

1. NAME OF THE MEDICINAL PRODUCT

CALQUENCE CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Acalabrutinib 100 mg

3. PHARMACEUTICAL FORM

Capsules.

A size 1 hard gelatin capsule, with a blue cap and yellow body, printed with 'ACA 100mg' in black ink.

4. INDICATIONS AND USAGE

4.1 Mantle Cell Lymphoma

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

4.2 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

CALQUENCE CAPSULES 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 CAPSULES as Monotherapy

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

CALQUENCE CAPSULES in Combination with Obinutuzumab

For patients with previously untreated CLL or SLL, the recommended dose of CALQUENCE CAPSULES is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start CALQUENCE CAPSULES 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 CAPSULES prior to obinutuzumab when given on the same day.

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

5.2 Recommended Dosage for Hepatic Impairment

Avoid administration of CALQUENCE CAPSULES in patients with severe hepatic impairment. Dose modifications are not required for patients with mild or moderate hepatic impairment [see Use in Specific Populations (11.6) and Clinical Pharmacology (13.3)].

5.3 Recommended Dosage for Drug Interactions

Dose Modifications for Use with CYP3A Inhibitors or Inducers

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

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

CYP3A	Co-administered Drug	Recommended CALQUENCE CAPSULES use
Inhibition	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 CAPSULES.
	Moderate CYP3A inhibitor	100 mg once daily.
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE CAPSULES dose to 200 mg approximately every 12 hours.

Concomitant Use with Gastric Acid Reducing Agents

Proton Pump Inhibitors: Avoid concomitant use [see Drug Interactions (10)].

H2-Receptor Antagonists: Take CALQUENCE CAPSULES 2 hours before taking a H2-receptor antagonist [see Drug Interactions (10)].

Antacids: Separate dosing by at least 2 hours [see Drug Interactions (10)].

5.4 Dose Modifications for Adverse Reactions

Recommended dose modifications of CALQUENCE CAPSULES for Grade 3 or greater adverse reactions are provided in Table 2.

Table 2: Recommended Dose Modifications for Adverse Reactions

Event	Adverse Reaction Occurrence	Dose 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 CAPSULES. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE CAPSULES may be resumed at 100 mg approximately every 12 hours.
	Third	Interrupt CALQUENCE CAPSULES. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE CAPSULES may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue CALQUENCE CAPSULES.

Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.

6. DOSAGE FORMS AND STRENGTHS

100 mg capsules.

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 CAPSULES.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE CAPSULES in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE CAPSULES 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 with hematologic malignancies treated with CALQUENCE CAPSULES. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE CAPSULES in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients. Use of antithrombotic agents concomitantly with CALQUENCE CAPSULES may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE CAPSULES without antithrombotic agents and 3.6% of patients taking CALQUENCE CAPSULES with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE CAPSULES. Monitor patients for signs of bleeding. Consider the benefit-risk of withholding CALQUENCE CAPSULES for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

8.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE CAPSULES. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted [see Dose Modifications for Adverse Reactions (5.4)].

8.4 Second Primary Malignancies

Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE CAPSULES in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

8.5 Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with CALQUENCE CAPSULES. Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE CAPSULES, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. Grade 3 or higher ventricular arrhythmia events were reported in 0.9% of patients. The risk 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 CAPSULES.

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

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

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.

The data in the Warnings and Precautions reflect exposure to CALQUENCE CAPSULES 100 mg approximately every 12 hours in 1029 patients with hematologic malignancies. Treatment includes CALQUENCE CAPSULES monotherapy in 820 patients in 6 trials, and CALQUENCE CAPSULES with obinutuzumab in 209 patients in 2 trials.

Among these recipients of CALQUENCE CAPSULES, 88% were exposed for at least 6 months and 79% were exposed for at least one year. In this pooled safety population, adverse reactions in $\geq 30\%$ of 1029 patients were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain.

Mantle Cell Lymphoma

The safety data described in this section reflect exposure to CALQUENCE CAPSULES (100 mg approximately every 12 hours) in 124 patients with previously treated MCL in Trial LY-004 [see Clinical Studies (15.1)]. The median duration of treatment with CALQUENCE CAPSULES was 16.6 (range 0.1 to 26.6) months. A total of 91 (73.4%) patients were treated with CALQUENCE CAPSULES for ≥ 6 months and 74 (59.7%) patients were treated for ≥ 1 year.

The most common adverse reactions ($\geq 20\%$) 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 3 and 4 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE CAPSULES.

Table 3: Non-Hematologic Adverse Reactions* in $\geq 5\%$ (All Grades) of Patients with MCL in Trial LY-004

Body System Adverse Reactions*	CALQUENCE CAPSULES 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	-

^aPer NCI CTCAE version 4.03.

^aBruising: Includes all terms containing 'bruise,' 'contusion,' 'petechiae,' or 'ecchymosis'

^bRash: Includes all terms containing 'rash'

^cHemorrhage: Includes all terms containing 'hemorrhage' or 'hematoma'

Table 4: Hematologic Adverse Reactions Reported* in ≥ 20% of Patients with MCL in Trial LY-004

Hematologic Adverse Reactions*	CALQUENCE CAPSULES 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 1.5 to 3 times the upper limit of normal occurred in 4.8% of patients.

Chronic Lymphocytic Leukemia

The safety data described below reflect exposure to CALQUENCE CAPSULES (100 mg approximately every 12 hours, with or without obinutuzumab) in 511 patients with CLL from two randomized controlled clinical trials [see Clinical Studies (15.2)].

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

ELEVATE-TN

The safety of CALQUENCE CAPSULES plus obinutuzumab (CALQUENCE CAPSULES +G), CALQUENCE CAPSULES monotherapy, and obinutuzumab plus chlorambucil (GC1b) was evaluated in a randomized, multicenter, open-label, actively controlled trial in 526 patients with previously untreated CLL [see Clinical Studies (15.2)].

Patients randomized to the CALQUENCE CAPSULES +G arm were treated with CALQUENCE CAPSULES and obinutuzumab in combination for six cycles, then with CALQUENCE CAPSULES 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 CAPSULES monotherapy received CALQUENCE CAPSULES 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 upper limit of normal (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 CAPSULES in the CALQUENCE CAPSULES +G and CALQUENCE CAPSULES 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 CAPSULES +G arm received at least 6 cycles of obinutuzumab.

In the CALQUENCE CAPSULES +G and CALQUENCE CAPSULES 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

CAPSULES +G arm and 32% in the CALQUENCE CAPSULES monotherapy arm, most often due to events of pneumonia (2.8% to 7%). In the CALQUENCE CAPSULES +G arm, adverse reactions led to treatment discontinuation in 11% of patients and a dose reduction of CALQUENCE CAPSULES in 7% of patients. In the CALQUENCE CAPSULES monotherapy arm, adverse reactions led to discontinuation in 10% and dose reduction in 4% of patients. Tables 5 and 6 presents adverse reactions and laboratory abnormalities identified in the ELEVATE-TN trial.

Table 5: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE CAPSULES in Patients with CLL (ELEVATE-TN)

Body System Adverse Reaction*	CALQUENCE CAPSULES plus Obinutuzumab N=178		CALQUENCE CAPSULES 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 ^a	39	2.8	35	0	17	1.2
Lower respiratory tract infection ^b	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[§]						
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 [†]	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

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 CAPSULES plus obinutuzumab arm, 3 fatal cases in the CALQUENCE CAPSULES monotherapy arm and 1 fatal case in the obinutuzumab plus chlorambucil arm

§ Derived from adverse reaction and laboratory data

^a Upper respiratory tract infection, nasopharyngitis and sinusitis

^b Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection

^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 CAPSULES (CALQUENCE 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 6: Select Non-Hematologic Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE CAPSULES (ELEVATE-TN)

Laboratory Abnormality ^{*,a}	CALQUENCE CAPSULES plus Obinutuzumab N=178	CALQUENCE CAPSULES 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 1.5 to 3 times the upper limit of normal occurred in 3.9% and 2.8% of patients in the CALQUENCE CAPSULES combination arm and monotherapy arm, respectively.

ASCEND

The safety of CALQUENCE CAPSULES in patients with relapsed or refractory CLL was evaluated in a randomized, open-label study (ASCEND) [see Clinical Studies (15.2)]. The trial enrolled patients with relapsed or refractory CLL after at least one prior therapy and required hepatic transaminases ≤ 2 times upper limit of normal (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 CAPSULES (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 CAPSULES arm, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in > 5% of patients who received CALQUENCE CAPSULES included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE CAPSULES occurred in 2.6% of patients, including from second primary malignancies and infection.

In recipients of CALQUENCE CAPSULES, 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 CAPSULES 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 7 and non-hematologic laboratory abnormalities are described in Table 8. These tables reflect exposure to CALQUENCE CAPSULES 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 7: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE CAPSULES in Patients with CLL (ASCEND)

Body System Adverse Reaction*	CALQUENCE CAPSULES 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 ^a	29	1.9	26	3.4	17	2.9
Lower respiratory tract infection ^b	23	6	26	15	14	6
Blood and lymphatic system disorders[§]						
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 CAPSULES monotherapy arm and 1 fatal case in the Idelalisib plus Rituximab arm

§ Derived from adverse reaction and laboratory data

^a Upper respiratory tract infection, rhinitis and nasopharyngitis

^b Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection.

^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 CAPSULES 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 8: Select Non-Hematologic Laboratory Abnormalities (≥ 10% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE CAPSULES (ASCEND)

Laboratory Abnormality ^a	CALQUENCE CAPSULES 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 CAPSULES.

9.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of CALQUENCE CAPSULES. 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 reactions events should be reported to the Ministry of Health according to the National Regulation by an online form:

<https://sideeffects.health.gov.il>

10. DRUG INTERACTIONS

Strong CYP3A Inhibitors	
Clinical Impact	<ul style="list-style-type: none"> • Co-administration of CALQUENCE CAPSULES with a strong CYP3A inhibitor (itraconazole) increased

	<p>acalabrutinib plasma concentrations [see Clinical Pharmacology (12.3)].</p> <ul style="list-style-type: none"> Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	<ul style="list-style-type: none"> Avoid co-administration of strong CYP3A inhibitors with CALQUENCE CAPSULES. Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE CAPSULES [see Dosage and Administration (5.3)].
Moderate CYP3A Inhibitors	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of CALQUENCE CAPSULES with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentrations [see Clinical Pharmacology 13.3]. Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	<ul style="list-style-type: none"> When CALQUENCE CAPSULES is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.
Strong CYP3A Inducers	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of CALQUENCE CAPSULES with a strong CYP3A inducer (rifampin) decreased acalabrutinib plasma concentrations [see Clinical Pharmacology 13.3]. Decreased acalabrutinib concentrations may reduce CALQUENCE CAPSULES activity.
Prevention or Management	<ul style="list-style-type: none"> Avoid co-administration of strong CYP3A inducers with CALQUENCE CAPSULES. If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg approximately every 12 hours.
Gastric Acid Reducing Agents	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of CALQUENCE CAPSULES with a proton pump inhibitor, H₂-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations [see Clinical Pharmacology 13.3].

	<ul style="list-style-type: none"> Decreased acalabrutinib concentrations may reduce CALQUENCE CAPSULES activity. If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (e.g., ranitidine or famotidine) or an antacid (e.g., calcium carbonate). 	
Prevention or Management	Antacids	Separate dosing by at least 2 hours [see Recommended Dosage for Drug Interactions (5.3)].
	H2-receptor antagonists	Take CALQUENCE CAPSULES 2 hours before taking the H2-receptor antagonist [see Recommended Dosage for Drug Interactions (5.3)].
	Proton pump inhibitors	Avoid co-administration. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with CALQUENCE CAPSULES.

11. USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk summary

Based on findings in animals, CALQUENCE CAPSULES 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 2-4% and 15-20%, 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 \geq 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 \geq 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 CAPSULES, advise lactating women not to breastfeed while taking CALQUENCE CAPSULES and for at least 2 weeks after the final dose.

11.3 Females and Males of Reproductive Potential

Pregnancy

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

Contraception

Females

CALQUENCE CAPSULES may cause embryo-fetal harm and dystocia when administered to pregnant women [see Use in Specific Populations 11.1]. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE CAPSULES and for at least 1 week following the last dose of CALQUENCE CAPSULES. 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 CAPSULES in pediatric patients have not been established.

11.5 Geriatric Use

Of the 929 patients with CLL or MCL in clinical trials of CALQUENCE CAPSULES, 68% were 65 years of age or older, and 24% were 75 years of age or older. Among patients 65 years of age or older, 59% had Grade 3 or higher adverse reactions and 39% had serious adverse reactions. Among patients younger than age 65, 45% had Grade 3 or higher adverse reactions and 25% had serious adverse reactions. No clinically relevant differences in efficacy were observed between patients \geq 65 years and younger.

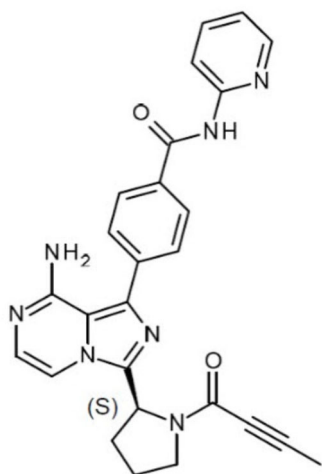
11.6 Hepatic Impairment

Avoid administration of CALQUENCE CAPSULES in patients with severe hepatic impairment. The safety of CALQUENCE CAPSULES has not been evaluated in patients with moderate or severe hepatic impairment [see Recommended Dosage for Hepatic Impairment (5.2) and Clinical Pharmacology (13.3)].

12. DESCRIPTION

CALQUENCE CAPSULES (acalabrutinib) is an inhibitor of Bruton tyrosine kinase (BTK). The molecular formula for acalabrutinib is $C_{26}H_{23}N_7O_2$, and the molecular weight is 465.51. The chemical name is 4-{8-amino-3-[(2S)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(pyridine-2-yl)benzamide.

The chemical structure of acalabrutinib is shown below:



Acalabrutinib is a white to yellow 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 CAPSULES for oral administration contains 100 mg acalabrutinib and the following inactive ingredients: silicified microcrystalline cellulose, partially pregelatinised starch, sodium starch glycolate Type A, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, iron oxide, yellow, Indigotine - FD&C Blue 2 and is imprinted with ink.

13. CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Acalabrutinib is a small-molecule inhibitor of 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 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

The effect of acalabrutinib on the QTc interval was evaluated in a randomized, 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).

13.3 Pharmacokinetics

Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and its active metabolite, ACP-5862, exposures increase with dose across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose) 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 acalabrutinib plasma concentrations (T_{max}) was 0.9 [0.5, 1.9] hours, and 1.6 [0.9, 2.7] hour for ACP-5862.

Effect of Food

In healthy subjects, administration of a single 75 mg dose of acalabrutinib (0.75 times the approved recommended single dose) with a high-fat, high-calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting C_{max} decreased by 73% and T_{max} was delayed 1-2 hours.

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 geometric mean (% CV) steady-state volume of distribution (V_{ss}) was approximately 101 (52%) L for acalabrutinib and 67 (32%) L for ACP-5862.

Elimination

The geometric mean (% CV) terminal elimination half-life ($t_{1/2}$) was 1 (59%) hour for acalabrutinib and 3.5 (24%) hours for ACP-5862. The geometric mean (%CV) apparent oral clearance (CL/F) was 71 (35%) L/hr for acalabrutinib and 13 (42%) L/hr for ACP-5862.

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 and 12% of the dose was recovered in the urine, with less than 2% of the dose excreted as unchanged acalabrutinib in urine and feces.

Specific Populations

Age, Race, and Body Weight

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

Renal Impairment

No clinically relevant PK difference was observed in patients with mild or moderate renal impairment (eGFR \geq 30 mL/min/1.73m², 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/1.73m², MDRD) or renal impairment requiring dialysis.

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 less and equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin greater than ULN and any AST) relative to patients with normal hepatic function (total bilirubin and AST within ULN).

Drug Interaction Studies

Effect of CYP3A Inhibitors on Acababrutinib

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 approximately 2- to 3-fold.

Effect of CYP3A Inducers on Acababrutinib

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.

Gastric Acid Reducing Agents

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

In Vitro Studies

Metabolic Pathways

Acalabrutinib is a weak inhibitor of CYP3A4/5, CYP2C8 and CYP2C9, but does not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, UGT1A1, and UGT2B7. ACP-5862 is a weak inhibitor of CYP2C8, CYP2C9 and CYP2C19, but does not inhibit CYP1A2, CYP2B6, CYP2D6, CYP3A4/5, UGT1A1, and UGT2B7.

Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4; ACP-5862 weakly induces CYP3A4.

Based on in vitro data and PBPK modeling, no interaction with CYP substrates is expected at clinically relevant concentrations.

Drug Transporter Systems

Acalabrutinib and its active metabolite, ACP-5862, are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1, and OATP1B3. ACP-5862 is not a substrate of OATP1B1 or OATP1B3.

Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, and MATE2-K at clinically relevant concentrations.

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP. ACP-5862 does not inhibit BCRP at clinically relevant concentrations. Acalabrutinib does not inhibit MATE1, while ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1.

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 Mantle Cell Lymphoma

The efficacy of CALQUENCE CAPSULES 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 \geq 5 cm, 73% had extra nodal involvement including 51% with bone marrow involvement. The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 44% and high in 17% of patients.

CALQUENCE CAPSULES 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 9: 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+]

*Per 2014 Lugano Classification.

CI= Confidence Interval; NE=Not Estimable; + indicates censored observations

The median time to best response was 1.9 months.

Lymphocytosis

Upon initiation of CALQUENCE CAPSULES, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count (ALC) increased \geq 50% from baseline and a post baseline assessment \geq 5×10^9) 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.

15.2 Chronic Lymphocytic Leukemia

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

ELEVATE-TN

The efficacy of CALQUENCE CAPSULES was evaluated in the ELEVATE-TN trial, a randomized, multicenter, open-label, actively controlled, 3 arm trial of CALQUENCE CAPSULES in combination with obinutuzumab, CALQUENCE CAPSULES 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 CAPSULES plus obinutuzumab (CALQUENCE CAPSULES +G): CALQUENCE CAPSULES 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 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 CAPSULES monotherapy: CALQUENCE CAPSULES 100 mg was administered approximately every 12 hours until disease progression or unacceptable toxicity.
- Obinutuzumab plus chlorambucil (GC1b): Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1000 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 1000 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 CAPSULES +G, 179 to CALQUENCE CAPSULES monotherapy, and 177 to GC1b. 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 10. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 10. Efficacy Results per IRC in Patients with CLL -- ITT population (ELEVATE-TN)

	CALQUENCE CAPSULES plus Obinutuzumab N=179	CALQUENCE CAPSULES 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.

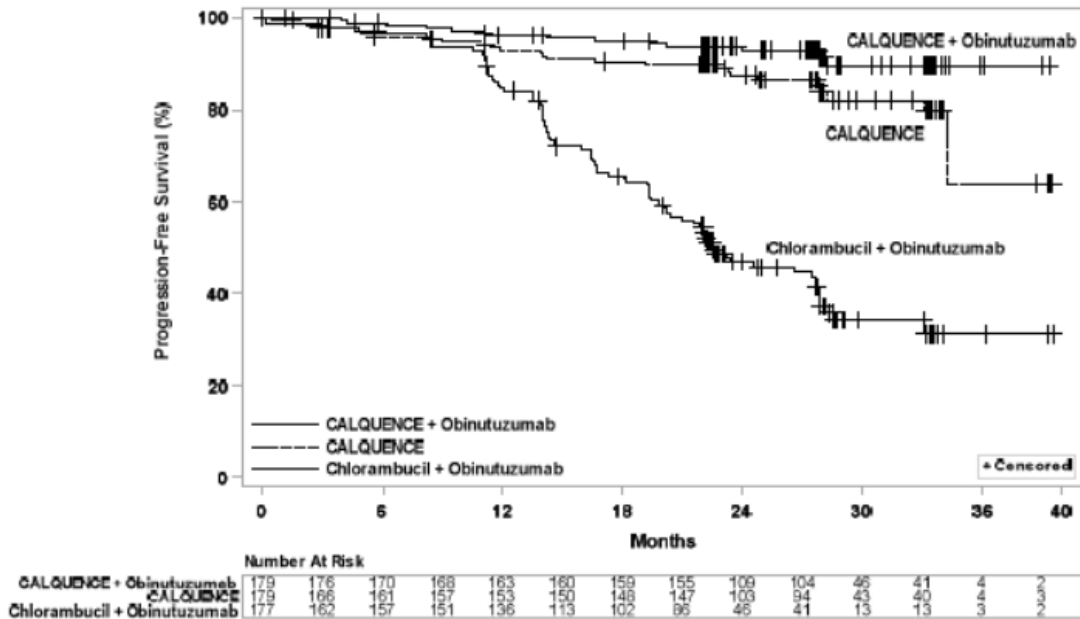
^b Kaplan-Meier estimate.

^cBased 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 1: Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL in ELEVATE-TN



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 CAPSULES 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, polymphocytic 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 CAPSULES 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/m² intravenously on Day 1 of Cycle 1, followed by 500 mg/m² every 2 weeks for 4 doses and then every 4 weeks for 3 doses), with a 28-day cycle length.
 - Bendamustine plus a rituximab product (BR): Bendamustine 70 mg/m² intravenously (Day 1 and 2 of each 28-day cycle), in combination with a rituximab product (375 mg/m² intravenously on Day 1 of Cycle 1, then 500 mg/m² 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 CAPSULES 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 CAPSULES arm had a median of 1 prior therapy (range 1-8), with 47% having at least 2 prior therapies. The investigator's choice arm had a median of 2 prior therapies (range 1-10), with 57% having at least 2 prior therapies.

In the CALQUENCE CAPSULES 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 11. The Kaplan-Meier curve for PFS is shown in Figure 2. There was no statistically significant difference in overall response rates between the two treatment arms.

Table 11: Efficacy Results per IRC in Patients with Relapsed or Refractory CLL – ITT Population (ASCEND)

	CALQUENCE CAPSULES 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 ^d	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 CAPSULES 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.

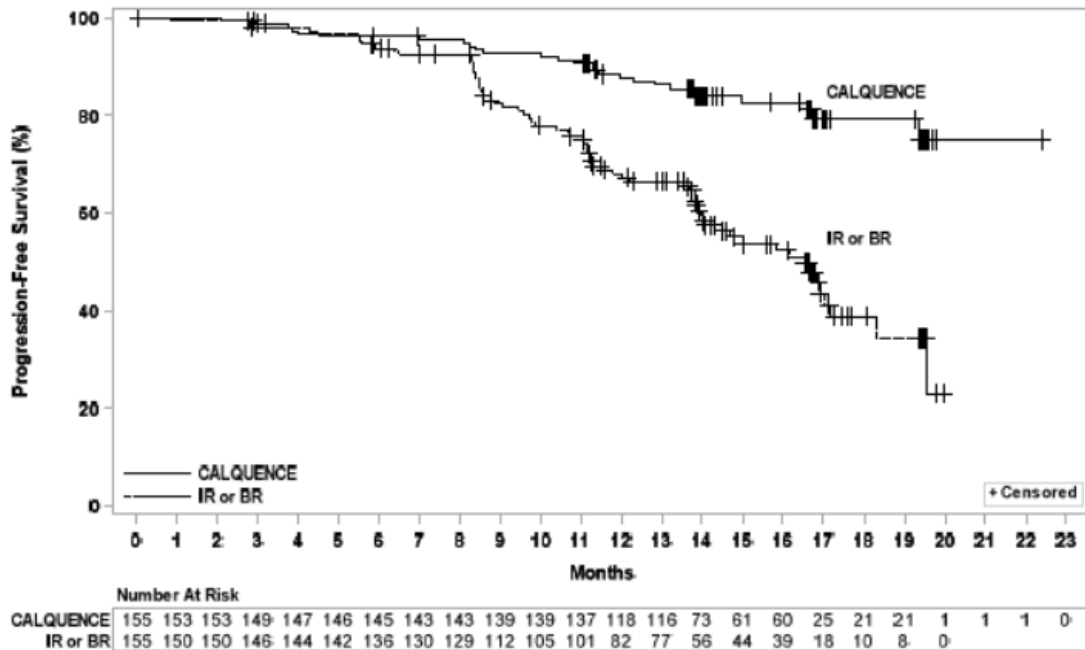
^b Kaplan-Meier estimate

^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 Haenzel test with adjustment for randomization stratification factors.

Figure 2: 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

How Supplied

Aluminum blister Pack.

Pack sizes of 56 capsules, 60 capsules

100 mg, hard gelatin capsules with yellow body and blue cap, marked in black ink with 'ACA 100 mg'

Registration number: 163-15-35692-00

Storage:

Do not store above 30°C.

Manufacturer:

AstraZeneca AB Gärtunavägen SE-151 85 Södertälje Sweden

License holder:

AstraZeneca (Israel) Ltd.,

1 Atirei Yeda St., Kfar Saba 4464301.

Revised in September 2024.