverse reactions that resulted in dosage modification in >10% included infections, cytopenias, rashes, and gastrointestinal toxicity. Adverse reactions which resulted in permanent discontinuation of CALQUENCE in ≥ 4% of patients included COVID-19 and neutropenia.

Table 5 and Table 6 present summaries of the most common adverse reactions and laboratory abnormalities observed in patients with MCL who received CALQUENCE in the ECHO study.

Table 5 Common adverse reactions (≥ 15% all grades) in patients with previously untreated MCL (ECHO)

Body system Adverse reaction [a]	**CALQUENCE + BR N=297**		**Placebo + BR N=297**	
	All grades (%)	**Grade ≥ 3 (%)**	**All grades (%)**	**Grade ≥ 3 (%)**
Skin and subcutaneous tissue disorders				
Rash [b]	47	12	31	3
Infections				
COVID-19 including COVID-19 pneumonia [d]	38	13	27	11
Upper respiratory tract infection [e]	30	0.7	29	1
Lower respiratory tract infection not including COVID-19 [f]	36	22	28	17
Gastrointestinal disorders				
Diarrhoea	37	3	28	2.4
Nausea	43	1.3	38	1.3
Constipation	25	1	25	0.3
Vomiting	26	0.7	14	1
General disorders and administrative site conditions				
Fatigue [g]	37	3.7	32	4.4
Pyrexia	29	2.4	24	1.3
Oedema	20	1.3	19	0
Nervous system disorders				
Headache	31	1.7	14	0.7
Dizziness	18	1	17	0.3
Musculoskeletal and connective tissue disorder				
Musculoskeletal pain [h]	34	3.7	25	1.3
Arthralgia	18	0.7	16	1
Respiratory, thoracic and mediastinal disorders				

Body system Adverse reaction [a]	CALQUENCE + BR N=297		Placebo + BR N=297	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Cough	27	0	20	0.3
Dyspnoea	17	1	11	2.7
Vascular disorders				
Haemorrhage [i]	20	1.7	11	3
Neoplasms benign, malignant and unspecified				
Second primary malignancy	19	7	15	7

[a] Excluding laboratory abnormalities. Severity grades per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

[b] Includes rash, dermatitis, and other related terms.

[c] Includes any adverse reactions involving infection or febrile neutropenia.

[d] Including fatal events of COVID-19 in both the investigational (n=24) and the comparator (n=16) arm.

[e] Includes upper respiratory tract infection, nasopharyngitis and sinusitis.

[f] Includes pneumonia, terms containing pneumonia, and related infections, except for COVID-19 pneumonia which is included under 'COVID-19' instead.

[g] Includes asthenia, fatigue, and lethargy.

[h] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain.

[i] Includes all terms containing haematoma or haemorrhage and related terms indicative of bleeding.

Other clinically relevant adverse reactions (all grades incidence < 15%) in patients receiving CALQUENCE + BR included: bruising (14%), abdominal pain (12%), atrial fibrillation or flutter (7%), and tumour lysis syndrome (1.3%).

Table 6 Selected laboratory abnormalities (≥ 15% all grades) in patients with previously untreated MCL (ECHO)

Laboratory abnormality	CALQUENCE + BR N=297		Placebo + BR alone N=297	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Haematological abnormalities				
Lymphocytes decreased	98	87	97	89
Haemoglobin decreased	80	11	65	11
Neutrophils decreased	76	56	77	51
Platelets decreased	69	18	60	16
Chemistry abnormalities				
AST increased	53	5	50	3.4
Uric acid increased	45	45	40	40
ALT increased	44	7	41	2.4
Potassium increased	40	2	38	2.7
Creatinine increased	37	3	28	2.4
Phosphate decreased	36	4.4	30	4.7
Potassium decreased	29	7	23	6
Bilirubin increased	19	2	12	2

ACE-LY-004 (acalabrutinib monotherapy in previously treated MCL)

The safety data described in this section reflect exposure to CALQUENCE (100 mg twice daily) in 124 patients with previously treated MCL in ACE-LY-004 (see Section 5.1 Pharmacodynamic properties / *Clinical trials*). The median duration of treatment with CALQUENCE was 16.6 (range 0.1 to 26.6) months. A total of 91 (73%) patients were treated with CALQUENCE for ≥6 months and 74 (60%) patients were treated for ≥1 year.

The most common adverse reactions (≥ 20%) of any grade were anaemia, thrombocytopenia, headache, neutropenia, diarrhoea, fatigue, myalgia, and bruising. Grade 1 severity for the non-haematologic, most common events were as follows: headache (25%), diarrhoea (16%), fatigue (20%), myalgia (15%), and bruising (19%). The most common Grade ≥3 non-haematological adverse reaction (reported in at least 2% of patients) was diarrhoea.

Dose reductions and discontinuation due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.

Table 7 and Table 8 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE.

Table 7 Non-haematological adverse reactions [a] in ≥ 5% (all grades) of patients with MCL in ACE-LY-004

Body system Adverse reaction	**CALQUENCE 100 mg twice daily N=124**	
	All grades (%)	**Grade ≥ 3 (%)**
Nervous system disorders		
Headache	39	1.6
Gastrointestinal disorders		
Diarrhoea	31	3.2
Nausea	19	0.8
Abdominal pain	15	1.6
Constipation	15	-
Vomiting	13	1.6
General disorders		
Fatigue	28	0.8
Musculoskeletal and connective tissue disorders		
Myalgia	21	0.8
Skin & subcutaneous tissue disorders		
Bruising [b]	21	-
Rash [c]	18	0.8
Vascular disorders		
Haemorrhage/haematoma [d]	8	0.8
Respiratory, thoracic & mediastinal disorders		
Epistaxis	6	-

[a] Per NCI CTCAE version 4.03.

[b] Bruising: Includes all preferred terms (PTs) containing ‘bruise,’ ‘contusion,’ ‘petechiae,’ or ‘ecchymosis’

[c] Rash: Includes all PTs containing ‘rash’

[d] Haemorrhage/haematoma: Includes all PTs containing ‘haemorrhage’ or ‘haematoma’

Table 8 Haematological adverse reactions reported [a] in ≥ 20% of patients with MCL in ACE-LY-004

Adverse reaction	CALQUENCE 100 mg twice daily N=124	
	All grades (%)	Grade ≥3 (%)
Haemoglobin decreased	46	10
Platelets decreased	44	12
Neutrophils decreased	36	15

[a] Per NCI CTCAE version 4.03; based on laboratory measurements and adverse reactions.

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 4.8% of patients.

Safety data from clinical trials in chronic lymphocytic leukaemia (CLL)

The safety data described below reflect exposure to CALQUENCE (100 mg twice daily) in three randomised controlled clinical trials (AMPLIFY, ELEVATE-TN and ASCEND) in patients with CLL (see Section 5.1 Pharmacodynamic properties / *Clinical trials*).

The most common adverse reactions (≥ 20%) of any grade were infection, neutropenia, anaemia, thrombocytopenia, headache, diarrhoea, musculoskeletal pain, bruising, and nausea. The most commonly reported Grade ≥ 3 adverse reactions were infection, neutropenia, and anaemia.

AMPLIFY (acalabrutinib+venetoclax+/-obinutuzumab in previously untreated CLL)

The safety of CALQUENCE in patients with previously untreated CLL has been studied in a 3-arm, randomised, multicentre, open-label Phase 3 trial (AMPLIFY). CALQUENCE plus venetoclax, CALQUENCE plus venetoclax and obinutuzumab, or Investigator's choice of chemoimmunotherapy, either FCR (fludarabine plus cyclophosphamide plus rituximab) or BR (bendamustine plus rituximab) were administered to 867 patients with previously untreated CLL (see Section 5.1 Pharmacodynamic properties / *Clinical trials*).

The adverse reactions described in Table 9 reflect exposure to CALQUENCE in the CALQUENCE plus venetoclax and CALQUENCE plus venetoclax with obinutuzumab arms with a median duration of exposure of 12.9 months in patients with previously untreated CLL. The tabulated adverse reactions were reported in ≥5% of patients in either CALQUENCE-containing treatment arm and are considered at least possibly related to study drug.

Table 9 Adverse drug reactions in ≥5% (all grades) of patients with previously untreated CLL (AMPLIFY)

	CALQUENCE + venetoclax (AV) (N=291)		CALQUENCE + venetoclax + obinutuzumab (AVO) (N=284)		Investigator's choice of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab (FCR/BR) (N=259)	
Body systems Adverse reactions	**All grades (%)**	**Grade ≥3 [a] (%)**	**All grades (%)**	**Grade ≥3 [a] (%)**	**All grades (%)**	**Grade ≥3 [a] (%)**
Blood and lymphatic system disorders						
Leukopenia [b]	37.5	32.6	51.8	47.5	54.1	46.3
Neutropenia [b]	37.1	32.3	50.4	46.1	51.0	43.2

Body systems Adverse reactions	CALQUENCE + venetoclax (AV) (N=291)		CALQUENCE + venetoclax + obinutuzumab (AVO) (N=284)		Investigator's choice of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab (FCR/BR) (N=259)	
	All grades (%)	Grade ≥3 [a] (%)	All grades (%)	Grade ≥3 [a] (%)	All grades (%)	Grade ≥3 [a] (%)
Anaemia [b]	6.9	3.8	4.6	2.1	9.7	6.6
Thrombocytopenia [b]	5.8	2.1	12.3	9.2	15.1	10.8
Gastrointestinal disorders						
Diarrhoea	32.6	1.7	36.3	1.4	10.8	0.4
Nausea	14.8	0	21.8	0.7	35.9	0
Constipation	6.5	0.3	8.1	0	12.0	0.4
Abdominal pain [b]	7.9	1.0	8.1	0.7	4.2	0.8
Vomiting	5.5	0	6.7	0	12.0	0
General disorders and administration site conditions						
Fatigue	14.8	0.3	14.4	0	13.5	0.8
Infections and Infestations						
Infection [b]	50.9	12.4	53.9	23.6	31.7	10.0
COVID-19	18.9	2.7	20.4	6.7	2.3	1.5
COVID-19 pneumonia	7.2	5.5	12.3	11.6	2.7	2.7
Musculoskeletal and connective tissue disorders						
Arthralgia	12.7	1.0	10.9	0.4	3.5	0
Musculoskeletal pain [b]	24.1	0.7	21.8	1.1	13.1	0.8
Neoplasms benign, malignant and unspecified						
Second primary malignancy (SPM) [b]	5.2	1.7	4.2	1.8	0.8	0
SPM excluding non-melanoma skin	2.7	1.7	2.5	1.4	0.4	0
Non-melanoma skin malignancy	3.1	0	1.8	0.4	0.4	0
Nervous system disorders						
Headache	35.1	1.4	28.2	0.4	7.7	0.4
Dizziness	5.5	0	6.7	0	3.1	0
Skin and subcutaneous tissue disorders						
Bruising [b]	20.6	0	21.8	0	1.5	0
Rash [b]	12.0	0.3	16.2	1.1	12.7	0.8
Vascular disorders						
Haemorrhage/ haematoma [b]	8.9	0.7	8.5	1.1	1.5	0

[a] Per NCI CTCAE version 5.0.

[b] Includes multiple ADR terms.

The following less common clinical trial adverse drug reactions were reported in the AMPLIFY study in ≥1 but <5% of patients with previously untreated CLL treated with CALQUENCE:

- *Cardiac disorders:* atrial fibrillation/flutter [*]
- *General disorders and administration site conditions:* asthenia

- *Metabolism and nutrition disorders:* tumour lysis syndrome
- *Respiratory, thoracic and mediastinal disorders:* epistaxis

* includes multiple ADR terms.

Table 10 Treatment-emergent haematological laboratory abnormalities in patients with previously untreated CLL (AMPLIFY)

	CALQUENCE + venetoclax (AV) (N=291)		CALQUENCE + venetoclax + obinutuzumab (AVO) (N=284)		Investigator's choice of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab (FCR/BR) (N=259)	
Laboratory abnormalities	**All grades (%)**	**Grade ≥3 [a] (%)**	**All grades (%)**	**Grade ≥3 [a] (%)**	**All grades (%)**	**Grade ≥3 [a] (%)**
Investigations (findings based on test results presented as CTCAE grade shifts)						
Absolute neutrophil count decreased	78.0	38.1	81.7	53.5	79.2	50.2
Haemoglobin decreased	34.7	6.5	45.8	3.5	54.8	8.1
Platelets decreased	42.6	5.2	54.9	13.7	58.3	14.3

[a] Per NCI CTCAE version 5.0.

Serious infections when treating patients with CALQUENCE in combination with venetoclax with or without obinutuzumab

Of the 291 patients treated with CALQUENCE in combination with venetoclax, severe (Grade ≥ 3) infections were reported in 12.4% of the patients (most frequently reported COVID-19 or COVID-19 pneumonia). Fatal infections occurred in 3.1% of patients (most frequently reported COVID-19 or COVID-19 pneumonia).

Of the 284 patients treated with CALQUENCE in combination with venetoclax and obinutuzumab, severe (Grade ≥3) infections were reported in 23.6% of the patients (most frequently reported COVID-19 or COVID-19 pneumonia). Fatal infections occurred in 5.6% of patients (most frequently reported COVID-19 or COVID-19 pneumonia).

Deaths from COVID-19 in the full analysis set during treatment emergent as well as follow-up periods were reported for 10 (3.4%) patients in the AV arm, 25 (8.7%) in the AVO arm and 21 (7.2%) in the FCR/BR arm.

ELEVATE-TN (acalabrutinib+/-obinutuzumab vs chlorambucil+obinutuzumab in previously untreated CLL)

The safety of CALQUENCE plus obinutuzumab (CALQUENCE+G), CALQUENCE monotherapy, and obinutuzumab plus chlorambucil (GClb) was evaluated in a randomised, multicentre, open-label, phase 3 study, in 526 patients with previously untreated CLL. Details of the study treatment are described in Section 5.1 (Pharmacodynamic properties / *Clinical trials*).

In the CALQUENCE+G arm, adverse events led to regimen discontinuation in 11% of patients and a dose reduction of CALQUENCE in 8% of patients. In the CALQUENCE monotherapy arm, adverse events led to discontinuation in 9% and dose reduction in 3% of patients. In the GClb arm,

adverse events led to regimen discontinuation in 14% of patients and a dose reduction of chlorambucil in 28% of patients. There were no dose reductions for obinutuzumab.

The adverse reactions described below in Table 11 and Table 12 reflect exposure to CALQUENCE in the CALQUENCE+G and CALQUENCE monotherapy arms with a median duration of exposure of 27.7 months in patients with previously untreated CLL. The median duration of exposure in the GClb arm was 5.6 months.

Table 11 Non-haematological adverse reactions [a] in ≥ 5% (all grades) of patients with CLL in ELEVATE-TN

Body system Adverse reaction	**CALQUENCE plus obinutuzumab N=178**		**CALQUENCE monotherapy N=179**		**Obinutuzumab plus chlorambucil N=169**	
	All grades (%)	**Grade ≥ 3 (%)**	**All grades (%)**	**Grade ≥ 3 (%)**	**All grades (%)**	**Grade ≥ 3 (%)**
Blood and lymphatic system disorders						
Leukopenia [b]	33	32	12	11	50	46
Nervous system disorders						
Headache	40	1	37	1	12	0
Dizziness	18	0	12	0	6	0
Gastrointestinal disorders						
Diarrhoea	39	5	35	1	21	2
Nausea	20	0	22	0	31	0
Constipation	14	0	11	0	10	1
Vomiting	14	1	12	1	11	1
Abdominal pain [b]	12	2	10	0	9	0
General disorders and administration site conditions						
Fatigue	28	2	18	1	17	1
Asthenia	10	1	5	0	6	1
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain [b]	37	2	32	1	16	2
Arthralgia	22	1	16	1	5	1
Infections and infestations						
Infection [b]	69	21	65	14	44	8
Neoplasms benign, malignant and unspecified						
Second primary malignancy [b]	11	4	8	1	4	2
SPM excluding non-melanoma skin [b]	6	3	3	1	2	1
Non-melanoma skin malignancy [b]	5	1	6	0	2	1
Skin and subcutaneous tissue disorders						
Bruising [b]	34	0	26	0	5	0
Rash [b]	22	2	19	1	7	1
Vascular disorders						
Haemorrhage/haematoma [b]	13	1	9	1	4	0

[a] Per NCI CTCAE version 4.03.

[b] Includes multiple ADR terms

Table 12 Haematological adverse reactions [a] in ≥ 20% of patients with CLL in ELEVATE-TN

Adverse reaction	CALQUENCE plus obinutuzumab N=178		CALQUENCE monotherapy N=179		Obinutuzumab plus chlorambucil N=169	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Absolute neutrophil count decreased	53	35	24	13	76	50
Haemoglobin decreased	51	11	52	10	53	13
Platelets decreased	51	12	32	3	60	16

[a] Per NCI CTCAE version 4.03 based on laboratory measurements and adverse reactions

Tumour lysis syndrome in ELEVATE-TN
Tumour lysis syndrome (TLS) was reported in 2% of patients treated with CALQUENCE+G. No patients experienced TLS in the CALQUENCE monotherapy arm.

Atrial fibrillation/atrial flutter in ELEVATE-TN
Atrial fibrillation/atrial flutter was reported in patients treated with CALQUENCE+G and CALQUENCE monotherapy with an incidence of 3% and 4%, respectively, including 1% with ≥ Grade 3 atrial fibrillation/atrial flutter in the CALQUENCE+G arm. No patients experienced ≥ Grade 3 atrial fibrillation/atrial flutter in the CALQUENCE monotherapy arm.

Infusion-related reaction in ELEVATE-TN
Infusion-related reaction was reported in 14% and 40% of patients in the CALQUENCE+G and GClb arms, respectively.

ASCEND (acalabrutinib monotherapy in relapsed/refractory CLL after at least one prior therapy)

The safety of CALQUENCE versus investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab was evaluated in a randomised, multicentre, open-label, phase 3 study, in 307 patients with relapsed or refractory CLL. Details of the study treatment are described in Section 5.1 (Pharmacodynamic properties / *Clinical trials*).

In the CALQUENCE arm, adverse events led to discontinuation in 10% and dose reduction in 3% of patients. In patients receiving idelalisib plus rituximab, adverse events led to regimen discontinuation in 9% of patients and a dose reduction of idelalisib in 24%. In patients receiving bendamustine plus rituximab, adverse events led to regimen discontinuation in 9% of patients and a dose reduction of bendamustine in 14% of patients. There were no dose reductions of rituximab.

The adverse reactions described below in Table 13 and Table 14 reflect exposure to CALQUENCE with a median duration of 15.7 months, exposure to idelalisib with a median duration of 11.5 months, exposure to rituximab with a median duration of 5.5 months, and exposure to bendamustine and a median duration of 5.6 months in patients with relapsed or refractory CLL.

Table 13 Non-haematological adverse reactions [a] in ≥ 5% (all grades) of patients with CLL in ASCEND

Body system Adverse reaction	CALQUENCE N=154		Idelalisib plus rituximab N=118		Bendamustine plus rituximab N=35	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders						
Leukopenia [b]	21	18	53	49	37	34
Cardiac disorders						
Atrial fibrillation/flutter [b]	5	1	3	1	3	3
Nervous system disorders						
Headache	22	1	6	0	0	0
Dizziness	6	0	3	0	0	0
Gastrointestinal disorders						
Diarrhoea	18	1	47	24	14	0
Nausea	7	0	13	1	20	0
Constipation	7	0	8	0	14	6
Abdominal pain [b]	8	0	9	1	3	0
General disorders and administration site conditions						
Fatigue	10	1	9	0	23	3
Asthenia	5	1	4	1	9	3
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain [b]	15	1	15	2	3	0
Arthralgia	8	1	6	0	3	0
Infections and Infestations						
Infection	57	15	65	28	49	11
Neoplasms benign, malignant and unspecified						
Second primary malignancy (SPM) [b]	12	4	3	0	3	3
SPM excluding non-melanoma skin [b]	7	3	3	0	3	3
Non-melanoma skin malignancy [b]	7	1	1	0	0	0
Skin and subcutaneous tissue disorders						
Bruising [b]	12	0	3	0	0	0
Rash [b]	7	0	16	3	9	0
Vascular disorders						
Haemorrhage/haematoma [b]	13	1	4	1	6	3

[a] Per NCI CTCAE version 4.03.

[b] Includes multiple ADR terms

Table 14 Haematological adverse reactions [a] in ≥ 20% of patients with CLL in ASCEND

Haematological adverse reactions	CALQUENCE N=154		Idelalisib plus rituximab N=118		Bendamustine plus ritixumab N=35	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Absolute neutrophil count decreased	47	22	79	48	80	40
Haemoglobin decreased	47	15	44	8	57	17
Platelets decreased	33	6	40	13	54	6

[a] Per NCI CTCAE version 4.03 based on laboratory measurements and adverse reactions

Tumour lysis syndrome in ASCEND
Tumour lysis syndrome (TLS) was reported in patients treated with CALQUENCE and idelalisib plus rituximab with an incidence of 1% in both arms. The one patient experiencing TLS treated with CALQUENCE had Grade 3 TLS and bulky disease.

Post-marketing experience

The following adverse reactions have been identified during post-approval use of CALQUENCE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Vascular disorders*: hypertension
- *Cardiac disorders*: cardiac arrhythmias
- *Hepatobiliary disorders*: hepatotoxicity, drug-induced liver injury

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Acalabrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signalling molecule of the B-cell antigen

receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signalling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and tumour growth in mouse xenograft models.

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

The effect of acalabrutinib on the QTc interval was evaluated in a randomised, double-blind, double-dummy, placebo- and positive-controlled, 4-way crossover thorough QTc study in 48 healthy adult subjects. Administration of a single dose of acalabrutinib that is the 4-fold maximum recommended single dose did not prolong the QTc interval to any clinically relevant extent (i.e. ≥10 ms).

Clinical trials

Mantle cell lymphoma (MCL)

Patients with previously untreated MCL – ECHO

The safety and efficacy of CALQUENCE in patients with previously untreated MCL was evaluated in ECHO, a randomised, double-blind, placebo controlled, multicentre phase 3 study. ECHO enrolled 598 patients who were at least 65 years of age and had no intention to undergo autologous haematopoietic stem cell transplant. The study excluded patients with total bilirubin > 1.5 × upper limit of normal (ULN), AST or ALT > 2.5 × ULN, or estimated creatinine clearance of ≤ 50 mL/min. Randomisation was stratified by geographic region and simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score. The study enrolled patients during the COVID-19 pandemic.

Patients were randomised in a 1:1 ratio to receive either CALQUENCE plus bendamustine and rituximab (CALQUENCE + BR) or placebo + BR. Treatment in both arms was continued until disease progression or unacceptable toxicity, and was administered in 28-day cycles as follows:

- Induction (maximum 6 cycles):
  - CALQUENCE 100 mg (or matching placebo) orally twice daily, every day of the cycle
  - Bendamustine 90 mg/m^2 administered IV over 30 minutes on Days 1 and 2 of each cycle
  - Rituximab 375 mg/m^2 administered IV on Day 1 of each cycle.
- Maintenance – for patients remaining in response (PR or CR) after induction:
  - CALQUENCE 100 mg (or matching placebo) orally twice daily, every day of the cycle
  - Rituximab 375 mg/m^2 administered IV on Day 1 of every other cycle; ceased after a maximum of 12 additional doses of rituximab (up to Cycle 30).
- After discontinuation of rituximab, patients continued CALQUENCE 100 mg (or matching placebo) as monotherapy, taken orally twice daily until disease progression or unacceptable toxicity.

Crossover to CALQUENCE monotherapy was permitted for patients in the placebo plus BR arm at disease progression.

The median age was 71 years (range 65-86), 71% were male, 78% were Caucasian, and 93% had an ECOG performance status of 0-1. The simplified MIPI score was low (0-3) in 33%, intermediate (4-5) in 43% and high (6-11) in 24% of patients. A total of 38% of patients had tumour bulk ≥ 5 cm and 86% had Ann Arbor stage IV disease. Most (80%) had classic MCL histology, whilst 7.7% had blastoid and 5.5% had pleomorphic forms. A total of 48% 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 efficacy endpoints were Investigator-assessed (INV) PFS, INV and IRC assessed overall response rate (ORR), IRC and INV assessed duration of response (DOR) and overall survival (OS).

Efficacy results are presented in Table 15 and Figure 1. At this prespecified interim analysis, the median follow-up for PFS was 49.8 months in both arms. 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.

Table 15 Efficacy results in patients with previously untreated MCL (ECHO)

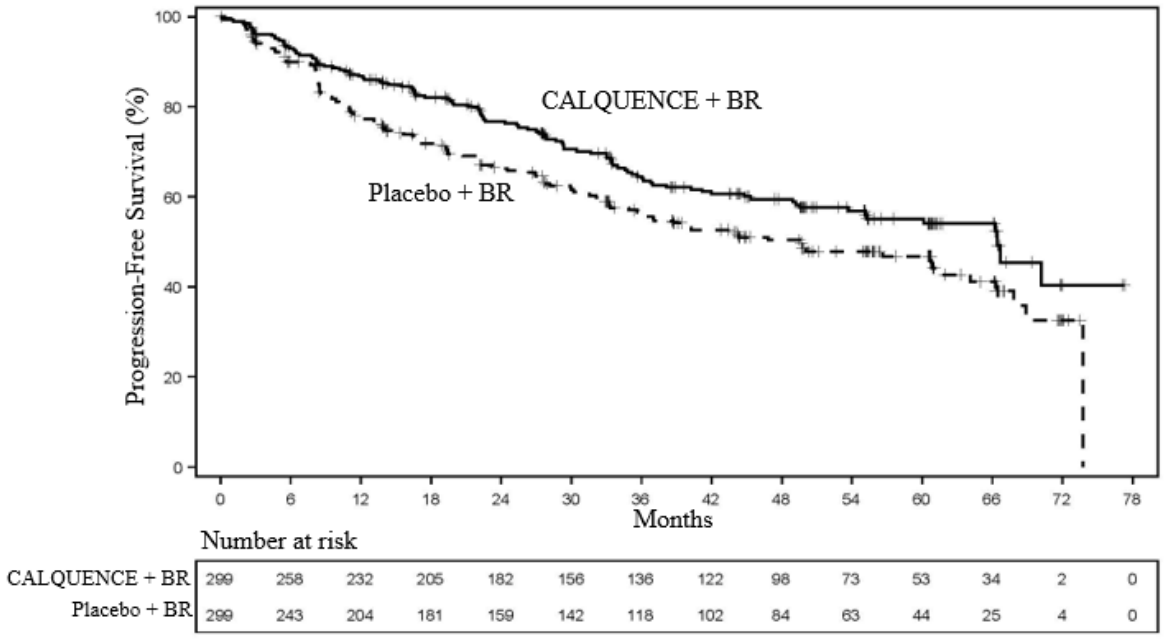
	CALQUENCE + BR N= 299	**Placebo + BR N= 299**
IRC-assessed progression-free survival (PFS)		
Median (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
HR (95% CI) (stratified) [a]	0.73 (0.57, 0.94)	
p-value [b]	0.0160	
IRC-assessed overall response rate (ORR)		
CR + PR n (%)	272 (91)	263 (88)
95% CI	87, 94	84, 91
CR n (%)	199 (67)	160 (54)
PR n (%)	73 (24)	103 (34)
p-value	0.2196	
IRC-assessed duration of response (DoR)		
Median (95% CI), months	63.5 (52.5, NE)	53.8 (37.6, 66.1)

IRC=Independent Review Committee; CI=Confidence Interval; HR=hazard ratio; CR=complete response; PR=partial response; NE=not evaluable

[a] Stratified by randomisation stratification factors: geographic region (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).

[b] 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)**



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

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.

The median age was 68 (range 42 to 90) years, 80% were male and 74% were Caucasian. At baseline, 93% of patients had an ECOG performance status of 0 or 1. The median time since diagnosis was 46 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 (52%) and ARA-C (34%). At baseline, 37% of patients had at least one tumour with a longest diameter ≥5 cm, 73% had extra nodal involvement including 51% with bone marrow involvement. The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 44% and high in 17% of patients. The median dose intensity was 98.5%.

Efficacy results are presented in Table 16 for the primary analysis, and at a 54-month final analysis (median follow-up 38.1 months).

Table 16 **Efficacy results in patients with MCL in ACE-LY-004**

	Primary analysis		**54-month final analysis**
	Investigator assessed N=124	**IRC assessed N=124**	**Investigator assessed N=124**
	n (%) (95% CI [b])	**n (%) (95% CI [b])**	**n (%) (95% CI)**
Overall response rate (ORR) [a]			
Overall response rate	100 (81%) (73, 87)	99 (80%) (72, 87)	101 (82%) (74, 88)

	Primary analysis		54-month final analysis
	Investigator assessed N=124	**IRC assessed N=124**	**Investigator assessed N=124**
	n (%) (95% CI [b])	**n (%) (95% CI [b])**	**n (%) (95% CI)**
Complete response	49 (40%) (31, 49)	49 (40%) (31, 49)	59 (48%) (39, 57)
Partial response	51 (41%) (32, 50)	50 (40%) (32, 50)	42 (34%) (26, 43)
Stable disease	11 (9%) (5, 15)	9 (7%) (3, 13)	10 (8%) (4, 14)
Progressive disease	10 (8%) (4, 14)	11 (9%) (5, 15)	10 (8%) (4, 14)
Non-evaluable [c]	3 (2%) (1, 7)	5 (4%) (1, 9)	3 (2%) (1, 7)
Duration of response (DoR)			
Median (months)	NR [1+ to 20+]	NR [0+ to 20+]	28.6 (17.5, 39.1)
% (95% CI) of responses lasting			
12 months	72 (62, 80)	72 (62, 80)	72.2 (62, 80)
18 months	63 (49, 74)	56 (38, 71)	59 (48, 68)

CI=confidence interval; NR=not reached; IRC= Independent Review Committee

[a] Per 2014 Lugano classification.

[b] 95% exact binomial confidence interval.

[c] Reasons for non-evaluable data included lack of adequate post-baseline disease assessment.

Lymphocytosis

Upon initiation of CALQUENCE, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count (ALC) increased ≥ 50% from baseline and a post baseline assessment ≥$5x10^9$) in 32% of patients in ACE-LY-004. The median time to onset of lymphocytosis was 1.1 weeks and the median duration of lymphocytosis was 6.7 weeks.

Chronic lymphocytic leukaemia (CLL)

Patients with previously untreated CLL - fixed duration therapy - AMPLIFY

The safety and efficacy of CALQUENCE in combination with venetoclax with or without obinutuzumab in previously untreated CLL was evaluated in a randomised, multicentre, open-label Phase 3 study (AMPLIFY) of 867 patients. Patients received CALQUENCE plus venetoclax, CALQUENCE plus venetoclax and obinutuzumab, or Investigator's choice of chemoimmunotherapy, either FCR (fludarabine plus cyclophosphamide plus rituximab) or BR (bendamustine plus rituximab).

Patients were randomised in a 1:1:1 ratio into 3 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 5 week 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.
- CALQUENCE plus venetoclax plus obinutuzumab (AVO): 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 5 week 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. Obinutuzumab 1,000 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 1,000 mg on Day 1 of Cycles 3-7. Each cycle was 28 days.

- Investigator's choice of chemoimmunotherapy (FCR/BR):
  - Fludarabine plus cyclophosphamide 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 years), IGHV mutational status (mutated versus unmutated), Rai stage (high risk [≥3] versus non-high risk) and geographic region (North America and Western Europe versus other). Table 17 summarises the baseline demographics and disease characteristics of the study population.

AMPLIFY included patients previously untreated for CLL without del(17p) or TP53 mutation that were 18 years of age and older. 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.

Table 17 Baseline patient characteristics in patients with previously untreated CLL (AMPLIFY)

Characteristic	**CALQUENCE + venetoclax (AV) N=291**	**CALQUENCE + venetoclax + obinutuzumab (AVO) N=286**	**Investigator's choice of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab (FCR/BR) N=290**
Age, years; median (range)	61 (31-84)	61 (29-81)	61 (26-86)
Male; %	61.2	69.2	63.1
Caucasian; %	91.1	86.7	86.9
ECOG performance status 0-1; %	90.0	95.1	90.3
Median time from diagnosis to randomisation (months)	28.5	26.1	29.6
Bulky disease with nodes ≥ 5 cm; %	38.8	35.0	42.8
Cytogenetics/FISH Category; %			
11q deletion	17.5	19.6	15.9
Complex karyotype (≥ 3 abnormalities)	15.5	16.1	14.5
Unmutated IGHV; %	57.4	59.1	59.3
Rai stage; %			
0	1.0	0.3	1.4
I	16.2	21.3	21.4
II	35.7	37.8	33.4
III	23.7	17.8	20.3
IV	23.4	22.7	23.4

The primary endpoint was IRC-assessed PFS for AV versus Investigator's choice of chemoimmunotherapy (FCR/BR) arm as assessed by International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) 2018 criteria. Additional efficacy endpoints were IRC-assessed PFS of AVO versus Investigator's choice (FCR/BR) arm and OS in both AV arm vs. Investigator's choice (FCR/BR) arm and AVO vs Investigator's choice (FCR/BR) arm.

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 in patients treated with AV compared to FCR/BR. The secondary endpoint median for Investigator-assessed PFS was not reached.

With a median follow-up of 42.0 months, IRC-assessed PFS indicated a 58% statistically significant reduction in risk of disease progression or death in patients treated with AVO compared to FCR/BR. The secondary endpoint median for Investigator-assessed PFS was not reached.

Efficacy results are presented in Table 18. The Kaplan-Meier curve for IRC-PFS is shown in Figure 2.

Table 18 Efficacy results in patients with previously untreated CLL (AMPLIFY) (ITT population)

	CALQUENCE + venetoclax (AV) N=291	**CALQUENCE + venetoclax + obinutuzumab (AVO) N=286**	**Investigator's choice of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab (FCR/BR) [b] N=290**
Progression-free survival (PFS) [a]			
Number of events (%)	89 (30.6)	56 (19.6)	95 (32.8)
PD, n (%)	77 (26.5)	23 (8.0)	66 (22.8)
Death events (%)	12 (4.1)	33 (11.5)	29 (10.0)
Median (95% CI), months	NC (51.1, NC)	NC (NC, NC)	47.6 (43.3, NC)
Hazard ratio [c] (95% CI)	0.65 (0.49, 0.87)	0.42 (0.30, 0.59)	-
P-value	0.0038	<0.0001	-
Overall Survival (OS) [d]			
Death events (%)	23 (7.9)	37 (12.9)	44 (15.2)
Hazard ratio [c] (95% CI)	0.42 (0.25, 0.70) [e]	0.75 (0.48, 1.16)	-

PD=progressive disease; NC=not calculable; CI=confidence interval; IRC= Independent Review Committee

[a] Per IRC assessment

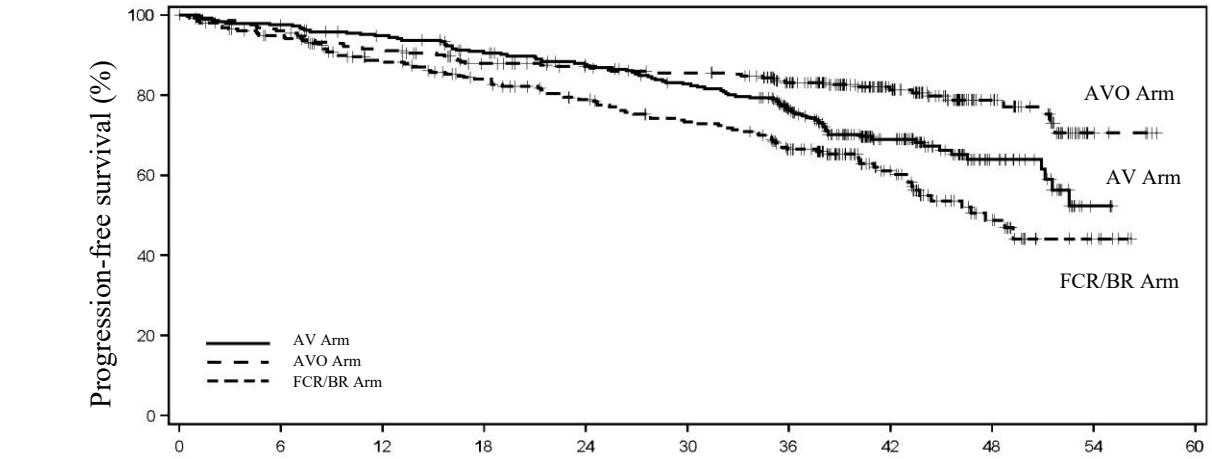
[b] Approximately 50% of patients were planned to be treated with FCR and 50% treated with BR per investigator's choice

[c] Based on stratified Cox-Proportional-Hazards model

[d] Based on data cutoff 30 Oct 2024

[e] The p-value is not significant after adjusting for multiplicity

Figure 2 **Kaplan-Meier curve of IRC-assessed PFS in patients with previously untreated CLL (AMPLIFY) (ITT population)**



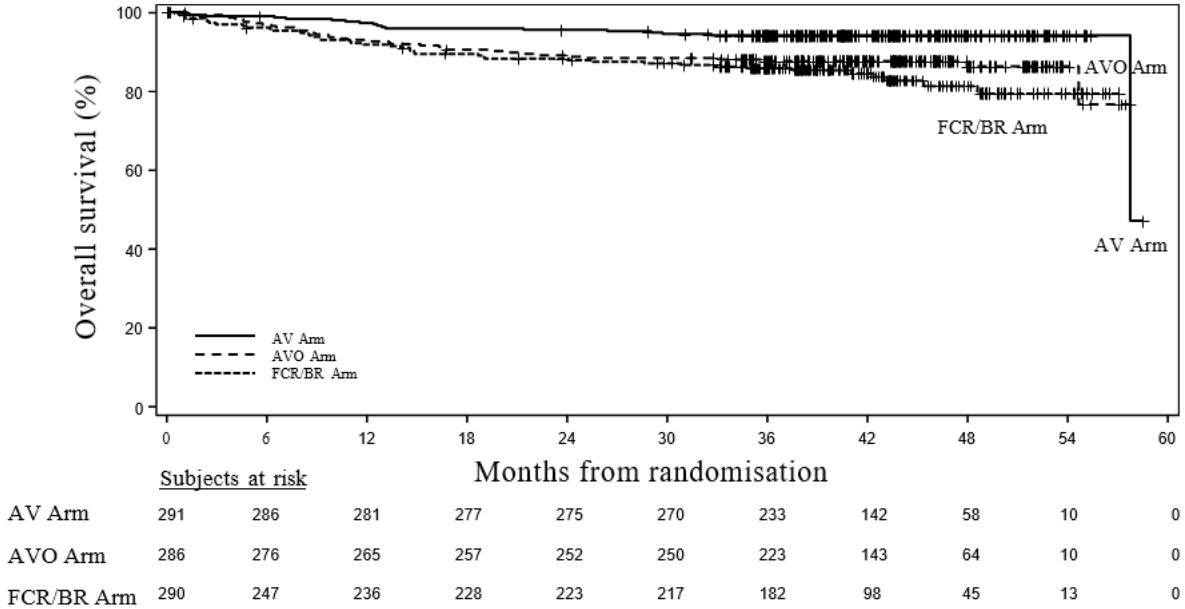
Subjects at risk											
AV Arm	291	282	269	251	237	219	177	102	35	3	0
AVO Arm	286	272	258	237	225	219	191	116	51	7	0
FCR/BR Arm	290	236	208	189	170	154	127	66	28	6	0

AV=acalabrutinib plus venetoclax; AVO=acalabrutinib plus venetoclax and obinutuzumab; BR=bendamustine plus rituximab; FCR=fludarabine plus cyclophosphamide and rituximab

The benefit of CALQUENCE in combination with venetoclax with or without obinutuzumab on PFS risk reduction was consistent across all clinically relevant subgroups. In patients with unmutated IGHV, the PFS HRs of CALQUENCE in combination with venetoclax or CALQUENCE in combination with venetoclax and obinutuzumab versus FCR/BR arm were 0.69 [95% CI (0.48, 0.97)] and 0.35 [95% CI (0.23, 0.53)], respectively.

As shown in Figure 3 at the time of the interim analysis (approximately 10% OS maturity), a total of 18 (6.2%) and 42 deaths (14.5%) were observed in Arm A (AV) and C (FCR/BR), respectively. OS HR was 0.33 (95% CI: 0.18–0.56; nominal p<0.0001). Additionally, at approximately 14% OS maturity, a total of 37 (12.9%) deaths were observed in Arm B (AVO). OS HR compared to Arm C was 0.76 (95% CI: 0.49- 1.18, nominal p=0.2224).

Figure 3 Kaplan-Meier curve of OS in patients with previously untreated CLL (AMPLIFY) (ITT population)



AV=acalabrutinib plus venetoclax; AVO=acalabrutinib plus venetoclax and obinutuzumab; BR=bendamustine plus rituximab; FCR=fludarabine plus cyclophosphamide and rituximab

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. 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 19 summarises the baseline demographics and disease characteristics of the study population.

Table 19 Baseline patient characteristics in patients with previously untreated CLL (ELEVATE-TN)

Characteristic	CALQUENCE + obinutuzumab (G) N=179	CALQUENCE monotherapy N=179	Obinutuzumab + chlorambucil (GClb)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) of CALQUENCE+G arm versus GClb arm as assessed by an IRC per 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 20. The Kaplan-Meier curves for PFS are shown in Figure 4.

Table 20 Efficacy results in patients with CLL (ELEVATE-TN)

	CALQUENCE plus obinutuzumab N=179	CALQUENCE monotherapy N=179	Obinutuzumab plus chlorambucil N=177
Progression-free survival (PFS) [a]			
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 [b] (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-

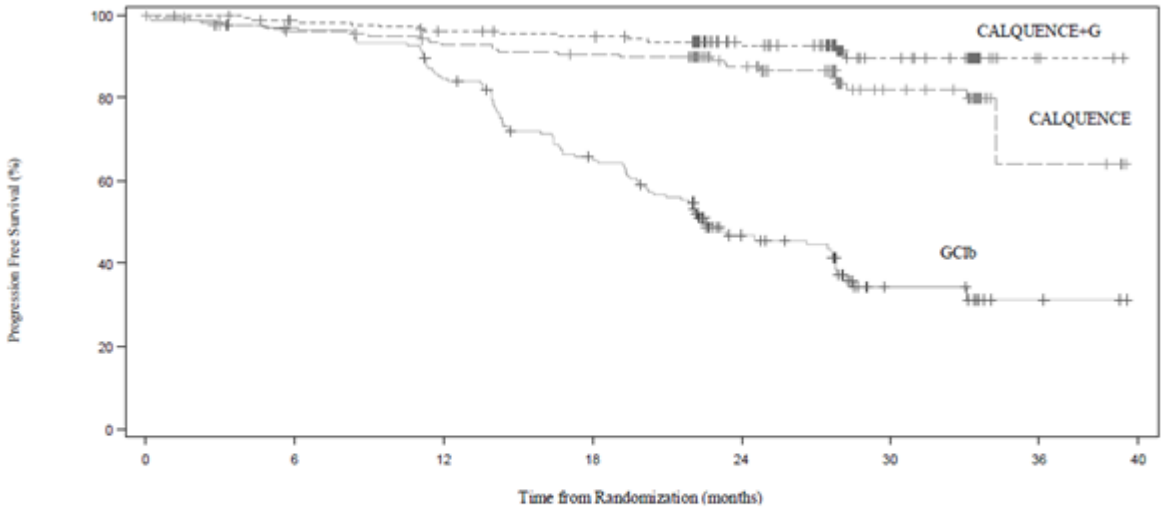
	CALQUENCE plus obinutuzumab N=179	CALQUENCE monotherapy N=179	Obinutuzumab plus chlorambucil N=177
P-value	< 0.0001	< 0.0001	-
24 months estimate, % (95% CI)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
Overall response rate (ORR) [a] (CR + CRi + nPR + PR)			
ORR, n (%); (95% CI)	168 (93.9); (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; IRC=independent review committee

[a] Per IRC assessment

[b] Based on stratified Cox proportional hazards model

Figure 4 Kaplan-Meier curve of IRC-assessed PFS in patients with CLL (ELEVATE-TN)(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 0.15 [95% CI (0.09, 0.25)], respectively.

With long term data, the median follow-up was 58.2 months for CALQUENCE+G arm, 58.1 months for CALQUENCE arm and 58.2 months for the GClb arm. The median investigator-assessed PFS for CALQUENCE+G and CALQUENCE monotherapy was not reached; and was 27.8 months in GClb arm. At the time of most recent data cut off, a total of 72 patients (40.7%) originally randomised to the GClb arm crossed over to CALQUENCE monotherapy. The median overall survival had not been reached in any arm with a total of 76 deaths: 18 (10.1%) in the CALQUENCE+G arm, 30 (16.8%) in the CALQUENCE monotherapy arm, and 28 (15.8%) in the GClb arm. The time to next treatment was prolonged for CALQUENCE+G arm (HR=0.14 [95% CI: 0.09, 0.21]) and CALQUENCE only arm (HR=0.27 [95% CI: 0.19, 0.38]) compared to GClb arm.

Table 21 Efficacy results per investigator assessment in patients with CLL (ELEVATE-TN)

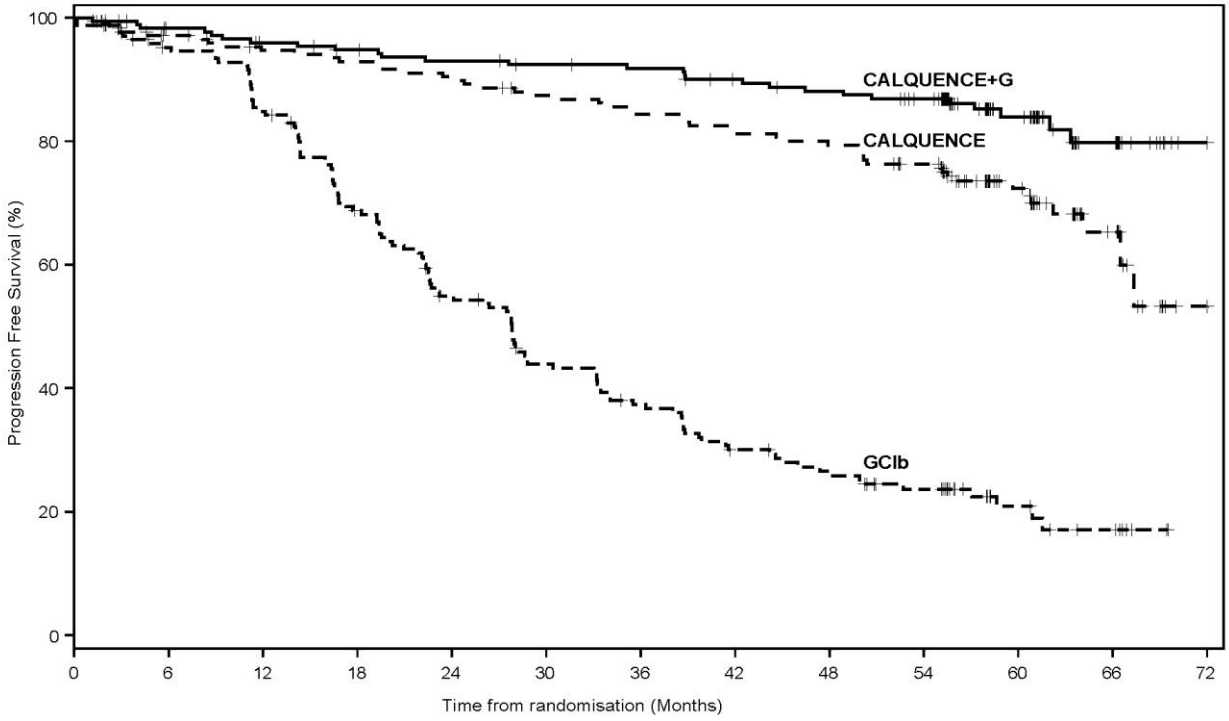
	CALQUENCE plus obinutuzumab N=179	**CALQUENCE monotherapy N=179**	**Obinutuzumab plus chlorambucil N=177**
Progression-free survival (PFS)			
Number of events (%)	27 (15.1)	50 (27.9)	124 (70.1)
PD, n (%)	14 (7.8)	30 (16.8)	112 (63.3)
Death events (%)	13 (7.3)	20 (11.2)	12 (6.8)
Median (95% CI), months [a]	NR	NR (66.5, NR)	27.8 (22.6, 33.2)
HR (95% CI) [b]	0.11 (0.07, 0.16)	0.21 (0.15, 0.30)	-
Overall survival (OS)			
Death events (%)	18 (10.1)	30 (16.8)	28 (15.8)
HR (95% CI) [b]	0.55 (0.30, 0.99)	0.98 (0.58, 1.64)	-

CI=confidence interval; HR=hazard ratio; NR=not reached; PD=progressive disease

[a] 95% confidence interval based on Kaplan-Meier estimation

[b] Estimate based on stratified Cox-Proportional-Hazards model for Hazard Ratio (95% CI) stratified by 17p deletion status (yes vs no)

Figure 5 Kaplan-Meier curve of Investigator-assessed PFS in patients with CLL (ELEVATE-TN)(ITT population)



Number of patients at risk																									
Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72
CALQUENCE	179	167	163	158	156	155	153	150	149	146	142	141	137	135	133	130	129	124	120	93	63	39	22	6	1
CALQUENCE+G	179	175	170	168	164	163	160	157	156	156	153	152	151	146	144	141	140	138	133	99	65	39	27	7	1
GClb	177	163	156	153	139	125	110	100	86	82	67	66	56	49	44	40	38	31	30	20	13	8	7	2	0

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. 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/m^2/500 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. Table 22 summarises the baseline demographics and disease characteristics of the study population.

Table 22 Baseline patient characteristics in patients with CLL (ASCEND)

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 23. The Kaplan-Meier curve for PFS is shown in Figure 6.

Table 23 Efficacy results in patients with CLL (ASCEND)

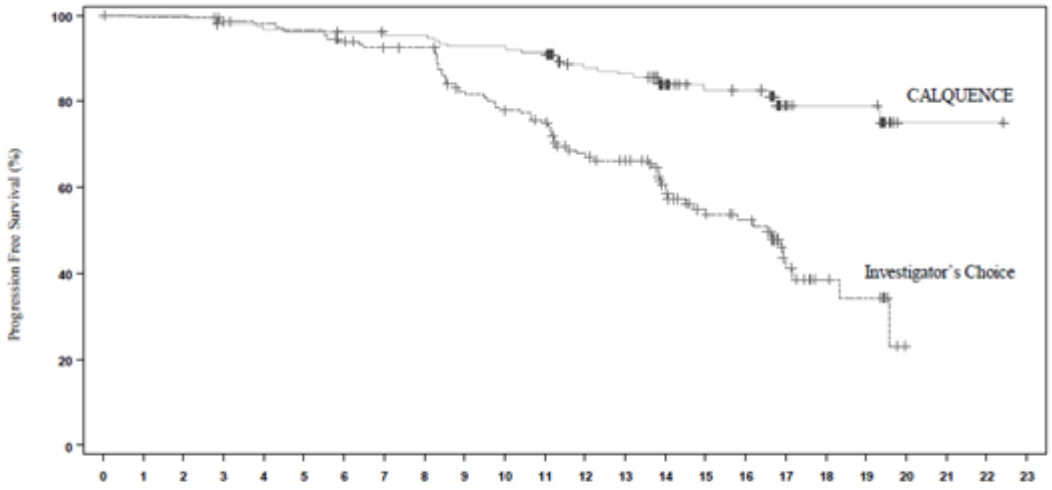
	CALQUENCE monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Progression-free survival (PFS) [a]		
Number of events (%)	27 (17.4)	68 (43.9)
PD, n (%)	19 (12.3)	59 (38.1)
Death events (%)	8 (5.2)	9 (5.8)
Median (95% CI), months	NR	16.5 (14.0, 17.1)
HR (95% CI) [b]	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 (ORR) [a] (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

[a] Per Independent Review Committee (IRC) assessment

[b] Based on stratified Cox-Proportional-Hazards model

Figure 6 **Kaplan-Meier curve of IRC-assessed PFS in patients with CLL (ASCEND)(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			

At the final analysis, with a median follow-up of 46.5 months for CALQUENCE and 45.3 months for the IR/BR, 72% reduction in risk of investigator-assessed disease progression or death was observed for patients in the CALQUENCE arm. The median investigator-assessed PFS was not reached in CALQUENCE and was 16.8 months in IR/BR. The median investigator-assessed PFS in patients with 17p deletion per IWCLL criteria was not reached in CALQUENCE arm and was 13.8 months in IR/BR arm.

At the time of final analysis, median overall survival had not been reached in any arm with a total of 95 deaths: 41 (26.5%) in the CALQUENCE monotherapy arm and 54 (34.8%) in the IR/BR arm.

Table 24 **Efficacy results at final analysis per INV assessments in patients with CLL (ASCEND)**

	CALQUENCE monotherapy N=155	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Progression-free survival (PFS) [a]		
Number of events (%)	62 (40.0)	119 (76.8)
PD, n (%)	43 (27.7)	102 (65.8)
Death events (%)	19 (12.3)	17 (11.0)
Median (95% CI), months	NR	16.8 (14.1, 22.5)
HR (95% CI) [c]	0.28 (0.20, 0.38)	
Overall survival (OS) [b]		
Death events (%)	41 (26.5)	54 (34.8%)
HR (95% CI) [c]	0.69 (0.46, 1.04)	-

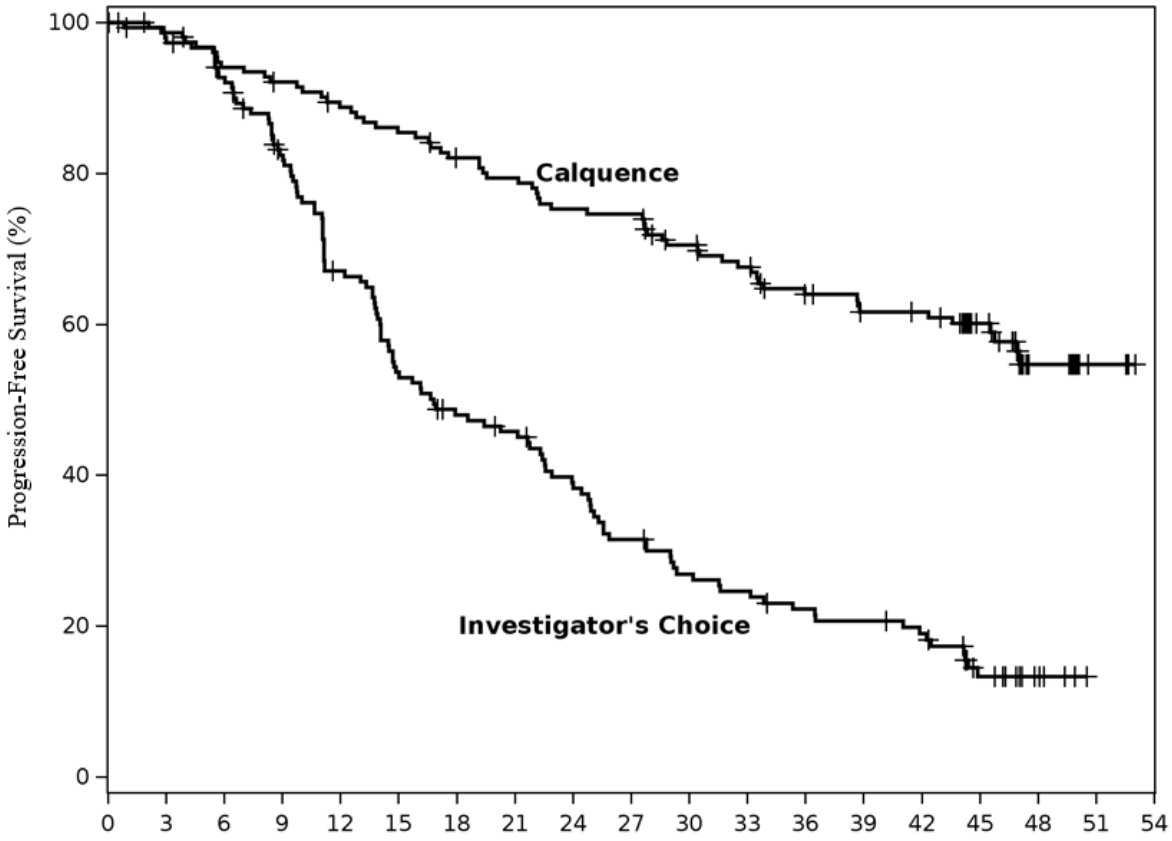
CI=confidence interval; HR=hazard ratio; NR=not reached; PD=progressive disease

[a] Per INV assessment

[b] Median OS not reached for both arms P=0.0783 for OS

[c] Based on stratified Cox-Proportional-Hazards model

Figure 7 Kaplan-Meier curve of Investigator-assessed PFS in patients with CLL (ASCEND)(ITT population)



Number of patients at risk																			
Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Calquence	155	151	143	139	133	128	121	117	111	110	100	94	85	80	79	52	21	4	0
Investigator's Choice	155	147	138	118	95	76	66	62	52	42	35	32	28	26	23	12	5	0	

Investigator-assessed PFS results for CALQUENCE at final analysis were consistent across subgroups, including high risk features and were consistent with the primary analysis.

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 (0.75 to 2.5 times the approved recommended single dose). 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 (AUC_{24h}) and maximum plasma 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.

CALQUENCE tablets and CALQUENCE capsules have been demonstrated to be bioequivalent. Geometric mean PK exposures (C_{max} and AUC_{last} or AUC_{inf}) of acalabrutinib and ACP-5862 were similar (< 4% difference) between the tablet and capsule, with the 90% confidence intervals for geometric mean ratios within the pre-defined bioequivalence margin of 80% and 125%.

Absorption

The median (min-max) time to peak plasma concentrations (T_{max}) was 0.5 (0.2, 3.0) hours for acalabrutinib, and 0.75 (0.5, 4.0) hours for ACP-5862, following administration of acalabrutinib tablet. The absolute bioavailability of CALQUENCE was 25% following oral administration of acalabrutinib capsule.

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 metabolised 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.

Acalabrutinib may inhibit intestinal BCRP substrates (see Section 4.5 Interactions with other medicines and other forms of interactions), while ACP-5862 may inhibit MATE1 (see Section 4.5 Interactions with other medicines and other forms of interactions) at clinically relevant concentrations. Acalabrutinib does not inhibit MATE1, while ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

Excretion

Following a single oral dose of 100 mg acalabrutinib tablet, the median terminal elimination half-life ($t_{½}$) of acalabrutinib was 1.3 (range: 0.8 to 9.0) hours. The median $t_{½}$ of the active metabolite, ACP-5862, was 7.3 hours (range: 2.5 to 10.1) 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 [^{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.

Specific populations

Age, race, and body weight

Age (32 to 90 years), sex, race (Caucasian, African American), and body weight (40 to 149 kg) did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862, based on population PK analysis.

Renal impairment

Acalabrutinib undergoes minimal renal elimination. Based on population PK analysis, no clinically relevant PK difference was observed in 543 patients with mild or moderate renal impairment (eGFR

≥30 mL/min/1.73 m^2, as estimated by MDRD (modification of diet in renal disease equation)). Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR <29 mL/min/1.73 m^2, MDRD) or renal impairment requiring dialysis.

Hepatic impairment

Acalabrutinib is metabolised in the liver. In 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 PK difference was observed in subjects with mild (n=79) or moderate (n=6) hepatic impairment (total bilirubin between 1.5 to 3 times the upper limit of normal [ULN] and any AST) relative to subjects with normal (n=651) hepatic function (total bilirubin and AST within ULN).

Drug interaction studies

Effect of CYP3A inhibitors on acalabrutinib

Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased the acalabrutinib C_{max} by 3.9-fold and AUC by 5.1-fold in healthy subjects.

Physiologically based pharmacokinetic (PBPK) simulations with acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased acalabrutinib C_{max} and AUC increased by 2- to almost 3-fold (see Section 4.5 Interactions with other medicines and other forms of interactions).

Effect of CYP3A inducers on acalabrutinib

Co-administration with a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} by 68% and AUC by 77% in healthy subjects (see Section 4.5 Interactions with other medicines and other forms of interactions).

Gastric acid reducing medicines

Co-administration of acalabrutinib tablet with a proton pump inhibitor (20 mg rabeprazole, twice daily for 3 days) increased AUC by 17% (up to 31% increase, based on upper limit of 90% confidence interval) and decreased C_{max} by 24% (up to 45% decrease, based on lower limit of 90% confidence interval), with a delay in T_{max} (up to 1 hour, approximately).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Acalabrutinib was not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or in an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core: mannitol, microcrystalline cellulose, hyprolose, and sodium stearylfumarate.

Tablet coating: hypromellose, copovidone, titanium dioxide, macrogol 3350, medium chain triglycerides, iron oxide yellow, iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Polyamide-aluminium-polyvinylchloride/aluminium blisters. Cartons of 56 tablets and 60 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

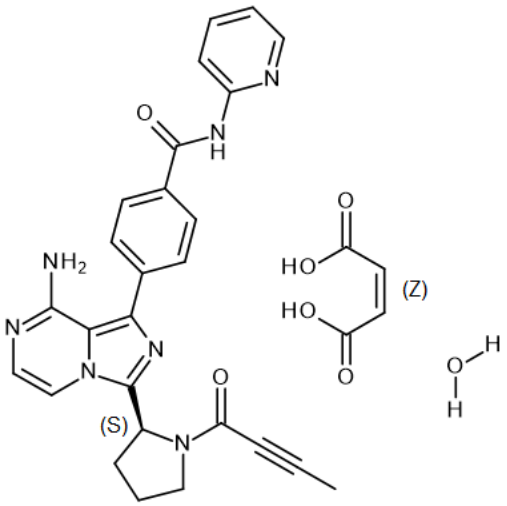
6.7 PHYSICOCHEMICAL PROPERTIES

Acalabrutinib maleate monohydrate is a white to pale brown powder with pH-dependent solubility. It is freely soluble in water at pH values below 3 and practically insoluble at pH values above 6.

Chemical structure

The chemical name is 4-{8-Amino-3-[(2*S*)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-*a*]pyrazin-1-yl}-*N*-(pyridin-2-yl)benzamide (2*Z*)-2-butenedioic acid hydrate (1:1:1).

Figure 8 Chemical structure of acalabrutinib maleate monohydrate



Molecular formula: $C_{26}H_{23}N_7O_2.C_4H_4O_4.H_2O$

Molecular weight: 599.59

CAS number

CAS 2641500-53-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

13 October 2022

10 DATE OF REVISION

16 July 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.5	Additional pack size – 60 tablets

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