NEW ZEALAND DATA SHEET

1. PRODUCT NAME

CALQUENCE® 100 mg Film-coated Tablets

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.

3. PHARMACEUTICAL FORM

Film-coated tablets

The CALQUENCE 100 mg film-coated tablet is 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 MCL who are ineligible for autologous hematopoietic stem cell transplantation (HSCT).

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).

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).

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 Data Sheet of each of the medicines for dosing information. For details of the combination regimens, see section 5.1 Pharmacodynamic Properties.

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 Data Sheet of each of the combination medicines for recommended dosing information (for details of the combination regimens, see section 5.1 Pharmacodynamic Properties).

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, instruct the patient to take the next dose at its regularly scheduled time. Extra tablets of CALQUENCE should not be taken to make up for a missed dose.

Dose adjustments

Adverse reactions

Recommended dose modifications of CALQUENCE for Grade 3 or greater adverse reactions in patients receiving CALQUENCE monotherapy and CALQUENCE in combination with obinutuzumab or in combination with venetoclax with or without obinutuzumab are provided in Table 1.

Table 1 Recommended dose adjustments for adverse reactions [a]

Event	**Adverse reaction occurrence**	**Dose modification** *(Starting dose = 100 mg twice daily)*
Grade 3 or greater non-haematologic 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

Dose modifications for adverse reactions in patients receiving CALQUENCE in combination with bendamustine and rituximab are listed in Table 2

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 occurrence). For 3rd occurrence with no significant bleeding, resume CALQUENCE with reduced dose (100 mg once daily). For 3rd occurrence with significant bleeding or 4th occurrence, discontinue CALQUENCE.
Other haematologic 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 greater non-haematologic 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 Data Sheet.

[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.

Refer to the Data Sheet of each of the medicines used in combination with CALQUENCE for additional information for management of toxicities.

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. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg twice daily.

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.

Use in the elderly

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

Use in 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

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 the combined safety database of 1478 patients with haematologic 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 haematologic malignancies treated with CALQUENCE monotherapy. Consider prophylaxis in patients who are at increased risk for opportunistic infections.

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. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Cytopenias

In the combined safety database of 1478 patients with haematologic malignancies, patients treated with CALQUENCE monotherapy 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 haematologic 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.

Atrial fibrillation and flutter

In the combined safety database of 1478 patients with haematologic malignancies treated with CALQUENCE monotherapy, atrial fibrillation/flutter of any grade occurred in 7.4% of patients and Grade 3 or higher occurred in 2.3% 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.

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 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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. If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg twice daily.

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 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Use in pregnancy - Category C
Based on findings in animals, CALQUENCE may cause foetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of acalabrutinib to pregnant rabbits during organogenesis resulted decreased fetal body weights and delayed skeletal ossification at maternal exposures (AUC) approximately 3.6 times exposures in patients at the recommended dose of 100 mg twice daily. This dose was maternotoxic. Dystocia was observed in a rat study (see below). Advise pregnant women of the potential risk to a foetus.

In a combined fertility and embryofoetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting prior to mating through the period of organogenesis. No effects on embryofoetal development or survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 16-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 a rat reproductive study involving dosing animals from implantation throughout gestation, parturition and lactation, dystocia (prolonged /difficult labour) was observed at ≥100 mg/kg/day, yielding exposures > 3.5-times the clinical exposure at 100 mg twice daily. Dystocia was not observed in rats at 50 mg/kg/day, associated with exposures approximately equivalent to the clinical exposure at 100 mg twice daily.

Breast-feeding

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 lactating women not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose.

Fertility

In a fertility study in rats, there were no effects of acalabrutinib on fertility in male rats at exposures 16-times, or in female rats at exposures 14-times the AUC observed in patients at the recommended dose of 100 mg twice daily.

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

Overall Summary of Adverse Drug Reactions

CALQUENCE Monotherapy

The overall safety profile of CALQUENCE monotherapy is based on pooled data from 1478 patients with haematologic malignancies receiving CALQUENCE monotherapy. The median duration of CALQUENCE monotherapy treatment across the pooled dataset was 38.2 months.

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

The most commonly reported (≥ 5%) Grade 3 or higher adverse drug reactions in patients receiving CALQUENCE monotherapy were infection, leukopenia, neutropenia, anaemia, second primary malignancies, thrombocytopenia and second primary malignancies excluding non-melanoma skin.

Dose reductions due to adverse events were reported in 5.9% of patients. Discontinuation due to adverse events were reported in 14.6% of the patients. The median dose intensity was 98.2%.

CALQUENCE in combination with obinutuzumab

The overall safety profile of CALQUENCE in combination with obinutuzumab is consistent with the known safety profile of CALQUENCE monotherapy and that of obinutuzumab.

CALQUENCE in combination with bendamustine and rituximab

The overall safety profile of CALQUENCE in combination with bendamustine and rituximab is based on pooled data from 297 patients receiving CALQUENCE in combination with bendamustine and rituximab. The median duration of CALQUENCE exposure in patients treated with CALQUENCE in combination with bendamustine and rituximab was 28.6 months.

The most common (≥ 20%) adverse drug reactions (ADRs) of any grade reported in patients receiving CALQUENCE in combination with bendamustine and rituximab were infection, leukopenia, neutropenia, nausea, rash, diarrhoea, musculoskeletal pain, headache, fatigue, vomiting, constipation, anaemia and thrombocytopenia.

The most commonly reported (≥ 5%) Grade 3 or higher adverse drug reactions were leukopenia, neutropenia, infection, rash, thrombocytopenia, anaemia, second primary malignancies and second primary malignancies excluding non-melanoma skin.

Dose reductions due to adverse events were reported in 10.1% of patients. Discontinuation due to adverse events were reported in 42.8% of the patients. The median dose intensity was 96.3%.

The adverse drug reactions for patients receiving CALQUENCE in combination with bendamustine or rituximab are listed in Table 5.

CALQUENCE in combination with venetoclax with or without obinutuzumab

The overall safety profile of CALQUENCE in combination with venetoclax with or without obinutuzumab is based on pooled data from 291 patients receiving CALQUENCE in combination with venetoclax and 284 patients receiving CALQUENCE in combination with venetoclax and obinutuzumab. The median duration of CALQUENCE exposure in patients treated with CALQUENCE in combination with venetoclax with or without obinutuzumab was 12.9 months.

The most common (≥ 20%) adverse drug reactions (ADRs) of any grade reported in patients receiving CALQUENCE in combination with venetoclax were infection, leukopenia, neutropenia, headache, diarrhoea, musculoskeletal pain and bruising.

The most commonly reported (≥ 5%) Grade 3 or higher adverse drug reactions in patients receiving CALQUENCE in combination with venetoclax were leukopenia and neutropenia.

CALQUENCE dose reductions in patients due to adverse events were reported in 5.8% of patients receiving CALQUENCE in combination with venetoclax. Discontinuation due to adverse events were reported in 7.6% of the patients. The median dose intensity was 99.5%.

The most common (≥ 20%) adverse drug reactions (ADRs) of any grade reported in patients receiving acalabrutinib in combination with venetoclax and obinutuzumab were infection, leukopenia, neutropenia, diarrhoea, headache, nausea, musculoskeletal pain and bruising.

The most commonly reported (≥ 5%) Grade 3 or higher adverse drug reactions in patients receiving CALQUENCE in combination with venetoclax and obinutuzumab were leukopenia, neutropenia, infection and thrombocytopenia.

CALQUENCE dose reductions due to adverse events were reported in 6.3% of patients receiving CALQUENCE in combination with venetoclax and obinutuzumab. Discontinuation due to adverse events were reported in 13.7% of the patients. The median dose intensity was 98.1%.

The adverse drug reactions for patients receiving CALQUENCE in combination with venetoclax with or without obinutuzumab are listed in Table 9.

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.

Adverse drug reactions are listed according to body system in MedDRA. Within each body system, 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 <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data).

Mantle Cell Lymphoma (MCL)

The safety data described below reflect exposure to CALQUENCE (100 mg twice daily with or without BR) in 421 patients with MCL (see section 5.1 Pharmacodynamic Properties - Clinical Efficacy and Safety).

ECHO

The safety data described in this section reflect exposure to CALQUENCE (100 mg approximately every 12 hours) in combination with bendamustine and rituximab in 297 patients with previously untreated MCL in ECHO (see Section 5.1). The median duration of treatment with CALQUENCE was 28.6 (range: 0.1 to 80) months. A total of 171 (57.6%) patients were treated with CALQUENCE for > 24 months and 122 (41.1%) 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 associated reactions (19.5%), pneumonia (9.4%), pyrexia (5.7%), febrile neutropenia (3.4%), atrial fibrillation (3.0%), sepsis (2.7%) and anaemia (2.4%).

Fatal adverse reactions were reported in 12.1% who received CALQUENCE including COVID-19 pneumonia (5.1%), COVID-19 (2.7%), pneumonia (1.0%), sepsis (0.3%), neuroendocrine carcinoma (0.3%) and pneumonitis (0.3%).

Dose reductions and discontinuation due to any adverse reaction were reported in 10.1% and 42.8% of patients, respectively.

Table 5 and Table 6 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE.

Table 5 Common Adverse Reactions (≥ 15% All Grades) in Patients with Previously Untreated MCL (ECHO)

Body System Adverse Reactions [a]	CALQUENCE + BR N=297		Placebo + BR N=297	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections				
Infection [b]	78.5	43.1	72.1	35.4
Upper respiratory tract infection [c]	26.3	0.3	22.2	1.0
Lower respiratory tract infection [d]	36.0	22.2	27.6	16.5
Blood and lymphatic system disorders				
Leukopenia [e]	58.9	53.2	61.3	54.5
Neutropenia [f]	77.4	57.9	78.5	52.5
Anaemia [g]	82.8	12.5	70.0	13.8
Thrombocytopenia [h]	70.7	18.9	62.3	16.5
Lymphocytosis [i]	97.6	87.2	96.6	88.9
Nervous system disorders				
Headache	30.3	1.3	14.1	0.7
Gastrointestinal disorders				
Diarrhoea	37.4	3.0	27.9	2.4
Nausea	42.8	1.3	37.7	1.3
Constipation	24.6	1.0	25.3	0.3
Vomiting	25.6	0.7	13.8	1.0

Body System Adverse Reactions [a]	CALQUENCE + BR N=297		Placebo + BR N=297	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Musculoskeletal and connective tissue disorder				
Musculoskeletal pain [j]	34.3	3.7	24.6	1.3
Arthralgia	17.5	0.7	16.5	1.0
General disorders and administrative site conditions				
Fatigue [k]	36.7	3.7	32.3	4.4
Neoplasms benign, malignant and unspecified				
SPM [l]	17.8	7.4	14.5	7.4
Skin and subcutaneous tissue disorders				
Rash [m]	39.1	9.8	25.9	2.4
Vascular disorders				
Haemorrhage/Haematoma [n]	15.5	1.0	7.7	2.4

[a] Per NCI CTCAE version 4.03.

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

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

[d] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection.

[e] Includes neutropenia, neutrophil count decreased, febrile neutropenia, lymphocyte count decreased, leukopenia, white blood cell count decreased, neutropenic sepsis, lymphopenia, granulocytopenia, monocyte count decreased, CD19 lymphocytes decreased.

[f] Includes neutropenia, neutrophil count decreased, and related laboratory data.

[g] Includes anaemia, red blood cell count decreased, and related laboratory data.

[h] Includes thrombocytopenia, platelet count decreased, and related laboratory data.

[i] Includes lymphocytosis, lymphocyte count increased, and related laboratory data.

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

[k] Includes asthenia, fatigue, and lethargy.

[l] Includes second primary malignancy excluding non-melanoma skin and non-melanoma skin malignancy.

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

[n] Includes haemorrhage, haematoma, haemoptysis, haematuria, menorrhagia, haemarthrosis, and epistaxis.

Other clinically relevant adverse reactions (all grades incidence < 15%) in patients receiving CALQUENCE + BR included:

- *Cardiac disorders:* Atrial Fibrillation/Flutter (6.7%)
- *Respiratory, thoracic and mediastinal disorders:* Epistaxis (2.7%)
- *Nervous system disorders:* Dizziness (14.5%)
- *Gastrointestinal disorders:* Abdominal pain (12.1%)
- *General disorders and administration site conditions:* Asthenia (10.4%)
- *Metabolism and nutrition disorders:* Tumour lysis syndrome (1.3%)
- *Neoplasms benign, malignant and unspecified:* Second primary malignancy excluding non-melanoma skin (9.8%), non-melanoma skin malignancy (11.1%)
- *Skin and subcutaneous tissue disorders:* Bruising (14.1%)

Table 6 Non-Haematologic 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 (%)
Uric acid increase	45.1	45.1	40.1	40.1
ALT increase	43.4	6.7	40.7	2.4
AST increase	52.9	5.4	49.8	3.4
Bilirubin increase	18.9	2.0	12.5	2.0

ACE-LY-004

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

Body System Adverse Reactions	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 National Cancer Institute Common Terminology Criteria for Adverse Events (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 Haematologic adverse reactions reported [a] in ≥20% of patients with MCL in ACE-LY-004

Haematologic Adverse Reactions	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 National Cancer Institute Common Terminology Criteria for Adverse Events (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.

Chronic Lymphocytic Leukaemia (CLL)

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

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 (Patients with Previously Untreated CLL)

The safety of CALQUENCE in patients with previously untreated CLL has been studied in a 3-arm, randomised, multi-centre, 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).

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 Chronic Lymphocytic Leukaemia (CLL) in the AMPLIFY Trial

Body systems Adverse Reactions	CALQUENCE + venetoclax (N=291)		CALQUENCE + venetoclax + obinutuzumab (N=284)		Investigator's choice of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab (N=259)	
	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

Body systems Adverse Reactions	CALQUENCE + venetoclax (N=291)		CALQUENCE + venetoclax + obinutuzumab (N=284)		Investigator's choice of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab (N=259)	
	All Grades (%)	Grade ≥3 [a] (%)	All Grades (%)	Grade ≥3 [a] (%)	All Grades (%)	Grade ≥3 [a] (%)
Neutropenia [b]	37.1	32.3	50.4	46.1	51.0	43.2
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
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 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

[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 for Patients receiving CALQUENCE in combination with venetoclax with or without obinutuzumab in AMPLIFY

	CALQUENCE + venetoclax (N=291)		CALQUENCE + venetoclax + obinutuzumab (N=284)		Investigator's choice of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab (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 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

ELEVATE-TN (Patients with 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 efficacy and safety*).

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 CALQENCE+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-Haematologic 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/Hematoma†	13	1	9	1	4	0

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

[b] Includes multiple ADR terms

Table 12 Haematologic Adverse Reactions[a] in ≥ 20% of Patients with CLL in ELEVATE-TN

Haematologic Adverse Reactions	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 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 based on laboratory measurements and adverse reactions

Tumour Lysis Syndrome
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
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
Infusion related reaction was reported in 14% and 40% of patients in the CALQUENCE+G and GClb arms, respectively.

ASCEND (Patients with CLL who received 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 efficacy and safety*).

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

[b] Includes multiple ADR terms

Table 14 Haematologic Adverse Reactions [a] in ≥ 20% of Patients with CLL in ASCEND

Haematologic 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 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 based on laboratory measurements and adverse reactions

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.

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. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s/.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EL02.

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 Efficacy and Safety

Mantle cell lymphoma (MCL)

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. Efficacy results are presented in Table 15.

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. The median dose intensity was 98.5%.

Table 15 Efficacy results in patients with MCL in ACE-LY-004

	Investigator Assessed N=124	**Independent Review Committee (IRC) Assessed N=124**
	n (%) (95% CI[b])	**n (%) (95% CI[b])**
Overall Response Rate (ORR) [a]		
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 [c]	3 (2.4%) (0.5, 6.9)	5 (4.0%) (1.3, 9.2)
Duration of Response (DoR)		
Median (months)	NR [1+ to 20+]	NR [0+ to 20+]

	Investigator Assessed N=124	Independent Review Committee (IRC) Assessed N=124
	n (%) (95% CI[b])	**n (%) (95% CI[b])**
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

[a] Per 2014 Lugano Classification.

[b] 95% exact binomial confidence interval.

[c] Includes subjects without any 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 ≥5x109) in 31.5% 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.

54-month final analysis of ACE-LY-004

The efficacy results at 54-month final analysis after the median follow-up of 38.1 months are presented in Table 16. At the final analysis the mPFS was 22 months (95% CI: 16.6, 33.3) and the mOS was 59.2 months (95% CI: 36.5, NE).

Table 16 Overall Response Rate and Duration of Response in (ACE-LY-004) Patients with MCL at 54-month final analysis

	Investigator Assessed N=124 n (%) (95% CI)
Overall Response Rate (ORR)	
Overall Response Rate	101 (81.5%) (73.5, 87.9)
Complete Response (CR)	59 (47.6%) (38.5, 56.7)
Partial Response (PR)	42 (33.9%) (25.6, 42.9)
Stable Disease	10 (8.1%) (3.9, 14.3)
Progressive Disease (PD)	10 (8.1%) (3.9, 14.3)
Non-Evaluable [a]	3 (2.4%) (0.5, 6.9)
Duration of Response (DoR)	
Median (months)	28.6 (17.5, 39.1)
Landmark DOR	
12 months estimate (%) (95% CI)	72.2 (62.0, 80.0)
18 months estimate (%) (95% CI)	59.0 (48.4, 68.2)

CI=Confidence Interval; NR = Not Reached

[a] **Included subjects without any adequate post-baseline disease assessment.**

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 included 598 patients 65 years of age and older with confirmed MCL that was previously untreated. Patient randomisation was stratified by geographic region (North America versus Western Europe versus Other) and simplified MIPI (Mantle Cell Lymphoma International Prognostic Index) score (0-3 versus 4-5 versus 6-11). The study enrolled patients during the COVID-19 pandemic.

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

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

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

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

The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) per Lugano Classification for NHL in subjects with previously untreated MCL. Additional 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).

With a median follow-up of 46.1 months in the CALQUENCE + BR arm and 44.4 months in the Placebo + BR arm, IRC-assessed PFS demonstrated 27% statistically significant reduction in risk of disease progression or death in patients treated with CALQUENCE + BR compared to Placebo + BR.

At the time of PFS analysis, median OS had not been reached in any arm with a total of 203 deaths: 97 (32.4%) in the CALQUENCE + BR arm, 106 (35.5%) in the Placebo + BR arm. Efficacy results are presented in Table 17. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 17 Efficacy Results in Patients with previously untreated MCL in ECHO

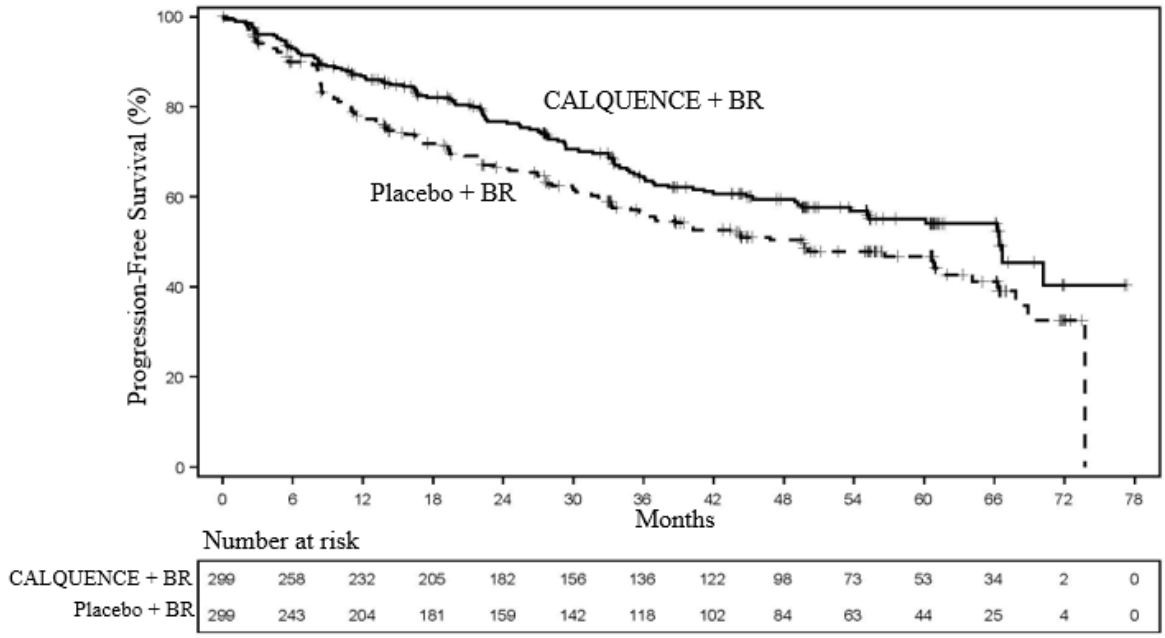
	CALQUENCE + BR N= 299	Placebo + BR N= 299
IRC-assessed PFS		
Median (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
HR (95% CI) (stratified) [a]	0.73 (0.57, 0.94)	
p-value [b]	0.0160	
IRC-assessed ORR		
CR + PR n (%)	272 (91.0)	263 (88.0)
95% CI	87.3,93.8	83.9, 91.3
CR n (%)	199 (66.6)	160 (53.5)
PR n (%)	73 (24.4)	103 (34.4)
ORR difference (vs PBR arm)	3.0%	-
p-value	0.2196	-
IRC-assessed DOR		
Median (95% CI), months	63.5 (52.5, NE)	53.8 (37.6, 66.1)

HR = hazard ratio, CR = complete response, PR = partial response, NE – not evaluable

[a] Stratified by randomization stratification factors: Geographic Regions (North American, Western Europe, Other) and simplified MIPI Score (Low risk [0 to 3], Intermediate risk [4 to 5], High Risk [6 to 11]) as collected via IXRS. Estimated based on stratified Cox Proportional Hazards model for hazard ratio (95% CI).

[b] Estimated based on stratified log-rank test for p-value.

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



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

Patients were stratified by age (>65 years or ≤65 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 18 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 18 Baseline Patient Characteristics in (AMPLIFY) Patients with Previously Untreated CLL

Characteristic	AV N=291	AVO N=286	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 randomization (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 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.

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.

Efficacy results are presented in Table 19. The Kaplan-Meier curve for IRC-PFS is shown in Figure 2.

Table 19 Efficacy results in (AMPLIFY) patients with previously untreated CLL

	AV N=291	AVO N=286	FCR/BR [b] N=290
Progression-free survival [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)

	AV N=291	AVO N=286	FCR/BR [b] N=290
HR [c] (95% CI)	0.65 (0.49, 0.87)	0.42 (0.30, 0.59)	-
P-value	0.0038	<0.0001	-
12 months estimate, % (95% CI)	94.8 (91.5, 96.8)	91.5 (87.6, 94.2)	88.3 (83.6, 91.7)
24 months estimate, % (95% CI)	87.6 (83.1, 90.9)	87.1 (82.6, 90.5)	79.0 (73.2, 83.6)
36 months estimate, % (95% CI)	76.5 (71.0, 81.1)	83.1 (78.1, 87.1)	66.5 (59.8, 72.3)
Overall Survival			
Death events (%)	18 (6.2)	37 (12.9)	42 (14.5)
HR [c] (95% CI)	0.33 (0.18, 0.56)	0.76 (0.49, 1.18)	-
12 months estimate, % (95% CI)	97.2 (94.5, 98.6)	93.0 (89.3, 95.4)	91.9 (87.8, 94.6)
24 months estimate, % (95% CI)	95.5 (92.4, 97.4)	89.1 (84.9, 92.2)	88.3 (83.7, 91.7)
36 months estimate, % (95% CI)	94.1 (90.7, 96.3)	87.7 (83.2, 91.0)	85.9 (81.0, 89.6)

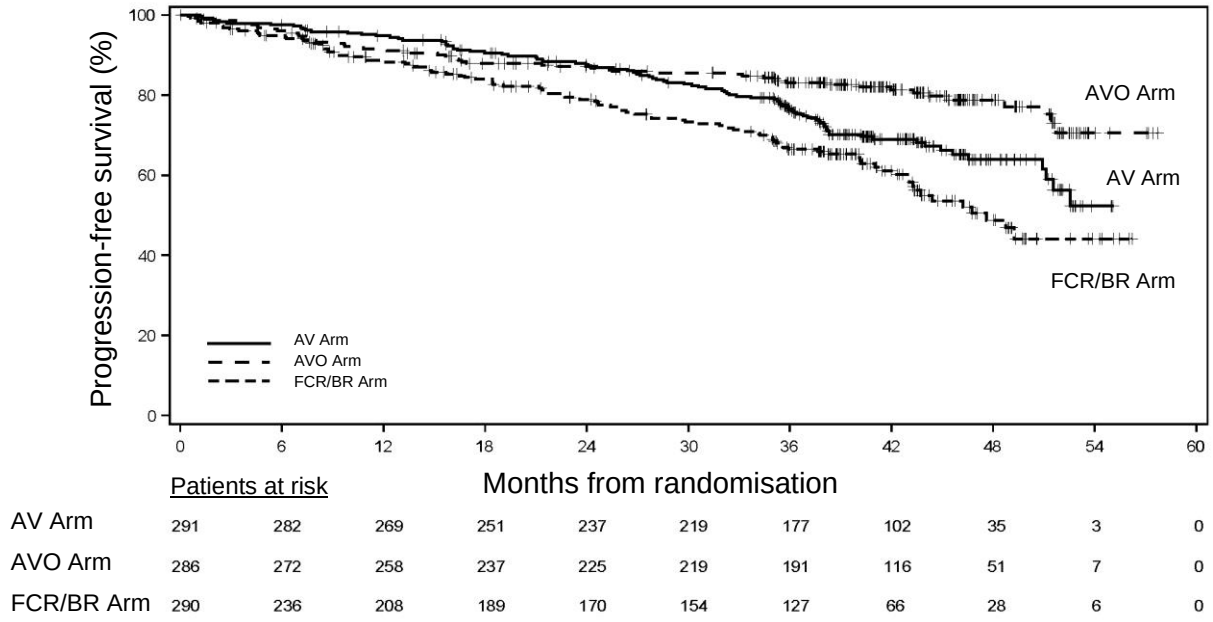
AV=acalabrutinib plus venetoclas; AVO=acalabrutinib plus venetoclax and obinutuzumabl
BR=bendamustine plus rituximab; FCR=fludarabine plus cyclophosphamide and rituximab;
PR=progressive disease; NC= Not calculable; HR=hazard ratio; CI=confidence interval

[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

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



The benefit of CALQUENCE in combination with venetoclax with or without obinutuzumab on PFS risk reduction was consistent across all clinically relevant subgroups, including higher risk

CLL patients (unmutated IGHV). 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.

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

Table 20 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; %			

Characteristic	CALQUENCE plus obinutuzumab N=179	CALQUENCE Monotherapy N=179	Obinutuzumab plus Chlorambucil N=177
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 Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 28.3 months, PFS by IRC indicated a 90% statistically significant reduction in the risk of disease progression or death for previously untreated CLL patients in the CALQUENCE+G arm compared to the GClb arm. At the time of analysis, median overall survival had not been reached in any arm with a total of 37 deaths: 9 (5%) in the CALQUENCE+G arm, 11 (6.1%) in the CALQUENCE monotherapy arm, and 17 (9.6%) in the GClb arm. Efficacy results are presented in Table 21. The Kaplan-Meier curves for PFS are shown in Figure 3.

Table 21 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 (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)	-
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

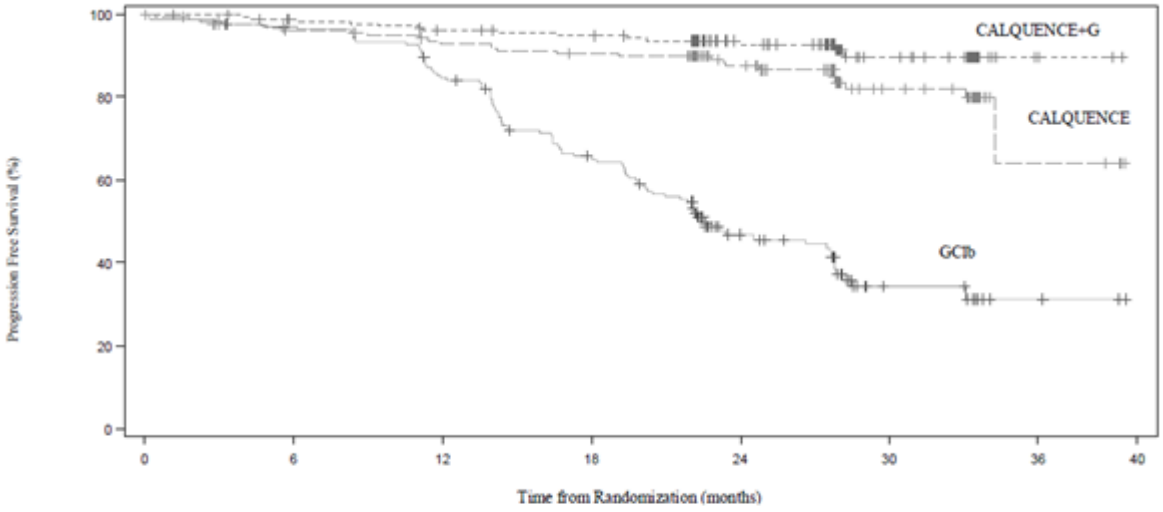
	CALQUENCE plus obinutuzumab N=179	CALQUENCE Monotherapy N=179	Obinutuzumab plus Chlorambucil N=177
nPR, n (%)	1 (0.6%)	2 (1.1%)	3 (1.7%)
PR, n (%)	143 (79.9)	150 (83.8)	128 (72.3)
PRL, n (%)	0	2 (1.1)	0
SD, n (%)	4 (2.2)	8 (4.5)	15 (8.5)
PD, n (%)	0	3 (1.7)	0
Non-evaluable, n (%)	0	1 (0.6)	8 (4.5)
Unknown, 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

[a] Per Independent Review Committee (IRC) assessment

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

Figure 3 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
GClb	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]; 0<0.0001) and CALQUENCE only arm (HR=0.27 [95% CI: 0.19, 0.38]; 0<0.0001) compared to GClb arm.

Table 22 Efficacy Results per INV assessment 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 (%)	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]	NE	NE (66.5, NE)	27.8 (22.6, 33.2)
HR (95% CI) [b]	0.11 (0.07, 0.16)	0.21 (0.15, 0.30)	-
24 months estimate, % (95% CI) [a]	93.0 (88.0, 96.0)	90.5 (84.9, 94.0)	55.0 (47.0, 62.3)
36 months estimate, % (95% CI) [a]	91.8 (86.6, 95.1)	84.3 (77.8, 89.1)	37.4 (29.8, 44.9)
48 months estimate, % (95% CI) [a]	88.1 (82.2, 92.2)	79.4 (72.4, 84.8)	26.5 (19.8, 33.7)
60 months estimate, % (95% CI) [a]	83.9 (76.8, 89.0)	72.4 (64.6, 78.8)	20.9 (14.3, 28.3)
Overall survival			
Death events (%)	18 (10.1)	30 (16.8)	28 (15.8)
Hazard Ratio (95% CI) [b]	0.55 (0.30, 0.99)	0.98 (0.58, 1.64)	-
Best overall response rate (CR + CRi + nPR + PR)			
ORR, n (%)	172 (96.1)	161 (89.9)	147 (83.1)
95% CI [c]	92.1, 98.1	84.7, 93.5	76.8, 87.9
P-value [d]	≤0.0001	0.0499	-
CR, n (%)	52 (29.1)	24 (13.4)	23 (13.0)
Cri, n (%)	6 (3.4)	2 (1.1)	1 (0.6)
nPR, n (%)	16 (8.9)	26 (14.5)	15 (8.5)
PR, n (%)	98 (54.7)	109 (60.9)	108 (61.0)

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

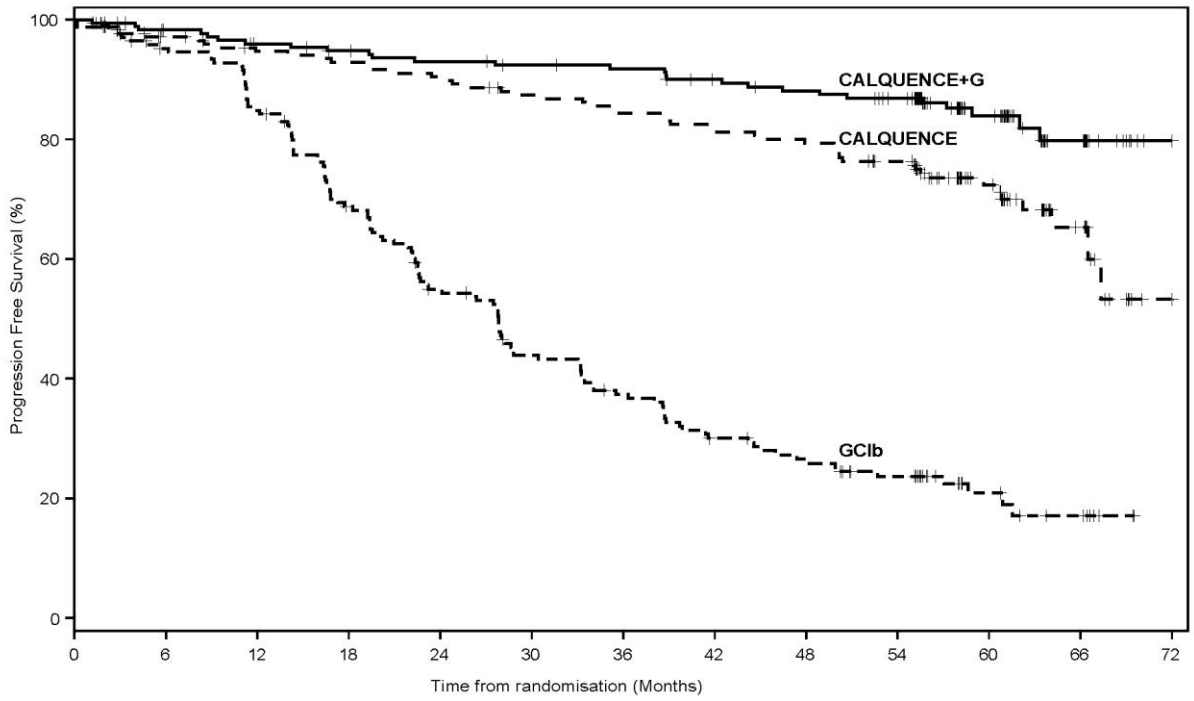
[a] 95% confidence interval based on Kaplan-Meier estimation.

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

[c] 95% confidence interval based on Normal approximation (with use of Wilson's score)

[d] Based on Cochran-Mantel-Haenzel test with adjustment for 17p deletion status (yes vs no)

Figure 4 Kaplan-Meier Curve of INV-Assessed PFS in (ELEVATE-TN) Patients with CLL (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 23 summarises the baseline demographics and disease characteristics of the study population.

Table 23 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 24. The Kaplan-Meier curve for PFS is shown in Figure 5.

Table 24 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 (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)

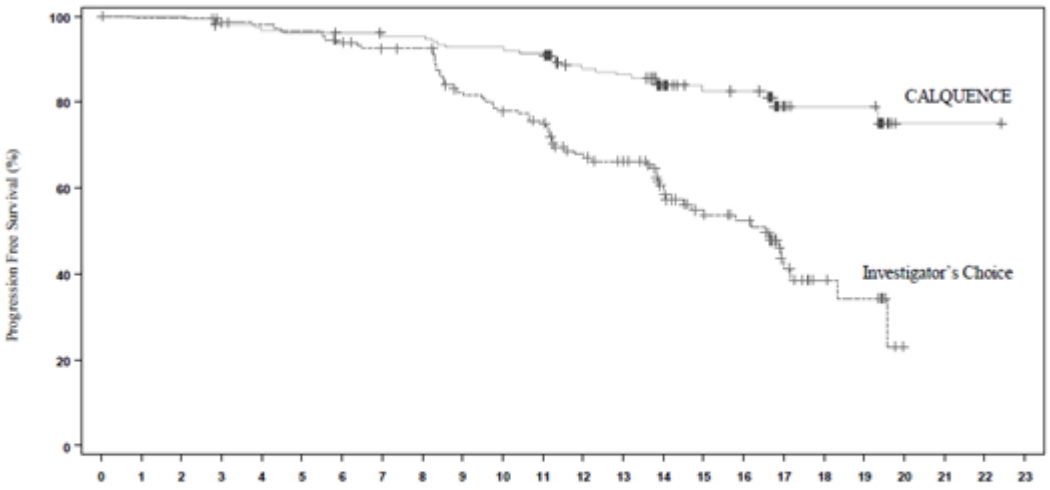
Median (95% CI), months	NR	16.5 (14.0, 17.1)
HR† [b] (95% CI)	0.31 (0.20, 0.49)	
P-value	< 0.0001	
15 months estimate, % (95% CI)	82.6 (75.0, 88.1)	54.9 (45.4, 63.5)
Overall Response Rate (ORR) [a] (CR + CRi + nPR + PR)		
ORR, n (%) (95% CI)	126 (81.3) (74.4, 86.6)	117 (75.5) (68.1, 81.6)
P-value	0.2248	-
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 5 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			

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 25 Efficacy results at final analysis per INV assessments in (ASCEND) patients with CLL

	CALQUENCE monotherapy N=155	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Progression-free survival [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)
Hazard Ratio (95% CI) [d]	0.28 (0.20, 0.38)	
24 months estimate, % (95% CI)	75.3 (67.6, 81.5)	39.0 (31.0, 47.0)
36 months estimate, % (95% CI)	64.0 (55.6, 71.2)	22.3 (15.7, 29.6)
42 months estimate, % (95% CI)	61.7 (53.2, 69.1)	19.0 (12.9, 26.1)
Overall survival [b]		
Death events (%)	41 (26.5)	54 (34.8%)
Hazard Ratio (95% CI) [d]	0.69 (0.46, 1.04)	-
Best overall response rate (CR + CRi + nPR + PR) [a,c]		
ORR, n (%) (95% CI)	128 (82.6) (75.8, 87.7)	130 (83.9) (77.3, 88.8)
P-value [e]	0.7340	-
CR, n (%)	8 (5.2)	8 (5.2)
Cri, n (%)	1 (0.6)	2 (1.3)
nPR, n (%)	6 (3.9)	0
PR, n (%)	113 (72.9)	120 (77.4)
Duration of Response (DoR)		
Median (95% CI), months	NR (41.5, NR)	18.3 (11.9, 21.7)

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; PD=progressive disease

[a] Per INV assessment

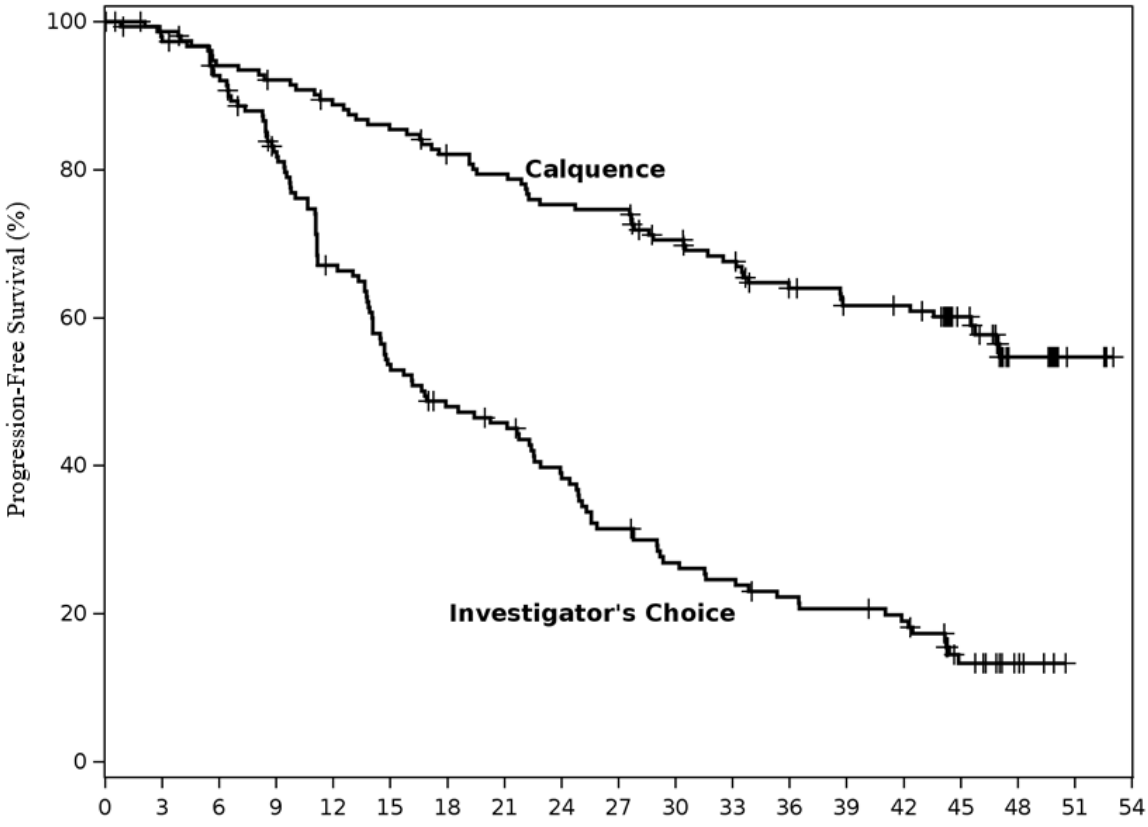
[b] Median OS not reached for both arms P=0.0783 for OS.

[c] CRi and nPR have values of 3 and 6.

[d] Based on stratified Cox-Proportional-Hazards model
Based on Cochran-Mantel-Haenzel test with adjustment for randomization stratification factors as recorded in IXRS.

[e] Based on Cochran-Mantel-Haenszel test with adjustment for randomization stratification factors as recorded in IXRS.

Figure 6 **Kaplan-Meier Curve of INV-Assessed PFS in (ASCEND) Patients with CLL (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. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation, and unmutated IGHV), the investigator assessed PFS HR was 0.26 [95% CI (0.19, 0.37)].

Table 26 Subgroup analysis of PFS per INV assessments (Study ASCEND)

	CALQUENCE monotherapy		
	N	**Hazard Ratio**	**95% CI**
All subjects	155	0.28	(0.20, 0.38)
Del 17P Yes No	 28 127	 0.13 0.32	 (0.06, 0.29) (0.23, 0.45)
TP53 mutation Yes No	 39 113	 0.25 0.28	 (0.14, 0.46) (0.19, 0.41)

	CALQUENCE monotherapy		
	N	**Hazard Ratio**	**95% CI**
Del 17P or TP53 mutation			
Yes	44	0.22	(0.12, 0.39)
No	108	0.30	(0.20, 0.44)
IGHV mutation			
Mutated	21	0.34	(0.13, 0.93)
Unmutated	109	0.29	(0.20, 0.41)
Del 11q			
Yes	39	0.33	(0.18, 0.62)
No	114	0.29	(0.20, 0.41)
Complex Karyotype			
Yes	3	0.18	(0.02, 1.84)
No	150	0.28	(0.21, 0.39)

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.

Absorption

The median time (min-max) to peak plasma concentrations (T_{max}) was 0.5 (0.2, 3.0) hours for CALQUENCE, and 0.75 (0.5, 4.0) hours 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 (Vss) 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 Interaction), while ACP-5862 may inhibit MATE1 (see Section 4.5 Interactions with Other Medicines and Other Forms of Interaction) 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, 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.

Special 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 Interaction).

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 Interaction).

Gastric acid reducing medicines

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

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
- sodium stearyl fumarate

Tablet coating

- Hypromellose
- Copovidone
- titanium dioxide
- macrogol 3350
- medium chain triglycerides
- iron oxide yellow
- iron oxide red
- purified water

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

36 months

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: 0800 684 432

9. DATE OF FIRST APPROVAL

21 March 2024

10. DATE OF REVISION OF THE TEXT

29 January 2026

VV-RIM-04953549 v 4.0

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1, 4.4 & 4.8	Extension of indication related texts based on AMPLIFY study
4.2	Section revised to incorporate monotherapy and combination regimens for CLL Revision to the table for dose modification when managing adverse reactions
4.8	Update to the CARM reporting link
5.1	Addition of extension of indication texts based on AMPLIFY study and update on long term efficacy for ELEVATE-TN and ASCEND studies