

CALQUENCE- acalabrutinib capsule, gelatin coated
AstraZeneca Pharmaceuticals LP

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CALQUENCE safely and effectively. See full prescribing information for CALQUENCE.

CALQUENCE® (acalabrutinib) capsules, for oral use

Initial U.S. Approval: 2017

----- **RECENT MAJOR CHANGES** -----

Indications and Usage (1.2) 11/2019
Dosage and Administration (2.2) 11/2019

----- **INDICATIONS AND USAGE** -----

CALQUENCE is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy. (1.1)
This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1,14.1)
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). (1.2)

----- **DOSAGE AND ADMINISTRATION** -----

- Recommended dose is 100 mg orally approximately every 12 hours; swallow whole with water and with or without food. (2.1)
- Advise patients not to break, open, or chew capsules. (2.1)
- Manage toxicities using treatment interruption, dose reduction, or discontinuation. (2.2)
- Avoid CALQUENCE in patients with severe hepatic impairment (2.2,8.6)

----- **DOSAGE FORMS AND STRENGTHS** -----

Capsules: 100 mg. (3)

----- **CONTRAINDICATIONS** -----

None. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Serious and Opportunistic Infections: Monitor for signs and symptoms of infection and treat promptly. (5.1)
- Hemorrhage: Monitor for bleeding and manage appropriately. (5.2)
- Cytopenias: Monitor complete blood counts regularly. (5.3)
- Second Primary Malignancies: Other malignancies have occurred, including skin cancers and other solid tumors. Advise patients to use sun protection. (5.4)
- Atrial Fibrillation and Flutter: Monitor for symptoms of arrhythmias and manage. (5.5)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (incidence \geq 30%) were: anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

- CYP3A Inhibitors: Avoid co-administration with strong CYP3A inhibitors. Dose adjustments may be recommended. (2.3,7,12.3)
- CYP3A Inducers: Avoid co-administration with strong CYP3A inducers. Dose adjustments may be recommended. (2.3,7,12.3)
- Gastric Acid Reducing Agents: Avoid co-administration with proton pump inhibitors (PPIs). Stagger dosing with H2-receptor antagonists and antacids. (2.4,7,12.3)

----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: May cause fetal harm and dystocia. (8.1)
- Lactation: Advise not to breastfeed (8.2)

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Mantle Cell Lymphoma
- 1.2 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Recommended Dosage for Hepatic Impairment
- 2.3 Recommended Dosage for Drug Interactions
- 2.4 Dose Modifications for Adverse Reactions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Serious and Opportunistic Infections
- 5.2 Hemorrhage
- 5.3 Cytopenias
- 5.4 Second Primary Malignancies
- 5.5 Atrial Fibrillation and Flutter

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Mantle Cell Lymphoma
- 14.2 Chronic Lymphocytic Leukemia

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

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

This indication is approved under accelerated approval based on overall response rate [see *Clinical Studies (14.1)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.2 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

CALQUENCE as Monotherapy

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

CALQUENCE in Combination with Obinutuzumab

For patients with previously untreated CLL or SLL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start CALQUENCE 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 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 may be taken with or without food. If a dose of CALQUENCE 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 should not be taken to make up for a missed dose.

2.2 Recommended Dosage for Hepatic Impairment

Avoid administration of CALQUENCE in patients with severe hepatic impairment.

Dose modifications are not required for patients with mild or moderate hepatic impairment [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

2.3 Recommended Dosage for Drug Interactions

Dose Modifications for Use with CYP3A Inhibitors or Inducers

These are described in Table 1 [see *Drug Interactions (7)*].

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

CYP3A	Co-administered Drug	Recommended CALQUENCE 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.
	Moderate CYP3A inhibitor	100 mg once daily.

Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg approximately every 12 hours.
-----------	----------------------	--

Concomitant Use with Gastric Acid Reducing Agents

Proton Pump Inhibitors: Avoid concomitant use [see Drug Interactions (7)].

H2-Receptor Antagonists: Take CALQUENCE 2 hours before taking a H2-receptor antagonist [see Drug Interactions (7)].

Antacids: Separate dosing by at least 2 hours [see Drug Interactions (7)].

2.4 Dose Modifications for Adverse Reactions

Recommended dose modifications of CALQUENCE 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. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at 100 mg approximately every 12 hours.
	Third	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue CALQUENCE.

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

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

3 DOSAGE FORMS AND STRENGTHS

100 mg capsules.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious and Opportunistic Infections

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

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE 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 have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jiroveci* 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.

5.2 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. 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 in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

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

5.3 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. 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 (2.4)*].

5.4 Second Primary Malignancies

Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE 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.

5.5 Atrial Fibrillation and Flutter

Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all 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.

6 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 (5.1)*]
- Hemorrhage [*see Warnings and Precautions (5.2)*]
- Cytopenias [*see Warnings and Precautions (5.3)*]
- Second Primary Malignancies [*see Warnings and Precautions (5.4)*]
- Atrial Fibrillation and Flutter [*see Warnings and Precautions (5.5)*]

6.1 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 100 mg approximately every 12 hours in 1029 patients with hematologic malignancies. Treatment includes CALQUENCE monotherapy in 820 patients in 6 trials, and CALQUENCE with obinutuzumab in 209 patients in 2 trials. Among these recipients of CALQUENCE, 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 (100 mg approximately every 12 hours) in 124 patients with previously treated MCL in Trial LY-004 [see *Clinical Studies (14.1)*]. The median duration of treatment with CALQUENCE was 16.6 (range: 0.1 to 26.6) months. A total of 91 (73.4%) patients were treated with CALQUENCE 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.

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

Body System Adverse Reactions *	CALQUENCE 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 [†]	21	-
Rash [‡]	18	0.8

Vascular disorders		
Hemorrhage [§]	8	0.8
Respiratory, thoracic and mediastinal disorders		
Epistaxis	6	-

* Per NCI CTCAE version 4.03.

† Bruising: Includes all terms containing ‘bruise,’ ‘contusion,’ ‘petechiae,’ or ‘ecchymosis’

‡ Rash: Includes all terms containing ‘rash’

§ Hemorrhage: 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 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 (100 mg approximately every 12 hours, with or without obinutuzumab) in 511 patients with CLL from two randomized controlled clinical trials [see *Clinical Studies (14.2)*].

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 plus obinutuzumab (CALQUENCE+G), CALQUENCE 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 (14.2)*].

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

In the CALQUENCE+G and CALQUENCE 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+G arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (2.8% to 7%).

In the CALQUENCE+G arm, adverse reactions led to treatment discontinuation in 11% of patients and a dose reduction of CALQUENCE in 7% of patients. In the CALQUENCE 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 in Patients with CLL (ELEVATE-TN)

Body System Adverse Reaction*	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections						
Infection [†]	69	22 [‡]	65	14 [‡]	46	13 [‡]
Upper respiratory tract infection [§]	39	2.8	35	0	17	1.2
Lower respiratory tract infection [¶]	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 [Ⓓ]	53	37	23	13	78	50
Anemia [Ⓑ]	52	12	53	10	54	14
Thrombocytopenia [Ⓐ]	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 ^δ	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 ^θ	34	2.2	23	1.1	24	1.2
Skin and subcutaneous tissue disorders						
Bruising ^γ	31	0	21	0	5	0
Rash [£]	26	2.2	25	0.6	9	0.6
Vascular disorders						
Hemorrhage [¥]	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 plus obinutuzumab arm, 3 fatal cases in the CALQUENCE monotherapy arm and 1 fatal case in the obinutuzumab plus chlorambucil arm

§ Upper respiratory tract infection, nasopharyngitis and sinusitis

- ¶ Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection
- # Derived from adverse reactions and laboratory data
- ᵀ Includes neutropenia, neutrophil count decreased, and related laboratory data
- β Includes anemia, red blood cell count decreased, and related laboratory data
- à Includes thrombocytopenia, platelet count decreased, and related laboratory data
- è Includes lymphocytosis, lymphocyte count increased, and related laboratory data
- ð Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain
- ø Includes asthenia, fatigue, and lethargy
- ý Includes bruise, contusion, and ecchymosis
- £ Includes rash, dermatitis, and other related terms
- ¥ Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE (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 (ELEVATE-TN)

Laboratory Abnormality*†	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
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

† 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 combination arm and monotherapy arm, respectively.

ASCEND

The safety of CALQUENCE in patients with relapsed or refractory CLL was evaluated in a randomized, open-label study (ASCEND) [see *Clinical Studies (14.2)*]. 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 (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 arm, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in > 5% of patients who received CALQUENCE included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE occurred in 2.6% of patients, including from second primary malignancies and infection.

In recipients of CALQUENCE, 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 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 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 in Patients with CLL (ASCEND)

Body System Adverse Reaction*	CALQUENCE 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¶	23	6	26	15	14	6
Blood and lymphatic system disorders#						
Neutropenia ^p	48	23	79	53	80	40
Anemia ^b	47	15	45	8	57	17
Thrombocytopenia ^a	33	6	41	13	54	6

Lymphocytosis ^è	26	19	23	18	2.9	2.9
Nervous system disorders						
Headache	22	0.6	6	0	0	0
Gastrointestinal disorders						
Diarrhea ^ð	18	1.3	49	25	14	0
Vascular disorders						
Hemorrhage ^ø	16	1.3	5	1.7	6	2.9
General disorders						
Fatigue ^ý	15	1.9	13	0.8	31	6
Musculoskeletal and connective tissue disorders						
Musculoskeletal Pain [£]	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 monotherapy arm and 1 fatal case in the Idelalisib plus Rituximab arm

§ Upper respiratory tract infection, rhinitis and nasopharyngitis

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

Derived from adverse reaction and laboratory data

Ð Includes neutropenia, neutrophil count decreased, and related laboratory data

ß Includes anemia, red blood cell decreased, and related laboratory data

à Includes thrombocytopenia, platelet count decreased, and related laboratory data

è Includes lymphocytosis, lymphocyte count increased and related laboratory data

ð Includes colitis, diarrhea, and enterocolitis

ø Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

ý Includes asthenia, fatigue, and lethargy

£ 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 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 (ASCEND)

Laboratory Abnormality*	CALQUENCE 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

* Excludes electrolytes

7 DRUG INTERACTIONS

Strong CYP3A Inhibitors	
<i>Clinical Impact</i>	<ul style="list-style-type: none"> • Co-administration of CALQUENCE with a strong CYP3A inhibitor (itraconazole) increased acalabrutinib plasma concentrations [see <i>Clinical Pharmacology</i> (12.3)]. • Increased acalabrutinib concentrations may result in increased toxicity.
<i>Prevention or Management</i>	<ul style="list-style-type: none"> • Avoid co-administration of strong CYP3A inhibitors with CALQUENCE. • Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE [see <i>Recommended Dosage for Drug Interactions</i> (2.3)].
Moderate CYP3A Inhibitors	
<i>Clinical Impact</i>	<ul style="list-style-type: none"> • Co-administration of CALQUENCE with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentrations [see <i>Clinical Pharmacology</i> (12.3)]. • Increased acalabrutinib concentrations may result in increased toxicity.
<i>Prevention or Management</i>	<ul style="list-style-type: none"> • When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.
Strong CYP3A Inducers	
<i>Clinical Impact</i>	<ul style="list-style-type: none"> • Co-administration of CALQUENCE with a strong CYP3A inducer (rifampin)

	decreased acalabrutinib plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>]. <ul style="list-style-type: none"> Decreased acalabrutinib concentrations may reduce CALQUENCE activity. 	
<i>Prevention or Management</i>	<ul style="list-style-type: none"> Avoid co-administration of strong CYP3A inducers with CALQUENCE. If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg approximately every 12 hours. 	
Gastric Acid Reducing Agents		
<i>Clinical Impact</i>	<ul style="list-style-type: none"> Co-administration of CALQUENCE with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>]. Decreased acalabrutinib concentrations may reduce CALQUENCE 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). 	
<i>Prevention or Management</i>	Antacids	Separate dosing by at least 2 hours [see <i>Recommended Dosage for Drug Interactions (2.3)</i>].
	H ₂ -receptor antagonists	Take CALQUENCE 2 hours before taking the H ₂ -receptor antagonist [see <i>Recommended Dosage for Drug Interactions (2.3)</i>].
	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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, CALQUENCE 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.

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

8.3 Females and Males of Reproductive Potential

Pregnancy

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

Contraception

Females

CALQUENCE may cause embryo-fetal harm and dystocia when administered to pregnant women [*see Use in Specific Populations (8.1)*]. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE. 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.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 929 patients with CLL or MCL in clinical trials of CALQUENCE, 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.

8.6 Hepatic Impairment

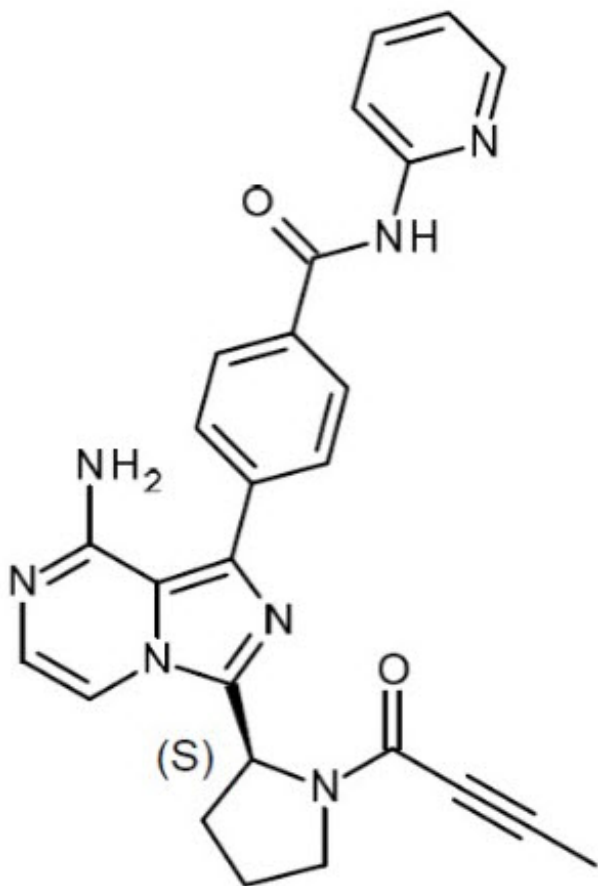
Avoid administration of CALQUENCE in patients with severe hepatic impairment. The safety of CALQUENCE has not been evaluated in patients with moderate or severe hepatic impairment [*see*

Recommended Dosage for Hepatic Impairment (2.2) and Clinical Pharmacology (12.3)].

11 DESCRIPTION

CALQUENCE (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 pregelatinized starch, magnesium stearate, and sodium starch glycolate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2 and is imprinted with edible black ink.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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).

12.3 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 Acalabrutinib

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

Physiologically based pharmacokinetic (PBPK) simulations with acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased acalabrutinib C_{max} and AUC approximately 2- to 3-fold.

Effect of CYP3A Inducers on Acalabrutinib

Co-administration with a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} by 68% and AUC by 77% in healthy subjects.

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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Mantle Cell Lymphoma

The efficacy of CALQUENCE 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 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+]

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, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count (ALC) increased $\geq 50\%$ from baseline and a post baseline assessment $\geq 5 \times 10^9$) 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.

14.2 Chronic Lymphocytic Leukemia

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

ELEVATE-TN

The efficacy of CALQUENCE was evaluated in the ELEVATE-TN trial, a randomized, multicenter, open-label, actively controlled, 3 arm trial of CALQUENCE in combination with obinutuzumab, CALQUENCE 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 plus obinutuzumab (CALQUENCE+G): CALQUENCE 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 monotherapy: CALQUENCE 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 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+G, 179 to CALQUENCE 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 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 plus Obinutuzumab N=179	CALQUENCE Monotherapy N=179	Obinutuzumab plus Chlorambucil N=177
Progression-Free Survival*			
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 [†]	NE	NE (34, NE)	22.6 (20, 28)
HR [‡] (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
p-value [§]	< 0.0001	< 0.0001	-
Overall Response Rate* (CR + CRi + nPR + PR)			
ORR, n (%)	168 (94)	153 (86)	139 (79)
(95% CI)	(89, 97)	(80, 90)	(72, 84)
p-value [¶]	< 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.

* Per 2008 International Workshop on CLL (IWCLL) criteria.

[†] Kaplan-Meier estimate.

[‡] Based on a stratified Cox-Proportional-Hazards model. Both hazard ratios are compared with the obinutuzumab and chlorambucil arm.

[§] 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.

[¶] 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

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

* Per 2008 IWCLL criteria.

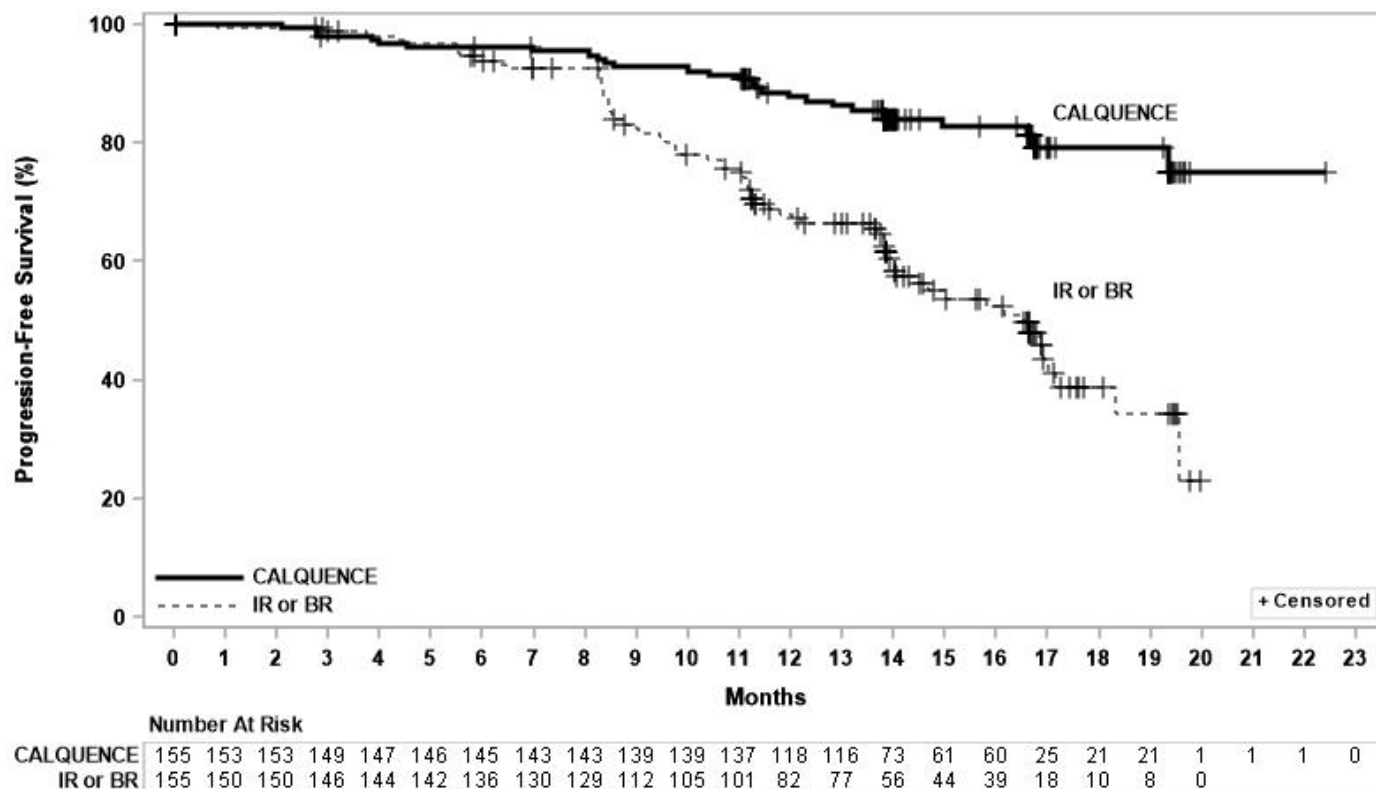
† Kaplan-Meier estimate

‡ Based on a stratified Cox-Proportional-Hazards model

§ 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

¶ 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

Pack Size	Contents	NDC Number
60-count bottle	Bottle containing 60 capsules 100 mg, hard gelatin capsules with yellow body and blue cap, marked in black ink with 'ACA 100 mg'	0310-0512-60

Storage

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Serious and Opportunistic Infections

Inform patients of the possibility of serious infection and to report signs or symptoms suggestive of infection [see Warnings and Precautions (5.1)].

Hemorrhage

Inform patients to report signs or symptoms of bleeding. Inform patients that CALQUENCE may need to be interrupted for major surgeries [see Warnings and Precautions (5.2)].

Cytopenias

Inform patients that they will need periodic blood tests to check blood counts during treatment with CALQUENCE [see *Warnings and Precautions (5.3)*].

Second Primary Malignancies

Inform patients that other malignancies have been reported in patients who have been treated with CALQUENCE, including skin cancer and other solid tumors. Advise patients to use sun protection [see *Warnings and Precautions (5.4)*].

Atrial Fibrillation and Flutter

Counsel patients to report any signs of palpitations, dizziness, fainting, chest discomfort, and shortness of breath [see *Warnings and Precautions (5.5)*].

Pregnancy Complication

CALQUENCE may cause fetal harm and dystocia. Advise women to avoid becoming pregnant during treatment and for at least 1 week after the last dose of CALQUENCE [see *Use in Specific Populations (8.3)*].

Lactation

Advise females not to breastfeed during treatment with CALQUENCE and for at least 2 weeks after the final dose [see *Use in Specific Populations (8.2)*].

Dosing Instructions

Instruct patients to take CALQUENCE orally twice daily, about 12 hours apart. CALQUENCE may be taken with or without food. Advise patients that CALQUENCE capsules should be swallowed whole with a glass of water, without being opened, broken, or chewed [see *Dosage and Administration (2.1)*].

Missed Dose

Advise patients that if they miss a dose of CALQUENCE, they may still take it up to 3 hours after the time they would normally take it. If more than 3 hours have elapsed, they should be instructed to skip that dose and take their next dose of CALQUENCE at the usual time. Warn patients they should not take extra capsules to make up for the dose that they missed [see *Dosage and Administration (2.1)*].

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins and herbal products [see *Drug Interactions (7)*].

Distributed by:

AstraZeneca Pharmaceuticals LP

Wilmington, DE 19850

CALQUENCE is a registered trademark of the AstraZeneca group of companies.

©AstraZeneca 2019

PATIENT INFORMATION CALQUENCE® (KAL-kwens) (acalabrutinib) Capsules
What is CALQUENCE? CALQUENCE is a prescription medicine used to treat adults with: <ul style="list-style-type: none">• Mantle cell lymphoma (MCL) who have received at least one prior treatment for their cancer.

- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

It is not known if CALQUENCE is safe and effective in children.

Before taking CALQUENCE, tell your healthcare provider about all of your medical conditions, including if you:

- have had recent surgery or plan to have surgery. Your healthcare provider may stop CALQUENCE for any planned medical, surgical, or dental procedure.
- have bleeding problems.
- have or had heart rhythm problems.
- have an infection.
- have or had liver problems, including hepatitis B virus (HBV) infection.
- are pregnant or plan to become pregnant. CALQUENCE may harm your unborn baby and problems during childbirth (dystocia).
 - If you are able to become pregnant, your healthcare provider may do a pregnancy test before you start treatment with CALQUENCE
 - Females who are able to become pregnant should use effective birth control (contraception) during treatment with CALQUENCE and for at least 1 week after the last dose of CALQUENCE.
- are breastfeeding or plan to breastfeed. It is not known if CALQUENCE passes into your breast milk. Do not breastfeed during treatment with CALQUENCE and for at least 2 weeks after your final dose of CALQUENCE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking CALQUENCE with certain other medications may affect how CALQUENCE works and can cause side effects. Especially tell your healthcare provider if you take a blood thinner medicine.

How should I take CALQUENCE?

- Take CALQUENCE exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking CALQUENCE unless your healthcare provider tells you to.
- Your healthcare provider may tell you to decrease your dose, temporarily stop, or completely stop taking CALQUENCE if you develop certain side effects.
- Take CALQUENCE 2 times a day (about 12 hours apart).
- Take CALQUENCE with or without food.
- Swallow CALQUENCE capsules whole with a glass of water. Do not open, break, or chew capsules.
- If you need to take an antacid medicine, take it either 2 hours before or 2 hours after you take CALQUENCE.
- If you need to take certain other medicines called acid reducers (H-2 receptor blockers), take CALQUENCE 2 hours before the acid reducer medicine.
- If you miss a dose of CALQUENCE, take it as soon as you remember. If it is more than 3 hours past your usual dosing time, skip the missed dose and take your next dose of CALQUENCE at your regularly scheduled time. Do not take an extra dose to make up for a missed dose.

What are the possible side effects of CALQUENCE?

CALQUENCE may cause serious side effects, including:

- **Serious infections** can happen during treatment with CALQUENCE and may lead to death. Your healthcare provider may prescribe certain medicines if you have an increased risk of getting infections. Tell your healthcare provider right away if you have any signs or symptoms of an infection, including fever, chills, or flu-like symptoms.
- **Bleeding problems (hemorrhage)** can happen during treatment with CALQUENCE and can be serious and may lead to death. Your risk of bleeding may increase if you are also taking a blood thinner medicine. Tell your healthcare provider if you have any signs or symptoms of bleeding, including:
 - blood in your stools or black stools (looks like tar)
 - pink or brown urine
 - unexpected bleeding, or bleeding that is severe or you cannot control
 - vomit blood or vomit that looks like coffee grounds
 - cough up blood or blood clots
 - dizziness
 - weakness
 - confusion
 - changes in your speech
 - headache that lasts a long time
 - bruising or red or purple skin marks
- **Decrease in blood cell counts.** Decreased blood counts (white blood cells, platelets, and red blood cells) are common with CALQUENCE, but can also be severe. Your healthcare provider should do blood tests to check your blood counts regularly during treatment with CALQUENCE.
- **Second primary cancers.** New cancers have happened in people during treatment with CALQUENCE, including cancers of the skin or other organs. Your healthcare provider will check you for skin cancers during treatment with CALQUENCE. Use sun protection when you are outside in sunlight.
- **Heart rhythm problems (atrial fibrillation and atrial flutter)** have happened in people treated with CALQUENCE. Tell your healthcare provider if you have any of the following signs or symptoms:
 - fast or irregular heartbeat
 - dizziness
 - feeling faint
 - chest discomfort
 - shortness of breath

The most common side effects of CALQUENCE include:

- headache
- diarrhea
- muscle and joint pain
- upper respiratory tract infection
- bruising

These are not all of the possible side effects of CALQUENCE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CALQUENCE?

- Store CALQUENCE at room temperature between 68°F to 77°F (20°C to 25°C).
Keep CALQUENCE and all medicines out of the reach of children.

General information about the safe and effective use of CALQUENCE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CALQUENCE for a condition for which it was not prescribed. Do not give CALQUENCE to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about CALQUENCE that is written for health professionals.

What are the ingredients in CALQUENCE?

Active ingredient: acalabrutinib

Inactive ingredients: silicified microcrystalline cellulose, pregelatinized starch, magnesium stearate, and sodium starch glycolate.

Capsule shell contains: gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2, and black ink.

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

CALQUENCE is a registered trademark of the AstraZeneca group of companies.

©AstraZeneca XXXX

For more information, go to www.CALQUENCE.com or call 1-800-236-9933.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 11/2019

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

NDC 0310-0512-60

60 capsules

CALQUENCE®

(acalabrutinib) capsules

100 mg

Rx only

Manufactured for:

AstraZeneca Pharmaceuticals LP

Wilmington, DE 19850

By: AstraZeneca AB

SE-151 85 Södertälje, Sweden

Product of Switzerland

Astra Zeneca

NDC 0310-0512-60

60 capsules



CALQUENCE[®]

(acalabrutinib) capsules

100 mg

00-89983

Rx only

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: AstraZeneca AB
SE-151 85 Södertälje, Sweden
Product of Switzerland

AstraZeneca 

CALQUENCE is a registered trademark of the AstraZeneca group of companies. © AstraZeneca 2019

GTIN 00303100512603

AREA RESERVED
FOR VARIABLE DATA

CALQUENCE

acalabrutinib capsule, gelatin coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0310-0512
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ACALABRUTINIB (UNII: I42748ELQW) (ACALABRUTINIB - UNII:I42748ELQW)	ACALABRUTINIB	100 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	YELLOW (blue cap)	Score	no score
Shape	CAPSULE	Size	1mm
Flavor		Imprint Code	ACA;100
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0310-0512-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	10/31/2017	
2	NDC:0310-0512-28	28 in 1 BOTTLE; Type 0: Not a Combination Product	04/01/2018	07/31/2021
3	NDC:0310-0512-95	60 in 1 BOTTLE; Type 0: Not a Combination Product	04/01/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210259	10/31/2017	

Labeler - AstraZeneca Pharmaceuticals LP (054743190)

Registrant - AstraZeneca PLC (230790719)

Revised: 11/2019

AstraZeneca Pharmaceuticals LP