1 NAME OF THE MEDICINAL PRODUCT

CALQUENCE TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of acalabrutinib (as acalabrutinib maleate). For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film Coated Tablets

4 INDICATIONS AND USAGE

4.1 Previously Untreated Mantle Cell Lymphoma

CALQUENCE TABLETS in combination with bendamustine and rituximab is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous hematopoietic stem cell transplantation (HSCT).

4.2 Mantle Cell Lymphoma

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

4.3 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

CALQUENCE TABLETS is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

5 DOSAGE AND ADMINISTRATION

5.1 Recommended Dosage

CALQUENCE TABLETS Administration Instructions

Advise patients to swallow tablet whole with water. Advise patients not to chew, crush, dissolve, or cut the tablets. CALQUENCE TABLETS may be taken with or without food. If a dose of CALQUENCE TABLETS is missed by more than 3 hours, it should be skipped, and the next dose should be taken at its regularly scheduled time. Extra tablets of CALQUENCE TABLETS should not be taken to make up for a missed dose.

CALQUENCE TABLETS as Monotherapy

For patients with MCL, CLL or SLL, the recommended dosage of CALQUENCE TABLETS is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

CALQUENCE TABLETS in Combination with Bendamustine and Rituximab

For patients with previously untreated MCL, the recommended dosage of CALQUENCE TABLETS is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

Start CALQUENCE TABLETS on Day 1 of Cycle 1 (each cycle is 28 days) and administer until disease progression or unacceptable toxicity. Administer bendamustine 90 mg/m^2 on Days 1 and 2 and rituximab 375 mg/m^2 on Day 1 of Cycle 1 and continue for a total of 6 cycles. Patients achieving a response (PR or CR) after the first 6 cycles may receive maintenance rituximab on Day 1 of every other cycle for a maximum of 12 additional doses, starting on Cycle 8 up to Cycle 30 *[see Clinical Studies (15.1)]*.

CALQUENCE TABLETS in Combination with Obinutuzumab

For patients with previously untreated CLL or SLL, the recommended dosage of CALQUENCE TABLETS is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start CALQUENCE TABLETS at Cycle 1 (each cycle is 28 days). Start obinutuzumab at Cycle 2 for a total of 6 cycles and refer to the obinutuzumab prescribing information for recommended dosing. Administer CALQUENCE TABLETS prior to obinutuzumab when given on the same day.

5.2 Recommended Dosage for Drug Interactions

Dosage Modifications for Use with CYP3A Inhibitors or Inducers

These are described in Table 1 *[see Drug Interactions (10)]*.

Table 1: Recommended Dosage Modifications for Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended CALQUENCE TABLETS use
Inhibition	Strong CYP3A inhibitor	Avoid co-administration. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE TABLETS. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of CALQUENCE TABLETS.
	Moderate CYP3A inhibitor	Reduce the CALQUENCE TABLETS 100 mg every 12 hours dosage to 100 mg once daily.
Induction	Strong CYP3A inducer	Avoid co-administration. If co-administration is unavoidable, increase CALQUENCE TABLETS dosage to 200 mg approximately every 12 hours.

5.3 Dosage Modifications for Adverse Reactions

Recommended dosage modifications are provided in Table 2 and 3.

Table 2: Recommended Dosage Modifications for Adverse Reactions in Patients Receiving CALQUENCE TABLETS Monotherapy and CALQUENCE TABLETS in Combination with Obinutuzumab

Event	Adverse Reaction Occurrence	Dosage Modification (Starting dose = 100 mg approximately every 12 hours)
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and Second	Interrupt CALQUENCE TABLETS. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE TABLETS may be resumed at 100 mg approximately every 12 hours.
	Third	Interrupt CALQUENCE TABLETS. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE TABLETS may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue CALQUENCE TABLETS.

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

Table 3: Recommended Dosage Modifications for Adverse Reactions in Patients Receiving CALQUENCE TABLETS in Combination with BR

Adverse Reaction	Severity[a]	Dosage Modification
		(Starting dosage of CALQUENCE TABLETS = 100 mg approximately every 12 hours)
Neutropenia[b] [see Warnings and Precautions (8.4)]	Absolute neutrophil count less than 0.5 x 10^9/L for greater than 7 days	Interrupt CALQUENCE TABLETS. Once toxicity has resolved to Grade ≤ 2, resume CALQUENCE TABLETS at starting dosage. Upon 2nd or 3rd occurrence, reduce dosage of CALQUENCE TABLETS to 100 mg once daily.[c] Discontinue CALQUENCE TABLETS at 4th occurrence. For bendamustine[b]: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2, resume bendamustine and consider dosage reduction to 70 mg/m^2.[d,e]
Thrombocytopenia[f] [see Warnings and Precautions (8.4)]	Platelet count 25 to 50 x 10^9/L with clinically significant	Interrupt CALQUENCE TABLETS. Once toxicity has resolved to Grade ≤ 2 or baseline, resume CALQUENCE TABLETS at starting dosage.

Adverse Reaction	Severity[a]	Dosage Modification
		(Starting dosage of CALQUENCE TABLETS = 100 mg approximately every 12 hours)
	bleeding or platelet count less than $25 \times 10^9/L$	If recurrence, reduce dosage of CALQUENCE TABLETS to 100 mg once daily.[c] Consider discontinuing CALQUENCE TABLETS at 3rd occurrence. For bendamustine[f]: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline, resume bendamustine and consider dose reduction to 70 mg/m^2.[e]
Non-hematologic adverse reactions [see Warnings and Precautions (8)]	Grade 3 or higher	Interrupt CALQUENCE TABLETS. Once toxicity has resolved to Grade ≤ 2 or baseline, resume CALQUENCE TABLETS at starting dosage. If recurrence, reduce dosage of CALQUENCE TABLETS to 100 mg once daily.[c] Discontinue CALQUENCE TABLETS at 3rd occurrence of Grade 4 toxicity. For Grade 3 toxicity, consider the risks and benefits of continuing CALQUENCE TABLETS. For bendamustine: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline, resume bendamustine and consider dose reduction to 70 mg/m^2.[e]

[a] Graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
[b] For neutropenia with ANC less than $1 \times 10^9/L$, consideration for bendamustine dose interruption and dosage reduction to 70 mg/m2 may be appropriate in certain circumstances.
[c] Dose may be re-escalated at the discretion of the physician if patient tolerates a reduced dose for ≥4 weeks.
[d] Consider use of myeloid growth factors before bendamustine dosage reduction.
[e] Consider discontinuing bendamustine if additional dosage reduction is required.
[f] For thrombocytopenia, a platelet count below $50 \times 10^9/L$ should prompt bendamustine dose interruption even in the absence of clinically significant bleeding.

Refer to the prescribing information of each of the products used in combination with CALQUENCE TABLETS for additional information for management of toxicities.

6 DOSAGE FORMS AND STRENGTHS

Film coated Tablets:100 mg acalabrutinib, orange, oval, film-coated, biconvex, debossed with 'ACA 100' on one side and plain on the other.

7 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 12.

8 WARNINGS AND PRECAUTIONS

8.1 Serious and Opportunistic Infections

Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE TABLETS.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 32% of 1,764 patients exposed to CALQUENCE TABLETS in clinical trials, most often due to respiratory tract infections (19% of all patients, including pneumonia in 9%) *[see Adverse Reactions (9.1)]*. These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 2.7% of all patients. Opportunistic infections in recipients of CALQUENCE TABLETS have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jirovecii* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

8.2 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients treated with CALQUENCE TABLETS. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 4.4% of patients, with fatal hemorrhage occurring in 0.2% of 1,764 patients exposed to CALQUENCE TABLETS in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 40% of patients *[see Adverse Reactions (9.1)]*.

Use of antithrombotic agents concomitantly with CALQUENCE TABLETS may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 7% of patients taking CALQUENCE TABLETS without antithrombotic agents and 4% of patients taking CALQUENCE TABLETS with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE TABLETS. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE TABLETS for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

8.3 Cytopenias

CALQUENCE TABLETS can cause Grade 3 or 4 cytopenias. Grade 3 or 4 cytopenias included absolute neutrophil count decreased (26%), platelets decreased (10%), hemoglobin decreased (10%), and absolute lymphocyte count decreased (10%) in patients treated with CALQUENCE TABLETS alone or in combination with obinutuzumab; Grade 4 neutropenia developed in 14% *[see Adverse Reactions (9.1)]*.

Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (5.3)]*.

8.4 Second Primary Malignancies

Second primary malignancies, including skin cancers and other solid tumors, occurred in 18% of 1,764 patients exposed to CALQUENCE TABLETS in clinical trials *[see Adverse Reactions (9.1)]*. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 10% of patients, followed by other solid tumors in 9% (including melanoma, lung cancer, gastrointestinal cancers, and genitourinary cancers) and hematologic malignancies (1%). Monitor patients for the development of second cancers and advise protection from sun exposure.

8.5 Cardiac Arrhythmias

Fatal and serious cardiac arrhythmias have occurred in patients treated with CALQUENCE TABLETS. Grade 3 or 4 atrial fibrillation or flutter was reported in 2.6% of 1,764 patients treated with CALQUENCE TABLETS, with all grades of atrial fibrillation or flutter reported in 7% of all patients *[see Adverse Reactions (9.1)]*. Grade 3 or higher ventricular arrhythmia events were reported in 0.6% of patients, including fatal cases in 0.3% of all patients. The risk of arrhythmias may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

8.6 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 TABLETS.

Evaluate bilirubin and transaminases at baseline and throughout treatment with CALQUENCE TABLETS. For patients who develop abnormal liver tests after CALQUENCE TABLETS, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold CALQUENCE TABLETS. Upon confirmation of DILI, discontinue CALQUENCE TABLETS.

9 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious and Opportunistic Infections *[see Warnings and Precautions (8.1)]*
- Hemorrhage *[see Warnings and Precautions (8.2)]*
- Cytopenias *[see Warnings and Precautions (8.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (8.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (8.5)]*
- Hepatotoxicity, including DILI *[see Warnings and Precautions (8.6)]*

9.1 Clinical Trials Experience

Because 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.

The data in the Warnings and Precautions reflect exposure to CALQUENCE TABLETS 100 mg approximately every 12 hours in 1,764 patients with hematologic malignancies. Treatment includes CALQUENCE TABLETS monotherapy in 1,256 patients in 9 trials, and CALQUENCE TABLETS combinations in 508 patients in 3 trials. Among these recipients of CALQUENCE TABLETS, 88% were exposed for at least 6 months and 80% were exposed for at least one year. In this pooled safety population, adverse reactions in ≥ 30% of 1,764 patients, excluding laboratory abnormalities, were diarrhea (37%), upper respiratory tract infection (36%), headache (35%), musculoskeletal pain (33%), lower respiratory tract infection (32%), and fatigue (32%). The most common grade 3 or 4 laboratory abnormalities (≥10%) were absolute neutrophil count decreased (31%), absolute lymphocyte count decreased (23%), platelets decreased (11%), and hemoglobin decreased (10%).

Previously Untreated Mantle Cell Lymphoma

The safety data described below reflect exposure to CALQUENCE TABLETS (100 mg approximately every 12 hours, with or without BR) in patients with MCL *[see Clinical Studies (15.1)]*.

ECHO

The safety of CALQUENCE TABLETS in combination with bendamustine and rituximab (CALQUENCE TABLETS plus BR) was evaluated in 297 patients with previously untreated MCL in ECHO *[see Clinical Studies (15.1)]*. The trial enrolled patients with previously untreated MCL, ≥ 65 years of age with no intention for transplant, total bilirubin ≤ 1.5 × ULN, AST or ALT ≤ 2.5 × ULN, and estimated creatinine clearance of > 50 mL/min. Patients received 6 cycles (as 28-day cycles) of CALQUENCE TABLETS 100 mg orally twice daily (n = 297) or placebo (n = 297) in combination with bendamustine and rituximab. Patients then received CALQUENCE TABLETS 100 mg orally twice daily or placebo continuously until progressive disease or unacceptable toxicity, with 12 additional dosages of rituximab every other cycle up to Cycle 30.

The median duration of treatment with CALQUENCE TABLETS was 28.6 months. A total of 171 (57.6%) patients were treated with CALQUENCE TABLETS for > 24 months and 122 (41.1%) patients were treated for > 36 months.

Serious adverse reactions occurred in 69% of patients who received CALQUENCE TABLETS plus BR. Serious adverse reactions reported in ≥ 2% of patients were pneumonia (23%; includes COVID-19 pneumonia), COVID-19 (20%; includes COVID-19 pneumonia), pyrexia (6%), second primary malignancy (7%), rash (3.4%), febrile neutropenia (3.4%), atrial fibrillation (3%), sepsis (2.7%), and anemia (2.4%). Fatal adverse reactions that occurred within 30 days of the last study treatment were reported in 12% who received CALQUENCE TABLETS plus BR including COVID-19 (6%; includes COVID-19 pneumonia), pneumonia (1%), sepsis (0.3%), second primary malignancy (0.7%), and pneumonitis (0.3%).

Adverse reactions led to permanent discontinuation of CALQUENCE TABLETS in 43%, dosage interruptions in 74%, and dosage reductions in 10% of patients. 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 TABLETS in ≥ 4% of patients included COVID-19 (includes COVID-19 pneumonia) and neutropenia.

Table 4 and Table 5 summarize select adverse reactions and laboratory abnormalities observed in patients treated in ECHO.

Table 4: Adverse Reactions* (≥ 15%) in Patients with Previously Untreated MCL Who Received CALQUENCE plus BR in ECHO

Body System Adverse Reactions*	CALQUENCE TABLETS plus BR N=297		Placebo plus BR N=297	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash[a]	47	12	31	3
Infections				
COVID-19[b]	38	13	27	11
Upper respiratory tract infection[c]	30	0.7	29	1
Pneumonia[d]	31	17	25	14
Gastrointestinal disorders				
Diarrhea	37	3	28	2.4
Vomiting	26	0.7	14	1
Constipation	25	1	25	0.3
General disorders				
Fatigue	37	3.7	32	4.4
Pyrexia	29	2.4	24	1.3
Edema	20	1.3	19	0
Nervous system disorders				
Headache	31	1.7	14	0.7
Dizziness	18	1	17	0.3
Respiratory, thoracic and mediastinal disorders				
Cough	27	0	20	0.3
Dyspnea	17	1	11	2.7
Neoplasms				
Secondary primary malignancy[e]	19	7	15	7
Musculoskeletal and connective tissue disorders				
Arthralgia	18	0.7	16	1
Vascular disorders				
Hemorrhage[f]	20	1.7	11	3

*Excludes laboratory terms.
[a] Includes rash, dermatitis, and other related terms.
[b] Includes the following fatal adverse reactions: n=24 for COVID-19.
[c] Includes upper respiratory tract infection, sinusitis, pharyngitis, and related terms.
[d] Includes pneumonia, terms containing pneumonia, and related infections. COVID-19 pneumonia is represented under both Pneumonia and COVID-19.
[e] Includes terms related to malignant neoplasms including cutaneous neoplasms.
[f] Includes all terms containing hematoma or hemorrhage and related terms indicative of bleeding.

Clinically relevant adverse reactions in < 15% of patients receiving CALQUENCE TABLETS plus BR included bruising, abdominal pain, atrial fibrillation or flutter, and tumor lysis syndrome.

Table 5: Select Laboratory Abnormalities (≥ 15%) in Patients with Previously Untreated MCL in ECHO

Laboratory Abnormality	CALQUENCE TABLETS plus BR[a]		Placebo plus BR[a]	
	All grade (%)	Grade 3 or 4 (%)	All grade (%)	Grade 3 or 4 (%)
Hematologic Abnormalities				
Lymphocytes decreased	98	87	97	89
Hemoglobin 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

[a] The denominator used to calculate the rate varied between 296 and 297 based on the number of patients with a baseline value and at least one post-treatment value.

Grade 4 laboratory abnormalities in > 15% of patients treated with CALQUENCE TABLETS plus BR include absolute lymphocyte count decreased (26%), absolute neutrophil count decreased (36%), and uric acid increased (17%).

Previously Treated Mantle Cell Lymphoma

ACE-LY-004

The safety data described in this section reflect exposure to CALQUENCE TABLETS (100 mg approximately every 12 hours) in 124 patients with previously treated MCL in Trial LY-004 *[see Clinical Studies (15.2)]*. The median duration of treatment with CALQUENCE TABLETS was 16.6 (range: 0.1 to 26.6) months. A total of 91 (73.4%) patients were treated with CALQUENCE TABLETS for ≥ 6 months and 74 (59.7%) patients were treated for ≥ 1 year.

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

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

Tables 6 and 7 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE TABLETS.

Table 6: Non-Hematologic Adverse Reactions in ≥ 5% (All Grades) of Patients with MCL in Trial LY-004

Body System Adverse Reactions[*]	CALQUENCE TABLETS Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Nervous system disorders		
Headache	39	1.6
Gastrointestinal disorders		
Diarrhea	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 and subcutaneous tissue disorders		
Bruising[a]	21	-
Rash[b]	18	0.8
Vascular disorders		
Hemorrhage[c]	8	0.8
Respiratory, thoracic and mediastinal disorders		
Epistaxis	6	-

[*] Per NCI CTCAE version 4.03.
[a] Bruising: Includes all terms containing 'bruise,' 'contusion,' 'petechiae,' or 'ecchymosis'
[b] Rash: Includes all terms containing 'rash'
[c] Hemorrhage: Includes all terms containing 'hemorrhage' or 'hematoma'

Table 7: Hematologic Adverse Reactions Reported in ≥ 20% of Patients with MCL in Trial LY-004

Hematologic Adverse Reactions[*]	CALQUENCE TABLETS Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Hemoglobin decreased	46	10
Platelets decreased	44	12
Neutrophils decreased	36	15

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

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

Chronic Lymphocytic Leukemia

The safety data described below reflect exposure to CALQUENCE TABLETS (100 mg approximately every 12 hours, with or without obinutuzumab) in 511 patients with CLL from two randomized controlled clinical trials *[see Clinical Studies (15.3)]*.

The most common adverse reactions (≥ 30%) of any grade in patients with CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

ELEVATE-TN

The safety of CALQUENCE TABLETS plus obinutuzumab (CALQUENCE TABLETS+G), CALQUENCE TABLETS monotherapy, and obinutuzumab plus chlorambucil (GClb) was evaluated in a randomized, multicenter, open-label, actively controlled trial in 526 patients with previously untreated CLL *[see Clinical Studies (15.3)]*.

Patients randomized to the CALQUENCE TABLETS+G arm were treated with CALQUENCE TABLETS and obinutuzumab in combination for six cycles, then with CALQUENCE TABLETS as monotherapy until disease progression or unacceptable toxicity. Patients initiated obinutuzumab on Day 1 of Cycle 2, continuing for a total of 6 cycles. Patient randomized to CALQUENCE TABLETS monotherapy received CALQUENCE TABLETS approximately every 12 hours until disease progression or unacceptable toxicity. The trial required age ≥ 65 years of age or 18 to < 65 years of age with a total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance of 30 to 69 mL/min, hepatic transaminases ≤ 3 times ULN and total bilirubin ≤ 1.5 times ULN, and allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

During randomized treatment, the median duration of exposure to CALQUENCE TABLETS in the CALQUENCE TABLETS+G and CALQUENCE TABLETS monotherapy arms was 27.7 months (range 0.3 to 40 months), with 95% and 92% and 89% and 86% of patients with at least 6 months and 12 months of exposure, respectively. In the obinutuzumab and chlorambucil arm the median number of cycles was 6 with 84% of patients receiving at least 6 cycles of obinutuzumab, 70% of patients received at least 6 cycles of chlorambucil. Eighty-five percent of patients in the CALQUENCE TABLETS+G arm received at least 6 cycles of obinutuzumab.

In the CALQUENCE TABLETS+G and CALQUENCE TABLETS monotherapy arms, fatal adverse reactions that occurred in the absence of disease progression and with onset within 30 days of the last

study treatment were reported in 2% for each treatment arm, most often from infection. Serious adverse reactions were reported in 39% of patients in the CALQUENCE TABLETS+G arm and 32% in the CALQUENCE TABLETS monotherapy arm, most often due to events of pneumonia (2.8% to 7%).

In the CALQUENCE TABLETS+G arm, adverse reactions led to treatment discontinuation in 11% of patients and a dose reduction of CALQUENCE TABLETS in 7% of patients. In the CALQUENCE TABLETS monotherapy arm, adverse reactions led to discontinuation in 10% and dose reduction in 4% of patients.

Tables 8 and 9 present adverse reactions and laboratory abnormalities identified in the ELEVATE-TN trial.

Table 8: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE TABLETS in Patients with CLL (ELEVATE-TN)

Body System Adverse Reaction[*]	CALQUENCE TABLETS plus Obinutuzumab N=178		CALQUENCE TABLETS Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections						
Infection[†]	69	22[‡]	65	14[‡]	46	13[‡]
Upper respiratory tract infection[§]	39	2.8	35	0	17	1.2
Lower respiratory tract infection[a]	24	8	18	4.5	7	1.8
Urinary tract infection	15	1.7	15	2.8	5	0.6
Blood and lymphatic system disorders[b]						
Neutropenia[c]	53	37	23	13	78	50
Anemia[d]	52	12	53	10	54	14
Thrombocytopenia[e]	51	12	32	3.4	61	16
Lymphocytosis[f]	12	11	16	15	0.6	0.6
Nervous system disorders						
Headache	40	1.1	39	1.1	12	0
Dizziness	20	0	12	0	7	0
Gastrointestinal disorders						
Diarrhea	39	4.5	35	0.6	21	1.8
Nausea	20	0	22	0	31	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[g]	37	2.2	32	1.1	16	2.4
Arthralgia	22	1.1	16	0.6	4.7	1.2
General disorders and administration site conditions						
Fatigue[h]	34	2.2	23	1.1	24	1.2
Skin and subcutaneous tissue disorders						
Bruising[i]	31	0	21	0	5	0
Rash[j]	26	2.2	25	0.6	9	0.6

Body System Adverse Reaction[*]	CALQUENCE TABLETS plus Obinutuzumab N=178		CALQUENCE TABLETS Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Vascular disorders						
Hemorrhage[k]	20	1.7	20	1.7	6	0

[*] Per NCI CTCAE version 4.03

[†] Includes any adverse reactions involving infection or febrile neutropenia

[‡] Includes 3 fatal cases in the CALQUENCE TABLETS plus obinutuzumab arm, 3 fatal cases in the CALQUENCE TABLETS monotherapy arm and 1 fatal case in the obinutuzumab plus chlorambucil arm

[§] Includes upper respiratory tract infection, nasopharyngitis and sinusitis

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

[b] Derived from adverse reaction and laboratory data

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

[d] Includes anemia, red blood cell count decreased, and related laboratory data

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

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

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

[h] Includes asthenia, fatigue, and lethargy

[i] Includes bruise, contusion, and ecchymosis

[j] Includes rash, dermatitis, and other related terms

[k] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE TABLETS (CALQUENCE TABLETS in combination with obinutuzumab and monotherapy) included:

- *Neoplasms:* second primary malignancy (10%), non-melanoma skin cancer (5%)
- *Cardiac disorders:* atrial fibrillation or flutter (3.6%), hypertension (5%)
- *Infection:* herpesvirus infection (6%)

Table 9: Select Non-Hematologic Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE TABLETS (ELEVATE-TN)

Laboratory Abnormality[*,a]	CALQUENCE TABLETS plus Obinutuzumab N=178		CALQUENCE TABLETS Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Uric acid increase	29	29	22	22	37	37
ALT increase	30	7	20	1.1	36	6
AST increase	38	5	17	0.6	60	8
Bilirubin increase	13	0.6	15	0.6	11	0.6

[*] Per NCI CTCAE version 4.03

[a] Excludes electrolytes

Increases in creatinine to 1.5 to 3 times ULN occurred in 3.9% and 2.8% of patients in the CALQUENCE TABLETS combination arm and monotherapy arm, respectively.

ASCEND

The safety of CALQUENCE TABLETS in patients with relapsed or refractory CLL was evaluated in a randomized, open-label study (ASCEND) *[see Clinical Studies (15.3)]*. The trial enrolled patients with relapsed or refractory CLL after at least one prior therapy and required hepatic transaminases ≤ 2 times ULN, total bilirubin ≤ 1.5 times ULN, and an estimated creatinine clearance ≥ 30 mL/min. The trial excluded patients having an absolute neutrophil count < 500/µL, platelet count < 30,000/µL, prothrombin time or activated partial thromboplastin time > 2 times ULN, significant cardiovascular disease, or a requirement for strong CYP3A inhibitors or inducers. Patients were allowed to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonist.

In ASCEND, 154 patients received CALQUENCE TABLETS (100 mg approximately every 12 hours until disease progression or unacceptable toxicity), 118 received idelalisib (150 mg approximately every 12 hours until disease progression or unacceptable toxicity) with up to 8 infusions of a rituximab product, and 35 received up to 6 cycles of bendamustine and a rituximab product. The median age overall was 68 years (range: 32-90); 67% were male; 92% were white; and 88% had an ECOG performance status of 0 or 1.

In the CALQUENCE TABLETS arm, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in > 5% of patients who received CALQUENCE TABLETS included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE TABLETS occurred in 2.6% of patients, including from second primary malignancies and infection.

In recipients of CALQUENCE TABLETS, permanent discontinuation due to an adverse reaction occurred in 10% of patients, most frequently due to second primary malignancies followed by infection. Adverse reactions led to dosage interruptions of CALQUENCE TABLETS in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and dose reduction in 3.9% of patients.

Selected adverse reactions are described in Table 10 and non-hematologic laboratory abnormalities are described in Table 11. These tables reflect exposure to CALQUENCE TABLETS with median duration of 15.7 months with 94% of patients on treatment for greater than 6 months and 86% of patients on treatment for greater than 12 months. The median duration of exposure to idelalisib was 11.5 months with 72% of patients on treatment for greater than 6 months and 48% of patients on treatment for greater than 12 months. Eighty-three percent of patients completed 6 cycles of bendamustine and rituximab product.

Table 10: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE TABLETS in Patients with CLL (ASCEND)

Body System Adverse Reaction[*]	CALQUENCE TABLETS N=154		Idelalisib plus Rituximab Product N=118		Bendamustine plus Rituximab Product N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections						
Infection[†]	56	15[‡]	65	28[‡]	49	11
Upper respiratory tract infection[§]	29	1.9	26	3.4	17	2.9
Lower respiratory tract infection [a]	23	6	26	15	14	6
Blood and lymphatic system disorders[b]						
Neutropenia[c]	48	23	79	53	80	40
Anemia[d]	47	15	45	8	57	17
Thrombocytopenia[e]	33	6	41	13	54	6
Lymphocytosis[f]	26	19	23	18	2.9	2.9
Nervous system disorders						
Headache	22	0.6	6	0	0	0
Gastrointestinal disorders						
Diarrhea[g]	18	1.3	49	25	14	0
Vascular disorders						
Hemorrhage[h]	16	1.3	5	1.7	6	2.9
General disorders						
Fatigue[i]	15	1.9	13	0.8	31	6
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[j]	15	1.3	15	1.7	2.9	0

[*] Per NCI CTCAE version 4.03

[†] Includes any adverse reactions involving infection or febrile neutropenia

[‡] Includes 1 fatal case in the CALQUENCE TABLETS monotherapy arm and 1 fatal case in the Idelalisib plus Rituximab arm

[§] Includes upper respiratory tract infection, rhinitis and nasopharyngitis

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

[b] Derived from adverse reaction and laboratory data

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

[d] Includes anemia, red blood cell decreased, and related laboratory data

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

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

[g] Includes colitis, diarrhea, and enterocolitis

[h] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

[i] Includes asthenia, fatigue, and lethargy

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

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE TABLETS included:

- *Skin and subcutaneous disorders:* bruising (10%), rash (9%)
- *Neoplasms:* second primary malignancy (12%), non-melanoma skin cancer (6%)
- *Musculoskeletal and connective tissue disorders:* arthralgia (8%)
- *Cardiac disorders:* atrial fibrillation or flutter (5%), hypertension (3.2%)
- *Infection:* herpesvirus infection (4.5%)

Table 11: Select Non-Hematologic Laboratory Abnormalities (≥ 10% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE TABLETS (ASCEND)

Laboratory abnormality [a]	CALQUENCE TABLETS N=154		Idelalisib plus Rituximab Product N=118		Bendamustine plus Rituximab Product N=35	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Uric acid increase	15	15	11	11	23	23
ALT increase	15	1.9	59	23	26	2.9
AST increase	13	0.6	48	13	31	2.9
Bilirubin increase	13	1.3	16	1.7	26	11

Per NCI CTCAE version 5

[a] Excludes electrolytes

Increases in creatinine to 1.5 to 3 times ULN occurred in 1.3% of patients who received CALQUENCE TABLETS.

9.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CALQUENCE TABLETS. 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.
- Cardiac disorders: ventricular arrhythmias
- Hepatobiliary disorders: drug-induced liver injury

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

10 DRUG INTERACTIONS

10.1 Effect of Other Drugs on CALQUENCE TABLETS

Strong CYP3A Inhibitors	
Clinical Effect	Co-administration of CALQUENCE TABLETS with a strong CYP3A inhibitor increased acalabrutinib plasma concentrations *[see Clinical Pharmacology (13.3)]*. Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	Avoid co-administration of CALQUENCE TABLETS with strong CYP3A inhibitors. Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE TABLETS *[see Dosage and Administration (5.2)]*.
Moderate CYP3A Inhibitors	
Clinical Effect	Co-administration of CALQUENCE TABLETS with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentration *[see Clinical Pharmacology (13.3)]*. Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	Reduce the dosage of CALQUENCE TABLETS when co-administered with a moderate CYP3A inhibitor *[see Dosage and Administration (5.2)]*.
Strong CYP3A Inducers	
Clinical Effect	Co-administration of CALQUENCE TABLETS with a strong CYP3A inducer decreased acalabrutinib plasma concentration *[see Clinical Pharmacology (13.3)]*. Decreased acalabrutinib concentrations may reduce CALQUENCE TABLETS activity.
Prevention or Management	Avoid co-administration of CALQUENCE TABLETS with strong CYP3A inducers. If co-administration is unavoidable, increase the dosage of CALQUENCE TABLETS *[see Dosage and Administration (5.2)]*.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

Based on findings in animals, CALQUENCE TABLETS may cause fetal harm and dystocia 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 animals during organogenesis resulted in dystocia in rats and reduced fetal growth in rabbits at maternal exposures (AUC) 2 times exposures in patients at the recommended dose of 100 mg approximately every 12 hours (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In a combined fertility and embryo-fetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryo-fetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 9 times the AUC in patients at the recommended dose of 100 mg approximately every 12 hours. The presence of acalabrutinib and its active metabolite were confirmed in fetal rat plasma.

In an embryo-fetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in decreased fetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 2 times the AUC in patients at 100 mg approximately every 12 hours.

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

11.2 Lactation

Risk Summary

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 TABLETS, advise lactating women not to breastfeed while taking CALQUENCE TABLETS and for 2 weeks after the last dose.

11.3 Females and Males of Reproductive Potential

CALQUENCE TABLETS may cause embryo-fetal harm and dystocia when administered to pregnant women *[see Use in Specific Populations (11.1)]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE TABLETS therapy.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE TABLETS and for 1 week following the last dose of CALQUENCE TABLETS. If this

drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

11.4 Pediatric Use

The safety and efficacy of CALQUENCE TABLETS in pediatric patients have not been established.

11.5 Geriatric Use

CLL and Previously Treated MCL

Of the 1,467 CALQUENCE TABLETS-treated patients with CLL or relapsed or refractory MCL in clinical trials, 977 (67%) were 65 years of age or older, and 328 (22%) were 75 years of age or older. Among patients 65 years of age or older, 74% had Grade 3 or higher adverse reactions and 58% had serious adverse reactions. Among patients younger than age 65, 61% had Grade 3 or higher adverse reactions and 39% had serious adverse reactions. No clinically relevant differences in efficacy were observed between patients ≥ 65 years and younger.

Previously Untreated MCL

Of the 297 CALQUENCE TABLETS-treated patients with previously untreated MCL, 214 (72%) were 65 to 74 years of age and 83 (28%) were 75 years of age and older. No clinically relevant differences in safety or efficacy were observed between patients ages 65 to 74 years and those who were 75 years of age and older.

11.6 Hepatic Impairment

Avoid use of CALQUENCE TABLETS in patients with severe hepatic impairment (Child-Pugh class C). No dosage adjustment of CALQUENCE TABLETS is recommended in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The safety of CALQUENCE TABLETS has not been evaluated in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (13.3)]*.

12 DESCRIPTION

CALQUENCE TABLETS (acalabrutinib) is a kinase inhibitor. The molecular formula for acalabrutinib maleate is $C_{26}H_{23}N_7O_2 \cdot C_4H_4O_4 \cdot H_2O$, and the molecular weight is 599.59. 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.

The chemical structure of acalabrutinib is shown below:
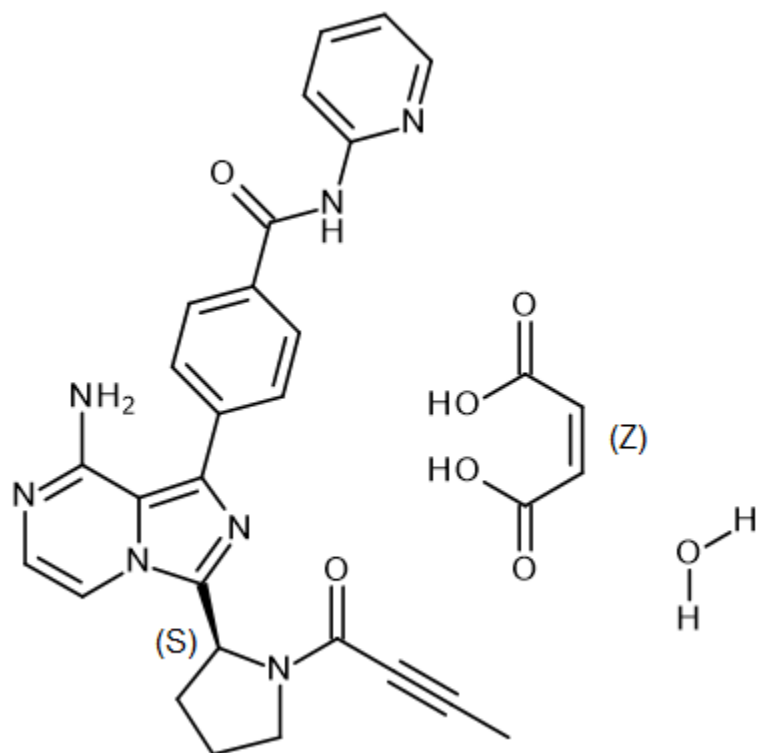
Acalabrutinib maleate is a white to pale brown powder with pH-dependent solubility. It is freely soluble in water at pH values below 3 and practically insoluble at pH values above 6.

CALQUENCE TABLETS are for oral administration. Each tablet contains 100 mg of acalabrutinib (equivalent to 129 mg of acalabrutinib maleate). Inactive ingredients in the tablet core are mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and sodium stearyl fumarate. The tablet coating consists of Hypromellose, copovidone, titanium dioxide, macrogol 3350, medium-chain triglycerides, iron oxide yellow and iron oxide red.

13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Acalabrutinib is a small-molecule inhibitor of Bruton 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 signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and tumor growth in mouse xenograft models.

13.2 Pharmacodynamics

In patients with B-cell malignancies dosed with acalabrutinib 100 mg approximately every 12 hours, median steady state BTK occupancy of $\geq 95\%$ in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

Cardiac Electrophysiology

At a dose 4 times the approved recommended dosage, CALQUENCE TABLETS does not prolong the QTc interval to any clinically relevant extent.

13.3 Pharmacokinetics

Acalabrutinib and its active metabolite, ACP-5862, exposures increase proportionally with dose across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dosage) in patients with B-cell malignancies. At the recommended dose of 100 mg twice daily, the geometric mean (% coefficient of variation [CV]) daily area under the plasma drug concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) for acalabrutinib were 1843 (38%) ng•h/mL and 563 (29%) ng/mL, respectively, and for ACP-5862 were 3947 (43%) ng•h/mL and 451 (52%) ng/mL, respectively.

Absorption

The geometric mean absolute bioavailability of acalabrutinib was 25%. Median (min, max) time to peak plasma concentration (T_{max}) of acalabrutinib and its active metabolite, ACP-5862 were 0.5 (0.2, 3.0) hours and 0.75 (0.5, 4.0) hours, respectively.

Effect of Food

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

Distribution

The geometric mean (% CV) steady-state volume of distribution (V_{ss}) of acalabrutinib and its active metabolite, ACP-5862 was approximately 101 (52%) L and 67 (32%) L, respectively. Reversible binding to human plasma protein of acalabrutinib and its active metabolite, ACP-5862, were 97.5% and 98.6%, respectively. The mean blood-to-plasma ratio of acalabrutinib and its active metabolite, ACP-5862, was 0.8 and 0.7, respectively.

Elimination

The geometric mean (% CV) terminal elimination half-life ($t_{1/2}$) of acalabrutinib and its active metabolite, ACP-5862, were 1.4 (50%) hours and 6.4 (37%) hours, respectively. The geometric mean (%CV)

apparent oral clearance (CL/F) of acalabrutinib and its active metabolite, ACP-5862, were 148 (33%) L/hr and 19 (23%) L/hr, respectively.

Metabolism

Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis, based on in vitro studies. ACP-5862 was identified as the major active 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.

Excretion

Following administration of a single 100 mg radiolabeled acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the feces (< 2% unchanged) and 12% of the dose was recovered in the urine (< 2% unchanged).

Specific Populations

There were no clinically significant differences in the pharmacokinetics of acalabrutinib and its active metabolite, ACP-5862, based on age (32 to 90 years), sex, race (Caucasian, African American), body weight (40 to 149 kg), or mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] by Modification of Diet in Renal Disease [MDRD] equation: 30 to < 90 mL/min). The effect of severe renal impairment (eGFR < 30 mL/min/, MDRD) or renal impairment requiring dialysis on the pharmacokinetics of acalabrutinib is unknown.

Patients with Hepatic Impairment

The AUC of acalabrutinib increased 1.9-fold in subjects with mild hepatic impairment (Child-Pugh class A), 1.5-fold in subjects with moderate hepatic impairment (Child-Pugh class B) and 5.3-fold in subjects with severe hepatic impairment (Child-Pugh class C) compared to subjects with normal liver function. No clinically relevant PK difference in ACP-5862 was observed in subjects with severe hepatic impairment (Child-Pugh Class C) compared to subjects with normal liver function. No clinically relevant PK differences in acalabrutinib and ACP-5862 were observed in patients with mild or moderate hepatic impairment (total bilirubin ≤ 3 x ULN and any AST) relative to patients with normal hepatic function (total bilirubin and AST ≤ ULN).

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A Inhibitors: Co-administration of acalabrutinib with itraconazole (strong CYP3A inhibitor) increase acalabrutinib C_{max} by 3.9-fold and AUC by 5.1-fold in healthy subjects.

Moderate CYP3A Inhibitors: Co-administration of acalabrutinib with erythromycin (moderate CYP3A inhibitor), fluconazole (moderate CYP3A inhibitor), diltiazem (moderate CYP3A inhibitor) is predicted to increase acalabrutinib C_{max} and AUC by approximately 2- to 3-fold.

Strong CYP3A Inducers: Co-administration of acalabrutinib with rifampin (strong CYP3A inducer) decreased acalabrutinib C_{max} by 68% and AUC by 77% in healthy subjects.

Acid-Reducing Agents: No clinically significant differences in the pharmacokinetics of acalabrutinib were observed when co-administered with rabeprazole (proton pump inhibitor).

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Acalabrutinib is an inhibitor of CYP3A4/5, CYP2C8 and CYP2C9, but not CYP1A2, CYP2B6, CYP2C19, or CYP2D6. Acalabrutinib's active metabolite, ACP-5862, is an inhibitor of CYP2C8, CYP2C9 and CYP2C19, but not CYP1A2, CYP2B6, CYP2D6, or CYP3A4/5. Acalabrutinib is an inducer of CYP1A2, CYP2B6, and CYP3A4. Acalabrutinib's active metabolite, ACP-5862, is an inducer of CYP3A4.

Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) Enzymes: Acalabrutinib and its active metabolite, ACP-5862, are not inhibitors of UGT1A1 or UGT2B7.

Transporter System: Acalabrutinib is an inhibitor of breast cancer resistance protein (BCRP), but not multidrug and toxin extrusion protein 1 (MATE1). Acalabrutinib's active metabolite, ACP-5862, is an inhibitor of MATE1, but not BCRP. Acalabrutinib and its active metabolite, ACP-5862, are not inhibitors of P-glycoprotein (P-gp), organic anion transporter (OAT) 1, OAT3, organic cation transporter 2 (OCT2), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, or MATE2-K.

Acalabrutinib and its active metabolite, ACP-5862, are substrates of P-gp and BCRP. Acalabrutinib is not a substrate of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3. Acalabrutinib's active metabolite, ACP-5862, is not a substrate of OATP1B1 or OATP1B3.

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with acalabrutinib.

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.

In a fertility study in rats, there were no effects of acalabrutinib on fertility in male rats at exposures 11 times, or in female rats at exposures 9 times, the AUC observed in patients at the recommended dose of 100 mg twice daily.

15 CLINICAL STUDIES

15.1 Previously Untreated Mantle Cell Lymphoma

ECHO

The efficacy of CALQUENCE TABLETS in patients with previously untreated MCL was evaluated in a randomized, double-blind, placebo controlled, multicenter study (ECHO; NCT02972840). The study

enrolled 598 patients who were ≥ 65 years of age and who had no intention for 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. Patients were randomized in a 1:1 ratio to receive CALQUENCE TABLETS plus bendamustine and rituximab (CALQUENCE TABLETS plus BR) or placebo plus BR. Dosing for both arms was administered in 28-day cycles as follows:

- CALQUENCE TABLETS plus BR was administered for a maximum of 6 treatment cycles. CALQUENCE TABLETS 100 mg orally was administered twice daily starting on Cycle 1 Day 1. Bendamustine was administered at 90 mg/m^2 intravenously over 30 minutes on Days 1 and 2 of each of 6 cycles. Rituximab was administered at 375 mg/m^2 intravenously on Day 1 of each cycle for 6 cycles.
- For patients achieving a response (PR or CR), CALQUENCE TABLETS 100 mg orally twice daily was administered continuously, in combination with rituximab given at 375 mg/m^2 on Day 1 every other cycle for a maximum of 12 additional doses up to Cycle 30. After discontinuation of rituximab, patients continued CALQUENCE TABLETS monotherapy at 100 mg orally twice daily until disease progression or unacceptable toxicity.

Patients on the control arm received the same regimen but placebo in lieu of CALQUENCE TABLETS. Crossover to CALQUENCE TABLETS monotherapy was permitted for patients in the placebo plus BR arm at disease progression.

Of all patients randomized, the median age was 71 years (range: 65-86); 71% were male; 78% were White, 16% Asian, 0.5% were Black or African American. In total, 80% had classic histology of MCL, 7.7% had blastoid MCL, and 5.5% had pleomorphic MCL. The simplified MIPI (Mantle Cell Lymphoma International Prognostic Index) score was low in 33%, intermediate in 43%, and high in 24% of patients. A total of 38% of patients had tumor bulk ≥ 5 cm and 86% had Ann Arbor stage IV disease.

The major efficacy outcome was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) using the Lugano Classification. Efficacy results are presented in Table 12. The Kaplan-Meier curves for PFS are shown in Figure 1. At this prespecified interim analysis, the median follow-up for PFS was 49.8 months in both arms.

Table 12. Efficacy Results in Patients with Previously Untreated MCL in ECHO

Outcomes per IRC	CALQUENCE TABLETS plus BR N=299	Placebo plus BR N=299
Progression-Free Survival[a]		
Median (95% CI), months	66.4 (55.1, NE)	49.6 (36.0, 64.1)
HR[b] (95%CI)	0.73 (0.57, 0.94)	
P-value[c]	0.016	
Overall Response Rate (ORR) (CR + PR)		
ORR 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	0.220	

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]).

[b] Estimated based on stratified Cox Proportional Hazards model for hazard ratio (95% CI).

[c] Estimated based on stratified log-rank test for p-value, with an alpha level of 0.039 derived by the O'Brien-Fleming method.

Figure 1. Kaplan-Meier Curve of IRC-Assessed PFS in Patients with Previously Untreated MCL in ECHO
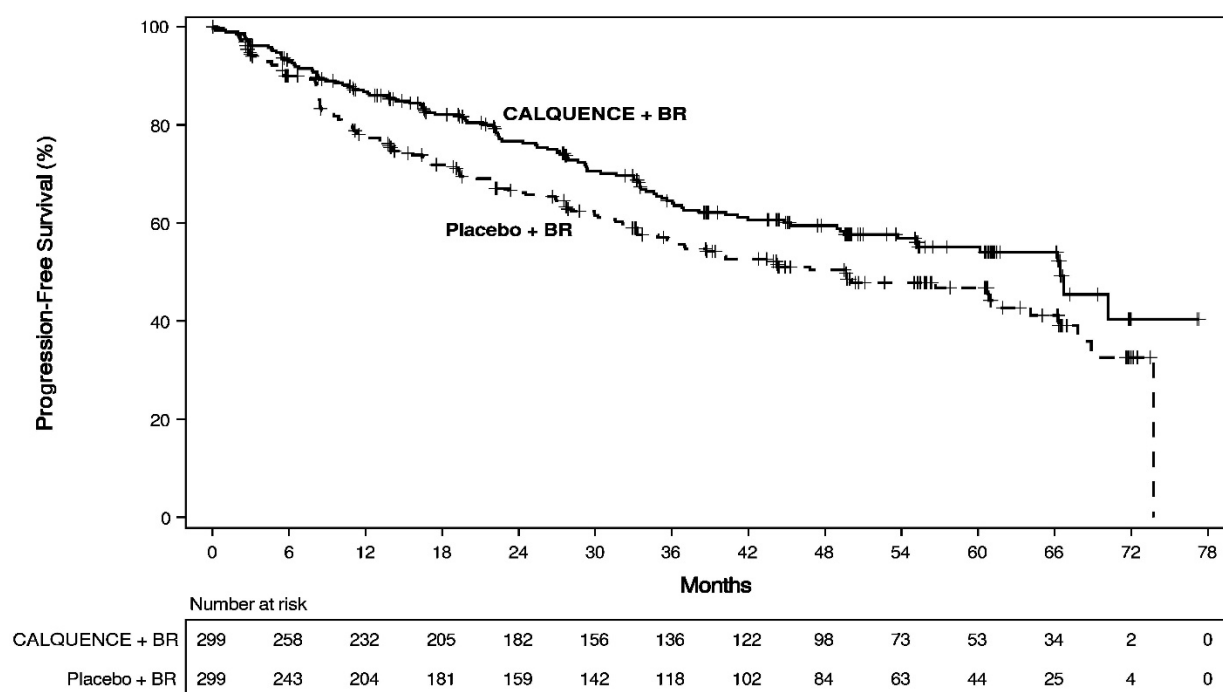
At the time of the PFS analysis, the median overall survival had not been reached in either arm with a total of 203 deaths: 97 (32%) patients in the CALQUENCE TABLETS plus BR arm and 106 (35%) patients in the placebo plus BR arm had died.

15.2 Previously Treated Mantle Cell Lymphoma

ACE-LY-004

The efficacy of CALQUENCE TABLETS was based upon Trial LY-004 titled "An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma" (NCT02213926). Trial LY-004 enrolled a total of 124 patients with MCL who had received at least one prior therapy.

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 46.3 months and the median number of prior treatments was 2 (range 1 to 5), including 18% with prior stem cell transplant. Patients who received prior treatment with BTK inhibitors were excluded. The most common prior regimens were CHOP-based (52%) and ARA-C (34%). At baseline, 37% of patients had at least one tumor with a longest diameter ≥ 5 cm, 73% had extra nodal involvement including 51% with bone marrow involvement. The simplified Mantle Cell Lymphoma International Prognostic Index (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.

CALQUENCE TABLETS was administered orally at 100 mg approximately every 12 hours until disease progression or unacceptable toxicity. The median dose intensity was 98.5%. The major efficacy outcome of Trial LY-004 was overall response rate and the median follow-up was 15.2 months.

Table 13: Efficacy Results in Patients with MCL in Trial LY-004

	Investigator Assessed N=124	Independent Review Committee (IRC) Assessed N=124
Overall Response Rate (ORR)*		
ORR (%) [95% CI]	81 [73, 87]	80 [72, 87]
Complete Response (%) [95% CI]	40 [31, 49]	40 [31, 49]
Partial Response (%) [95% CI]	41 [32, 50]	40 [32, 50]
Duration of Response (DoR)		
Median DoR in months [range]	NE [1+ to 20+]	NE [0+ to 20+]

CI= Confidence Interval; NE=Not Estimable; + indicates censored observations.
*Per 2014 Lugano Classification.

The median time to best response was 1.9 months.

Lymphocytosis

Upon initiation of CALQUENCE TABLETS, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count increased ≥ 50% from baseline and a post-baseline assessment ≥ 5 x 10^9/L) in 31.5% of patients in Trial LY-004. The median time to onset of lymphocytosis was 1.1 weeks, and the median duration of lymphocytosis was 6.7 weeks.

15.3 Chronic Lymphocytic Leukemia

The efficacy of CALQUENCE TABLETS in patients with CLL was demonstrated in two randomized, controlled trials. The indication for CALQUENCE TABLETS includes patients with SLL because it is the same disease.

ELEVATE-TN

The efficacy of CALQUENCE TABLETS was evaluated in the ELEVATE-TN trial, a randomized, multicenter, open-label, actively controlled, 3 arm trial of CALQUENCE TABLETS in combination with obinutuzumab, CALQUENCE TABLETS monotherapy, and obinutuzumab in combination with chlorambucil in 535 patients with previously untreated chronic lymphocytic leukemia (NCT02475681). Patients 65 years of age or older or between 18 and 65 years of age with a total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance of 30 to 69 mL/min were enrolled. The trial also required hepatic transaminases ≤ 3 times upper limit of normal (ULN) and total bilirubin ≤ 1.5 times ULN, and excluded patients with Richter's transformation.

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

- CALQUENCE TABLETS plus obinutuzumab (CALQUENCE TABLETS+G): CALQUENCE TABLETS 100 mg was administered approximately every 12 hours 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 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 up to 7. Each cycle was 28 days.

- CALQUENCE TABLETS monotherapy: CALQUENCE TABLETS 100 mg was administered approximately every 12 hours until disease progression or unacceptable toxicity.

- Obinutuzumab plus chlorambucil (GClb): Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1,000 mg was administered intravenously on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by 1,000 mg on Day 1 of Cycles 2 to 6. Chlorambucil 0.5 mg/kg was administered orally on Days 1 and 15 of Cycles 1 to 6. Each cycle was 28 days.

Randomization was stratified by 17p deletion mutation status, ECOG performance status (0 or 1 versus 2), and geographic region. A total of 535 patients were randomized, 179 to CALQUENCE TABLETS+G, 179 to CALQUENCE TABLETS monotherapy, and 177 to GClb. The overall median age was 70 years (range: 41 to 91 years), 47% had Rai stage III or IV disease, 14% had 17p deletion or TP53 mutation, 63% of patients had an unmutated IGVH, and 18% had 11q deletion. Baseline demographic and disease characteristics were similar between treatment arms.

Efficacy was based on progression-free survival (PFS) as assessed by an Independent Review Committee (IRC). The median duration of follow-up was 28.3 months (range: 0.0 to 40.8 months). Efficacy results are presented in Table 14. The Kaplan-Meier curves for PFS are shown in Figure 2.

Table 14. Efficacy Results per IRC in Patients with CLL − ITT population (ELEVATE-TN)

	CALQUENCE TABLETS plus Obinutuzumab N=179	CALQUENCE TABLETS Monotherapy N=179	Obinutuzumab plus Chlorambucil N=177
Progression-Free Survival [a]			
Number of events (%)	14 (8)	26 (15)	93 (53)
PD, n (%)	9 (5)	20 (11)	82 (46)
Death events, n (%)	5 (3)	6 (3)	11 (6)
Median (95% CI), months [b]	NE	NE (34, NE)	22.6 (20, 28)
HR[c] (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
p-value [d]	< 0.0001	< 0.0001	-
Overall Response Rate[a] (CR + CRi + nPR + PR)			
ORR, n (%)	168 (94)	153 (86)	139 (79)
(95% CI)	(89, 97)	(80, 90)	(72, 84)
p-value [e]	< 0.0001	0.0763	-
CR, n (%)	23 (13)	1 (1)	8 (5)
CRi, n (%)	1 (1)	0	0
nPR, n (%)	1 (1)	2 (1)	3 (2)
PR, n (%)	143 (80)	150 (84)	128 (72)

ITT=intent-to-treat; CI=confidence interval; HR=hazard ratio; NE=not estimable; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response.
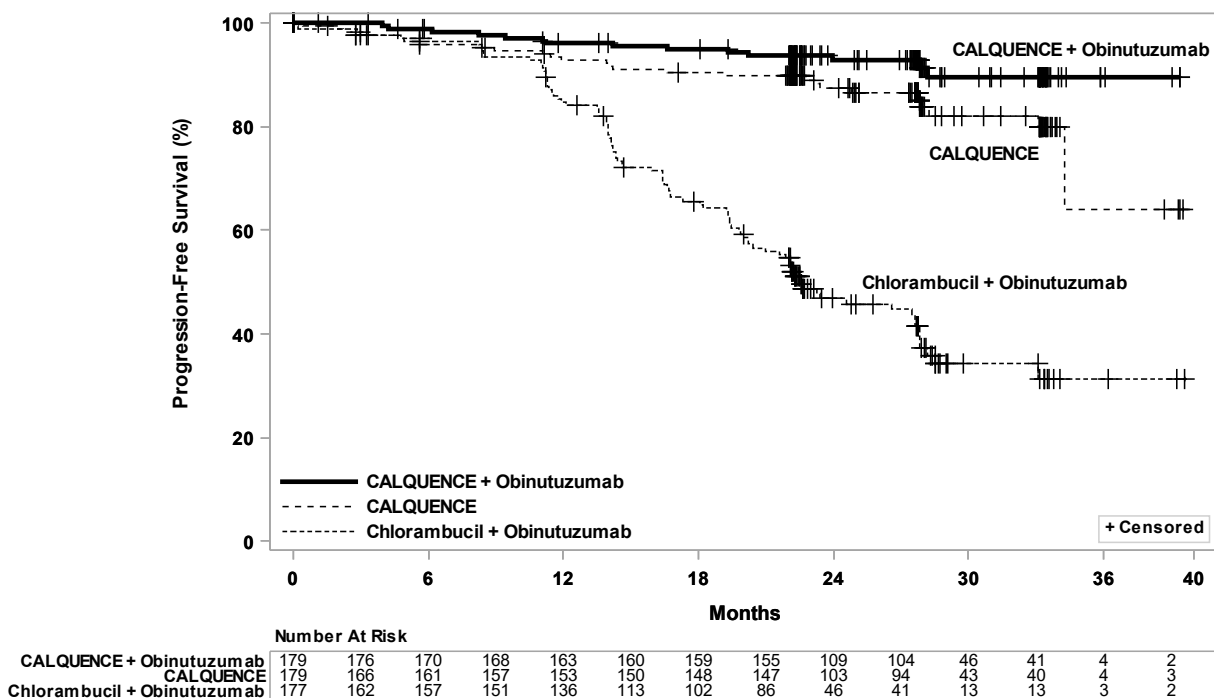[a] Per 2008 International Workshop on CLL (IWCLL) criteria.
[b] Kaplan-Meier estimate.
[c] Based on a stratified Cox-Proportional-Hazards model. Both hazard ratios are compared with the obinutuzumab and chlorambucil arm.
[d] Based on a stratified log-rank test, with an alpha level of 0.012 derived from alpha spending function by the O'Brien-Fleming method.
[e] Based on a stratified Cochran–Mantel–Haenszel test, for the comparison with the obinutuzumab and chlorambucil arm.

Figure 2: Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL in ELEVATE-TN

Number At Risk													
CALQUENCE + Obinutuzumab	179	176	170	168	163	160	159	155	109	104	46	41	4	2
CALQUENCE	179	166	161	157	153	150	148	147	103	94	43	40	4	3
Chlorambucil + Obinutuzumab	177	162	157	151	136	113	102	86	46	41	13	13	3	2

With a median follow-up of 28.3 months, median overall survival was not reached in any arm, with fewer than 10% of patients experiencing an event.

ASCEND

The efficacy of CALQUENCE TABLETS in patients with relapsed or refractory CLL was based upon a multicenter, randomized, open-label trial (ASCEND; NCT02970318). The trial enrolled 310 patients with relapsed or refractory CLL after at least 1 prior systemic therapy. The trial excluded patients with transformed disease, prolymphocytic leukemia, or previous treatment with venetoclax, a Bruton tyrosine kinase inhibitor, or a phosphoinositide-3 kinase inhibitor.

Patients were randomized in a 1:1 ratio to receive either:

- CALQUENCE TABLETS 100 mg approximately every 12 hours until disease progression or unacceptable toxicity, or

- Investigator's choice:

  - Idelalisib plus a rituximab product (IR): Idelalisib 150 mg orally approximately every 12 hours until disease progression or unacceptable toxicity, in combination with 8 infusions of a rituximab product (375 mg/m^2 intravenously on Day 1 of Cycle 1, followed by 500 mg/m^2 every 2 weeks for 4 doses and then every 4 weeks for 3 doses), with a 28-day cycle length.

    o   Bendamustine plus a rituximab product (BR): Bendamustine 70 mg/m^2 intravenously (Day 1 and 2 of each 28-day cycle), in combination with a rituximab product (375 mg/m^2 intravenously on Day 1 of Cycle 1, then 500 mg/m^2 on Day 1 of subsequent cycles), for up to 6 cycles.

Randomization was stratified by 17p deletion mutation status, ECOG performance status (0 or 1 versus 2), and number of prior therapies (1 to 3 versus ≥ 4). Of 310 patients total, 155 were assigned to CALQUENCE TABLETS monotherapy, 119 to IR, and 36 to BR. The median age overall was 67 years (range: 32 to 90 years), 42% had Rai stage III or IV disease, 28% had 17p deletion or TP53 mutation, 78% of patients had an unmutated IGVH, and 27% had a 11q deletion. The CALQUENCE TABLETS arm had a median of 1 prior therapy (range: 1 to 8), with 47% having at least 2 prior therapies. The investigator's choice arm had a median of 2 prior therapies (range: 1 to 10), with 57% having at least 2 prior therapies.

In the CALQUENCE TABLETS arm, the median treatment duration was 15.7 months, with 94% of patients treated for at least 6 months and 86% of patients treated for at least 1 year. In the investigator's choice arm, the median treatment duration was 8.4 months, with 59% of patients treated for at least 6 months and 37% treated for at least 1 year.

Efficacy was based on PFS as assessed by an IRC, with a median follow-up of 16.1 months (range 0.03 to 22.4 months). Efficacy results are presented in Table 15. The Kaplan-Meier curve for PFS is shown in Figure 3. There was no statistically significant difference in overall response rates between the two treatment arms.

Table 15: Efficacy Results per IRC in Patients with Relapsed or Refractory CLL – ITT Population (ASCEND)

	CALQUENCE TABLETS Monotherapy N=155	Investigator's Choice of Idelalisib + Rituximab Product or Bendamustine + Rituximab Product N=155
Progression-Free Survival [a]		
Number of events, n (%)	27 (17)	68 (44)
Disease progression, n	19	59
Death, n	8	9
Median (95% CI), months [b]	NE (NE, NE)	16.5 (14.0, 17.1)
HR (95% CI) [c]	0.31 (0.20, 0.49)	
P-value [d]	< 0.0001	
Overall Response Rate (CR + CRi + nPR + PR) [a, e]		
ORR, n (%) [e]	126 (81)	117 (75)
(95% CI)	(74, 87)	(68, 82)
CR, n (%)	0	2 (1)
CRi, n (%)	0	0

	CALQUENCE TABLETS Monotherapy N=155	Investigator's Choice of Idelalisib + Rituximab Product or Bendamustine + Rituximab Product N=155
nPR, n (%)	0	0
PR, n (%)	126 (81)	115 (74)

ITT=intent-to-treat; CI=confidence interval; HR=hazard ratio; NE=not estimable; CR=complete response;
CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response
[a] Per 2008 IWCLL criteria.
[b] Kaplan-Meier estimate.
[c] Based on a stratified Cox-Proportional-Hazards model.
[d] Based on a stratified Log-rank test. The pre-specified type I error rate (α) for this interim analysis is 0.012 derived from a Lan-DeMets alpha spending function with O'Brien-Fleming boundary.
[e] Through a hierarchical testing procedure, the difference in ORR was not statistically significant, based on a Cochran-Mantel-Haenszel test with adjustment for randomization stratification factors.

Figure 3: Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL in ASCEND
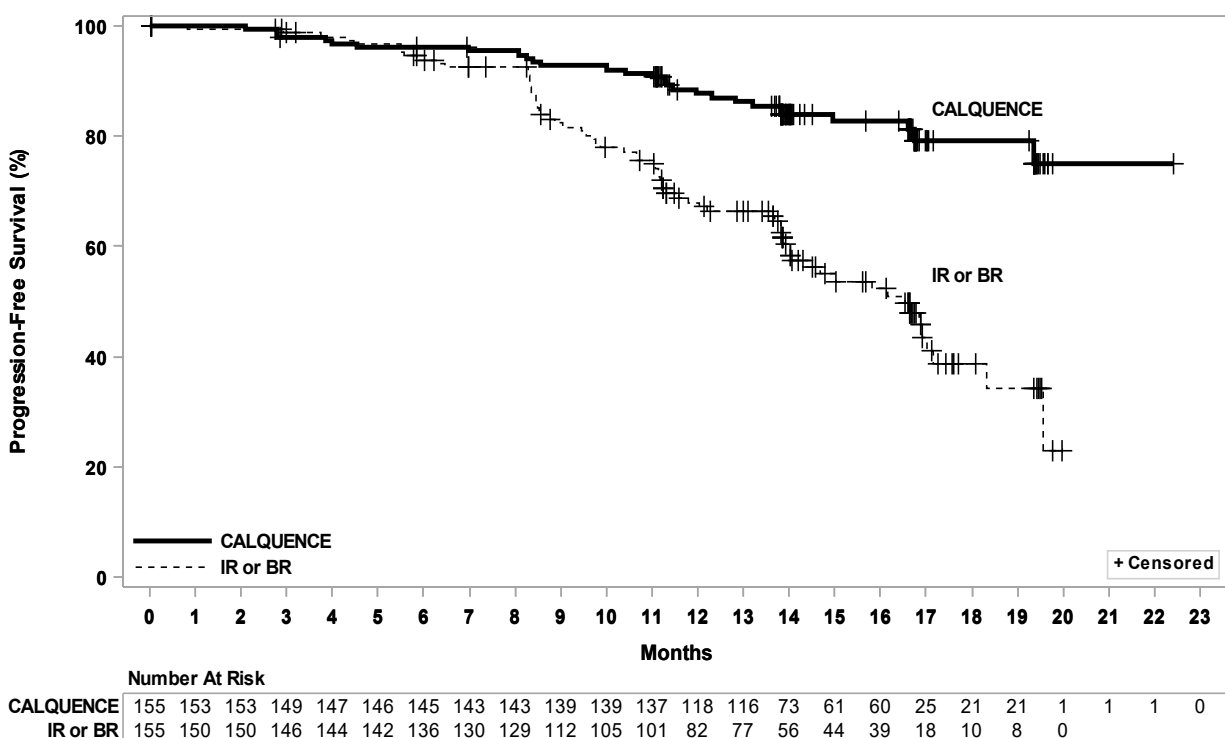
With a median follow-up of 16.1 months, median overall survival was not reached in either arm, with fewer than 11% of patients experiencing an event.

16 HOW SUPPLIED/STORAGE AND HANDLING

<u>How Supplied</u>

Blister Aluminium laminate foil.
Pack size of 60 tablets.

<u>Storage</u>

Do not store above 30°C.
The expiry date of the product is indicated on the packaging materials.

Registration number: 176-50-37586-99

Manufacturer:
AstraZeneca AB 152 57 Södertälje Sweden

License holder:
AstraZeneca (Israel) Ltd.,
1 Atirei Yeda St., Kfar Saba 4464301.

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