PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrCALQUENCE®

acalabrutinib tablets

Tablets, 100 mg acalabrutinib (as acalabrutinib maleate), Oral

Antineoplastic agent

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Date of Initial Authorization:
FEB 24, 2023

Submission Control Number: 259246

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RECENT MAJOR LABEL CHANGES

Not Applicable.

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CALQUENCE® (acalabrutinib tablets) is indicated:

- in combination with obinutuzumab or as monotherapy for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
- as monotherapy for the treatment of patients with CLL who have received at least one prior therapy
- for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

1.1 Pediatrics

Pediatrics (**<18 years of age)**: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and those younger than 65 years. See 7.1 Special Populations.

2 CONTRAINDICATIONS

CALQUENCE (acalabrutinib) is contraindicated in patients who are hypersensitive to acalabrutinib or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Treatment with CALQUENCE (acalabrutinib) should be initiated and supervised by a qualified physician experienced in the use of anticancer therapies.
- Concomitant use of CALQUENCE with a strong CYP3A inhibitor should be avoided (see 9 DRUG INTERACTIONS).
- Serious Hemorrhage: Monitor for bleeding and manage appropriately (see 7 WARNINGS AND PRECAUTIONS, Hemorrhage).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Avoid concomitant use with strong CYP3A4 inhibitors (see 9 DRUG INTERACTIONS).
- Avoid concomitant use with strong CYP3A4 inducers (see 9 DRUG INTERACTIONS).
- Consider the benefit-risk of withholding CALQUENCE for at least 3 days pre-and post-

surgery.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of CALQUENCE for patients with CLL or MCL is 100 mg (1 tablet) twice daily.

Doses should be separated by approximately 12 hours.

In patients with previously untreated CLL, CALQUENCE can be used as monotherapy or in combination with obinutuzumab. Start CALQUENCE at cycle 1 (each cycle is 28 days). Start obinutuzumab at cycle 2 for a total of 6 cycles. Consult the obinutuzumab Product Monograph for recommended dosing information. For details of the combination regimen, see 14 CLINICAL TRIALS.

Treatment with CALQUENCE should continue until disease progression or unacceptable toxicity.

Dosage Adjustment
Recommended dose modifications of CALQUENCE for Grade ≥3 adverse reactions are provided in Table 1.

Table 1 Recommended Dose Adjustments for Adverse Reactions[a]

Adverse Reaction	Adverse Reaction Occurrence	Dose Modification (Starting dose = 100 mg twice daily)
Grade ≥3 non-hematologic toxicities, or Grade 3 thrombocytopenia with significant bleeding, or 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 therapy may be resumed at 100 mg twice daily
	Third	Interrupt CALQUENCE Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE therapy may be resumed at a reduced dose of 100 mg once daily
	Fourth	Discontinue CALQUENCE

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

Recommended dose modifications of CALQUENCE for use with CYP3A inhibitors is provided in Table 2.

Table 2 Use with CYP3A Inhibitors

	Co-administered Drug	Recommended CALQUENCE Use
CYP3A Inhibitors	Strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE.
	Moderate CYP3A inhibitors	100 mg once daily. Patients should be monitored for adverse reactions.
	Mild CYP3A inhibitors	No dose adjustment. Patients should be monitored for adverse reactions.

Special Populations

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): No dose adjustment is necessary based on age (see 10 CLINICAL PHARMACOLOGY).

Renal Impairment: No dose adjustment is recommended in patients with mild to moderate renal impairment (eGFR ≥30 mL/min/1.73m^2 as estimated by MDRD (modification of diet in renal disease equation)).

The pharmacokinetics and safety of CALQUENCE in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end-stage renal disease have not been studied (see 10 CLINICAL PHARMACOLOGY).

Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment (Child-Pugh A, Child-Pugh B, or total bilirubin between 1.5-3 times the upper limit of normal [ULN] regardless of aspartate aminotransferase [AST] levels).

Avoid the administration of CALQUENCE in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3 times ULN regardless of AST levels) (see 10 CLINICAL PHARMACOLOGY).

4.4 Administration

CALQUENCE should be swallowed whole with water at approximately the same time each day. CALQUENCE can be taken with or without food. The tablet should not be chewed, crushed, dissolved, or divided.

4.5 Missed Dose

If a patient misses a dose of CALQUENCE by more than 3 hours, instruct the patient to take the next dose at its regularly scheduled time. Extra tablets of CALQUENCE should not be taken to make up for a missed dose.

5 OVERDOSAGE

There is no specific treatment for CALQUENCE overdose and symptoms of overdose have not been established. In the event of an overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	100 mg acalabrutinib (as acalabrutinib maleate) tablet	Copovidone, hypromellose, iron oxide red (E172), iron oxide yellow (E172), Low-substituted hydroxypropyl cellulose, mannitol, macrogol 3350, microcrystalline cellulose, purified water, sodium stearyl fumarate, titanium dioxide and triglycerides (medium-chain).

Description
CALQUENCE (acalabrutinib) 100 mg tablet is an orange, 7.5 x 13 mm, oval, biconvex tablet, debossed with ‘ACA 100’ on one side and plain on the reverse.

Packaging
CALQUENCE 100 mg tablets are provided in white high density polyethylene (HDPE) plastic bottles, containing desiccant, with a child-resistant closure containing 60 tablets.

CALQUENCE (acalabrutinib tablets) is also available as 100 mg acalabrutinib capsules. Do not substitute CALQUENCE tablets with CALQUENCE capsules without prior consideration of the CALQUENCE capsules Product Monograph, Dosage and Administration section regarding drug interactions with gastric acid reducing agents.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

Second Primary Malignancies

Second primary malignancies, including skin and other solid tumours, have been reported more frequently in patients treated with CALQUENCE than in patients treated in the control arms of clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Advise protection from the sun.

Cardiovascular

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

Atrial Fibrillation

In clinical studies of patients with hematologic malignancies who were treated with CALQUENCE (n=1029), events of atrial fibrillation or atrial flutter were reported in 4.1% of patients, including Grade 3 events in 1.1% of patients. The risk of these events may be increased in patients with risk factors, such as pre-existing cardiovascular disease, hypertension, previous history of atrial fibrillation, and infection/pneumonia. Monitor all patients for symptoms of cardiac arrhythmia (e.g., palpitations, light-headedness, syncope, chest discomfort, or dyspnea) and manage appropriately.

Driving and Operating Machinery

CALQUENCE has no or negligible influence on the ability to drive and use machines. However, during treatment with CALQUENCE in clinical trials, fatigue and dizziness have been reported. Patients who experience these symptoms should observe caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Cytopenias

Treatment-emergent Grade 3 or 4 neutropenia (including febrile neutropenia), anemia, and thrombocytopenia, based on laboratory measurements, occurred in patients with hematologic malignancies treated with CALQUENCE (see 8 ADVERSE REACTIONS). Monitor complete blood counts regularly during CALQUENCE treatment (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Interrupt treatment, reduce the dose, or discontinue treatment as necessary (see 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment).

Hemorrhage

Serious hemorrhagic events, including fatal events, have been reported in patients with hematologic malignancies (n=1029) treated with CALQUENCE in clinical trials.

Major hemorrhagic events (serious or Grade 3 or higher bleeding events or any central nervous system bleeding events) occurred in 3.3% of patients. Overall, bleeding events including bruising and petechiae of any grade, occurred in 44% of patients with hematological malignancies.

The mechanism for the bleeding events is not well understood.

Patients receiving antithrombotic agents concomitantly with CALQUENCE may be at increased risk of hemorrhage. Patients were excluded from CALQUENCE clinical trials if they required warfarin or other vitamin K antagonists, or if they had a recent history of stroke or intracranial hemorrhage. In clinical trials, major hemorrhagic events were reported in 3.8% of patients taking CALQUENCE with other antithrombotic agents, and in 3.0% of patients taking

CALQUENCE without any concomitant antithrombotic agents.

Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE (see 9.4 Drug-Drug Interactions). Monitor all patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for at least 3 days pre- and post-surgery.

Immune

Infections

Serious and fatal infections (bacterial, viral or fungal) have occurred in patients with hematologic malignancies treated with CALQUENCE. The most frequently reported Grade 3 or 4 infection was pneumonia.

Monitor patients for signs and symptoms of infection and treat promptly.

Opportunistic infections

Cases of progressive multifocal leukoencephalopathy (PML), including fatal events, have been reported in patients treated with CALQUENCE in clinical trials. Patients should be monitored for symptoms (chills, weakness, confusion), and appropriate therapy should be instituted as indicated.

Infections due to hepatitis B virus (HBV) reactivation have been reported in patients treated with CALQUENCE in clinical trials. Patients should be monitored for signs and symptoms (jaundice, abdominal pain, weakness, fatigue, nausea, and vomiting), and appropriate therapy should be instituted as indicated.

Other opportunistic infections, including aspergillosis, fungal pneumonia, and Pneumocystis Jiroveci Pneumonia have also been reported. Consider prophylaxis in patients who are at increased risk for opportunistic infections.

Monitoring and Laboratory Tests

- Monitor complete blood counts as per routine clinical practice.
- Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an echocardiogram (ECG) as appropriate.
- Monitor patients for the appearance of skin cancers.
- Monitor patients for signs and symptoms of infection and treat as medically appropriate.
- Monitor patients for signs of bleeding.

Reproductive Health: Female and Male Potential

There are no data on the effect of CALQUENCE on human fertility.

7.1 Special Populations

7.1.1 Pregnant Women

CALQUENCE should not be used during pregnancy and women of childbearing potential should be advised to avoid becoming pregnant while receiving CALQUENCE. There are insufficient clinical data on CALQUENCE use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Based on findings from animal studies, there may be a risk to the

fetus from exposure to acalabrutinib during pregnancy. Administration of acalabrutinib to pregnant rabbits at exposures 4-times the human exposure at the recommended dose was associated with reduced foetal growth (see 16 NON-CLINICAL TOXICOLOGY). Dystocia was observed in a rat study involving dosing animals from implantation throughout gestation, parturition and lactation at exposures >2.3-times the human AUC at the recommended dose (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

It is not known whether acalabrutinib is excreted in human milk. There are no data on the effect of acalabrutinib on the breast-fed infant or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. A risk to the suckling child cannot be excluded. Breast-feeding mothers are advised not to breast-feed during treatment with CALQUENCE and for 2 weeks after receiving the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of CALQUENCE in children and adolescents aged less than 18 years have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): No dose adjustment is necessary based on age (see 10 CLINICAL PHARMACOLOGY). Of the 1029 patients in clinical trials of CALQUENCE, 68% were 65 years of age or older, and 24% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and those younger than 65 years.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety profile of CALQUENCE is based on pooled data from 1029 patients with hematologic malignancies receiving CALQUENCE as monotherapy (n=820) or in combination with obinutuzumab (n=209).

The most common (≥20%) adverse reactions (ARs) of any grade reported in this pooled safety population of patients receiving CALQUENCE were infection, headache, diarrhea, musculoskeletal pain, bruising, fatigue, nausea, and rash.

The most frequently reported (≥2%) serious adverse reaction was pneumonia (5%).

Dose reductions and interruptions due to adverse events (AEs) were reported in 5% and 39% of patients, respectively. Discontinuation due to AEs were reported in 10% of the patients. The median dose intensity was 99%.

Lymphocytosis
Upon initiation of CALQUENCE, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count [ALC] increased ≥50% from baseline and a post baseline

assessment ≥5 x 10^9/L) has occurred in 54% (N=552/1029) of patients. The median time to onset of lymphocytosis was 1.1 weeks and the median duration of lymphocytosis was 7 weeks.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Previously Untreated Chronic Lymphocytic Leukemia (CLL) – ELEVATE-TN

The safety of CALQUENCE in patients with previously untreated CLL has been studied in a 3-arm, randomized, multi-centre, open-label Phase 3 trial (ELEVATE-TN). CALQUENCE plus obinutuzumab, CALQUENCE monotherapy, or obinutuzumab plus chlorambucil were administered to 526 patients with previously untreated CLL (see 14 CLINICAL TRIALS).

In the CALQUENCE plus obinutuzumab arm, adverse events led to regimen discontinuation in 11% of patients, and dose reduction of CALQUENCE in 7% of patients. In the CALQUENCE monotherapy arm, adverse events led to discontinuation in 10% and dose reduction in 4% of patients.

The adverse reactions described in Table 4 reflect exposure to CALQUENCE in the CALQUENCE plus obinutuzumab and CALQUENCE monotherapy arms with a median duration of exposure of 27.7 months in patients with previously untreated CLL. The median duration of exposure in the obinutuzumab plus chlorambucil arm was 5.6 months. The tabulated adverse reactions were reported in ≥5% of patients in either CALQUENCE-containing treatment arm, and are considered at least possibly related to study drug.

Table 4 Adverse Reactions in ≥5% (All Grades) of Patients with Chronic Lymphocytic Leukemia (CLL) in the ELEVATE-TN Trial.

System Organ Class Preferred Term[a]	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades[b] (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood and lymphatic system disorders[c]						
Neutropenia[c]	33	32	12	11	49	46
Thrombocytopenia[c]	15	9	10	3	15	13
Anemia[c]	13	6	16	7	12	7
Gastrointestinal disorders						
Diarrhea	39	5	35	1	21	2
Nausea	20	0	22	0	31	0
Constipation	14	0	11	0	10	1
Vomiting	14	1	12	1	11	1
Abdominal pain[c]	12	2	10	0	9	0
General disorders and administration site conditions						
Fatigue	28	2	18	1	17	1

System Organ Class Preferred Term[a]	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades[b] (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Pyrexia	13	0	7	1	21	1
Edema peripheral	12	1	9	1	7	0
Asthenia	10	1	5	0	6	1
Infections and Infestations						
Infection[c]	69	21	65	14	44	8
Upper respiratory tract infection	21	2	18	0	8	1
Lower respiratory tract infection (including pneumonia)[c]	15	7	10	2	5	0
Urinary tract infection	12	1	12	2	5	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[c]	37	2	32	1	16	2
Arthralgia	22	1	16	1	5	1
Neoplasms benign, malignant and unspecified						
Second Primary Malignancy (SPM)[c]	11	4	8	1	4	2
SPM excluding non-melanoma skin	6	3	3	1	2	1
Non-Melanoma Skin Malignancy	5	1	6	0	2	1
Nervous system disorders						
Headache	40	1	37	1	12	0
Dizziness	18	0	12	0	6	0
Skin and subcutaneous tissue disorders						
Bruising[c]	34	0	26	0	5	0
Rash[c]	22	2	19	1	7	1
Vascular disorders						
Hemorrhage/Hematoma[c]	13	1	9	1	4	0

[a] Based on MedDRA version 21.1.

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

[c] Includes multiple ADR terms:

Neutropenia: includes neutropenia, neutrophil count decreased.

Thrombocytopenia: includes thrombocytopenia, platelet count decreased.

Anemia: includes anemia, red blood cell decreased.

Abdominal pain: includes abdominal pain, abdominal pain upper, and abdominal pain lower.

Musculoskeletal pain: includes back pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, neck pain, pain in extremity, myalgia, spinal pain, bone pain.

Infection: includes any adverse reactions involving infection.

Lower respiratory infection: includes lower respiratory tract infection, pneumonia.

Second Primary Malignancy: includes any adverse reactions involving malignancy.

Bruising: includes bruise, contusion, and ecchymosis.

Rash: includes rash, dermatitis, and other related terms.

Hemorrhage/Hematoma: includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis and epitstaxis.

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) was reported in 3 (2%) patients treated with CALQUENCE plus obinutuzumab. No patients experienced TLS in the CALQUENCE monotherapy arm.

Previously Treated Chronic Lymphocytic Leukemia (CLL) - ASCEND

The safety of CALQUENCE in patients with previously treated CLL has been studied in a randomized, multi-centre, open-label, Phase 3 trial (ASCEND) in 307 patients with relapsed or refractory CLL. Patients were treated with CALQUENCE monotherapy or investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab (see 14 CLINICAL TRIALS).

In the CALQUENCE arm, adverse events led to discontinuation in 10% and dose reduction in 4% of patients.

The adverse reactions described in Table 5 reflect exposure to CALQUENCE with a median duration of 15.7 months, exposure to idelalisib with a median duration of 11.5 months, exposure to rituximab with a median duration of 5.5 months, and exposure to bendamustine with a median duration of 5.6 months in patients with relapsed or refractory CLL. The tabulated adverse reactions were reported in ≥5% of patients in the CALQUENCE arm, and are considered at least possibly related to study drug.

Table 5 Adverse Reactions in ≥5% (All Grades) of Patients with Chronic Lymphocytic Leukemia (CLL) in the ASCEND Trial.

System Organ Class Preferred Term[a]	CALQUENCE N=154		Idelalisib plus Rituximab N=118		Bendamustine plus Rituximab N=35	
	All Grades[b] (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders[c]						
Neutropenia[c]	21	18	51	47	37	34
Thrombocytopenia[C]	14	5	17	8	17	3
Anemia[c]	15	12	9	7	11	9
Cardiac disorders						
Atrial Fibrillation/Flutter[c]	5	1	3	1	3	3
Gastrointestinal disorders						
Diarrhea	18	1	47	24	14	0
Nausea	7	0	13	1	20	0
Constipation	7	0	8	0	14	6
Abdominal pain[c]	8	0	9	1	3	0
General disorders and administration site conditions						
Pyrexia	12	1	18	7	17	3
Fatigue	10	1	9	0	23	3
Asthenia	5	1	4	1	9	3
Infections and Infestations						
Infection[c]	57	15	65	28	49	11

System Organ Class Preferred Term[a]	CALQUENCE N=154		Idelalisib plus Rituximab N=118		Bendamustine plus Rituximab N=35	
	All Grades[b] (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥ 3 (%)
Upper respiratory tract infection	14	2	14	3	11	3
Lower respiratory tract infection (including pneumonia)[c]	12	5	13	10	6	3
Neoplasms benign, malignant and unspecified						
Second Primary Malignancy (SPM)[c]	12	4	3	0	3	3
SPM excluding non-melanoma skin	7	3	3	0	3	3
Non-Melanoma Skin Malignancy	7	1	1	0	0	0
Nervous system disorders						
Headache	22	1	6	0	0	0
Dizziness	6	0	3	0	0	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal Pain[c]	15	1	15	2	3	0
Arthralgia	8	1	6	0	3	0
Skin and subcutaneous tissue disorders						
Bruising[c]	12	0	3	0	0	0
Rash[c]	7	0	16	3	9	0
Vascular disorders						
Hemorrhage/Hematoma[c]	13	1	4	1	6	3

[a] Based on MedDRA version 21.1.

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

[c] Includes multiple ADR terms:

Neutropenia: Includes Neutropenia, Neutrophil count decreased

Anemia: Includes anemia, red blood cell decreased,

Thrombocytopenia: Includes Thrombocytopenia, Platelet count decreased

Abdominal pain: Includes abdominal pain, abdominal pain upper, and abdominal pain lower.

Musculoskeletal pain: Includes back pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, pain in extremity, myalgia, spinal pain and bone pain

Infection: Includes any adverse reactions involving infection

Lower respiratory tract infection: Includes lower respiratory tract infection, Pneumonia

Second primary malignancy: Includes any adverse reactions involving malignancy

Bruising: Includes bruise, contusion, and ecchymosis

Rash: Includes rash, dermatitis, and other related terms

Hemorrhage/Hematoma: Includes hemorrhage, hematoma, Hemoptysis, Hematuria, Menorrhagia, hemarthrosis, and epistaxis

Tumour Lysis Syndrome

TLS was reported in 1 patient treated with CALQUENCE and 1 patient treated with idelalisib plus rituximab, with an incidence of 1% in both arms. The one patient experiencing TLS treated with CALQUENCE had Grade 3 TLS and bulky disease.

Mantle Cell Lymphoma (MCL) – ACE-LY-004

The safety of CALQUENCE in patients with MCL has been studied in 124 patients at a dose of 100 mg twice daily in a single-arm Phase 2 trial (ACE-LY-004). The median dose intensity was 99%.

The frequencies of treatment-emergent adverse events reported (regardless of causality) in the ACE-LY-004 study have been included in Table 6. The median duration of CALQUENCE treatment in patients with MCL (ACE-LY-004) was 17.3 months.

Table 6 Treatment-Emergent Adverse Events reported at ≥10% incidence (frequencies reported regardless of causality) in ACE-LY-004 Study (100 mg twice daily)

	CALQUENCE (N=124)	
System Organ Class Preferred Term[a]	**All CTCAE[b] Grades (%)**	**CTCAE Grade ≥3[c] (%)**
Blood and lymphatic system disorders		
Anemia	13	10
Neutropenia	10	10
Gastrointestinal disorders		
Diarrhea	36	3
Nausea	19	2
Constipation	15	0
Vomiting	15	2
Abdominal Pain[d]	15	2
General disorders and administration site conditions		
Asthenia	17	2
Fatigue	28	2
Pyrexia	16	0
Infections and infestations		
Sinusitis	12	0
Upper respiratory tract infection	10	0
Musculoskeletal and connective tissue disorders		
Myalgia	21	2
Nervous system disorders		
Headache	38	2
Dizziness	12	0
Respiratory, thoracic and mediastinal disorders		
Cough	22	0
Dyspnoea	10	2
Skin and subcutaneous tissue disorders		
Bruising[d]	21	0
Rash[d]	19	2

System Organ Class Preferred Term[a]	CALQUENCE (N=124)	
	All CTCAE[b] Grades (%)	CTCAE Grade ≥3[c] (%)

[a] Based on MedDRA version 20.1.
[b] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
[c] All events were Grade 3, except one Grade 4 intracranial hemorrhage and one Grade 5 intracranial hematoma.
[d] AEs based on grouping of individual preferred terms (PTs):
Abdominal pain: Any PT containing 'abdominal pain'
Bruising: Any PT containing 'bruise', 'contusion', 'petechiae', or 'ecchymosis'
Rash: Any PT containing 'rash'

Contusion, a common finding in B cell malignancies, was reported at a lower rate in the ACE-LY-004 population (13%) than in the overall safety analysis (N=1029) population (20%), while myalgia was reported at a higher rate in the ACE-LY-004 population (21%) than in the overall safety analysis (10%) population. Overall, the most commonly reported AEs were consistent between the ACE-LY-004 and overall safety analysis populations.

8.3 Less Common Clinical Trial Adverse Reactions

Chronic Lymphocytic Leukemia (CLL)

The following less common clinical trial adverse reactions were reported in patients with previously untreated CLL (ELEVATE-TN study), or in patients with previously treated CLL (ASCEND study), at a frequency of ≥1 but <5% in either study, and are considered at least possibly related to study drug.

Blood and lymphatic system disorders: lymphocytosis, febrile neutropenia

Endocrine and metabolism: Tumour Lysis Syndrome

Mantle Cell Lymphoma (MCL)

The following treatment-emergent adverse events (regardless of causality) have been reported in the ACE-LY-004 study (100 mg twice daily) in ≥5 - <10% of patients.

Eye disorders: lacrimation increased, vision blurred

Gastrointestinal disorders: stomatitis

General disorders and administration site conditions: peripheral oedema

Infections and infestations: bronchitis, nasopharyngitis, pneumonia

Injury, poisoning and procedural complications: fall

Metabolism and nutrition disorders: decreased appetite

Musculoskeletal and connective tissue disorders: arthralgia, back pain, muscle

spasms, musculoskeletal pain, pain in extremity

Nervous system disorders: paraesthesia, memory impairment

Psychiatric disorders: insomnia

Respiratory, thoracic and mediastinal disorders: epistaxis

Skin and subcutaneous tissue disorders: erythema

Vascular disorders: hemorrhage/hematoma*, hypotension

*AEs based on grouping of individual preferred terms: any preferred term containing 'hemorrhage' or 'hematoma'

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Previously Untreated CLL:

Table 7 Hematologic Laboratory Abnormalities in ≥20% of Patients with Chronic Lymphocytic Leukemia (CLL) in the ELEVATE-TN Trial

Laboratory Abnormalities[a]	CALQUENCE plus Obinutuzumab N=178		CALQUENCE Monotherapy N=179		Obinutuzumab plus Chlorambucil N=169	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Absolute Neutrophil Count decreased	53	35	24	13	76	47
Hemoglobin decreased	48	8	44	6	49	11
Platelets decreased	48	12	28	3	60	15

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

Table 8 Chemistry Laboratory Abnormalities (≥15% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ELEVATE-TN)

Laboratory Abnormalities [a,b]	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	36	6
AST increase	38	5	17	1	60	8
Bilirubin increase	13	1	15	1	11	1

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

Increases in creatinine of 1.5 to 3 times the upper level of normal (ULN) occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

Previously Treated CLL:

Table 9 Hematologic Laboratory Abnormalities[a] in ≥20% of Patients with CLL in the ASCEND Trial

Hematologic Laboratory Abnormalities	CALQUENCE N=154		Idelalisib plus Rituximab N=118		Bendamustine plus Ritixumab N=35	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Absolute Neutrophil Count decreased	47	25	79	51	80	40
Hemoglobin decreased	46	13	42	4	54	11
Platelets decreased	25	4	36	11	51	6
Absolute Lymphocyte Count increased	26	20	22	17	3	3

[a] Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 based on laboratory measurements and adverse reactions.

Table 10 Chemistry Laboratory Abnormalities (≥10% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ASCEND)

Laboratory Abnormalities [a,b]	CALQUENCE N=154		Idelalisib plus Rituximab N=118		Bendamustine plus Rituximab N=35	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Uric acid increase	15	15	11	11	23	23
ALT increase	15	2	59	23	26	3
AST increase	13	1	48	13	31	3
Bilirubin increase	13	1	16	2	26	11

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

Increases in creatinine of 1.5 to 3 times the ULN occurred in 1.3% of patients.

Mantle Cell Lymphoma:

Table 11 Treatment-Emergent Hematological Laboratory Abnormalities in ACE-LY-004 Study (N=124)

Hematological Adverse Reaction[a]	All Grades (%)	Grade ≥3 (%)
Absolute neutrophil count decreased	36	13
Hemoglobin decreased	42	6
Platelets decreased	44	11

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant use of CALQUENCE with a strong CYP3A inhibitor should be avoided (see 4.1 Dosing Considerations)

9.2 Drug Interactions Overview

Co-administration of CALQUENCE with strong CYP3A inhibitors may increase acalabrutinib plasma concentrations. Consider alternative therapies that do not have strong inhibition of CYP3A activity in order to prevent an increased risk of toxicity with CALQUENCE.

Co-administration of CALQUENCE with strong CYP3A inducers decreases acalabrutinib plasma concentrations. Consider alternative therapies that do not strongly induce CYP3A activity in order to prevent a reduction of CALQUENCE activity.

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g. methotrexate) by inhibition of intestinal BCRP.

9.4 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 12 Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
CYP3A inhibitors (eg. Itraconazole, erythromycin, fluconazole, diltiazem)	CT, T	Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased acalabrutinib C_{max} and AUC by 3.7-fold and 5.1-fold, respectively, in healthy subjects (N=17). Physiologically based pharmacokinetic (PBPK) simulations with acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased acalabrutinib C_{max}, and AUC by 2 to almost 3-fold.	Consider alternative therapies that do not strongly inhibit CYP3A activity. Alternatively, if the strong CYP3A inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole) will be used short-term, interrupt CALQUENCE. When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce the acalabrutinib dose to 100 mg once daily.
CYP3A Inducers (e.g., phenytoin, rifampin, carbamazepine)	CT	Co-administration of a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} and AUC by 68% and 77%, respectively, in healthy subjects (N=24).	Strong inducers of CYP3A activity (e.g., phenytoin, rifampin, carbamazepine) should be avoided during treatment with CALQUENCE.
Antithrombotic agents	T	Use of CALQUENCE in patients receiving antithrombotic agents may increase the risk of bleeding.	Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE (see 7 WARNINGS AND PRECAUTIONS, Hemorrhage).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Clinical Studies

Effect of Gastric Acid Reducing Medications on acalabrutinib
No clinically significant differences in acalabrutinib (given as acalabrutinib maleate) pharmacokinetics were observed when used concomitantly with rabeprazole, a proton pump inhibitor. Acalabrutinib tablet can be co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids).

***In Vitro* Studies**

Effects of acalabrutinib and its active metabolite, ACP-5862, on CYP3A Substrates

CYP3A Substrates
Based on *in vitro* data and PBPK modelling, no interaction with CYP substrates is expected at the clinically relevant concentration (see 10 CLINICAL PHARMACOLOGY).

Effects of acalabrutinib and ACP-5862 on Drug Transport Systems

BCRP Substrates
Based on *in vitro* data, clinically relevant drug-drug interactions with BCRP substrates via inhibition of intestinal BCRP transport activity cannot be discounted (see 10 CLINICAL PHARMACOLOGY).

MATE1 substrates
ACP-5862, may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1 (see 10 CLINICAL PHARMACOLOGY).

9.5 Drug-Food Interactions

CALQUENCE tablets may be administered with or without food.

9.6 Drug-Herb Interactions

Avoid St. John's wort which may unpredictably decrease acalabrutinib plasma concentrations.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Acalabrutinib is a potent, highly selective small-molecule inhibitor of Bruton's tyrosine kinase (BTK), with minimal off-target kinase activity. Bruton's tyrosine kinase is a signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis. Acalabrutinib was selected to exhibit high potency against BTK and few interactions with other kinases.

Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK (IC50 ≤ 5 nM) with minimal off-target interactions. In a screen of >380 mammalian wild-type kinases, the only additional kinase interactions at clinically relevant concentrations of acalabrutinib and ACP-5862 were with non-receptor tyrosine kinase (BMX) and erb-b2 receptor tyrosine kinase 4 (ERBB4), with 3- to 4-fold less potency than with BTK.

In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signalling proteins CD86 and CD69, inhibited malignant B-cell proliferation and tumour growth in mouse

xenograft models, and had minimal activity on other immune cells (T cells and NK cells).

10.2 Pharmacodynamics

In patients with B-cell malignancies dosed with 100 mg CALQUENCE twice daily, median steady state BTK occupancy of ≥95% in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

Cardiac Electrophysiology
In a randomized, double-blind, double-dummy, placebo- and positive-controlled, 4-way crossover ECG assessment study, single dose administration of acalabrutinib 100 mg and 400 mg (4X maximum recommended single dose) was not demonstrated to have a clinically meaningful effect on the QTcF interval, the QRS duration, or the PR interval in healthy subjects (N=44).

10.3 Pharmacokinetics

Table 13 Pharmacokinetic Parameters of acalabrutinib and its active metabolite, ACP-5862, following administration of CALQUENCE 100mg twice daily

	C_{max} (ng/mL)[a]	T_{max} (h)[b]	$t_{½}$ (h)[a]	AUC_{24h} (ng.h/mL)[a]	CL/F (L/h)[a]	Vd/F (L)[a]
acalabrutinib	563 (29%)	0.5 (0.2, 3.0)	1.4 (50%)	1843 (38%)	71 (35%)	101 (52%)
ACP-5862*	451 (52%)	0.75 (0.5, 4.0)	6.6 (32%)	3947 (43%)	13 (42%)	67 (32%)

[a] geometric mean (percentage coefficient of variation) is shown.

[b] median (range) is shown.

The pharmacokinetics (PK) of acalabrutinib and its active metabolite, ACP-5862, were studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and ACP-5862 exhibit almost linear PK across a dose range of 75 to 250 mg. Population PK modeling suggests that the PK of acalabrutinib and ACP-5862 does not differ significantly in patients with different B-cell malignancies. At the recommended dose of 100 mg twice daily in patients with B-cell malignancies (including, MCL and CLL), the geometric mean (% coefficient of variation [CV]) daily area under the plasma 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.

CALQUENCE tablets and CALQUENCE capsules have been demonstrated to be bioequivalent and have equivalent oral bioavailability except when administered concomitantly with proton pump inhibitors and other acid reducing agents.

Absorption: The absolute bioavailability of acalabrutinib was 25%. The median [min, max] time

to peak acalabrutinib plasma concentrations (T_{max}) was 0.5 [0.2, 3.0] hours, and 0.75 [0.5, 4.0] hours for ACP-5862. In healthy subjects, administration of CALQUENCE (1 x 100 mg tablet) with a high-fat, high-calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions, although Cmax was decreased by 54% and Tmax was delayed by 1-2 hours. CALQUENCE tablets may be administered with or without food. CALQUENCE is available as a capsule or tablet formulation with equivalent oral bioavailability except when administered concomitantly with proton pump inhibitors or acid reducing agents.

Distribution: Reversible binding of acalabrutinib to human plasma protein was 97.5% and for ACP-5862 was 98.6%. The *in vitro* mean blood-to-plasma ratio was 0.8 for acalabrutinib and 0.7 for ACP-5862. The geometric mean (%CV) apparent steady state volume of distribution (V_{ss}/F) was 101 (52%) L for acalabrutinib and 67 (32%) L for ACP-5862.

Metabolism: *In vitro*, acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent by glutathione conjugation and amide hydrolysis. ACP-5862 was identified as the major metabolite in plasma with a geometric mean exposure (AUC) that was approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50% less potent than acalabrutinib with regard to BTK inhibition.

In vitro, 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 *in vitro*. Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4 mRNA; ACP-5862 weakly induces CYP3A4.

In vitro, 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, *in vitro*. ACP-5862 is not a substrate of OATP1B1 or OATP1B3.

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

Acalabrutinib may inhibit intestinal BCRP transport activity, while ACP-5862 may inhibit MATE1 at clinically relevant concentrations (see 9 DRUG INTERACTIONS).

Elimination: The geometric mean (%CV) terminal elimination half-life ($t_{1/2}$) was 1.4 (50%) hours for acalabrutinib and 6.6 (32%) 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, with similar PK between patients and healthy subjects based on population PK analysis.

Following administration of a single 100 mg radiolabelled [^{14}C]-acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the faeces and 12% of the dose was recovered in the urine, with less than 2% of the dose excreted as unchanged acalabrutinib in urine and feces.

Special Populations and Conditions
Based on population PK analysis, age, sex, race (Caucasian, Black or African American), and body weight did not have clinically meaningful effects on the PK of acalabrutinib and its active

metabolite, ACP-5862.

- ***Pediatrics:*** No pharmacokinetic studies were performed with acalabrutinib in patients under 18 years of age.

- ***Geriatrics:*** Based on population pharmacokinetic analysis, age (42 to 90 years) did not have a clinically meaningful effect on the PK of acalabrutinib.

- ***Hepatic Insufficiency:*** Acalabrutinib is metabolized in the liver. In dedicated hepatic impairment studies, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by 1.9-fold, 1.5-fold and 5.3 fold in subjects with mild (n=6) (Child-Pugh A), moderate (n=6) (Child-Pugh B), and severe (n=8) (Child-Pugh C) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant difference was observed between subjects with mild (n=79) or moderate (n=6) hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST) relative to subjects with normal (n=651) hepatic function (total bilirubin and AST within ULN).

- ***Renal Insufficiency:*** Acalabrutinib undergoes minimal renal elimination. A PK study in patients with renal impairment has not been conducted. Based on population PK analysis, no clinically relevant PK difference was observed in 433 patients with mild renal impairment (eGFR between 60 and 89 mL/min/1.73m^2 as estimated by MDRD), 110 patients with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73m^2) relative to 204 patients with normal renal function (eGFR greater than or equal to 90 mL/min/1.73m^2). The pharmacokinetics of acalabrutinib has not been characterized in patients with severe renal impairment (eGFR less than 29 mL/min/1.73m^2) or renal impairment requiring dialysis. Patients with creatinine levels greater than 2.5 times the institutional ULN were not included in the clinical trials (see 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

Store CALQUENCE at room temperature, between 15°C-30°C, in original bottle.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

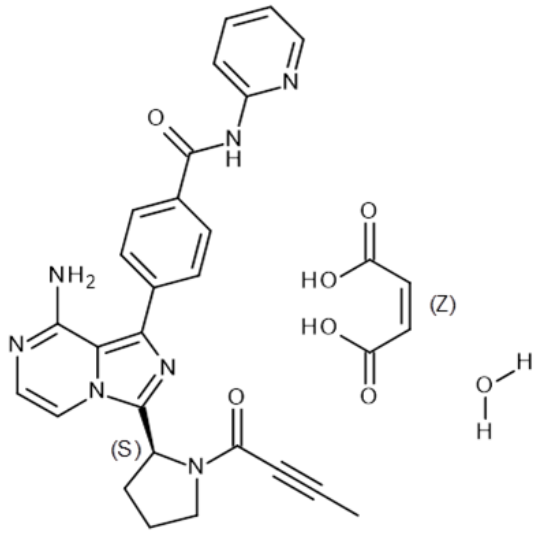
Drug Substance

Proper/Common name: Acalabrutinib maleate

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

Molecular formula and molecular mass: $C_{26}H_{23}N_7O_2.C_4H_4O_4.H_2O$, 599.59 (acalabrutinib free base is 465.51)

Structural formula:



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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

<u>Previously Untreated Chronic Lymphocytic Leukemia (CLL) (ELEVATE-TN)</u>

Table 14 Summary of patient demographics for clinical trials in patients with previously untreated CLL

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex

ELEVATE-TN (ACE-CL-007)	Randomized (1:1:1), open-label, Phase 3 Study	Arm A: obinutuzumab + chlorambucil[a]	177	70 (41-91)	M: 61% F: 39%
		Arm B: CALQUENCE 100 mg orally twice daily + obinutuzumab[b],	179		
		Arm C: CALQUENCE monotherapy, 100 mg orally twice daily[c]	179		
			Total: N=535		

[a] Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by 1000 mg on Day 1 of Cycles 2 up to 6. Chlorambucil 0.5 mg/kg was administered on Days 1 and 15 of Cycles 1 up to 6. Each cycle was 28 days.
[b] CALQUENCE 100 mg was administered twice daily starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. Obinutuzumab was administered starting on Cycle 2 Day 1 for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 2 followed by 1000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days.
[c] CALQUENCE monotherapy: CALQUENCE 100 mg was administered twice daily until disease progression or unacceptable toxicity.

The safety and efficacy of CALQUENCE in patients with previously untreated CLL were evaluated in a randomized, multi-centre, open-label Phase 3 study (ELEVATE-TN) of 535 patients. Patients were randomized to receive either CALQUENCE plus obinutuzumab, CALQUENCE monotherapy, or obinutuzumab plus chlorambucil.

Patients 65 years of age or older or between 18 and 65 years of age with coexisting medical conditions were included in ELEVATE-TN. The trial also allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists. Key inclusion criteria included confirmed diagnosis of CD20+ CLL and active disease that met ≥1 of the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria for requiring treatment. Key exclusion criteria included prior systemic treatment of CLL, known central nervous system (CNS) lymphoma or leukemia, and known prolymphocytic leukemia or Richter's syndrome.

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and geographic region (North America and Western Europe versus Other). At baseline, the majority of subjects (84%) were ≥65 years old, 94% of patients had an ECOG score of 0 or 1, 32% presented with lymph nodes ≥5 cm, 47% had Rai stage III or IV disease, 9% had 17p deletion, 11% had TP53 mutation, 63% of patients had an unmutated IGHV, and 18% had 11q deletion. The median time from initial CLL diagnosis to randomization was 27.6 months. Baseline demographic and disease characteristics were similar between treatment arms.

The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) in the CALQUENCE + obinutuzumab arm compared with the obinutuzumab + chlorambucil arm. PFS was defined as the time from the date of randomization to the date of first IRC-assessed disease progression or death due to any cause. The assessment of progressive disease was per IWCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis. Secondary endpoints included PFS as assessed by IRC in the CALQUENCE monotherapy arm compared with the obinutuzumab + chlorambucil arm, and ORR as assessed by IRC per IWCLL 2008 criteria.

With a median follow-up of 28.3 months in the ELEVATE-TN trial, PFS by IRC indicated a 90% statistically significant reduction in the risk of a PFS event for previously untreated CLL patients in the CALQUENCE plus obinutuzumab arm compared to obinutuzumab plus chlorambucil arm (HR=0.10 [95% CI: 0.06–0.17]; p<0.0001). At the time of analysis, median overall survival was not reached in any arm, with fewer than 10% of patients experiencing an event.

Efficacy results are presented in Table 15. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 15 Results from the ELEVATE-TN Trial in Patients with Previously Untreated CLL (Intention to Treat Population)

Efficacy Parameter	CALQUENCE plus Obinutuzumab N=179	CALQUENCE Monotherapy N=179	Obinutuzumab plus Chlorambucil N=177
Progression-Free Survival (PFS)[a]			
Number of events, n (%)	14 (7.8%)	26 (14.5%)	93 (52.5%)
Disease progression, n (%)	9 (5%)	20 (11.2%)	82 (46.3%)
Death events, n (%)	5 (2.8%)	6 (3.4%)	11 (6.2%)
Median (95% CI), months	NR	NR (34.2, NR)	22.6 (20.2, 27.6)
HR[b] (95% CI)	0.10 (0.06, 0.17)[c]	0.20 (0.13, 0.30)[d]	--
p-value	p<0.0001	p<0.0001	--
Overall Response Rate (ORR)[e,f]			
n (%) (95% CI)	168 (93.9%) (89.3, 96.5)	153 (85.5%) (79.6, 89.9)	139 (78.5%) (71.9, 83.9)
p-value	<0.0001	0.0763	--
CR, n(%)[g]	24 (13.4%)	1 (0.6%)	8 (4.5%)
PR, n(%)[h]	144 (80.4%)	152 (84.9%)	131 (74%)

CI=Confidence Interval; CR=Complete Response; CRi=Complete Response with incomplete marrow recovery; HR=Hazard Ratio; NR=Not Reached; ORR=Overall Response Rate; PR=Partial Response; nPR=nodular Partial Response.

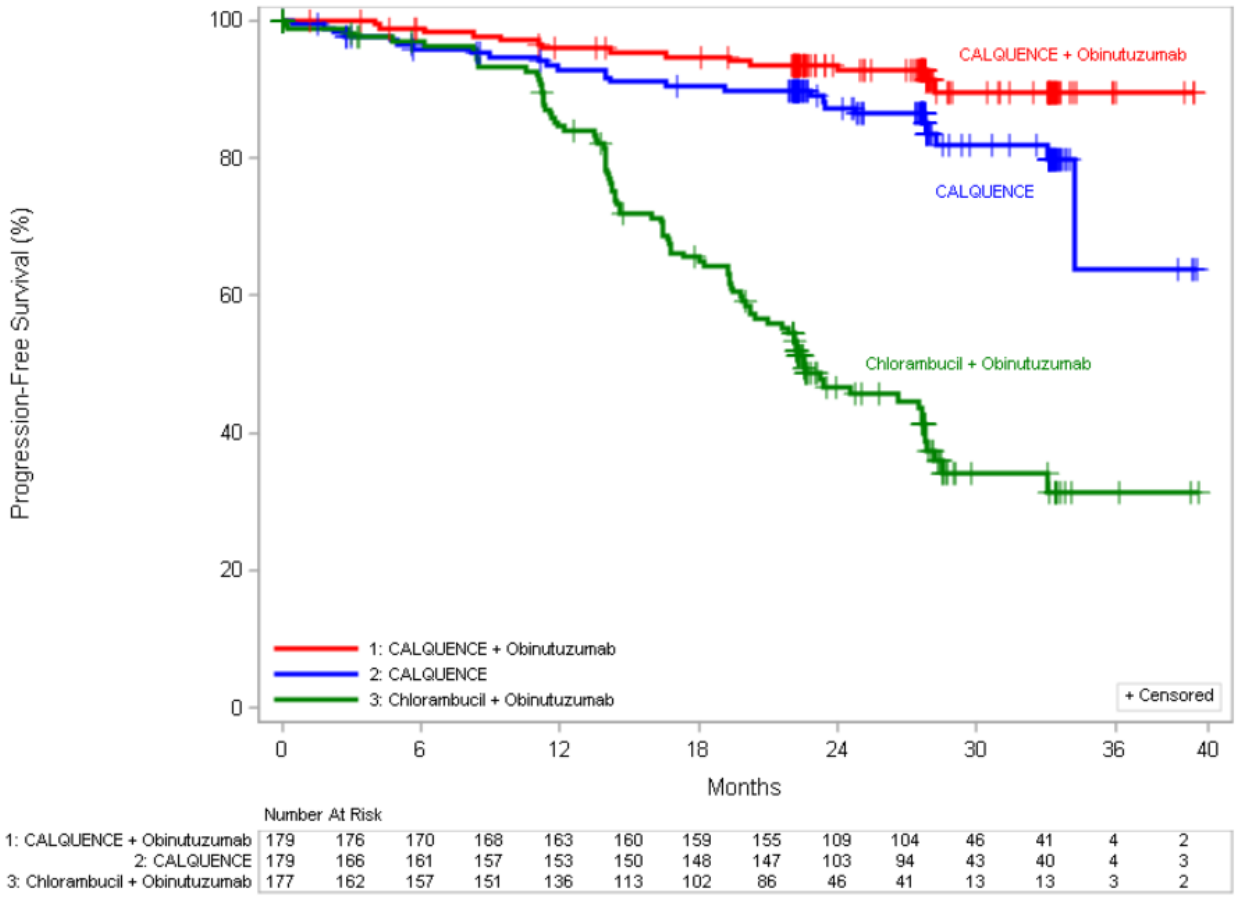
a Independent Review Committee (IRC) assessment per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis.

b Based on stratified Cox-Proportional Hazards model.

c CALQUENCE + obinutuzumab compared to obinutuzumab + chlorambucil.

[d] CALQUENCE monotherapy compared to obinutuzumab + chlorambucil.
[e] ORR: (CR + CRi + nPR + PR).
[f] Per IRC assessment.
[g] Includes 1 patient in the CALQUENCE + obinutuzumab arm with CRi.
[h] PR = PR + nPR; 1 patient with nPR in the CALQUENCE + obinutuzumab arm, 2 patients with nPR in the CALQUENCE monotherapy arm, and 3 patients with nPR in the obinutuzumab + chlorambucil arm.

Figure 1 Kaplan-Meier Curve of IRC-Assessed Progression-Free Survival in Patients with Previously Untreated CLL (ELEVATE-TN) (ITT Population)



The PFS benefit for CALQUENCE with or without obinutuzumab was consistent in the following subgroups: <65 and ≥65 years of age, patients with and without 17p deletion, patients with and without TP53 mutation, patients with and without 11q deletion, patients with unmutated IGHV, patients with and without advanced disease (Rai stage 0-II and stage III-IV), and patients with and without bulky lymphadenopathy (<5cm and ≥5cm).

Previously Treated CLL (ASCEND)

Table 16 Summary of patient demographics for clinical trials in patients with CLL who have received at least one prior therapy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ASCEND (ACE-CL-309)	Randomized (1:1), open-label, Phase 3 Study	Arm A: CALQUENCE 100 mg orally twice daily[a]	155	67 (32-90)	M: 67% F: 33%
		Arm B (Investigator's Choice): -Idelalisib + rituximab (IR)[b] or -Bendamustine + rituximab (BR)[c]	155		
			Total N= 310		

[a] CALQUENCE 100 mg approximately every 12 hours until disease progression or unacceptable toxicity.

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

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

The safety and efficacy of CALQUENCE in patients with relapsed or refractory CLL were evaluated in a randomized, multi-centre, open-label Phase 3 study (ASCEND) of 310 patients who received at least one prior therapy. Patients were randomized to receive CALQUENCE monotherapy or investigator's choice of either idelalisib plus rituximab (IR) or bendamustine plus rituximab (BR).

Key inclusion criteria included diagnosis of CD20+ CLL, ≥1 prior systemic therapy for CLL, active disease that met ≥1 of the IWCLL 2008 criteria for requiring treatment. The trial allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists. The trial excluded patients with known CNS lymphoma or leukemia, transformed disease, prolymphocytic leukemia, or previous treatment with a Bruton's Tyrosine Kinase inhibitor, venetoclax, or a phosphoinositide-3 kinase inhibitor.

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and number of prior therapies (1 to 3 versus ≥4). The median time from diagnosis to randomization was 79 months. At baseline, about two-thirds (63%) of patients were ≥65 years of age, 87% had an ECOG score of 0 or 1, 49% had tumour bulk ≥5cm, 42% had Rai stage III or IV disease, 16% had 17p deletion, 24% had TP53 mutation, 78% had an unmutated IGHV, and 27% had an 11q deletion. The CALQUENCE 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 arm, the median treatment duration was 15.7 months, with 86% of patients treated for at least 1 year. In the control arm (IR/BR), the median treatment duration was 11.5 months for idelalisib, 5.6 months for bendamustine and 5.5 months for rituximab.

The primary endpoint was PFS as assessed by IRC. PFS was defined as the time from the date of randomization to the date of first IRC-assessed disease progression or death due to any cause. The assessment of progressive disease was per the IWCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis. IRC-assessed ORR per IWCLL 2008 criteria was a secondary endpoint.

At a median follow-up of 16.1 months in the ASCEND trial which enrolled patients with CLL who had received at least one prior therapy, PFS as assessed by IRC indicated a 69% statistically significant reduction in the risk of a PFS event for patients who received CALQUENCE compared to patients who received the investigator's choice of therapy (HR=0.31 [95% CI: 0.20-0.49], p<0.0001). At the time of analysis, overall survival had not been reached in any arm. Efficacy results are presented in Table 17. The Kaplan-Meier curve for PFS is shown in Figure 2. The difference in overall response rate between the two arms did not reach statistical significance.

Table 17 Results from the ASCEND Trial in Patients with Previously Treated CLL (ITT population)

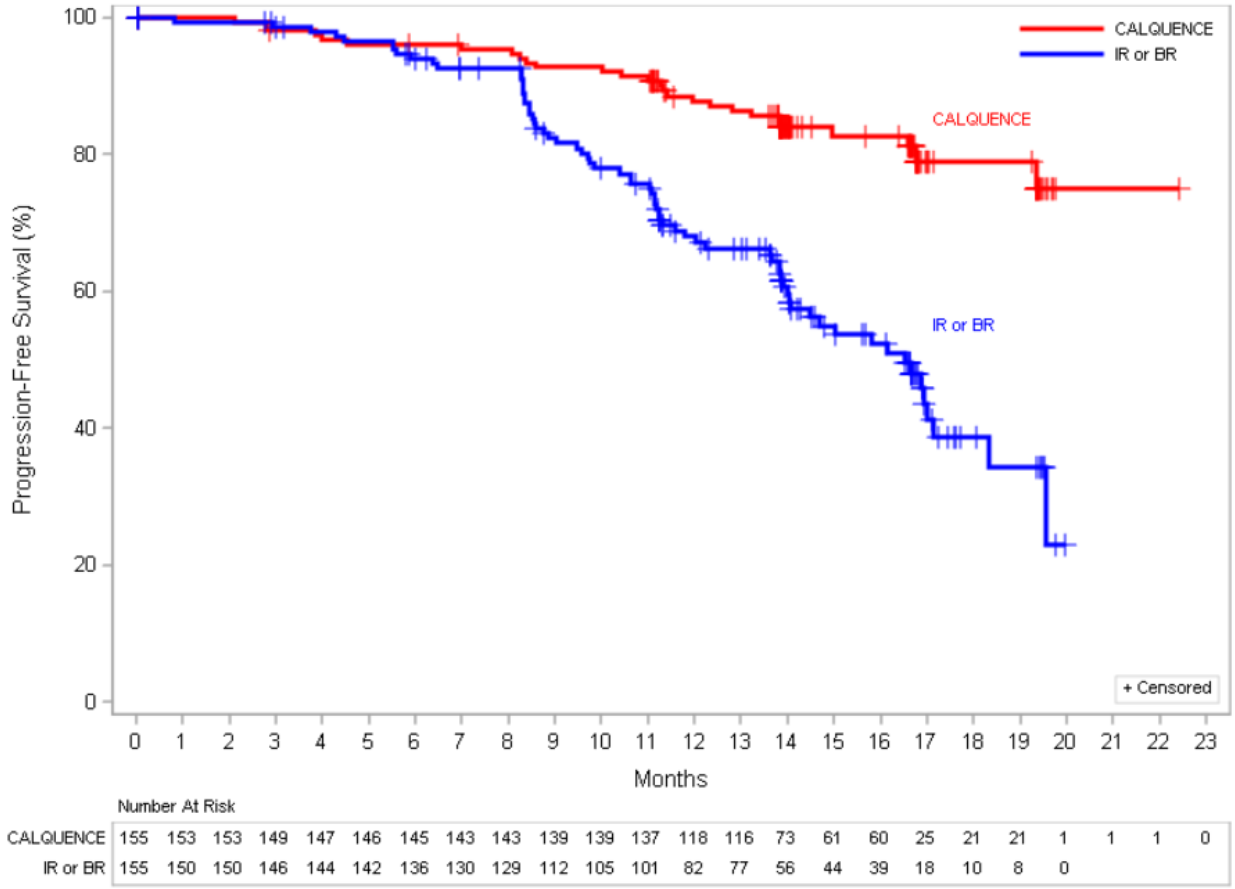
	CALQUENCE monotherapy N=155	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Progression-Free Survival (PFS)[a]		
Number of events (%)	27 (17.4)	68 (43.9)
Disease Progression, n (%)	19 (12.3)	59 (38.1)
Death events (%)	8 (5.2)	9 (5.8)
Median (95% CI), months[b]	NR	16.5 (14.0, 17.1)
HR[c] (95% CI)	0.31 (0.20, 0.49)	
P-value	< 0.0001	
Overall Response Rate (ORR)[d,e]		
n (%) (95% CI)	126 (81.3) (74.4, 86.6)	117 (75.5) (68.1, 81.6)
ORR Difference, % (95% CI)	5.8 (-3.3, 14.9)	--
P-value	0.2248	--
CR, n(%)	0	2 (1.3%)
PR, n(%)	126 (81.3%)	115 (74.2%)

CI=Confidence Interval; CR=Complete Response; CRi=Complete Response with incomplete blood count recovery; HR=hazard ratio; nPR=nodular Partial Response; NR=not reached; PR=partial response.

[a] Independent Review Committee (IRC) assessment per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis.

[b] Kaplan-Meier estimate.
[c] Based on stratified Cox-Proportional-Hazards model.
[d] Per IRC assessment.
[e] ORR: (CR + CRi + nPR + PR); there were no patients with CRi or nPR.

Figure 2 Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL Who Have Received At Least One Prior Therapy (ASCEND) (ITT Population)



The PFS benefit of CALQUENCE was consistent in the following subgroups: <65 and ≥65 years of age, patients with and without 17p deletion, patients with and without 11q deletion, patients with or without TP53 mutation, patients with mutated and unmutated IGHV, patients with and without advanced disease (Rai stage 0-II and stage III-IV), and patients with and without bulky lymphadenopathy (<5cm and ≥5cm).

Mantle Cell Lymphoma (ACE-LY-004)

Table 18 Summary of patient demographics for clinical trial in patients with MCL who have received at least one prior therapy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ACE-LY-004	Open-label, multi-centre, single-arm Phase 2 Study	CALQUENCE 100 mg orally twice daily until disease progression or unacceptable toxicity	124	68 (range 42 to 90) years	M: 80% F: 20%

The safety and efficacy of CALQUENCE in patients with MCL were evaluated in an open-label, multi-centre, single-arm Phase 2 study (ACE-LY-004) of 124 previously treated patients.

In Study ACE-LY-004, the median age was 68 (range 42 to 90) years, 80% were male and 74% were Caucasian. At baseline, 93% of patients had an ECOG performance status of 0 or 1. The median time since diagnosis was 46 months and the median number of prior treatments was 2 (range 1 to 5), including 18% with prior stem cell transplant. The majority of patients (95%) had previously received rituximab as a single agent or part of a regimen. Common prior regimens included CHOP-based regimen (52%), cytarabine (34%), bendamustine and rituximab-based regimens (22%), and Hyper-CVAD (21%). At baseline, 24% and 76% of patients had refractory and relapsed disease, respectively, and 37% of patients had at least one tumour with a longest diameter ≥5 cm, 73% had extra nodal involvement including 51% with bone marrow involvement. The Simplified MCL International Prognostic Index (MIPI) score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 44% and high in 17% of patients, and 75% of subject had Ann Arbor Stage IV disease.

Patients were to receive CALQUENCE 100 mg orally twice daily until disease progression or unacceptable toxicity. The median duration of treatment was 17.3 months and the median dose intensity was 98.7%. The median duration of follow-up was 26.3 months.

The trial did not include patients who received prior treatment with BTK inhibitors.

The primary endpoint was investigator-assessed overall response rate (ORR) per the Lugano classification for non-Hodgkin's lymphoma (NHL). Duration of Response (DoR) was an additional outcome measure.

The efficacy analysis for patients with MCL who have received at least one prior therapy was conducted at a median follow-up of 26.3 months, and the results are summarized below and presented in

Table 19. At time of analysis, 39.5% of patients remained on study. The ORR was 80.6% with a median time to documented response of 1.9 months and a median DoR of 25.7 months.

Table 19 Efficacy Results of Study ACE-LY-004 (N=124) in Patients with Mantle Cell Lymphoma Who Have Received At Least One Prior Therapy

Efficacy Parameter	Investigator Assessed[a] n (%) (95% CI[b])
Overall Response Rate (ORR)[c]	
Overall Response Rate	100 (80.6%) (72.6, 87.2)
Complete Response	53 (42.7%) (33.9, 51.9)
Partial Response	47 (37.9%) (29.3, 47.1)
Stable Disease	11 (8.9%) (4.5, 15.3)
Progressive Disease	10 (8.1%) (3.9, 14.3)
Duration of Response (DoR)	
Median (months)	25.7 (17.5, NE)

CI=Confidence Interval; NE=Not Estimable
[a] Per Lugano classification for non-Hodgkin's lymphoma.
[b] 95% exact binomial confidence interval.
[c] Non-Evaluable: 3 subjects were non-evaluable due to inadequate post-baseline disease assessment.

14.2 Comparative Bioavailability Studies

A randomized, multi-centre, open-label, single dose, two-way, cross-over, comparative bioavailability study of CALQUENCE 100 mg tablets and CALQUENCE 100 mg capsules was conducted in 66 healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 63 subjects that were included in the statistical analysis are presented in the following table.

Table 20 Acalabrutinib Comparative Bioavailability Data

Acalabrutinib (1 x 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	563.9 599.5 (2.81)	566.8 605.8 (2.71)	98. 8	93.6 – 104.2
AUC_I (ng·h/mL)	567.8 603.7 (2.80)	572.2 610.6 (2.73)	98.6	93.4 – 104.0
C_{max} (ng/mL)	537.2 581.6 (2.52)	535.7 606.8 (2.16)	100.4	90.8 – 111.0
T_{max}[3] (h)	0.52 (0.23 – 2.97)	0.58 (0.47 – 3.98)		

Acalabrutinib (1 x 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
$T_{½}$[4] (h)	1.64 (1.39)	2.24 (0.79)		

[1] CALQUENCE (acalabrutinib as acalabrutinib maleate) tablets, 100 mg (AstraZeneca Canada Inc.)
[2] CALQUENCE (acalabrutinib as acalabrutinib base) capsules, 100 mg (AstraZeneca Canada Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Daily oral administration of acalabrutinib for up to 6 months duration in rats and 9 months in dogs, was tolerated at exposure levels that exceed human therapeutic exposures at the recommended dose (2.5-fold in rats, 8.2-fold in dogs, based on AUC).

Kidney, liver and heart were identified as the target organs of toxicities in rats and dogs. In rats, liver and kidney findings were observed at exposures 4.2 times the total clinical exposures. More severe toxicities including cardiac findings were observed in both species at exposures ≥6.8 times the total clinical exposure. Reversibility was demonstrated for liver and kidney findings in both species. Reversibility for the heart findings could not be assessed as these findings were only observed at doses above the maximum tolerated dose (MTD).

Toxicology species were exposed to relevant metabolites of acalabrutinib, including the active metabolite ACP-5862.

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

Genotoxicity

Acalabrutinib was not mutagenic in a bacterial reverse mutation assay, in an *in vitro* chromosome aberration assay, or in an *in vivo* mouse bone marrow micronucleus assay.

Reproductive and Developmental toxicology

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

In a combined fertility and embryofetal 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 embryofoetal 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 twice daily. The presence of acalabrutinib and its active metabolite were confirmed in foetal rat plasma.

In an embryofoetal study in pregnant rabbits, acalabrutinib was administered orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Acalabrutinib produced no maternal toxicity and no evidence of teratogenicity or foetal development, growth, or survival at doses of 50 mg/kg/day (approximately equivalent to the human AUC exposure at the recommended dose). Decreased foetal body weight and delayed ossification were observed at exposure levels that produced maternal toxicity (doses ≥100 mg/kg/day), which were 2.4-times greater than the human exposure levels at the recommended dose.

In a rat reproductive study involving dosing animals from implantation throughout gestation, parturition and lactation, dystocia (prolonged /difficult labor) was observed at exposures >2.3-times the clinical exposure at 100 mg twice daily.

17 SUPPORTING PRODUCT MONOGRAPHS

1. CALQUENCE® (capsules, 100 mg), submission control number 231228, Product Monograph, AstraZeneca Canada Inc. (NOV 28, 2019)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ℙCALQUENCE®

acalabrutinib tablets

Read this carefully before you start taking **CALQUENCE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CALQUENCE**.

Serious Warnings and Precautions

- Take CALQUENCE only under the care of a healthcare professional who knows how to use anti-cancer drugs.
- **Hemorrhage (serious bleeding problems)** may occur when you take CALQUENCE. This can mean bleeding a lot, or bleeding that is difficult to stop.

What is CALQUENCE used for?

CALQUENCE is used to treat:

- patients with a kind of cancer called chronic lymphocytic leukemia (CLL) who have not had any previous treatment for their disease. These patients may take CALQUENCE alone or with the medication, obinutuzumab.
- patients with CLL who have had at least one previous treatment for their disease.
- patients with a kind of cancer called mantle cell lymphoma (MCL). It is only used in patients who received at least one other MCL therapy before using CALQUENCE.

How does CALQUENCE work?

CALQUENCE blocks a specific protein in the body that helps cancer cells live and grow. This protein is called “Bruton's Tyrosine Kinase.” By blocking this protein, CALQUENCE may help kill and reduce the number of cancer cells and slow the spread of the cancer.

What are the ingredients in CALQUENCE?

Medicinal ingredient: acalabrutinib (as acalabrutinib maleate)

Non-medicinal ingredients: copovidone, hypromellose, iron oxide red (E172), iron oxide yellow (E172), low-substituted hydroxypropyl cellulose, macrogol 3350, mannitol, microcrystalline cellulose, purified water, sodium stearyl fumarate, titanium dioxide, triglycerides (mediumchain).

CALQUENCE comes in the following dosage forms:

100 mg tablets

Please note: CALQUENCE is also available as a 100 mg capsule which should NOT be interchanged with CALQUENCE tablets.

Do not use CALQUENCE if:

- You are allergic to acalabrutinib, any other ingredients in CALQUENCE or the container it is

provided in.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CALQUENCE. Talk about any health conditions or problems you may have, including if you:

- have had recent surgery or plan to have surgery. Your healthcare professional 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.
- have severe liver or kidney disease or are on dialysis.
- are pregnant or plan to become pregnant. CALQUENCE may harm your unborn baby. Avoid getting pregnant while on 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 2 weeks after your final dose of CALQUENCE.

New cancers have happened in people during treatment with CALQUENCE, including cancers of the skin or other organs. Use sun protection when you are outside in sunlight.

Other warnings you should know about:
CALQUENCE is not for use in patients under the age of 18.

Driving and Using Machines:
Before you do tasks which may require special attention, wait until you know how you respond to CALQUENCE. If you have blurred vision, feel tired or dizzy, do not drive or use tools or machines.

Check-ups and Testing:
CALQUENCE can cause abnormal blood test results. Your healthcare professional may do blood tests before you start CALQUENCE and while you take it. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Before you start any new medication, tell your healthcare professional who prescribed CALQUENCE for you. You must not take CALQUENCE with certain medications. The combination can increase the amount of CALQUENCE in your blood. Your healthcare professional can decide and tell you if it is safe to take the new medication while you are taking CALQUENCE.

The following may interact with CALQUENCE:

- Antibiotics used to treat bacterial infections (clarithromycin, erythromycin, rifampin).
- Medicines for fungal infections (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole).

- Medicines for HIV infection (indinavir, ritonavir).
- Medicines to treat low blood sodium levels (conivaptan).
- Medicines to treat hepatitis C (telaprevir).
- Medicines used to prevent seizures or to treat epilepsy or medicines used to treat a painful condition of the face called trigeminal neuralgia (carbamazepine, phenytoin).
- Medicines used to treat cancer, rheumatoid arthritis and psoriasis (methotrexate).
- Medicines used to treat heart conditions or high blood pressure (diltiazem, verapamil).
- Medicines that may increase your risk of bleeding, including:
  - aspirin and anti-inflammatories such as ibuprofen or naproxen.
  - blood thinners such as warfarin, heparin or other medicines to treat or prevent blood clots such as dabigatran, rivaroxaban, apixaban.
  - supplements such as fish oil, vitamin E and flaxseed.
- An herbal medicine used for depression (St. John's Wort).

How to take CALQUENCE:
- Take it exactly as your healthcare professional tells you.
- If you are on 2 tablets a day, take them about 12 hours apart.
- Take at about the same time each day.
- Take with or without food.
- Swallow whole with a glass of water. Do NOT chew, crush, dissolve or divide the tablets.

Usual Adult Dose:
One tablet twice a day. Do not change your dose or stop taking CALQUENCE unless your healthcare care professional tells you to.

If you need to take other medications or develop certain side effects the healthcare professional may tell you to reduce or stop your dose. Sometimes the stop is temporary.

Overdose:

If you think you, or a person you are caring for, have taken too much CALQUENCE, contact your healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
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 possible side effects from using CALQUENCE?
These are not all the possible side effects you may feel when taking CALQUENCE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- tiny red or purple spots on the skin, bruising
- rash or redness of the skin
- watery eyes
- blurry vision
- constipation

- decreased appetite
- headache
- dizziness
- tiredness
- weakness
- falls
- abdominal pain, joint pain, muscle pain/aches, pain in the arms and legs, back pain
- tingling, pain, or numbness in hands, feet, legs
- swelling
- sores in mouth
- trouble with falling asleep
- memory loss

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Infections (from bacteria, a virus or fungus): Cough, infection in your nose (sinus infection), sore throat, fatigue, loss of appetite, fever, chills and flu-like symptoms.		✓	
Anemia (low red blood cells): Being short of breath. Feeling very tired. Having pale skin. Fast heartbeat. Loss of energy, or weakness.		✓	
Neutropenia (low white blood cells, neutrophils): Fever or infection. Fatigue. Aches and pains. Flu-like symptoms.		✓	
Thrombocytopenia (low blood platelets): Bruising or bleeding for longer than usual if you hurt yourself. Fatigue and weakness.		✓	
Nausea and Vomiting: Severe, feeling sick. Severe, being sick or throwing up.	✓		
Diarrhea: Increased number of bowel movements. Watery stool. Stomach pain and/or cramps.	✓		
Urinary tract infection: Pain or burning when urinating, bloody or cloudy urine, foul smelling urine.		✓	
New cancers of skin and other types of cancer.		✓	
COMMON			
Hemorrhage (serious bleeding problems): Bleeding a lot or uncontrollably. Blood in your stool or urine. Long-lasting headache. Feeling dizzy or confused. Nose bleeds. Coughing up blood. Increased bruising.		✓	
Pneumonia, Bronchitis (infection in the lungs): Cough with or without mucus. Fever, chills.		✓	

Shortness of breath that may only occur when you climb stairs. Difficult and painful breathing.			
Arrhythmia (heart rhythm problems): Racing or uncomfortable or irregular heartbeat. Flip-flop feeling, or pain in your chest. Feeling dizzy or confused.		✓	
Hypotension (low blood pressure): Dizziness, fainting, lightheadedness.		✓	
Tumour Lysis Syndrome (sudden, rapid death of cancer cells due to treatment): Nausea, vomiting, decreased urination, irregular heartbeat, confusion, delirium, seizures.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature between 15 to 30°C in original bottle.

Keep out of reach and sight of children.

If you want more information about CALQUENCE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.astrazeneca.ca), or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4.

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Last Revised: FEB 24, 2023