EU RMP

Drug substance	Acalabrutinib
EMA version number	8
AZ version number, succession number	8, 2
Data lock point	30 April 2024
Date of final sign off	19 February 2025

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for CALQUENCE® (ACALABRUTINIB)

The content of this RMP has been reviewed and approved by the deputy QPPV. Anne Lappareau-Gallot.

ADMINISTRATIVE INFORMATION

Rationale for Submitting an Updated RMP

Submitting a variation for a new indication, treatment in combination with venetoclax with or without obinutuzumab of adult patients with previously untreated CLL.

Summary of Significant Changes in this RMP

Part I

- Added proposed new indication.

Part II.1

- Updated epidemiology information for CLL.
- Updated epidemiology information for MCL.

Part II.3

- Exposure information was added for AV and AVO combination therapies.
- Updated clinical trial exposure information for CALQUENCE monotherapy population, including addition of studies ACE-CL-006 and ACE-LY-308 (ECHO) crossover patients.
- AO exposure data were added to provide data relevant for all indications and to correct a previous omission.
- Exposure information was added for ABR combination therapy.
- Wording was added to clarify that the exposure data for the pivotal study in R/R MCL (ACE-LY-004) were final as summarised in the monotherapy population in EU Version 5; thus, no new exposure data are presented for R/R MCL.

Part II.4

- Added important exclusion criteria from pivotal Study ACE-CL-311 (AMPLIFY).
- Removed some exclusion criteria in order to focus on important exclusion criteria.
- Added important exclusion criteria from pivotal study ACE-LY-308 (ECHO).
- Added important exclusion criteria from pivotal study ACE-LY-004 (R/R MCL).

Part II.7.3

- Added details for important identified and potential risks, including frequency, severity, and outcomes data, for the AV and AVO combination therapy populations (AMPLIFY).

- Calculations for all populations were updated such that a subject with multiple severity grades for a given AE was counted only once under the maximum severity.
- Updated details for important identified and potential risks, including frequency, severity, and outcomes data, for the monotherapy population.
- Added details for important identified and potential risks, including frequency, severity, and outcomes data in the AO population.
- Added details for important identified and potential risks, including frequency, severity, and outcomes data, in the ABR population (ECHO).
- Wording was added to clarify that findings from the pivotal study in R/R MCL (ACE-LY-004) were similar to the overall CALQUENCE monotherapy population.

Part III

- Added completion dates for milestones where applicable.

Part VI

- Updated in line with the changes above.

Part VII.2, Annex 2

- Added completion dates for milestones where applicable.

Other RMP versions under evaluation	**Version number:** 7[a] **Submitted:** 26 August 2024 **Procedure number:** EMEA/H/C/005299/II/0026 **Version number:** 6[b] **Submitted:** 22 August 2024 **Procedure number:** EMEA/H/C/005299/II/0025[a]
Details of currently approved RMP	**Version number**: 5 **Approved with procedure**: EMEA/H/C/PSUSA/00010887/202310 **Date of approval:** 16 May 2024

[a] EU RMP Version 7 was submitted for the proposed indication based on data from the Phase 3 ACE-LY-004 study: CALQUENCE monotherapy for the treatment of adult patients with R/R MCL (refer to eCTD sequence 0075).

[b] EU RMP Version 6 was submitted for the proposed indication based on data from the Phase 3 ECHO study: CALQUENCE in combination with bendamustine and rituximab for the treatment of adult patients with previously untreated MCL (refer to eCTD sequence 0074).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special Term	Definition/Explanation
ABR	acalabrutinib + bendamustine + rituximab
ACP-196	acalabrutinib
ACP-5862	metabolite of acalabrutinib
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AO	acalabrutinib + obinutuzumab (formerly abbreviated as AG)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
AUC_{last}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
AV	acalabrutinib + venetoclax
AVO	acalabrutinib + venetoclax + obinutuzumab
AZ	AstraZeneca
BCR	B-cell antigen receptor
BMI	body mass index
BP	blood pressure
BR	bendamustine + rituximab
BTK	Bruton tyrosine kinase
CHOP	cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin), and prednisolone
CIOMS	Council for International Organizations of Medical Sciences
CLL	chronic lymphocytic leukaemia
C_{max}	maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CrCl	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident

Abbreviation/ Special Term	Definition/Explanation
CYP	cytochrome P450
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	haematopoietic stem cell transplantation
IGHV	immunoglobulin heavy chain variable region genes
IL-2	interleukin 2
ILD	interstitial lung disease
INN	international nonproprietary name
INR	international normalised ratio
IRC	independent review committee
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LVEF	left ventricular ejection fraction
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NA	not applicable
NHL	non-Hodgkin's lymphoma
NYHA	New York Heart Association
PBR	placebo + bendamustine + rituximab
PEY	patient exposure years
PFS	progression-free survival
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy

Abbreviation/ Special Term	Definition/Explanation
PPI	proton pump inhibitor
PT	preferred term
QPPV	Qualified Person for Pharmacovigilance
QT	time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	QT correction
QTcF	QT corrected using the Fridericia formula
RMP	Risk Management Plan
R/R	relapsed/refractory
SAE	serious adverse event
SDF-1	stromal cell-derived factor 1
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	system organ class
SPM	second primary malignancy
Tec	tyrosine kinase expressed in hepatocellular carcinoma
TIA	transient ischaemic attack
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
XLA	X-linked agammaglobulinaemia

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Acalabrutinib
Pharmacotherapeutic group(s) (ATC Code)	L01EL02
Marketing Authorisation Applicant	AstraZeneca
Medicinal products to which this RMP refers	CALQUENCE
Invented name(s) in the European Economic Area (EEA)	CALQUENCE
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: CALQUENCE is a selective, irreversible small molecule inhibitor of Bruton tyrosine kinase (BTK).
	Summary of mode of action: BTK is expressed in the cells of all haematopoietic lineages except for T and plasma cells. It is a cytoplasmic tyrosine kinase in the Tec family. This tyrosine kinase lies downstream of the B-cell antigen receptor (BCR). Upon activation of BCR, BTK becomes activated through interacting with the partner molecules through the pleckstrin-homology (PH) and Src-homology (SH) domains. This in turn leads to calcium release. BTK is a critical effector molecule and is involved in all aspects of B cell development, including proliferation, maturation, differentiation, apoptosis, and cell migration. BTK is critical in the initiation, survival, and progression of B-cell lymphoproliferative disorders (Wu et al 2016). CALQUENCE inhibits BTK by covalent binding to the Cysteine 481 residue in the BTK ATP-binding pocket.
	Important information about its composition: **Capsule:** Each capsule also contains compendial inactive ingredients: silicified microcrystalline cellulose, which is composed of microcrystalline cellulose and colloidal silicon dioxide, partially pregelatinised starch, sodium starch glycolate, and magnesium stearate. The gelatine capsule shell contains the following colourants: titanium dioxide, yellow iron oxide and indigotine (Federal Food, Drug, and Cosmetic [FD&C] Blue 2). **Tablet:** Each tablet contains the following inactive ingredients mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and sodium stearyl fumarate. The tablet coating consists of hypromellose, copovidone, titanium oxide, polyethylene glycol 3350, medium-chain triglycerides, yellow iron oxide, red iron oxide, and purified water.
Hyperlink to the Product Information	CALQUENCE, Summary of Product Characteristics

Table I-1 Product Overview

Indication(s) in the EEA	Current: Treatment as monotherapy or in combination with obinutuzumab of adult patients with chronic lymphocytic leukaemia (CLL)
	Proposed: • Treatment in combination with venetoclax with or without obinutuzumab of adult patients with previously untreated CLL • Treatment in combination with bendamustine and rituximab of adult patients with previously untreated MCL • Treatment as monotherapy of adult patients with relapsed or refractory MCL
Dosage in the EEA	Current: The recommended dose is 100 mg twice daily (equivalent to a total daily dose of 200 mg). Doses should be separated by approximately 12 hours.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Capsule:** Each capsule contains 100 mg acalabrutinib. Size 1 hard gelatine capsule with a yellow body and blue cap, marked in black ink with 'ACA 100 mg' **Tablet:** Each film-coated tablet contains acalabrutinib maleate equivalent to 100 mg of acalabrutinib. Orange, 7.5 x 13 mm, oval, biconvex tablet, debossed with 'ACA 100' on one side and plain on the reverse.
Is/will the product be subject to additional monitoring in the EU?	Yes

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATION

II.1.1 Mantle Cell Lymphoma

Incidence

MCL represents 5% to 7% of malignant lymphoma in Western Europe. The annual incidence of MCL has increased during recent decades to 1 to 2 cases per 100,000 population (Dreyling et al 2017). In the Netherlands in 2001 and 2010, the age-standardised incidence of MCL was 1.3 and 1.4 per 100,000 person-years, respectively, in males, and was 0.4 and 0.4, respectively, in females (Issa et al 2015). Incidence rates were ~1.0 to ~1.3 per 100,000 in Denmark and ~0.7 to ~1.1 per 100,000 in Sweden (Monga et al 2020). In Europe, crude and age-standardised (European) MCL incidence (95% confidence interval) per 100,000 population was 0.86 (0.76-0.98) and 0.65 (0.62-0.69), respectively, overall; 1.15 (0.98-1.34) and 0.99 (0.93-1.05), respectively, in males; and 0.60 (0.48-0.74) and 0.39 (0.35-0.42), respectively, in females (Smith et al 2015).

Prevalence

Data on prevalence are not readily available.

Demographics of the Population in the Authorised Indication — Age, Gender, Racial and/or Ethnic Origin, and Risk Factors for the Disease

Age

Issa et al (Netherlands) reported that the mean age of patients with MCL was 71 years (Issa et al 2015). Smith et al (UK) reported that the median age was 73.5 years (range 64.3-80.3) (Smith et al 2015).

Gender

MCL is more common in males than in females with a 3:1 ratio (Dreyling et al 2017). Based on Haematological Malignancy Research Network (UK) data from 2004 to 2012, 64.4% of MCL cases occurred in men (159/247 cases) compared with 35.6% (88/247 cases) in women (Smith et al 2015).

Racial and/or Ethnic Origin

Racial differences exist among MCL patients in the US in terms of patient characteristics, incidence, and survival. Overall, MCL is typically reported in White patients by a 2:1 ratio over other races (Wang and Ma 2014). Based on an analysis of 18,120 patients diagnosed with MCL between 2004 and 2013 in the US National Cancer Database, the majority of patients (83%) were non-Hispanic White; 4% of patients were non-Hispanic Black, 6% were Hispanic,

and the remaining 7% identified as some other race (Shah et al 2019). Median age at diagnosis was higher (68 years) for non-Hispanic White patients compared with non-Hispanic Black and Hispanic patients (65 years in both groups).

Risk Factors

In a pooled analysis of case-control studies in the International Lymphoma Epidemiology (InterLymph) Consortium, which included 150 to 400 MCL cases and a large number of controls, BMI, and lifestyle factors such as cigarette smoking and alcohol intake were associated with increased risk of NHL overall and multiple NHL subtypes; however, BMI and lifestyle factors were not specifically implicated as risk factors for MCL.

Immune suppression has been associated with the risk of developing aggressive lymphomas. Some viruses have been implicated in the development of NHL overall. There is a lack of solid evidence for an association between these viral agents and the risk of MCL, but there is increasing evidence for the role of antigenic drive, by exogenous or endogenous antigens, in the aetiology of at least a subset of MCL cases (Wang and Ma 2014).

Family history of haematopoietic malignancies has been linked with a 2-fold increased risk of MCL (Wang and Ma 2014).

Main Existing Treatment Options for MCL

Front Line Settings: In patients eligible for stem cell transplant, dose intensified chemoimmunotherapy, including high-dose cytarabine followed by autologous transplant and rituximab maintenance, is generally the preferred therapeutic approach. For transplant-ineligible patients, a number of different chemoimmunotherapy regimens are appropriate as first-line therapy. Bendamustine and rituximab are considered a standard regimen in the first-line treatment of patients who are not candidates for intensive treatment (Eyre et al 2024, NCCN 2024).

The standard-of-care treatment for elderly patients with MCL is rituximab-based chemoimmunotherapy followed by rituximab maintenance (Flinn et al 2019, Kluin-Nelemans et al 2012, Robak et al 2018, Visco et al 2017) providing a median PFS of 3 to 5 years. Real-world data indicates that BR is the most administered first-line regimen in elderly MCL patients.

R/R MCL: BTK is a non-receptor kinase downstream from the BCR; it is critical for normal B-cell maturation, proliferation, and survival. The emergence of BTK inhibitors has had a great impact on patient outcomes in the past decade, including those patients who were previously heavily treated. Currently approved covalent BTK inhibitors for use in the R/R setting are ibrutinib, CALQUENCE, zanubrutinib (Burkart and Karmali 2022). Pirtobrutinib is an approved non-covalent BTK inhibitor.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

The clinical course of MCL varies between a slowly progressive, relatively indolent condition amenable to expectant management, to a rapidly progressive condition requiring immediate treatment (Alaggio et al 2022, Campo et al 2022, Dreyling et al 2018, Martin et al 2009). In addition to the Mantle Cell Lymphoma International Prognostic Index (MIPI), blastoid morphology, high Ki-67, and TP53 alterations have been identified as the most important high-risk biological risk factors for poor prognosis (including shorter overall survival) among MCL patients (Aukema et al 2018, Eskelund et al 2017, Hoster et al 2008, Hoster et al 2016, Jain et al 2020, Scheubeck et al 2023).

The most common presentation of MCL is painless enlargement of lymph glands, most commonly in the neck. Patients with MCL are often asymptomatic but may experience the following symptoms: decreased appetite, weight loss, fever, night sweats, nausea and/or vomiting, indigestion, abdominal pain or bloating, a feeling of "fullness" or discomfort due to enlarged tonsils, liver, or spleen, or fatigue, which may be associated with developing anaemia (Leukemia and Lymphoma Society 2014).

Aggressive therapy of MCL in younger patients can result in a median PFS of 7 to 10 years, but not all patients qualify for this approach, and eventually, all patients will experience a relapse (Hermine et al 2023, Martin et al 2022, Sarkozy et al 2023, Zoellner et al 2021).

Important Comorbidities

Comorbidities identified for patients with MCL (eg, cardiac disease 29%, hypertension 28%, diabetes 11%, and renal impairment 7%) (Schmidt et al 2011) are consistent with the comorbidities expected in an elderly and predominantly male population.

II.1.2 Chronic Lymphocytic Leukaemia

Incidence

The number of incident CLL cases in 2019 was approximately 4 times higher in Western Europe (n = 27,560) compared with Central Europe (n = 6,436) and Eastern Europe (n = 7,424) (Ou et al 2022; Yao et al 2022). Comparisons of age-standardized rates within the same year also indicate higher incidence of CLL in Western Europe versus Central and Eastern Europe (Yao et al 2022).

Prevalence

In the UK, more than 20,000 prevalent cases were estimated at the end of 2010 (Cancer Research UK 2019). The US, France, Germany, Italy, Spain, and the UK had a combined 150,800 five-year diagnosed prevalent cases of CLL in 2013

(EpiCast Report 2014). The prevalence of CLL is estimated to be 215,107 cases in the US (SEER 2024).

Demographics of the Population in the Proposed Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease

Age

CLL predominantly affects older adults, with reported median age at diagnosis between 70 and 72 years (Eichhorst et al 2021, Shadman 2023). CLL is rarely seen in people under age 40 and is extremely rare in children (American Cancer Society 2024).

Gender

The incidence of CLL is approximately 1.7 to 2 times higher in males compared with females (Hallek 2017, Kipps et al 2017).

Racial and/or Ethnic Origin

The incidence of CLL (per 100,000 person-years) is highest among non-Hispanic White individuals (6.88), followed by Black individuals (4.70), Hispanic White individuals (2.92), and Asian and Pacific Islander individuals (1.45) (Li et al 2015).

Risk Factors

Genetic factors contribute to CLL risk; individuals who have a family history of CLL have an approximately 5- to 9-fold increased risk of developing the disease (Eichhorst et al 2021, Sud et al 2019). Whole genome sequencing studies have identified over 40 single nucleotide polymorphisms that are associated with susceptibility to CLL (Berndt et al 2016).

Main Existing Treatment Options

The choice of frontline treatment options for CLL depends on patient characteristics, such as patient's age and overall health, and disease characteristics, including the presence of certain chromosomal abnormalities and mutations (Eichhorst et al 2024, Wierda et al 2024).

According to ESMO guidelines, watchful waiting is appropriate for patients with early asymptomatic disease (Eichhorst et al 2024). Depending on mutation status and stage of disease, treatment options include monotherapy with ibrutinib, zanubrutinib, acalabrutinib, or venetoclax. Time-limited combination therapies include ibrutinib + venetoclax, venetoclax + obinutuzumab, idelalisib + rituximab, venetoclax + rituximab, chemoimmunotherapy, or allogeneic stem cell transplant.

According to NCCN (Wierda et al 2024), depending on mutation status and stage of disease, treatment options include acalabrutinib with or without obinutuzumab, zanubrutinib, ibrutinib, venetoclax + obinutuzumab, ibrutinib + obinutuzumab, ibrutinib + rituximab, or ibrutinib + venetoclax.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias (Langerbeins et al 2023). Despite the relatively long life expectancy for early-stage disease, CLL remains an incurable disease.

As of 2019, the age-standardized death rate (95% confidence interval) from CLL was 1.18 (1, 1.42), 0.9 (0.79, 1.01), and 0.93, (0.82, 1.12) per 100,000 in Central Europe, Eastern Europe, and Western Europe, respectively, and the age-standardized disability-adjusted life-year burden was 25.09 (21.23, 30.39), 21.56 (18.85, 24.43), and 17.13 (15.32, 20.79) per 100,000, respectively (Ou et al 2022).

During the initial asymptomatic phase, patients can maintain their usual lifestyles, but during the terminal phase the performance status is poor, with recurring need for hospitalization. The most frequent causes of death are severe systemic infection (especially pneumonia and septicaemia), bleeding, and inanition with cachexia. Spontaneous clinical regression has been reported but is rare (Thomas et al 2002).

The natural history of CLL is extremely variable, with survival times from initial diagnosis that range from approximately 2 to 20 years, and a median survival of approximately 10 years. Until the mid-1970s, there were no reliable clinically applicable criteria that would allow the prospective separation of patients with a poor outlook for survival from those with an excellent prognosis. Certain high-risk genetic features (ie, deletion 17p/TP53 mutation, IGHV mutational status, complex karyotypes) have since been identified, allowing more informed treatment decisions to be made and leading to improved clinical outcomes, mostly because of a greater proportion of patients in the low-risk clinical stage and a relatively longer survival of the high-risk group.

Morbidities of CLL may include:

- More than 10% weight loss in 6 months
- Extreme tiredness
- Fever for more than 2 weeks without any signs of infection
- Night sweats for longer than 1 month
- Bone marrow failure that gets worse and lower numbers of healthy red blood cells (anaemia) or platelets (thrombocytopenia)
- Anaemia and/or thrombocytopenia that does not respond to steroids
- A spleen that is larger than normal and may be causing symptoms such as abdominal discomfort or a feeling of fullness

- More areas of enlarged lymph nodes
- An enlarged liver
- The number of lymphocytes increases by more than 50% in 2 months, or doubles in less than 6 months (rapid doubling time)

In rare cases, CLL develops into a high-grade lymphoma called Richter's syndrome or a Richter transformation. If this happens, it usually develops into a diffuse large B-cell lymphoma, which is treated like a lymphoma (Canadian Cancer Society 2024).

Important Comorbidities

In an observational study of 400 patients with CLL in Spain, nearly all participants (99.5%) presented with at least one comorbidity at diagnosis, with diabetes without end organ damage being the most common comorbidity (21%) followed by congestive heart failure (18%), chronic lung disease (11%), and malignant tumours (11%) (Villavicencio et al 2021).

A German study investigated comorbidity burden of 555 CLL patients from 2 trials of the German CLL Study Group. Top comorbidity conditions include: metabolic/endocrine (26%), vascular (21%), cardiac (12%), respiratory (5%), and musculoskeletal (5%) (Goede et al 2014).

II.2 MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of Key Findings from Nonclinical Data

Toxicity

Key Issues Identified From Acute or Repeat-Dose Toxicity Studies

No adverse changes were observed in mice dosed with up to 100 mg/kg/day CALQUENCE for 4 weeks.

In repeat-dose oral toxicity studies of up to 6 months duration in rats and 9 months in dogs, the kidney, liver, and heart were identified as target organs of toxicity in both species. Expected pharmacological changes in lymphoid tissues and blood lymphocyte populations were noted in these studies, however the observed effects were not considered to be toxicologically significant. In rats, minimal liver and kidney findings were observed at exposures 4 times the total clinical exposure. In both species, kidney findings included clinical and anatomical pathology changes. In rats, microscopic changes in the liver were associated with changes in clinical pathology parameters. In dogs, liver findings consisted of transient changes in clinical chemistry parameters. More severe toxicities including microscopic changes in the heart were observed at exposures ≥7-fold the total clinical exposure. Partial or complete reversibility was demonstrated for liver and kidney findings in both species. Heart

findings were only observed at doses greater than the maximum tolerated dose and therefore reversibility could not be demonstrated.

The findings in nonclinical studies occurred at exposures higher than those achieved in patients at the recommended therapeutic dose.

Reproductive/Developmental Toxicity

In an embryofoetal study in pregnant rats, no effects on embryofoetal survival, growth, and development were observed at exposures 9 times the human exposure at the recommended dose.

In an embryofoetal study in pregnant rabbits, daily oral administration of CALQUENCE during the period of organogenesis produced maternal toxicity, decreased foetal body weight, and delayed skeletal ossification at exposures 2.4-fold greater than the human exposure.

Administration of CALQUENCE to rats during pregnancy, parturition, and lactation was associated with dystocia (prolonged/difficult labour)/incomplete delivery at exposures 2.3 times the human AUC at the recommended dose.

In a pilot pre- and post-natal development study, CALQUENCE and its active metabolite, ACP-5862, were detected in foetal rat plasma, in the milk of lactating rats, and in plasma of the pups of nursing dams.

In the absence of clinical data in pregnant women, CALQUENCE is considered a potential human teratogenic/fetotoxic drug.

Fertility

There were no effects of CALQUENCE on fertility in male or female rats at exposures 16 to 18 times, respectively, the clinical exposure, at the therapeutic dose of 100 mg twice daily.

No key findings were identified.

Genotoxicity

CALQUENCE was negative for genotoxicity and clastogenicity in a standard panel of in vitro and in vivo assays.

No key findings were identified.

Carcinogenicity

No studies conducted.

Phototoxicity

Based on phototoxicity assays using 3T3 cell line in vitro, CALQUENCE is considered to have a low risk for phototoxicity in humans.

Safety Pharmacology

Cardiovascular System, Including Potential Effect on the QT Interval

CALQUENCE did not significantly affect the cardiovascular system, body temperature, ECG intervals, or physical condition of the dogs.

At a concentration of 10 μM (294 times the clinical unbound C_{max}), CALQUENCE showed 25% inhibition of human ether à-go-go-related (hERG) in stably transfected human embryonic kidney (HEK)-293 cells.

A slightly greater than dose-proportional increase in AUC from 100 to 400 mg established a supratherapeutic CALQUENCE exposure suitable to explore the relationship between the PK of CALQUENCE and corresponding QTc intervals.

Nervous System

CALQUENCE had no significant effects on the central nervous system (CNS) function.

No key findings identified.

Respiratory System

No key findings identified.

Drug-Drug Interaction

Based on interaction studies, inhibition of CALQUENCE metabolism by specific CYP3A4/5 inhibitors (ketoconazole and troleandomycin) indicates that CYP3A4/5 is the predominant CYP isoform responsible for metabolism of CALQUENCE.

Coadministration with moderate CYP3A inhibitor, fluconazole (400-mg single dose), increased CALQUENCE C_{max} and AUC by 1.5- and 2-fold, with a corresponding decrease in ACP-5862 C_{max} and AUC to 0.65- and 0.85-fold (of control), respectively, relative to when CALQUENCE was dosed alone (n = 14 healthy volunteers). Similarly, following administration with moderate CYP3A inhibitor isavuconazole (200 mg 3 times daily followed by 200 mg once daily for additional 4 days), CALQUENCE C_{max} and AUC increased by 1.37- and 1.60-fold, with a corresponding decrease in ACP-5862 C_{max} and AUC to 0.72- and 0.88-fold (of control), respectively (n = 14 healthy volunteers).

Other specific chemical inhibitors for CYP1A2, CYP2E1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 had minimal effect on the metabolic consumption of CALQUENCE in human liver microsomes.

CALQUENCE did not appreciably inhibit CYP1A2, CYP2B6, CYP2C19, or CYP2D6, or CYP2C8, CYP2C9, or CYP3A4/5.

CALQUENCE is not a potent direct inhibitor of CYP3A4 and is not anticipated to be a perpetrator of drug interactions at the level of systemic inhibition of CYP3A4. CALQUENCE is not expected to increase exposure of coadministered therapeutics that are substrates for other CYP isoforms.

CALQUENCE is not anticipated to be a moderate or strong inducer of CYP isoforms in humans.

CALQUENCE is unlikely to be a perpetrator of a DDI at the level of inhibition or induction of CYP isoforms.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

Clinical trial exposure is summarised using 5 populations, a monotherapy population and 4 combination therapy populations. To be included in any population, the patient had to receive at least 1 dose of the assigned treatment.

- CALQUENCE monotherapy population (data cutoff 15 February 2024; N = 1478): patients from 11 studies in various haematologic malignancies in both previously untreated and R/R settings, in which patients received at least 1 dose of CALQUENCE monotherapy, including studies with patients initially assigned to CALQUENCE monotherapy treatment (ACE-LY-004, ACE-CL-007, ACE-CL-309, ACE-CL-001, 15-H-0016, ACE-CL-006, ACE-LY-002, ACE-LY-003, ACE-MY-001, and ACE-WM-001) and studies in which some patients crossed over from control arms to CALQUENCE monotherapy (ACE-LY-308, ACE-CL-007, and ACE-CL-309).
- The combination therapy populations consist of:
  - Patients with previously untreated CLL in the AV arm of ACE-CL-311 (AMPLIFY) (data cutoff 30 April 2024; N = 291).
  - Patients with previously untreated CLL in the AVO arm of ACE-CL-311 (AMPLIFY) (data cutoff 30 April 2024; N = 284).
  - Patients with previously untreated R/R CLL, small lymphocytic lymphoma, or prolymphocytic leukaemia in the AO arm from Study ACE-CL-003 (data cutoff 08 February 2019; N = 223).
  - Patients with previously untreated MCL in the ABR arm of Study ACE-LY-308 (ECHO) (data cutoff 15 February 2024; N = 297).

Exposure data for the pivotal study in R/R MCL (ACE-LY-004; N =124) are included in the CALQUENCE monotherapy population. Note that data for ACE-LY-004 were final as summarised in the monotherapy population in EU RMP Version 5; thus, no new exposure data are presented for R/R MCL.

Table II-1 Duration of Exposure to CALQUENCE

Duration of exposure	CALQUENCE monotherapy (N = 1478)		Combination therapy							
			ABR (N = 297)		AO (N = 223)		AV (N = 291)		AVO (N = 284)	
	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)
≤ 6 months	231	51.6	51	11.9	9	2.5	12	3.6	19	4.6
> 6 to ≤ 12 months	98	72.8	33	24.8	10	8.2	14	11.7	26	18.5
> 12 to ≤ 24 months	173	256.4	42	60.8	8	11.5	265	291.4	239	265.8
> 24 to ≤ 36 months	210	532.6	49	121.7	93	251.7	0	0	0	0
> 36 months	766	3727.8	122	584.1	58	194.1	0	0	0	0
Total	1478	4641.2	297	803.4	178	467.9	291	306.8	284	289.0

Person time was calculated from first dose of CALQUENCE to last dose or data cutoff date.

Table II-2 Exposure to CALQUENCE by Age Group and Gender

Age group (years)	CALQUENCE monotherapy (N = 1478)				Combination therapy															
					ABR (N = 297)				AO (N = 223)				AV (N = 291)				AVO (N = 284)			
	Male		Female		Male		Female		Male		Female		Male		Female		Male		Female	
	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)
0 to 17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18 to 64	383	1301.2	167	484.9	0	0	0	0	38	56.8	23	43.6	120	127.2	74	79.9	138	143.4	60	65.0
65 to 74	422	1383.2	201	651.8	151	406.4	63	202.9	68	149.0	36	84.9	51	52.7	33	34.5	48	46.0	20	20.1
75 to 84	176	448.4	102	309.8	60	132.4	21	55.9	33	73.1	19	47.6	7	7.5	6	5.2	12	8.9	6	5.6

Table II-2 Exposure to CALQUENCE by Age Group and Gender

Age group (years)	CALQUENCE monotherapy (N = 1478)				Combination therapy															
					ABR (N = 297)				AO (N = 223)				AV (N = 291)				AVO (N = 284)			
	Male		Female		Male		Female		Male		Female		Male		Female		Male		Female	
	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)	No. of Pts	Person time (PEY)
> 85	17	34.0	10	27.8	1	3.6	1	2.2	4	11.4	2	1.5	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	998	3166.9	480	1474.3	212	542.4	85	261.0	143	290.3	80	177.6	178	187.3	113	119.6	198	198.3	86	90.7

Person time was calculated from first dose of CALQUENCE to last dose or data cutoff date.

Table II-3 Exposure to CALQUENCE by Dose

Dose	CALQUENCE monotherapy (N = 1478)		Combination therapy							
			ABR (N = 297)		AO (N = 223)		AV (N = 291)		AVO (N = 284)	
	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)
100 mg twice daily	1302	4016.5	297	803.4	223	467.9	291	306.8	284	289.0
200 mg once daily and 100 mg twice daily	70	345.2	0	0	0	0	0	0	0	0
200 mg twice daily	35	26.2	0	0	0	0	0	0	0	0
200 mg once daily	35	109.4	0	0	0	0	0	0	0	0
100 mg once daily	9	31.4	0	0	0	0	0	0	0	0
175 mg once daily	8	26.2	0	0	0	0	0	0	0	0

Table II-3 Exposure to CALQUENCE by Dose

Dose	CALQUENCE monotherapy (N = 1478)		Combination therapy							
			ABR (N = 297)		AO (N = 223)		AV (N = 291)		AVO (N = 284)	
	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)
250 mg once daily	7	24.2	0	0	0	0	0	0	0	0
200 mg twice daily and 100 mg twice daily	6	29.1	0	0	0	0	0	0	0	0
400 mg once daily	6	33.0	0	0	0	0	0	0	0	0
Total	1478	4641.2	297	803.4	223	467.9	291	306.8	284	289.0

Person time was calculated from first dose of CALQUENCE to last dose or data cutoff date.

Table II-4 Exposure to CALQUENCE by Race

Race	CALQUENCE monotherapy (N = 1478)		Combination therapy							
			ABR (N = 297)		AO (N = 223)		AV (N = 291)		AVO (N = 284)	
	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)
American Indian or Alaska Native	2	9.1	2	7.8	0	0	1	1.1	0	0
Asian	24	40.3	44	88.7	3	9.1	4	3.7	9	10.1
Black or African American	43	130.1	1	2.0	5	12.1	3	3.5	11	11.4
Native Hawaiian or Other Pacific Islander	1	5.0	0	0	0	0	0	0	0	0
White	1333	4241.3	232	640.8	208	428.6	265	279.3	246	249.1

Table II-4 Exposure to CALQUENCE by Race

Race	CALQUENCE monotherapy (N = 1478)		Combination therapy							
			ABR (N = 297)		AO (N = 223)		AV (N = 291)		AVO (N = 284)	
	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)
Multiple	0	0	5	21.3	0	0	0	0	2	2.2
Other	15	71.0	0	0	0	0	0	0	0	0
Not reported	60	144.5	13	42.8	7	18.1	18	19.3	16	16.2
Total	1478	4641.2	297	803.4	223	467.9	291	306.8	284	289.0

Person time was calculated from first dose of CALQUENCE to last dose or data cutoff date.

Table II-5 Exposure to CALQUENCE by Ethnicity

Ethnicity	CALQUENCE monotherapy (N = 1478)		Combination therapy							
			ABR (N = 297)		AO (N = 223)		AV (N = 291)		AVO (N = 284)	
	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)	Number of patients	Person time (PEY)
Hispanic	47	129.3	34	96.1	3	5.4	21	21.5	15	13.6
Non-Hispanic	1327	4211.7	244	649.1	212	443.9	246	259.7	248	254.3
Missing/NA	104	300.2	19	58.2	8	18.6	24	25.7	21	21.0
Total	1478	4641.2	297	803.4	223	467.9	291	306.8	284	289.0

Person time was calculated from first dose of CALQUENCE to last dose or data cutoff date.

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table II-6 Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale
Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer; adequately treated lentigo melanoma or carcinoma in situ (Study ACE-LY-308); or other cancer from which the patient has been disease-free for ≥ 2 years (≥ 3 years without further treatment in ACE-CL-311).	Excluded to allow for adequate evaluation of efficacy and safety outcomes.	No	Use in this population is not predicted to be associated with safety concerns different than those of the general target population.
Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or Class 4 cardiac disease as defined by the NYHA Functional Classification, or QTc > 480 ms.	Excluded to allow for adequate evaluation of safety outcomes.	Yes	
Known history of HIV, active infection with HCV or HBV, CMV (Study ACE-LY-308), or any uncontrolled active systemic infection.	Excluded to allow for adequate evaluation of safety outcomes.	No	It can be anticipated that use in these patients may increase the risk of infections. Based on the known safety profile of CALQUENCE, serious infections with or without association with neutropenia are considered to be an important identified risk for CALQUENCE.

Table II-6 Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale
Uncontrolled autoimmune haemolytic anaemia or idiopathic thrombocytopenia purpura.	Based on the mechanism of action of CALQUENCE and its predicted impact on the haematological system, these patients were excluded to allow for adequate evaluation of efficacy and safety outcomes.	No	It can be anticipated that use in these patients would increase the risk of clinically significant cytopenia. Based on the known safety profile of CALQUENCE, cytopenia (which includes anaemia and thrombocytopenia) is considered an identified risk for CALQUENCE and is included in Table II-9.
Known history of a bleeding diathesis (eg, haemophilia, von Willebrand disease).	Based on the mechanism of action of CALQUENCE and its predicted impact on the haematological system, these patients were excluded to allow for adequate evaluation of efficacy and safety outcomes.	No	It can be anticipated that use in these patients may increase the risk of haemorrhage. Based on the known safety profile of CALQUENCE, haemorrhage with or without association with thrombocytopenia is considered to be an important identified risk for CALQUENCE.
History of stroke or intracranial haemorrhage within 6 months before the first dose of study drug.	Based on the mechanism of action of CALQUENCE and its predicted impact on the haematological system, these patients were excluded to allow for adequate evaluation of efficacy and safety outcomes.	No	It can be anticipated that use in these patients would increase the risk of clinically significant haemorrhage. Based on the known safety profile of CALQUENCE, haemorrhage with or without association with thrombocytopenia is considered to be an important identified risk for CALQUENCE.

Table II-6 Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale
Required or was receiving anticoagulation with warfarin or equivalent vitamin K antagonist (eg, phenprocoumon) within 7 days of first dose of study drug.	Based on the mechanism of action of CALQUENCE and its predicted impact on the haematological system, these patients were excluded to allow for adequate evaluation of efficacy and safety outcomes.	No	It can be anticipated that use in these patients may increase the risk of haemorrhage. Based on the known safety profile of CALQUENCE, haemorrhage with or without association with thrombocytopenia is considered to be an important identified risk for CALQUENCE.
Required treatment with PPIs (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).	The capsule formulation of CALQUENCE absorption may be lower in individuals being treated with PPIs, histamine 2 antagonists, or antacids. NOTE: The tablet formulation of CALQUENCE absorption is not impacted by acid reducing agents.	No	Concomitant use of PPIs has been shown to decrease the AUC of CALQUENCE capsules by 43% in healthy volunteers and could therefore result in reduced efficacy. As this effect has been described in the SmPC for CALQUENCE capsules and patients are advised to avoid concomitant use of PPIs, use in this population is not expected for the capsule formulation and hence it is not considered missing information.
Breastfeeding or pregnant female patients: unwilling to utilise effective contraceptive methods or refrain from becoming pregnant if of childbearing potential or currently breastfeeding.	Patients excluded for safety reasons.	No	CALQUENCE should not be used during pregnancy and women of childbearing potential should be advised to avoid becoming pregnant while receiving CALQUENCE. Breastfeeding mothers are advised not to breastfeed during treatment with CALQUENCE and for 2 days after receiving the last dose. As this effect has been described in the SmPC, use in this population is not expected and hence it is not considered missing information.

Table II-6 Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale
Required treatment with a strong CYP3A inhibitor/inducer.	CALQUENCE is metabolised primarily by CYP3A4/5 and thus DDI is possible with strong CYP3A inhibitors/inducers.	No	CALQUENCE C_{max} and AUC were increased with coadministration with a strong CYP3A inhibitor, while coadministration of a strong CYP3A inducer decreased these parameters. The SmPC includes recommendations to consider alternative therapies that do not strongly inhibit or induce CYP3A activity and patients taking strong CYP3A inhibitors with CALQUENCE should be monitored more closely for adverse reactions. As this effect has been described in the SmPC, use in this population is not expected, hence it is not considered missing information.
Uncontrolled active systemic fungal, bacterial, viral, or other infection or ongoing intravenous anti-infective treatment.	Excluded to allow for adequate evaluation of efficacy and safety outcomes.	No	It can be anticipated that use in these patients may increase the risk of infections. Based on the known safety profile of CALQUENCE, serious infections with or without association with neutropenia are considered to be an important identified risk for CALQUENCE.
History of confirmed PML.	Excluded (in Studies ACE-CL-309, ACE-LY-308, and ACE-CL-311) to allow for adequate evaluation of efficacy and safety outcomes.	No	It can be anticipated that use in these patients may increase the risk of reactivation of PML infection. Based on the known safety profile of CALQUENCE, serious infections with or without association with neutropenia are considered to be an important identified risk for CALQUENCE.

Table II-6 Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale
Active CMV infection (active viremia as evidenced by positive polymerase chain reaction result for CMV DNA).	Excluded (in Studies ACE-CL-309, ACE-LY-308, and ACE-CL-311) to allow for adequate evaluation of efficacy and safety outcomes.	No	It can be anticipated that use in these patients may increase the risk of infection. Based on the known safety profile of CALQUENCE, serious infections with or without association with neutropenia are considered to be an important identified risk for CALQUENCE.
Prothrombin time/INR or aPTT (in the absence of a lupus anticoagulant) > 2.0 × ULN.	Excluded (in Studies ACE-CL-309, ACE-LY-308) to allow for adequate evaluation of efficacy and safety outcomes.	No	It can be anticipated that use in these patients may increase the risk of haemorrhage. Based on the known safety profile of CALQUENCE, haemorrhage with or without association with thrombocytopenia is considered to be an important identified risk for CALQUENCE.
Presence of a GI ulcer diagnosed by endoscopy within 3 months prior to screening.	Based on the mechanism of action of CALQUENCE and its predicted impact on the haematological system, these patients were excluded (in Studies ACE-LY-004 and ACE-CL-309) to allow for adequate evaluation of efficacy and safety outcomes.	No	One of the major complications of GI ulcers is haemorrhage and it can be anticipated that use in patients with GI ulcers would increase the risk of clinically significant haemorrhage. Based on the known safety profile of CALQUENCE, haemorrhage with or without association with thrombocytopenia is considered to be an important identified risk for CALQUENCE.

Table II-6 Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale
ANC < 0.75 × 10^9/L or platelet count < 50 × 10^9/L; for patients with disease involvement in the bone marrow, ANC < 0.50 × 10^9/L and platelet count < 30 × 10^9/L (Studies ACE-LY-004 and ACE-CL-311). ANC < 1.0 × 10^9/L or platelet count < 75 × 10^9/L; for patients with disease involvement in the bone marrow, ANC < 0.75 × 10^9/L or platelet count < 50 × 10^9/L (Studies ACE-LY-308 and ACE-CL-311).	Excluded (in Studies ACE-LY-004, ACE-LY-308, and ACE-CL-311) to allow for adequate evaluation of safety outcomes. In addition, cytopenias are a risk of ibrutinib and thus cytopenias were suspected to be a class effect.	No	It can be anticipated that use in these patients would increase the risk of clinically significant cytopenias. Based on the known safety profile of CALQUENCE, cytopenia (which includes anaemia and thrombocytopenia) is considered an identified risk for CALQUENCE and is included in Table II-9.
Estimated CrCl of < 30 mL/min (Study ACE-LY-004) or < 50 mL/min (Studies ACE-LY-308 and ACE-CL-311), calculated using the formula of Cockcroft and Gault Creatinine > 2.5 × ULN (Study ACE-LY-004).	Excluded (in Studies ACE-LY-004, ACE-LY-308, and ACE-CL-311) to allow for adequate evaluation of safety outcomes.	No	In a human radiolabelled mass balance study, approximately 12% of CALQUENCE was excreted in urine, mainly as metabolites, thus the safety profile in this population is not anticipated to be different to that of the general target population.
Total bilirubin > 2.5 × ULN (Study ACE-LY-004) or >1.5 × ULN (Study ACE-LY-308), or > 2 × ULN unless directly attributable to Gilbert's syndrome (Study ACE-CL-311). AST or ALT > 3.0 × ULN (Study ACE-LY-004) or >2.5 × ULN (Studies ACE-LY-308 and ACE-CL-311).	Excluded (in Studies ACE-LY-004, ACE-LY-308, and ACE-CL-311) to allow for adequate evaluation of safety outcomes.	No	Use in these patients might increase the risk of hepatoxicity, which is considered to be an important potential risk for CALQUENCE. In addition, increased ALT and AST are considered ADRs for the ABR combination.

II.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as uncommon (1/100 to 1/1000) adverse reactions or adverse reactions with a long latency, or those caused by prolonged exposure.

II.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table II-7 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Paediatric population	Not included in the clinical development programme.
Pregnant women	Not included in the clinical development programme. There has been one reported pregnancy in a patient exposed to CALQUENCE, in which the patient was exposed during the first trimester; the pregnancy went to full term with no complications/abnormalities.
Breastfeeding women	
Patients with relevant comorbidities:	
Patients with hepatic impairment	12 patients with mild to moderate hepatic impairment who received CALQUENCE in PK/pharmacodynamics studies.
Patients with severe renal impairment (creatinine > 2.5 × ULN, estimated CrCl < 30, estimated glomerular filtration rate ≤ 50)	Not included in the clinical development programme.
Patients with severe cardiovascular impairment (uncontrolled arrhythmias, Class 3-4 NYHA functional classification, significant screening ECG abnormalities)	Not included in the clinical development programme.
Immunocompromised patients (ongoing immunosuppressive therapy or known history of HIV infection)	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	The majority of patients studied were non-Hispanic and White by race.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II.5.1 Method Used to Calculate Exposure

The post-marketing patient exposure data presented is estimated based on monthly actual ex-factory sales volume for CALQUENCE from the US and other countries where CALQUENCE is available. These data represent all CALQUENCE formulations delivered to various distribution channels (eg, wholesalers, pharmacies, etc) worldwide.

The sales volume is provided as the number of capsules and tablets distributed. The estimated post-marketing patient exposure data for the reporting period is an approximation based on the assumption that each patient took 2 capsules/tablets of CALQUENCE a day. Therefore, a patient-year worth of exposure is calculated by multiplying 2 capsules/tablets per day by 365 days (730 capsules/tablets per patient year).

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to CALQUENCE. More detailed patient-level data (eg, sex, ethnicity, age category, off-label use, specific populations) are not available.

II.5.2 Exposure

The cumulative global post-marketing patient exposure to CALQUENCE (acalabrutinib) 100-mg capsules and 100-mg tablets since their respective launches to 30 October 2023, has been estimated to be approximately 48,107 patient-years and 14,072 patient-years, respectively. The cumulative overall global post-marketing patient exposure to CALQUENCE (100-mg) capsule and tablet was estimated to be approximately 62,179 patient-years.

The cumulative regional sales figures are presented in **Table II-8**.

Table II-8 CALQUENCE (acalabrutinib) Cumulative Sales: Number of 100-mg Capsules and 100-mg Tablets, by Region, From First Launches to 30 October 2023

Formulation	Europe	North America	CCI	Rest of the world	Total
CALQUENCE capsule 100 mg	13,211,918	18,611,100	[redacted]	3,034,818	35,118,208
CALQUENCE tablet 100 mg	582,801	9,631,800	[redacted]	57,600	10,272,201
Total	13,794,719	28,242,900	[redacted]	3,092,418	45,390,409

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Based on mechanism of action, CALQUENCE is not anticipated to show a potential for drug abuse or dependence and hence there is no anticipated potential for misuse for illegal purposes.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of Safety Concerns in the Initial RMP Submission

II.7.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP

Table II-9 Risks with Minimal Clinical Impact on Patients (in Relation to Severity of Indication Treated)

MedDRA SOC	MedDRA Term	Overall Frequency (All CTCAE Grades) (N=1040)	Frequency of CTCAE Grade ≥3 (N=1040)
Blood and lymphatic system disorders	Leukopenia[a]	Very common (16.2%)	14%
	Neutropenia	Very common (15.7%)	14%
	Anaemia	Very common (13.8%)	8%
	Thrombocytopenia	Common (8.9%)	4.8%
GI disorders	Diarrhoea	Very common (36.7%)	2.6%
	Nausea	Very common (21.7%)	1.2%
	Constipation	Very common (14.5%)	0.1%
	Vomiting	Very common (13.3%)	0.9%
	Abdominal pain[a]	Very common (12.5%)	1.0%
Nervous system disorders	Headache	Very common (37.8%)	1.1%
	Dizziness	Very common (13.4%)	0.2%
Skin and subcutaneous tissue disorders	Bruising[a]	Very common (34.1%)	0
	Rash[a]	Very common (20.3%)	0.6%
General disorders	Fatigue	Very common (21.3%)	1.7%
	Asthenia	Common (5.3%)	0.8%
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[a]	Very common (33.1%)	1.5%
	Arthralgia	Very common (19.1%)	0.7%

CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class; National Cancer Institute CTCAE, version 4.03.

[a] Adverse drug reactions (ADRs) are provided by MedDRA preferred term (PT) or by bundled terms:

- Leukopenia: Any PT contained within the MedDRA SMQ Haematopoietic leukopenia
- Abdominal pain: Any PT containing 'abdominal pain'
- Bruising: Any PT containing 'bruise', 'contusion', 'petechiae', or 'ecchymosis'
- Rash: Any PT containing 'rash'
- Musculoskeletal pain: Following PTs 'Back pain', 'Bone pain', 'Musculoskeletal chest pain', 'Musculoskeletal pain', 'Musculoskeletal discomfort', 'Myofascial pain syndrome', 'Neck pain', 'Pain in extremity', 'Myalgia', and 'Spinal pain'

Table II-10 Adverse Reactions With Clinical Consequences, Even Serious, but Occurring with a Low Frequency and Considered to be Acceptable in Relation to the Severity of the Indication Treated

MedDRA SOC	MedDRA Term	Overall Frequency (all CTCAE grades) (N=1040)	Frequency of CTCAE Grade ≥3 (N=1040)
Metabolism and nutrition disorders	Tumour lysis syndrome	Rare (0.5%)	0.4%

Risks common to other members of the pharmacological class

The currently available BTK inhibitor, ibrutinib, has off-target kinase activity across all tyrosine-protein kinase TEC-family kinases and all mammalian Src-family kinases, as well as Janus kinase 3, epidermal growth factor receptor, receptor tyrosine-protein kinase erbB-2, receptor tyrosine-protein kinase erbB-4, and B-lymphocyte kinase, which are structurally related to BTK (Byrd et al 2015). This off-target kinase activity may contribute to some of its reported pharmacological effects.

Table II-11 Risks for Drugs from Same Pharmacological Class Not Included as Risks or Important Risks

Risk ***(drug from same pharmacological class: risk type)***	**Incidence with CALQUENCE Mono HemMalig (N=1040)**		**Rationale for Not Including as a Risk or an Important Risk**
	All Grades n (%)	**Grade ≥3 n (%)**	
Ventricular tachyarrhythmia *(ibrutinib: important identified risk)*	1 (0.1)	1 (0.1)	Events of ventricular tachyarrhythmia were observed at very low frequency. Detailed review of reported event did not support a causal association with CALQUENCE. Based on review of the QTcF intervals and other ECG data from a Phase 1 thorough QT/QTc study conducted in 48 healthy adult subjects, and a cardiac substudy conducted as part of Phase 1/2 dose-escalation/expansion study in subjects with CLL and Richter

Table II-11 Risks for Drugs from Same Pharmacological Class Not Included as Risks or Important Risks

Risk ***(drug from same pharmacological class: risk type)***	**Incidence with CALQUENCE Mono HemMalig (N=1040)**		**Rationale for Not Including as a Risk or an Important Risk**
	All Grades n (%)	**Grade ≥3 n (%)**	
			syndrome, there was no significant effect of CALQUENCE on cardiac repolarisation or other relevant ECG parameters. Ventricular tachyarrhythmia is not considered to be a risk for CALQUENCE.
Hypertension *(ibrutinib: important identified risk)*	79 (7.6%)	36 (3.5%)	Although events of hypertension were observed, the event is common in the underlying population, including older subjects (worldwide prevalence is 3.4% to 72.5%, with prevalence in US general adult population of 27.1% in men and 30.1% in women [Kearney et al 2004]). Furthermore, there are various risk factors for the development of hypertension, which include tobacco use, alcohol consumption, increased intake of salt, low physical activity, obesity, and diabetes (Dhungana et al 2016). A review of vital signs data for shifts from baseline in comparison to maximum BP on study revealed that 60.5% of subjects showed a shift to a higher systolic BP and 51.3% showed a shift to a higher diastolic BP. This data, however, reflects isolated BP measurements and is not consistent with an actual diagnosis of hypertension. Additionally, isolated BP measurements are subject to variation based on various factors including physiology, responses to the environment, and lifestyle factors (Frazier 2000). In considering the overall prevalence of hypertension, its multifactorial aetiology, and the results of detailed analyses based on both AE data and BP values (vital signs data), a causal association between hypertension and CALQUENCE was not supported. In addition, it is anticipated that there would be minimal clinical impact on patients in relation to the severity of the indication treated. Hypertension is not considered to be a risk for CALQUENCE.
Teratogenicity/ embryofoetal toxicity *(ibrutinib: important potential risk)*	0	0	Nonclinical reproductive studies with CALQUENCE have not supported teratogenicity as an important risk for humans. The specificity of CALQUENCE for BTK compared to ibrutinib does not support there being a risk of teratogenicity. There has been one reported pregnancy in a subject exposed to CALQUENCE (first trimester exposure, CALQUENCE discontinued, followed to normal delivery with no associated adverse events). The SmPC includes recommendations that CALQUENCE should not be used during pregnancy and women

Table II-11 Risks for Drugs from Same Pharmacological Class Not Included as Risks or Important Risks

Risk ***(drug from same pharmacological class: risk type)***	**Incidence with CALQUENCE Mono HemMalig (N=1040)**		**Rationale for Not Including as a Risk or an Important Risk**
	All Grades n (%)	**Grade ≥3 n (%)**	
			of childbearing potential should be advised to avoid becoming pregnant while receiving CALQUENCE; breastfeeding mothers are advised not to breastfeed during treatment with CALQUENCE and for 2 days after receiving the last dose. Use in pregnant and breastfeeding population is not expected. Teratogenicity/embryofoetal toxicity is considered to be a potential risk but not considered an important potential risk for CALQUENCE.
Leukostasis *(ibrutinib: important identified risk)*	1 (0.1)	1 (0.1)	Leukostasis has been reported at a very low frequency. A single subject experienced leukostasis in the setting of leucocytosis, which was considered due to disease progression. Additionally, leukostasis has rarely been reported with ibrutinib treatment; isolated cases have occurred in the setting of disease progression or transformation (Barrientos et al 2019). Based on this data, leukostasis is not a common event seen in patients treated with BTK inhibitors, and of the few observed cases, the event is likely secondary to disease progression. Leukostasis is not considered to be a risk for CALQUENCE.
Interstitial lung disease (ILD) *(ibrutinib: important identified risk)*	10 (1.0)	3 (0.3)	Events of ILD, based on the MedDRA SMQ of ILD, have been reported at low frequency, most of which were low-grade (Grade 1-2) in severity. Of the reported events, detailed case reviews revealed various confounding factors for each event, thus making a drug-induced event of ILD unlikely in each case. Additional review of literature has shown that ILD/pneumonitis has been reported in patients who received tyrosine kinase inhibitors (Shah 2016); however, there has been no established mechanism between ILD and BTK inhibition specifically. ILD is not considered to be a risk for CALQUENCE.

Table II-11 Risks for Drugs from Same Pharmacological Class Not Included as Risks or Important Risks

Risk ***(drug from same pharmacological class: risk type)***	**Incidence with CALQUENCE Mono HemMalig (N=1040)**		**Rationale for Not Including as a Risk or an Important Risk**
	All Grades n (%)	**Grade ≥3 n (%)**	
DDI with CYP3A inhibitors and inducers *(ibrutinib: important potential risk)*	Not applicable		Effects of CYP3A inhibitors/inducers on ibrutinib: There was an increase in ibrutinib concentration following coadministration with the strong CYP3A inhibitor ketoconazole. Under fasted condition, ketoconazole increased ibrutinib dose-normalised AUC_{last} by 24-fold and C_{max} by 29-fold; the strong CYP3A inducer rifampin decreased ibrutinib C_{max} by 13-fold and AUC_{last} by 10-fold (de Jong et al 2015). Effects of CYP3A inhibitors/inducers on CALQUENCE: Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased CALQUENCE C_{max} and AUC by 3.7-fold and 5.1-fold in healthy subjects (N=17), respectively. Co-administration of a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased CALQUENCE C_{max} and AUC by 68% and 77% in healthy subjects (N=24), respectively. The SmPC includes recommendations to consider alternative therapies that do not strongly inhibit or induce CYP3A activity and patients taking strong CYP3A inhibitors with CALQUENCE should be monitored more closely for adverse reactions. As this effect has been described in the SmPC, use in this population is not expected and DDI is not considered to be a risk for CALQUENCE.

AE=adverse event; AUC=area under the curve; BP=blood pressure; BTK=Bruton tyrosine kinase; CLL=chronic lymphocytic leukaemia; CTCAE=Common Terminology Criteria for Adverse Events; DDI=drug-drug interaction; ECG=electrocardiogram; ILD=interstitial lung disease; MedDRA=Medical Dictionary for Regulatory Activities; QD=once daily; QT=time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; QTc=QT correction; QTcF=Fridericia's correction; SmPC=Summary of Product Characteristics; SMQ= Standardised MedDRA Queries; SOC=system organ class.

II.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Haemorrhage with or without association with thrombocytopenia

Risk-benefit impact

Haemorrhage can be serious, life-threatening, or fatal. As such, haemorrhage may lead to adverse outcomes that negatively impact the risk-benefit balance.

Important identified risk: Serious infections with or without association with neutropenia

Risk-benefit impact

Infections can be serious, life-threatening, or fatal. Some infections can result in treatment interruptions, which may potentially impact the benefit received by the patient.

Important identified risk: Second primary malignancy

Risk-benefit impact

Second primary malignancy (SPM) can be serious, life-threatening, or fatal, and lack of proper treatment may lead to outcomes that will negatively impact the risk-benefit balance. Early detection of SPM is important, as it can affect patient outcome.

Important identified risk: Atrial fibrillation/flutter

Risk-benefit impact

Atrial fibrillation/flutter can be a serious condition and lack of proper treatment may lead to outcomes (such as stroke and cardiac failure) that will negatively impact the risk-benefit balance.

Important potential risk: Cerebrovascular events

Risk-benefit impact

Cerebrovascular events can be serious, life-threatening, or fatal, and lack of proper treatment may lead to outcomes that will negatively impact the risk-benefit balance. However as potential risk the causality with CALQUENCE is not established.

Missing information: Long-term safety

Risk-benefit impact

Targeted cancer therapy with agents such as CALQUENCE, may be given for a long duration. Based on long-term risks for ibrutinib (a drug in the same pharmacological class) there is a possibility that the safety profile of CALQUENCE may be different in patients with long-term exposure.

The safety profile for long-term use will be derived from routine pharmacovigilance activities and from results of an ongoing Study D8220C00008.

Missing information: Use in patients with moderate-to-severe cardiac impairment

Risk-benefit impact

Considering the cardiovascular risks for ibrutinib (a drug in the same pharmacological class), there is a possibility that safety profile of CALQUENCE may be different when used in a population with significant cardiovascular disease.

The safety profile for this population will be derived from routine pharmacovigilance activities and from results of a planned cohort in an ongoing Study D8220C00008.

II.7.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

II.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks and important potential risks were analysed in the CALQUENCE monotherapy population, and the ABR, AO, AV, and AVO combination therapy populations. These populations are defined in Section II.3.

Safety findings for the pivotal study in R/R MCL (ACE-LY-004) (not presented separately but included in the CALQUENCE monotherapy population) were consistent with results for the overall CALQUENCE monotherapy population. Note that data for Study ACE-LY-004 were final in the EU RMP Version 5; thus, no new data are presented for R/R MCL.

II.7.3.1 Important Identified Risk: Haemorrhage With or Without Association With Thrombocytopenia

Potential Mechanisms

BTK is present on platelets and is required for collagen- or shear stress-induced platelet aggregation (Visco et al 2017). Long-term BTK inhibition is also associated with increased megakaryocytes and giant platelets in peripheral blood, potentially leading to additional platelet dysfunction.

Ex vivo experiments showed that ibrutinib at clinically achievable concentrations inhibited platelet signalling downstream of the collagen receptor glycoprotein VI and interfered with platelet adhesion on von Willebrand factor under arterial flow (Bye et al 2015, Levade et al 2014). Another study confirmed these data and found a correlation between the degree of BTK inhibition and the occurrence of clinical bleeding (Kamel et al 2015).

Evidence Source(s) and Strength of Evidence

Based on evidence that BTK inhibition is associated with platelet aggregation, there is a plausible mechanism of action for how CALQUENCE may lead to haemorrhage. Furthermore, in the CALQUENCE monotherapy population and in all 4 combination therapy populations, the reported rate of haemorrhage of any grade was very common and the reported rate of Grade ≥ 3 haemorrhage was common (per CIOMS-defined frequencies). Additionally, haemorrhage has been described with other BTK inhibitors.

Characterisation of the Risk

Table II-12 Frequency, Severity, and Outcomes: Haemorrhage

	CALQUENCE monotherapy (N = 1478) n (%)	Combination therapy			
		ABR (N = 297) n (%)	AO (N = 223) n (%)	AV (N = 291) n (%)	AVO (N = 284) n (%)
Haemorrhage [a]					
Frequency					
Any AE	681 (46.1)	84 (28.3)	113 (50.7)	94 (32.3)	86 (30.3)
With concurrent thrombocytopenia [b]	101 (14.8) [c]	16 (19.0) [c]	17 (15.0) [c]	15 (16.0)	21 (24.4)
With concurrent Grade ≥ 3 thrombocytopenia [b]	26 (3.8) [c]	3 (3.6) [c]	6 (5.3) [c]	0	4 (4.7) [c]
SAEs	53 (3.6)	4 (1.3)	5 (2.2)	3 (1.0)	5 (1.8)
Severity					
Grade 1-2	614 (41.5)	78 (26.3)	108 (48.4)	91 (31.3)	80 (28.2)
Grade ≥ 3	67 (4.5)	6 (2.0)	5 (2.2)	3 (1.0)	6 (2.1)
Outcome					
Fatal	2 (0.1)	0	0	0	0
Ongoing	220 (14.9)	22 (7.4)	34 (15.2)	5 (1.7)	8 (2.8)
Recovered/resolved	459 (31.1)	62 (20.9)	79 (35.4)	89 (30.6)	78 (27.5)
Major haemorrhage [d]					
Frequency					
Any AE	81 (5.5)	7 (2.4)	8 (3.6)	3 (1.0)	8 (2.8)
With concurrent thrombocytopenia [b]	11 (13.6) [e]	1 (14.3) [e]	2 (25.0) [e]	0	0
With concurrent Grade ≥ 3 thrombocytopenia [b]	6 (7.4) [e]	1 (14.3) [e]	2 (25.0) [e]	0	0

A subject with multiple severity grades for a given AE was counted only once under the maximum severity. Only treatment-emergent AEs were included.

[a] Haemorrhage events were identified using the SMQ Haemorrhages (excluding laboratory terms). [Note: includes bruising events.]
[b] Concurrent thrombocytopenia was defined as treatment-emergent thrombocytopenia based on laboratory values within 2 weeks prior to or on the same day of haemorrhage onset date.
[c] The denominator for percent is the total number of patients with any AE of haemorrhage.
[d] Major haemorrhage was defined as any haemorrhagic event that was serious, Grade ≥ 3, or CNS haemorrhage.
[e] The denominator for percent is the total number of patients with any AE of major haemorrhage.

Impact on Quality of Life

Non-serious, low-severity bleeding events may have no or little impact on the patient's quality of life. More severe haemorrhage can be associated with greater morbidity and mortality, as events may be serious, life-threatening, or fatal.

Risk Factors and Risk Groups

Patient Factors

General risk factors not specific to CALQUENCE include advanced age, comorbid medical conditions (eg, cerebrovascular disease, hepatic or renal disease, and diabetes mellitus), a history of bleeding (especially in the GI tract), and anaemia, and are predictive of subsequent bleeding complications (Shoeb and Fang 2013). Lower levels of von Willebrand factor activity and Factor VIII (Lipsky et al 2015) are also risks.

Preventability

The SmPC informs that serious haemorrhagic events, including fatal events, have been reported in patients treated with CALQUENCE monotherapy. In addition, the SmPC advises that patients receiving antithrombotic agents may be at increased risk of haemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. Consider the benefit-risk of withholding CALQUENCE for at least 3 days pre- and post-surgery.

Impact on the Risk-Benefit Balance of the Product

Haemorrhage impacts the risk-benefit balance of CALQUENCE because severe haemorrhage can be serious, life-threatening, or fatal.

Public Health Impact

As the impact is to the treated population only there is no public health impact.

II.7.3.2 Important Identified Risk: Serious Infections With or Without Association With Neutropenia

Potential Mechanisms

Inactivating mutations of the BTK are the cause of X-linked agammaglobulinaemia and lead to deficient development of B lymphocytes, thus causing hypogammaglobulinaemia, profoundly reduced levels of serum antibodies, and reduced levels of circulating B cells. BTK deficiency impairs B cell, monocytic, and dendritic cell functions, which leads to a markedly increased incidence and severity of infections, often causing even lethal complications. The importance of BTK in the defence against a variety of organisms such as bacteria, virus, and even fungi has been demonstrated nonclinically (Reinwald et al 2015). The chemokine SDF-1 induced activation of BTK and integrin-mediated adhesion and migration in response to SDF-1 or CXC motif chemokine ligand 13, as well as in vivo homing to lymphoid organs, was impaired in BTK-deficient (pre-)B cells (de Gorter et al 2007).

Evidence Source(s) and Strength of Evidence

There is a plausible mechanism of action between BTK and infections, based on nonclinical evidence examining the role of BTK in XLA patients. Furthermore, the reported rate of infections (both any grade and Grade ≥3) for patients in the CALQUENCE monotherapy population and all 4 combination therapy populations was very common (per CIOMS-defined frequencies). Additionally, infection has been described with other BTK inhibitors.

Infections due to hepatitis B virus reactivation and opportunistic infections have been reported. Also, progressive multifocal leukoencephalopathy has been reported in the CLL combination setting.

Characterisation of the Risk

Table II-13 Frequency, Severity, and Outcomes: Serious Infections With and Without Neutropenia

	CALQUENCE monotherapy (N = 1478) n (%)	Combination therapy			
		ABR (N = 297) n (%)	AO (N = 223) n (%)	AV (N = 291) n (%)	AVO (N = 284) n (%)
Frequency					
Any AE of infection	1098 (74.3)	232 (78.1)	171 (76.7)	148 (50.9)	153 (53.9)
Any AE with concurrent neutropenia [a]	111 (10.1) [b]	67 (28.9) [b]	32 (18.7) [b]	42 (28.4) [b]	51 (33.3) [b]
Any AE with concurrent Grade ≥3 neutropenia [a]	59 (5.4) [b]	41 (17.7) [b]	14 (8.2) [b]	13 (8.8) [b]	25 (16.3) [b]
Any AE with concurrent neutropenia SAE [a]	32 (2.9) [b]	24 (10.3) [b]	8 (4.7) [b]	8 (5.4) [b]	16 (10.5) [b]
Any SAE of infection	374 (25.3)	120 (40.4)	50 (22.4)	36 (12.4)	67 (23.6)
Severity					
Grade 1-2 infection	708 (47.9)	110 (37.0)	119 (53.4)	112 (38.5)	86 (30.3)
Grade ≥ 3 infection	390 (26.4)	122 (41.1)	52 (23.3)	36 (12.4)	67 (23.6)
Grade ≥ 3 AE with concurrent neutropenia [a]	30 (7.7) [c]	23 (18.9) [c]	8 (15.4) [c]	6 (16.7) [c]	15 (22.4) [c]
Grade ≥ 3 AE with concurrent Grade ≥3 neutropenia [a]	18 (4.6) [c]	14 (11.5) [c]	3 (5.8) [c]	1 (2.8) [c]	8 (11.9) [c]
Grade ≥ 3 AE with concurrent neutropenia SAE [a]	29 (7.4) [c]	22 (18.0) [c]	8 (15.4) [c]	6 (16.7) [c]	12 (17.9) [c]
Outcome, any AE of infection					
Fatal	58 (3.9)	31 (10.4)	3 (1.3)	9 (3.1)	16 (5.6)
Ongoing	99 (6.7)	16 (5.4)	21 (9.4)	5 (1.7)	3 (1.1)
Recovered/resolved	941 (63.7)	185 (62.3)	147 (65.9)	134 (46.0)	134 (47.2)

Infection events were identified using the Infections and Infestations SOC. A subject with multiple severity grades for a given AE was counted only once under the maximum severity. Only treatment-emergent AEs were included.

[a] Concurrent neutropenia was defined as treatment-emergent neutropenia based on laboratory values within 2 weeks prior to or on the same day of infection onset date.

[b] Denominator is the number of patients with any AE of infection.

[c] Denominator is the number of patients with any Grade ≥ 3 AE of infection.

Impact on Quality of Life

Mild infections may have minimal impact on the patient. More severe or serious infections can be debilitating for patients and require intensive medical support. Severe infections in immunocompromised patients can be fatal.

Risk Factors and Risk Groups

General risk factors not specific to CALQUENCE are divided into those that are host-associated and those that are treatment-associated. Host-associated factors include underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, psychological stress (Zembower 2014), and the underlying haematological malignancy. Treatment-associated factors include surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures.

Preventability

The SmPC informs that serious infections, including fatal events, have been reported in patients treated with CALQUENCE monotherapy. In addition, the SmPC advises to consider prophylaxis in patients who are at increased risk for opportunistic infections and to monitor patients for signs and symptoms of infection and treat as medically appropriate.

Impact on the Risk-Benefit Balance of the Product

Infections may impact the benefit-risk balance of CALQUENCE. Serious infections have been reported in patients who received CALQUENCE, and some serious infections have been life-threatening/fatal. Some infections may result in hospitalisations and possible interruptions in treatment with CALQUENCE, which may potentially impact the benefit received by the patient (CIOMS 2020).

Public Health Impact

As the impact is to the treated population only, there is no public health impact.

II.7.3.3 Important Identified Risk: Second Primary Malignancy

Potential Mechanisms

B cells have dual role in promoting and inhibiting cancer progression depending on the different B-cell subpopulation (Visco et al 2017, Wang et al 2016). Eliminating B cells, as with BTK inhibitors, may potentially promote cancer progression by removing the B-cell cancer-inhibitory effect and their role in anti-tumour immune surveillance.

Evidence Source(s) and Strength of Evidence

Based on evidence that eliminating B cells, as with BTK inhibitors, may potentially promote cancer progression, there is a plausible mechanism of action for how CALQUENCE may lead to SPM.

In the CALQUENCE monotherapy, ABR combination therapy, and AO combination therapy populations, the reported rates of SPM (per CIOMS-defined frequencies) were very common and in the AV and AVO fixed-duration combination therapy populations, the reported rates of SPMs were common. Results from 2 pivotal Phase III studies for CLL (ACE-CL-007 and ACE-CL-309) demonstrated higher incidence rates of SPM (skin and non-skin) in the CALQUENCE monotherapy arm as compared with rates in the comparator arms. In the pivotal study for previously untreated MCL (ACE-LY-308), the incidence rate of SPMs was slightly higher in the ABR arm than in the PBR comparator arm, and the incidence rate excluding non-melanoma skin SPMs in the ABR arm was similar to the incidence rate in the PBR comparator arm.

It has been reported in literature that the incidence of SPM in patients treated with BTK inhibitors for CLL was increased relative to the general population (Bond et al 2019). Additionally, SPM has been described with other BTK inhibitors.

Characterisation of the Risk

Table II-14 Frequency, Severity, and Outcomes: Second Primary Malignancy

	CALQUENCE monotherapy (N = 1478) n (%)	Combination therapy			
		ABR (N = 297) n (%)	AO (N = 223) n (%)	AV (N = 291) n (%)	AVO (N = 284) n (%)
Frequency					
Any SPM	260 (17.6)	53 (17.8)	34 (15.2)	15 (5.2)	12 (4.2)
Non-melanoma skin	146 (9.9)	33 (11.1)	20 (9.0)	9 (3.1)	5 (1.8)
Excluding non-melanoma skin	143 (9.7)	29 (9.8)	17 (7.6)	8 (2.7)	7 (2.5)
SAEs	105 (7.1)	22 (7.4)	11 (4.9)	8 (2.7)	7 (2.5)
Severity					
Grade 1-2	158 (10.7)	31 (10.4)	22 (9.9)	10 (3.4)	7 (2.5)
Grade ≥ 3	99 (6.7)	22 (7.4)	11 (4.9)	5 (1.7)	5 (1.8)
Outcome					
Fatal	17 (1.2)	2 (0.7)	2 (0.9)	0	0
Ongoing	64 (4.3)	13 (4.4)	10 (4.5)	0	2 (0.7)
Recovered/resolved	179 (12.1)	38 (12.8)	22 (9.9)	15 (5.2)	10 (3.5)

SPM events were identified using the following SMQs: Haematological malignant tumours [narrow], Non-haematological malignant tumours [narrow], Malignant lymphomas [narrow], and Myelodysplastic syndrome [narrow]. A subject with multiple severity grades for a given AE was counted only once under the maximum severity. Only treatment-emergent AEs were included.

Impact on Quality of Life

SPM may have low impact on patient quality of life, when low-grade and easily treated, such as small localised skin cancers amenable to curative resection as an outpatient procedure. However, SPM may involve long-term debilitating and life-threatening conditions that can require patients to undergo further treatments and are associated with poor long-term survival.

Risk Factors and Risk Groups

Patient Factors

General risk factors not specific to CALQUENCE include age (André et al 2004, Moser et al 2006). Incidence of SPM in patients treated with BTK inhibitors for CLL was increased relative to the general population (Bond et al 2019).

Additive or Synergistic Factors

Use of any type of chemotherapy alone was associated with higher risk for secondary malignant neoplasms. A similar result was observed in the sub-analysis on patients treated only with alkylating agents, while the pooled relative risk of secondary malignant neoplasms for patients who underwent treatment with CHOP, or CHOP-like or radiotherapy alone, was raised but not statistically significant. A combined modality of treatment was significantly associated with the risk for overall secondary malignant neoplasms but not for solid tumours (Pirani et al 2011).

Preventability

The SmPC informs that SPMs, including skin carcinomas, have been reported in patients treated with CALQUENCE monotherapy. The most frequent SPM was skin cancer. In addition, the SmPC advises on the need to monitor patients for appearance of skin cancer.

Impact on the Risk-Benefit Balance of the Product

SPMs can be serious, life-threatening, or fatal and lack of proper treatment may lead to serious outcomes that will negatively impact the risk-benefit balance.

Public Health Impact

As the impact is to the treated population only, there is no public health impact.

II.7.3.4 Important Identified Risk: Atrial Fibrillation/Flutter

Potential Mechanisms

The aetiology of atrial fibrillation/flutter remains largely unknown (Falchi et al 2016). Studies with ibrutinib showed that one of the pathways regulated by BTK and Tec Kinase is the PI3K-protein kinase B (Akt) pathway, which mediates cardiac protection under stress conditions (McMullen et al 2007, McMullen et al 2014). In rat ventricular myocytes, therapeutic doses of ibrutinib caused reduced PI3K protein expression and Akt activation (McMullen et al 2014). Evidence of direct inhibition of PI3K activity by ibrutinib, direct involvement of BTK in the PI3K-Akt pathway, or direct cellular effects of ibrutinib on myocytes, however, is lacking (Byrd et al 2015). CALQUENCE has minimal off-target effect including on Tec and interleukin-2-inducible T-cell kinases. Hence, the mechanism underlying atrial fibrillation/flutter events for CALQUENCE is currently unknown.

Evidence Source(s) and Strength of Evidence

In Phase III pivotal studies for CLL (ACE-CL-007 and ACE-CL-309), the incidence of atrial fibrillation/flutter events was higher in the CALQUENCE monotherapy arm as compared with the comparator arm. Similarly, in the pivotal study for ABR combination therapy in previously untreated MCL (ACE-LY-308), the incidence of atrial fibrillation/flutter events was higher in the ABR group as compared with the PBR group. In the pivotal study for previously untreated CLL (ACE-CL-311), the incidence of atrial fibrillation (all grades) was significantly lower in the AV and AVO arms compared with CALQUENCE monotherapy. The reported rates of atrial fibrillation/flutter for patients in the CALQUENCE monotherapy population and the ABR, AO, and AVO combination therapy populations were common (per CIOMS-defined frequencies), and the reported rate in the AV combination therapy population was uncommon. Additionally, atrial fibrillation/flutter has been described with other BTK inhibitors.

Characterisation of the Risk

Table II-15 Frequency, Severity, and Outcomes: Atrial Fibrillation/Atrial Flutter

	CALQUENCE monotherapy (N = 1478) n (%)	Combination therapy			
		ABR (N = 297) n (%)	AO (N = 223) n (%)	AV (N = 291) n (%)	AVO (N = 284) n (%)
Frequency[a]					
Any AE	109 (7.4)	20 (6.7)	7 (3.1)	2 (0.7)	6 (2.1)
SAEs	25 (1.7)	9 (3.0)	3 (1.3)	0	1 (0.4)
Severity					
Grade 1-2	75 (5.1)	8 (2.7)	5 (2.2)	1 (0.3)	4 (1.4)
Grade ≥ 3	34 (2.3)	12 (4.0)	2 (0.9)	1 (0.3)	2 (0.7)

Table II-15 Frequency, Severity, and Outcomes: Atrial Fibrillation/Atrial Flutter

	CALQUENCE monotherapy (N = 1478) n (%)	Combination therapy			
		ABR (N = 297) n (%)	AO (N = 223) n (%)	AV (N = 291) n (%)	AVO (N = 284) n (%)
Outcome					
Fatal	0	0	0	0	0
Ongoing	48 (3.2)	5 (1.7)	5 (2.2)	2 (0.7)	1 (0.4)
Recovered/resolved	61 (4.1)	15 (5.1)	2 (0.9)	0	5 (1.8)

Events of atrial fibrillation and atrial flutter were identified using the corresponding MedDRA PTs. A subject with multiple severity grades for a given AE was counted only once under the maximum severity. Only treatment-emergent AEs were included.

Impact on Quality of Life

While atrial fibrillation/flutter is rarely life-threatening in itself, if left untreated it can lead to other sequelae including stroke or heart failure, which can be fatal or result in a major reduction in quality of life.

Risk Factors and Risk Groups

Patient Factors

General risk factors not specific to CALQUENCE include advancing age, male sex, diabetes mellitus, hypertension, valvular disease, myocardial infarction, heart failure, obesity, elevated inflammatory marker concentrations, hypoxia, hypercapnia, acidosis, electrolyte disturbances, autonomic dysfunction, and PR-interval prolongation (Ferreira et al 2015, Rienstra et al 2012). In recent years, increasing data have been reported supporting the notion that atrial fibrillation/flutter in the general population is heritable (Rienstra et al 2012). Several classes of cancer chemotherapeutic agents appear to be associated with cardiac arrhythmias like anthracyclines (rate of 2% to 10% of cases), melphalan (rate of 7% to 12% of cases), and IL-2 (Guglin et al 2009).

Preventability

The SmPC informs that atrial fibrillation/flutter have been reported in patients treated with CALQUENCE monotherapy, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. In addition, the SmPC advises on the need to monitor patients for symptoms (eg, palpitations, dizziness, syncope, chest pain) of atrial fibrillation/flutter and obtain an ECG as appropriate.

Impact on the Risk-Benefit Balance of the Product

Atrial fibrillation/flutter can be a serious condition and lack of proper treatment may lead to outcomes (such as stroke and cardiac failure) that will negatively impact the risk-benefit balance. In addition, the SmPC advises on the need to monitor patients for signs and symptom of atrial fibrillation/flutter and treat as medically appropriate.

Public Health Impact

As the impact is to the treated population only, there is no public health impact.

II.7.3.5 Important Potential Risk: Cerebrovascular Events

Potential Mechanisms

The current mechanism for the development of cardiovascular events in association with the use of BTK inhibitors to include CALQUENCE is not confirmed.

Evidence Source(s) and Strength of Evidence

Cerebrovascular events have been observed with ibrutinib but are not considered causally associated (not listed in section 4.8 of SmPC). Cerebrovascular events have been observed with CALQUENCE; however, a causal relationship seems unlikely, since in most cases other significant confounding factors were present as well as the long time to event onset in some cases.

Characterisation of the Risk

Table II-16 Frequency, Severity, and Outcomes: Cerebrovascular Events

	CALQUENCE monotherapy (N = 1478) n (%)	Combination therapy			
		ABR (N = 297) n (%)	AO (N = 223) n (%)	AV (N = 291) n (%)	AVO (N = 284) n (%)
Frequency					
Any AE	37 (2.5)	7 (2.4)	2 (0.9)	1 (0.3)	1 (0.4)
SAEs	17 (1.2)	2 (0.7)	2 (0.9)	0	0
Severity					
Grade 1-2	25 (1.7)	4 (1.3)	0	1 (0.3)	1 (0.4)
Grade ≥3	12 (0.8)	3 (1.0)	2 (0.9)	0	0
Outcome					
Fatal	5 (0.3)	0	0	0	0
Ongoing	13 (0.9)	2 (0.7)	0	1 (0.3)	0
Recovered/resolved	19 (1.3)	5 (1.7)	2 (0.9)	0	1 (0.4)

Cerebrovascular events were identified using the SMQ Ischaemic central nervous system vascular conditions [narrow]. A subject with multiple severity grades for a given AE was counted only once under the maximum severity. Only treatment-emergent AEs were included.

Impact on Quality of Life

Cerebrovascular events can be fatal or result in a major reduction in quality of life.

Risk Factors and Risk Groups

Many general risk factors for cerebrovascular events have been described, some of them are biological traits such as age and sex, some of them are physiological or pathological characteristics such as high blood pressure, serum cholesterol and fibrinogen and some are behavioural such as smoking, diet, alcohol consumption, and physical inactivity; some are social characteristics such as education, social class and ethnicity; and some are environmental factors that may be physical (temperature, altitude), geographical, or psychosocial. In addition, medical factors including previous TIA or stroke, ischaemic heart disease, atrial fibrillation, and glucose intolerance, all increase the risk of stroke (Marmot and Poulter 1992).

Overall, atrial fibrillation (an important identified risk for CALQUENCE) may be associated with higher risk of cardiovascular events.

Preventability

There are no specific preventative actions for cerebrovascular events with CALQUENCE but general routine prevention measures should be applied.

Impact on the Risk-Benefit Balance of the Product

Cerebrovascular events can be serious, life-threatening, or fatal, and lack of proper treatment may lead to outcomes that will negatively impact the risk-benefit balance. However, as potential risk the causality with CALQUENCE is not established.

Public Health Impact

As the impact is to the treated population only, there is no public health impact.

II.7.3.6 Important Potential Risk: Hepatotoxicity

Potential Mechanisms

Several mechanisms have been proposed, including immune mechanisms due to genetic variants, oxidative damage, direct hepatotoxicity via mitochondrial dysfunction, and metabolic bioactivation of small molecule kinase inhibitors by CYP enzymes and generating chemically reactive products (Atallah et al 2021).

Evidence Source(s) and Strength of Evidence

In January 2021, there were 2 case reports of Potential Hy's Law. After a comprehensive review of hepatotoxicity events, 1 case of Hy's Law was confirmed. In addition, hepatotoxicity has been observed in clinical studies; in the majority of cases, there were no clinical symptoms and confounding factors, but in a minority, there was positive dechallenge and/or rechallenge.

In the pivotal study for previously untreated MCL (ACE-LY-308), a slight imbalance was noted between arms for transaminase elevations (ALT/AST increased) (see Section 12.2.3.4, ACE-LY-308 CSR). These transaminase elevations were not accompanied by symptoms and signs of liver injury or clinically significant increases of serum bilirubin. There is insufficient evidence that these transaminase elevations are associated with overt liver injury.

Characterisation of the Risk

Table II-17 Frequency, Severity, and Outcomes: Hepatotoxicity

	CALQUENCE monotherapy (N = 1478) n (%)	Combination therapy			
		ABR (N = 297) n (%)	AO (N = 223) n (%)	AV (N = 291) n (%)	AVO (N = 284) n (%)
Frequency					
Any AE	87 (5.9)	42 (14.1)	15 (6.7)	17 (5.8)	19 (6.7)
SAEs	6 (0.4)	5 (1.7)	2 (0.9)	2 (0.7)	3 (1.1)
Severity					
Grade 1-2	56 (3.8)	22 (7.4)	7 (3.1)	7 (2.4)	11 (3.9)
Grade ≥ 3	31 (2.1)	20 (6.7)	8 (3.6)	10 (3.4)	8 (2.8)
Outcome					
Fatal	1 (0.1)	0	0	0	0
Ongoing	27 (1.8)	5 (1.7)	0	0	0
Recovered/resolved	59 (4.0)	37 (12.5)	15 (6.7)	17 (5.8)	19 (6.7)

Hepatotoxicity events were identified using the following SMQs: Hepatic failure, Fibrosis, and Cirrhosis and Other Liver Damage-related Conditions [narrow]; Hepatitis, Non-infectious [narrow], and Liver-related Investigations Signs [narrow]. A subject with multiple severity grades for a given AE was counted only once under the maximum severity. Only treatment-emergent AEs were included.

Characterisation of the patients who experienced events of Potential Hy's Law in January 2021 are included below:

The first Potential Hy's Law event involved a 59-year-old male with a rapid elevation in AST, ALT, and total bilirubin elevation < 2 months after starting CALQUENCE. The subject had a

positive dechallenge/rechallenge for CALQUENCE, and serology testing ruled out viral infection aetiologies. However, this case was confounded by the subject's past medical history of Gilbert's syndrome and more than 10 years of heavy alcohol use of 500 mL consumed per day. This case was reclassified as an event of hepatic enzyme increased as the subject's baseline bilirubin was high and did not meet the definition of Potential Hy's Law. The transaminase elevations were considered causally related per the investigator.

The second Potential Hy's Law event involved an 87-year-old female with a rapid elevation of AST, ALT, and total bilirubin approximately 2 months after starting CALQUENCE. This subject had a positive dechallenge of CALQUENCE, and her laboratory elevations returned to baseline levels after stopping treatment with CALQUENCE with no other intervention. Despite the subject's advanced age, all serology testing and alternative aetiologies did not explain the rapid transaminase elevation while taking CALQUENCE. The event was considered to be causally related per the investigator.

Impact on Quality of Life

The development of hepatotoxicity, if left untreated, can lead to sequelae such as acute liver failure. This could result in a decreased quality of life due to the potential need for liver transplantation or can lead to a fatal outcome.

Risk Factors and Risk Groups

Risk factors for the development of hepatotoxicity that are non-specific to CALQUENCE include increasing age, the female gender, chronic HBV and HCV, and HIV. Additional risk factors include the daily dose and metabolism of the offending drug, and the potential to develop toxic reactive metabolites secondary to hepatic metabolism (Chalasani and Bjornsson 2010). Chronic alcohol consumption, underlying nonalcoholic fatty liver disease, and concomitant medication use, such as some nonsteroidal anti-inflammatory drugs, antibiotics, and seizure medications may increase the risk for a patient to develop hepatotoxicity (Sandhu and Navarro 2020).

Preventability

Adherence to recommended general dose modification guidance for adverse reactions (SmPC Section 4.2) would allow for the detection and appropriate management of more severe events of hepatotoxicity and prevent more severe liver injury.

Impact on the Risk-Benefit Balance of the Product

Hepatotoxicity may result in increased toxicities and treatment interruption in patients, impacting the benefit/risk profile. If left untreated or undetected, hepatotoxicity could lead to more severe consequences such as hepatic failure and/or death (Christensen et al 2022).

Public Health Impact

Because the impact is to the treated population only, there is no public health impact.

II.7.3.7 Missing Information: Long-Term Safety

Evidence Source

In the CALQUENCE monotherapy population, 66.0% of patients had more than 24 months of CALQUENCE treatment. In these patients, the safety profile of CALQUENCE was not different from the general established safety profile.

Late-onset cardiovascular AEs have been reported with use of ibrutinib and other BTK inhibitors (Christensen et al 2022, Gülsaran et al 2019, Ng et al 2023, Quartermaine et al 2023), which may be given for durations of more than 41 months (Byrd et al 2019). Considering the cardiovascular risks for a drug in the same pharmacological class, there is a possibility that the safety profile of CALQUENCE may be different in patients with long-term exposure (Bond et al 2020).

The long-term risk of SPM has not been well characterised.

Population in Need of Further Characterisation

This utilisation will be further characterised from routine pharmacovigilance activities and from results of an ongoing study, ACE-CL-007.

II.7.3.8 Missing Information: Use in Patients With Moderate to Severe Cardiac Impairment

Evidence Source

Fatal and serious cardiac arrhythmia have occurred with ibrutinib therapy (Imbruvica USPI). Considering the cardiovascular risks for a drug in the same pharmacological class, there is a possibility that safety profile of CALQUENCE may be different when used in a population with significant cardiovascular disease. In addition, patients with haematological malignancies may have cardiovascular comorbidities (Park et al 2019).

Population in Need of Further Characterisation

This utilisation will be further characterised from routine pharmacovigilance activities and from results of planned study D8223C00016.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the Safety Concerns

Table II-18 Summary of Safety Concerns

Important identified risks	Haemorrhage with or without association with thrombocytopenia Serious infections with or without association with neutropenia Second primary malignancy Atrial fibrillation/flutter
Important potential risks	Cerebrovascular events Hepatoxicity
Missing information	Long-term safety Use in patients with moderate to severe cardiac impairment

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific Adverse Reaction Follow-up Questionnaires

Specific AE follow-up questionnaires for the following safety concerns are provided in Annex 4 (Section VII.4):

- Cerebrovascular accidents (CVA)
- Major haemorrhages
- Hepatotoxicity

Follow-up questionnaires will be used to facilitate the post-marketing safety data collection for the above safety concerns. The purpose is to collect additional information related to the history of these events, which will allow for more accurate assessment of the post-marketing safety profile of CALQUENCE. The questionnaire will be sent as follow-up to the healthcare professionals for respective reported events that are coded to the MedDRA PTs for each safety concern.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Study ACE-CL-007

Study Short Name and Title

A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination With Obinutuzumab, and ACP-196 Monotherapy in Subjects With Previously Untreated Chronic Lymphocytic Leukemia

Rationale

This randomised controlled Phase III study in previously untreated patients with CLL is designed to determine whether treatment with CALQUENCE in combination with obinutuzumab (Arm B) results in a clinically significant improvement in PFS as compared with treatment with obinutuzumab in combination with chlorambucil (Arm A), and whether treatment with CALQUENCE monotherapy (Arm C) results in a clinically significant improvement in PFS as compared with treatment with Arm A.

Study Objectives

- Primary objective: To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with acalabrutinib in combination with obinutuzumab (Arm B) based on IRC assessment of PFS per IWCLL 2008 criteria in subjects with previously untreated CLL.
- Secondary objectives:
  - To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) based on IRC assessment of PFS per IWCLL 2008 criteria.
  - To compare obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib plus obinutuzumab (Arm B), and obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) in terms of:
    - IRC-assessed objective response rate per IWCLL 2008 criteria;
    - Time to next treatment (defined as the time from randomisation to institution of non-protocol-specified treatment for CLL); and
    - Overall survival.
- Safety objective: Incidence of AEs, including AEs, ECIs, and AESIs, SAEs and changes in laboratory measurements.

Study Design and Study Populations

This randomised, multicentre (ie, approximately 200 global centres), open-label, 3-arm Phase III study is designed to evaluate the safety and efficacy of Arm A, Arm B, and Arm C in patients with previously untreated CLL.

Approximately 510 eligible patients will be randomised in a 1:1:1 ratio into 3 arms (n = 170 each) to receive either Arm A (obinutuzumab in combination with chlorambucil per the package inserts), Arm B (CALQUENCE 100 mg twice daily in combination with obinutuzumab per the package insert), or Arm C (CALQUENCE 100 mg twice daily).

Milestones:

The milestones listed below are for submission to EMA.

- Interim report …… Q3 2022 [submitted 30 September 2022]
- Final report submission …… Q1 2026

This study was amended from a duration of 4.5 years to up to 10 years in order to collect additional long-term safety information. The results from this ongoing Study ACE-CL-007 will be used to further characterise the missing information of long-term safety in patients treated with CALQUENCE.

D8223C00016

Study Short Name and Title

Acalabrutinib Monotherapy vs Investigator's Choice of Treatment in Patients With Chronic Lymphocytic Leukemia and Moderate to Severe Cardiac Impairment

Rationale

CLL is the most prevalent adult leukaemia in Europe and the Western societies (Yao et al 2022). As of 2019, the global incidence of CLL was over 100,000 cases with an estimated 200,000 people with CLL living in the US alone (SEER 2024). The median age at diagnosis for CLL is ~70 years (American Society of Clinical Oncology 2024). While the prevalence of people with both CLL and cardiovascular disease is unreported, patients with CLL are likely to have at least the same risk of cardiovascular disease as the general population (Park et al 2019), estimated as 75% in people between 60 and 79 years of age and 86% in those > 80 years (Rodgers et al 2019).

BTK inhibitors are better tolerated than chemoimmunotherapy in patients with CLL; however, serious and fatal cardiac arrhythmias beyond atrial fibrillation have occurred with ibrutinib and have limited its use in cardiac-impaired patients (Imbruvica SmPC). The second generation, more selective BTK inhibitor CALQUENCE has shown a lower incidence of atrial fibrillation and cardiac adverse events (AEs) than ibrutinib (Byrd et al 2021). A review of the safety data for CALQUENCE suggests that it is well tolerated in patients with risk factors for developing cardiovascular diseases at screening, yet the safety profile of CALQUENCE in CLL patients with significant cardiovascular diseases or with moderate to severe cardiac impairment has not been established.

Study Objectives

- Primary objective: To evaluate the safety and tolerability of acalabrutinib monotherapy vs investigator's choice of treatment in patients with treatment-naïve or R/R CLL and moderate to severe cardiac impairment.
- Secondary objective: To evaluate the extent and duration of tumour response and survival after acalabrutinib vs investigator's choice of treatment in patients with treatment-naïve or R/R CLL and moderate to severe cardiac impairment.

Study Design and Study Population

Approximately 60 eligible patients will be randomised in a 1 to 1 ratio to Arm A (CALQUENCE monotherapy, n = 30) or Arm B (investigator's choice of treatment, n = 30). Randomisation will be stratified by LVEF > 40% vs ≤ 40%.

The target population of interest is patients with CLL and moderate to severe cardiac impairment.

Randomisation will be stratified by LVEF > 40% vs ≤ 40% to stratify for moderate and severe cardiac impairment, which for this study are defined as follows: severe cardiac impairment in those with LVEF ≤ 40% and moderate cardiac impairment in those with LVEF ≥ 40% to < 50%.

Milestones

The milestones listed below are for submissions to EMA.

- Protocol submission …….. April 2024 [submitted 04 April 2024]
- Final report submission …… Q4 2029

Results from the planned study D8223C00016 will be used to characterise the missing information of safety of CALQUENCE in CLL patients with moderate to severe cardiac impairment.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table III-1 Ongoing and Planned Additional Pharmacovigilance Activities

Study & status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
ACE-CL-007 Ongoing	The primary objective of this study is to evaluate the efficacy and safety of CALQUENCE in treatment-naïve CLL patients (as monotherapy or combination therapy with obinutuzumab).	Long-term safety including SPM	Interim report	Q3 2022 [submitted 30Sep2022]
			Final report	Q1 2026
D8223C00016	The primary objective is this study is to evaluate the safety and tolerability of acalabrutinib monotherapy vs investigator's choice of treatment in patients	Safety in patients with pre-existing moderate to severe	Protocol submission	Apr2024 [a] [submitted 04Apr2024]
			Final report	Q4 2029

Table III-1 Ongoing and Planned Additional Pharmacovigilance Activities

Study & status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	with treatment-naïve or R/R CLL and moderate to severe cardiac impairment.	cardiac impairment		

[a] Submitted to Clinical Trial Regulation (EU) No 536/2014.

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Table V-1 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Haemorrhage with or without association with thrombocytopenia (important identified risk)	**Routine risk communication**: SmPC section(s) 4.4 and 4.8
Serious infections with or without association with neutropenia (important identified risk)	**Routine risk communication**: SmPC section(s) 4.4 and 4.8
Second primary malignancy (Important identified risk)	**Routine risk communication**: SmPC section(s) 4.4 and 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4: Monitor patients for appearance of skin cancer.
Atrial fibrillation/flutter (important identified risk)	**Routine risk communication**: SmPC section(s) 4.4 and 4.8
Cerebrovascular events (important potential risk)	None

Table V-1 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Hepatotoxicity (important potential risk)	**Routine risk communication:** SmPC section 4.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.2: It is not recommended to administer CALQUENCE in patients with severe hepatic impairment (Child-Pugh C or total bilirubin > 3 times ULN and any AST).
Long-term safety (missing information)	None
Use in patients with moderate to severe cardiac impairment (missing information)	**Routine risk communication:** SmPC section 4.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.2: Patients with severe cardiovascular disease were excluded from CALQUENCE clinical studies

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Haemorrhage with or without association with thrombocytopenia	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction
Serious infections with or without association with neutropenia	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8	None
Second primary malignancy	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8	Additional pharmacovigilance activities: Submission of final study report for ACE-CL-007

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Atrial fibrillation/flutter	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8	None
Cerebrovascular events	None	Routine pharmacovigilance activities beyond adverse event reporting and signal detection: AE follow-up form for adverse reaction
Hepatotoxicity	**Routine risk communication:** SmPC section 4.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction
Long-term safety	None	Additional pharmacovigilance activities: Study ACE-CL-007
Use in patients with moderate to severe cardiac impairment	**Routine risk communication:** SmPC section 4.2	Additional pharmacovigilance activities: Study D8223C00016

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR CALQUENCE (ACALABRUTINIB)

This is a summary of the Risk Management Plan (RMP) for CALQUENCE. The RMP details important risks of CALQUENCE, how these risks can be minimised, and how more information will be obtained about CALQUENCE risks and uncertainties (missing information).

The CALQUENCE Summary of Product Characteristics (SmPC) and package leaflet for CALQUENCE give essential information to healthcare professionals and patients on how CALQUENCE should be used.

This summary of the RMP for CALQUENCE should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current risks will be included in updates to the CALQUENCE RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

CALQUENCE is authorised for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL) (see SmPC for full indications). CALQUENCE contains acalabrutinib as the active substance and it is given orally by capsule or tablet.

Further information about the evaluation of CALQUENCE's benefits can be found in CALQUENCE's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage. <*link to the EPAR summary landing page*>

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of CALQUENCE, together with measures to minimise such risks and the proposed studies for learning more about the risks of CALQUENCE, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of CALQUENCE is not yet available, it is listed under 'missing information' below.

VI.2.1 List of Important Risks and Missing Information

Important risks of CALQUENCE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely

administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CALQUENCE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table VI-1 List of Important Risks and Missing Information

Important identified risks	Haemorrhage with or without association with thrombocytopenia Serious infections with or without association with neutropenia Second primary malignancy Atrial fibrillation/flutter
Important potential risks	Cerebrovascular events Hepatoxicity
Missing information	Long-term safety Use in patients with moderate to severe cardiac impairment

VI.2.2 Summary of Important Risks

Table VI-2 Important Identified Risks

Important Identified Risk: Haemorrhage With or Without Association With Thrombocytopenia	
Evidence for linking the risk to the medicine	Based on evidence that BTK inhibition is associated with platelet aggregation, there is a plausible mechanism of action for how CALQUENCE may lead to haemorrhage. Furthermore, in the CALQUENCE monotherapy population and in all 4 combination therapy populations, the reported rate of haemorrhage of any grade was very common and the reported rate of Grade ≥ 3 haemorrhage was common (per CIOMS-defined frequencies). Additionally, haemorrhage has been described with other BTK inhibitors. Infections due to hepatitis B virus reactivation and opportunistic infections have been reported. Also, progressive multifocal leukoencephalopathy has been reported in the CLL combination setting.
Risk factors and risk groups	**Patient factors** Advanced age, comorbid medical conditions (eg, cerebrovascular disease, hepatic or renal disease, and diabetes mellitus), a history of bleeding (especially in the GI tract), and anaemia are predictive of subsequent bleeding complications (Shoeb and Fang 2013). Lower levels of von Willebrand factor activity, and factor VIII (Lipsky et al 2015) are also risks.

Table VI-2 Important Identified Risks

Risk minimisation measures	**Routine risk minimisation measures:** SmPC section(s) 4.4 and 4.8 **Additional risk minimisation measures:** None
Important Identified Risk: Serious Infections With or Without Association With Neutropenia	
Evidence for linking the risk to the medicine	There is a plausible mechanism of action between BTK and infections, based on nonclinical evidence examining the role of BTK in XLA patients. Furthermore, the reported rates of infections (both any grade and Grade ≥3) for patients in the CALQUENCE monotherapy and all 4 combination therapy populations were very common (per CIOMS-defined frequencies). Additionally, infection has been described with other BTK inhibitors.
Risk factors and risk groups	General risk factors not specific to CALQUENCE are divided into those that are host-associated and those that are treatment-associated. Host-associated factors include underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, psychological stress (Zembower 2014), and the underlying haematological malignancy. Treatment-associated factors include surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section(s) 4.4 and 4.8 **Additional risk minimisation measures:** None
Important Identified Risk: Second Primary Malignancy	
Evidence for linking the risk to the medicine	Based on evidence that eliminating B cells, as with BTK inhibitors, may potentially promote cancer progression, there is a plausible mechanism of action for how CALQUENCE may lead to SPM. In the CALQUENCE monotherapy, ABR combination therapy, and AO combination therapy populations, the reported rates of SPM were very common (per CIOMS-defined frequencies), and in the AV and AVO fixed-duration combination therapy populations, the reported rates of SPMs were common. Results from 2 pivotal Phase III studies for CLL (ACE-CL-007 and ACE-CL-309) demonstrated higher incidence rates of SPM (skin and non-skin) in the CALQUENCE monotherapy arm compared with rates in the comparator arms. In the pivotal study for previously untreated MCL (ACE-LY-308), the incidence rate of SPMs was slightly higher in the ABR arm than in the PBR comparator arm, and the incidence rate excluding non-melanoma skin SPMs in the ABR arm was similar to the incidence rate in the PBR comparator arm. It has been reported in the literature that the incidence of SPM in patients treated with BTK inhibitors for CLL was increased relative to the general population (Bond et al 2019). Additionally, SPM has been described with other BTK inhibitors.

Table VI-2 Important Identified Risks

Risk factors and risk groups	**Patient factors** Age is a risk factor for secondary malignancy (André et al 2004, Moser et al 2006). Incidence of SPM in patients treated with BTK inhibitors for CLL was increased relative to the general population (Bond et al 2019). **Additive or synergistic factors** Use of any type of chemotherapy alone was associated with higher risk for secondary malignant neoplasms. A similar result was observed in the sub-analysis on patients treated only with alkylating agents, while the pooled relative risk of secondary malignant neoplasms for patients who underwent treatment with CHOP, or CHOP-like or radiotherapy alone, was raised but not statistically significant. A combined modality of treatment was significantly associated with the risk for overall secondary malignant neoplasms but not for solid tumours (Pirani et al 2011).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section(s) 4.4 and 4.8 **Additional risk minimisation measures:** None
Important Identified Risk: Atrial Fibrillation/Flutter	
Evidence for linking the risk to the medicine	The mechanism underlying atrial fibrillation/flutter events is currently unknown. In 2 Phase III pivotal studies for CLL (ACE-CL-007 and ACE-CL-309), the incidence of atrial fibrillation/flutter events was higher in the CALQUENCE monotherapy arm as compared with the comparator arm. Similarly, in the pivotal study for ABR combination therapy in previously untreated MCL (ACE-LY-308), the incidence of atrial fibrillation/flutter events was higher in the ABR group as compared with the PBR group. In the pivotal study for previously untreated CLL (ACE-CL-311), the incidence of atrial fibrillation/flutter (all grades) was significantly lower in the AV and AVO arms compared with CALQUENCE monotherapy. The reported rates of atrial fibrillation/flutter for patients in the CALQUENCE monotherapy population and the ABR, AO, and AVO combination therapy populations were common (per CIOMS-defined frequencies), and the reported rate in the AV combination therapy population was uncommon. Additionally, atrial fibrillation/flutter has been described with other BTK inhibitors.
Risk factors and risk groups	General risk factors not specific to CALQUENCE include advancing age, male sex, diabetes mellitus, hypertension, valvular disease, myocardial infarction, heart failure, obesity, elevated inflammatory marker concentrations, hypoxia, hypercapnia, acidosis, electrolyte disturbances, autonomic dysfunction, and PR-interval prolongation (Ferreira et al 2015, Rienstra et al 2012). In recent years, increasing data have been reported supporting the notion that atrial fibrillation/flutter in the general population is heritable (Rienstra et al 2012). Several classes of cancer chemotherapeutic agents appear to be associated with cardiac arrhythmias

Table VI-2 Important Identified Risks

	like anthracyclines (rate of 2% to 10% of cases), melphalan (rate of 7% to 12% of cases), and IL-2 (Guglin et al 2009).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section(s) 4.4 and 4.8 **Additional risk minimisation measures:** None

ABR = acalabrutinib + bendamustine + rituximab; AO = acalabrutinib + obinutuzumab; AV = acalabrutinib + venetoclax; AVO = acalabrutinib + venetoclax + obinutuzumab; BTK = Bruton tyrosine kinase; CHOP = cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin), and prednisolone; CIOMS = Council for International Organizations of Medical Sciences; CLL = chronic lymphocytic leukaemia; GI = gastrointestinal; IL-2 = interleukin 2; MCL = mantle cell lymphoma; PBR = placebo + bendamustine + rituximab; SmPC = Summary of Product Characteristics; SPM = second primary malignancy; XLA = X-linked agammaglobulinaemia.

Table VI-3 Important Potential Risks

Important Potential Risk: Cerebrovascular Events	
Evidence for linking the risk to the medicine	Cerebrovascular events have been observed with ibrutinib but are not considered causally associated (not listed in section 4.8 of SmPC). Cerebrovascular events have been observed with CALQUENCE; however, a causal relationship seems unlikely, since in most cases other significant confounding factors were present as well as the long time to event onset in some cases.
Risk factors and risk groups	Many risk factors for cerebrovascular events have been described, some of them are biological traits such as age and sex, some of them are physiological or pathological characteristics such as high blood pressure, serum cholesterol and fibrinogen and some are behavioural such as smoking, diet, alcohol consumption, and physical inactivity; some are social characteristics such as education, social class and ethnicity; and some are environmental factors that may be physical (temperature, altitude), geographical, or psychosocial. In addition, medical factors including previous TIA or stroke, ischaemic heart disease, atrial fibrillation, and glucose intolerance, all increase the risk of stroke. Overall, atrial fibrillation (an important identified risk for CALQUENCE) may be associated with higher risk of cardiovascular events.
Risk minimisation measures	None

Table VI-3 Important Potential Risks

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	The mechanism underlying hepatotoxicity events is currently unknown. Following a comprehensive review of hepatotoxicity events in the CALQUENCE clinical programme, there was insufficient evidence to establish an association between hepatotoxicity and CALQUENCE due to the contribution of confounding factors, absence of clinical symptoms, and quick recovery without treatment for patients with transaminase elevations. There is limited evidence regarding hepatotoxicity from literature for other BTK inhibitors. In the pivotal study for previously untreated MCL (ACE-LY-308), a slight imbalance was noted between arms for transaminase elevations (ALT/AST increased). These transaminase elevations were not accompanied by symptoms and signs of liver injury or clinically significant increases of serum bilirubin. There is insufficient evidence that these transaminase elevations are associated with overt liver injury.
Risk factors and risk groups	Risk factors for the development of hepatotoxicity that are non-specific to CALQUENCE include increasing age, the female gender, chronic hepatitis B and C, and HIV. Additional risk factors include the daily dose and metabolism of the offending drug and the potential to develop toxic reactive metabolites secondary to hepatic metabolism (Chalasani and Bjornsson 2010). Chronic alcohol consumption, underlying nonalcoholic fatty liver disease, and concomitant medication use, such as some nonsteroidal anti-inflammatory drugs, antibiotics, and seizure medications may increase the risk for a patient to develop hepatotoxicity (Sandhu and Navarro 2020).
Risk minimisation measures	**Routine risk communication:** SmPC section 4.2

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BTK = Bruton tyrosine kinase; HIV = human immunodeficiency virus; SmPC = Summary of Product Characteristics; TIA = transient ischaemic attack.

Table VI-4 Missing Information

Missing Information: Long-Term Safety	
Risk minimisation measures	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** Study ACE-CL-007 This utilisation will be further characterised from routine pharmacovigilance activities and from results of an ongoing Study ACE-CL-007, a randomised, multicentre, open-label, 3 arm Phase III study of obinutuzumab in combination with chlorambucil, CALQUENCE in combination with obinutuzumab, and CALQUENCE monotherapy in patients with previously untreated CLL. The primary objective of this study

Table VI-4 Missing Information

	is to evaluate the efficacy and safety of CALQUENCE in treatment-naïve CLL patients (as monotherapy or combination therapy with obinutuzumab).
Missing Information: Use in Patients With Moderate to Severe Cardiac Impairment	
Risk minimisation measures	**Routine risk communication:** SmPC section: 4.2
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** D8223C00016 This utilisation will be further characterised from routine pharmacovigilance activities and from results of Study D8223C00016, which is a multicentre, open-label, randomised, Phase IV study to investigate CALQUENCE monotherapy compared with investigator's choice of treatment in approximately 60 adults (> 18 years) with CLL and moderate to severe cardiac impairment. All patients are required to have a left ventricular ejection fraction < 50% assessed by echocardiography. Safety assessments will include AEs, SAEs, ECIs, AESIs, laboratory parameters (haematology, clinical chemistry, urinalysis, and others as clinically indicated), physical examinations and vital signs, cardiac assessments (ECG, Holter, echocardiography, cardiac biomarkers, and cardiac MRI) and other tests deemed critical to the safety evaluation of the study treatment.

AE = adverse event; AESI = adverse event of special interest; CLL = chronic lymphocytic leukaemia; ECG = electrocardiogram; ECI = event of clinical interest; MRI = magnetic resonance imaging; SAE = serious adverse event.

VI.2.3 Post-Authorisation Development Plan

VI.2.3.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligations of CALQUENCE.

VI.2.3.2 Other Studies in Post-Authorisation Development Plan

ACE-CL-007

Study Short Name and Title

A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP-196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia

Rationale

This randomised controlled Phase III study in previously untreated patients with CLL is designed to determine whether treatment with CALQUENCE in combination with

obinutuzumab (Arm B) results in a clinically significant improvement in progression-free survival (PFS) as compared with treatment with obinutuzumab in combination with chlorambucil (Arm A), and whether treatment with CALQUENCE monotherapy (Arm C) results in a clinically significant improvement in PFS as compared with treatment with Arm A.

Study Objectives

- Primary objective: To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with CALQUENCE in combination with obinutuzumab (Arm B), based on independent review committee (IRC) assessment of PFS per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria, in subjects with previously untreated CLL.
- Secondary objectives:
  - To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) versus CALQUENCE monotherapy (Arm C) based on IRC assessment of PFS per IWCLL 2008 criteria.
  - To compare obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib plus obinutuzumab (Arm B), and obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) in terms of:
    - IRC-assessed objective response rate per IWCLL 2008 criteria;
    - Time to next treatment (defined as the time from randomisation to institution of non-protocol-specified treatment for CLL; and
    - Overall survival.
- Safety objective: Incidence of adverse events (AEs) including AEs, events of clinical interest (ECIs), and adverse events of special interest (AESIs), and serious adverse events (SAEs) and changes in laboratory measurements.

This study was amended from a duration of 4.5 years to up to 10 years in order to collect additional long-term safety information. The results from this ongoing study will be used to further characterise the missing information of long-term safety in patients treated with CALQUENCE.

D8223C00016

Study Short Name and Title

Acalabrutinib Monotherapy vs Investigator's Choice of Treatment in Patients With Chronic Lymphocytic Leukaemia and Moderate to Severe Cardiac Impairment

Rationale

CLL is the most prevalent adult leukaemia in Europe and the Western societies (Yao et al 2022). As of 2019, the global incidence of CLL was over 100,000 cases, with an estimated

200,000 people with CLL living in the US alone (SEER 2024). The median age at diagnosis for CLL is ~70 years (American Society of Clinical Oncology 2024). While the prevalence of people with both CLL and cardiovascular disease is unreported, patients with CLL are likely to have at least the same risk of cardiovascular disease as the general population (Park et al 2019), estimated as 75% in people between 60 and 79 years of age and 86% in those > 80 years (Rodgers et al 2019).

Bruton tyrosine kinase (BTK) inhibitors are better tolerated than chemoimmunotherapy in patients with CLL; however, serious and fatal cardiac arrhythmias beyond atrial fibrillation have occurred with ibrutinib and have limited its use in cardiac-impaired patients (Imbruvica SmPC). The second generation, more selective BTK inhibitor CALQUENCE has shown a lower incidence of atrial fibrillation and cardiac AEs than ibrutinib (Byrd et al 2021). A review of the safety data for CALQUENCE suggests that it is well tolerated in patients with risk factors for developing cardiovascular diseases at screening, yet the safety profile of CALQUENCE in CLL patients with significant cardiovascular diseases or with moderate to severe cardiac impairment has not been established.

Study Objectives

- Primary objective: To evaluate the safety and tolerability of acalabrutinib monotherapy vs investigator's choice of treatment in patients with treatment-naïve or relapsed/refractory (R/R) CLL and moderate to severe cardiac impairment.
- Secondary objective: To evaluate the extent and duration of tumour response and survival after acalabrutinib vs investigator's choice of treatment in patients with treatment-naïve or R/R CLL and moderate to severe cardiac impairment.

VII. PART VII: ANNEXES

VII.1 ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Please see below the follow-up questionnaires to further characterise the important potential or identified risks on cerebrovascular events (Section VII.4.1), major haemorrhages (Section VII.4.2), and hepatotoxicity (Section VII.4.3).

VII.1.1 Cerebrovascular Event

Cerebrovascular Event

Patient Demographic information

Initials: …….....

Date of Birth (dd/mm/yy): …….....

Reporter information Contact details :

Details of CVA/ TIA

Date of onset:...../...../.....
Symptoms: Y / N
If TIA, duration of symptoms……seconds/minutes/days (please delete as necessary)

Please tick the signs and symptoms observed:

Motor-related symptoms	**Yes/No**
• Arm or leg weakness	
• Facial weakness	
• Impaired gait	
• Ataxia (malcoordination)	
• abnormal eye movements	
• Dysarthria (slurred speech), Dysphagia (difficulty swallowing)	
Sensory-type symptoms	
• Dizziness/vertigo	
• Impaired vision, visual field defect, diplopia (double vision)	
• Sensory deficit in face, arm or leg	
Cognitive or other symptoms	
• Sensory neglect	
• Amnesia or impaired memory	
• Seizures	
• Aphasia	

• Impaired consciousness or coma	
• Vegetative state	
OTHER: Please specify:	

Risk Factors and current or past medical history

Disorder or risk factor	**Current Y/N**	**Past Y/N**	**Onset date mm/yy (dd/mm/yy if known)**	**Relevant Clinical details**
Transient ischemic attack (TIA)/ Cerebrovascular accident (CVA)				
Prior Myocardial infarction (MI)				
Coronary artery disease (CAD)				
Hypertension				
Atrial fibrillation				
Heart valve malformation				
Mitral valve stenosis				
Diabetes				
Antiphospholipid antibodies				
Obesity				
Hyperlipidemia				
Alcohol/ drug abuse				

Disorder or risk factor	**Current Y/N**	**Past Y/N**	**Onset date mm/yy (dd/mm/yy if known)**	**Relevant Clinical details**
Smoker				
Sickle cell disease				
Vascular stenosis				
Hypercoagulable state				
Cardiomyopathy/heart failure				
Other relevant past medical history?				
Any contributory family medical history? Please specify				

Investigations (if performed):

Test	**Date (dd/mm/yy)**	**Results**
Carotid Doppler		
Head CT/ MRI		
Other		

Outcome	Yes	No
Hospitalised		
Full recovery		
Partial Recovery with mild residual symptoms		
Partial Recovery with disabling residual symptoms		
No recovery		
Death Date:..... Cause of death :…….....		

Drugs suspected of being associated with the CVA/ TIA

	Indication	**Start date dd/mm/yy**	**Stop date dd/mm/yy**	**Dose and dosing regimes**
Calquence (acalabrutinib)				
Other suspect drugs (please specify)				

Concomitant therapy:

Drug	**Dose and regime**	**Start date**	**Stop date**	**Indication**

Please continue overleaf if necessary

VII.1.2 Major Haemorrhage

1. Patient Details

Initials:	Age: Date of Birth:	Drug Indication:	☐ Male ☐ Female

2. Details of Acalabrutinib Therapy

Start Date _____ Stop Date: **Dosage mg/kg (QD/BID/TID):**

Date of last dose of acalabrutinib received: **Number of Doses prior to Adverse Event (AE):**

3. Details of Adverse Event(s) (Haemorrhage)

Adverse Event(s):	Start Date dd/mm/yyyy	Stop Date dd/mm/yyyy	Intensity/Grade	Outcome of AE	Causally Related?	Action taken with acalabrutinib
				☐ Recovered ☐ Ongoing ☐ Recovered with sequelae ☐ Died	☐ Yes ☐ No	☐ Discontinued ☐ Delayed ☐ None
				☐ Recovered ☐ Ongoing ☐ Recovered with sequelae ☐ Died	☐ Yes ☐ No	☐ Discontinued ☐ Delayed ☐ None
				☐ Recovered ☐ Ongoing ☐ Recovered with sequelae ☐ Died	☐ Yes ☐ No	☐ Discontinued ☐ Delayed ☐ None

If dose was delayed, did the AEs improve after delaying the drug? ☐ Yes ☐ No ☐ N/A ☐ Unknown

Was the drug re-introduced?	☐ Yes ☐ No Date if yes _____ **If yes, did the event reoccur or worsen after re-introduction?** ☐ Yes ☐ No

Was there any complication caused by the AE or AE treatments? ☐ Yes ☐ No If yes, provide a brief statement

Does the reporter consider there to be a causal relationship between the suspect drug and adverse event? ☐ Yes ☐ No Please explain:

Please describe AE and treatment, including blood transfusions:

4. Concomitant Drugs							
Drug Name	**Indication**	**Dose/Frequency**	**Route of administration**	**Was this an AE treatment**	**Start date**	**Stop date**	**Suspect medication?**
							☐ Yes ☐ No
							☐ Yes ☐ No
							☐ Yes ☐ No
							☐ Yes ☐ No
							☐ Yes ☐ No
							☐ Yes ☐ No

5. Relevant Medical History *Please provide details of any other relevant medical history/concurrent diseases, including approximate dates of diagnosis and resolution if applicable.*

Medical history/concurrent diseases	**Comments**

6. Risk factors for the haemorrhage		
Risk factor	**History Current/Past**	**If yes, provide details**
Anticoagulant therapy		
History of coagulopathy		
Medications and supplements		
Hepatic disease		
Other		

7. Laboratory Results *Please provide details of the following relevant lab tests (attach test results if available)*

Test	**Reference Values** (provide units)	**Baseline Value (pre-treatment)** (dd/mm/yyyy)	**Event Onset Value** date (dd/mm/yyyy)	**Peak or Worst Value** (dd/mm/yyyy)	**Post-drug withdrawal**	**Return to Normal Value** (dd/mm/yyyy)

					Value (dd/mm/yyyy)	
Prothrombin time [sec] (test/control)						
Prothrombin activity (%) (test/control)						
INR						
Activated partial thromboplastin time [sec]						
Partial thromboplastin time [sec]						
Thrombin time (sec)						
Platelets						
Haemoglobin						
Haematocrit						
Reticulocyte						
Other						

8. Other Investigations

Other Investigations	**Performed**	**Date**	**Results**
Ultrasound	☐		
Biopsy	☐		
CT/MRI	☐		
Autopsy	☐		
Other, please specify	☐		

Reporter Details

Reporter's name: Reporter's Address:	Is the reporter a healthcare professional (HCP)? No ☐ Yes ☐ If yes, please provide specialty:

Telephone#: Fax#/Email address:	If no, please confirm if we can contact the HCP? No ☐ Yes ☐ If yes, please provide contact information of the HCP
Thank you for completing this form.	

VII.1.3 Hepatotoxicity

1. Patient Details

Initials: **Age:** **Drug Indication:** ☐ **Male** ☐ **Female**

Date of Birth: **Height:** **Weight:**

2. Details of Acalabrutinib Therapy

Start Date **Stop Date:** **Dosage (mg/kg) (QD/BID/TID):**

Date of last dose of acalabrutinib received: **Number of Doses prior to Adverse Event (AE):**

3. Details of Adverse Event(s) (Hepatoxicity)

Adverse Event(s):	**Start Date** dd/mm/yyyy	**Stop Date** dd/mm/yyyy	**Intensity/Grade**	**Outcome of AE**	**Causally Related?**	**Action taken with acalabrutinib**
				☐ Recovered ☐ Ongoing ☐ Recovered with sequelae ☐ Died	☐ Yes ☐ No	☐ Discontinued ☐ Delayed ☐ None
				☐ Recovered ☐ Ongoing ☐ Recovered with sequelae ☐ Died	☐ Yes ☐ No	☐ Discontinued ☐ Delayed ☐ None
				☐ Recovered ☐ Ongoing ☐ Recovered with sequelae ☐ Died	☐ Yes ☐ No	☐ Discontinued ☐ Delayed ☐ None

If dose was delayed, did the AEs improve after delaying the drug? ☐ Yes ☐ No ☐ N/A ☐ Unknown

Was the drug re-introduced? ☐ Yes ☐ No Date if yes _____

If yes, did the event reoccur or worsen after re-introduction? ☐ Yes ☐ No

Was there any complication caused by the AE or AE treatments? ☐ Yes ☐ No If yes, provide a brief statement

Does the reporter consider there to be a causal relationship between the suspect drug and adverse event? ☐ Yes ☐ No Please explain:

Please describe AE including signs/symptoms:

4. AE Treatment

Drug Name	Dose/Frequency	Route of Administration	Start date	Stop date

5. Concomitant Drugs

Drug Name	Indication	Dose/Frequency	Route of administration	Was this an AE treatment?	Start date	Stop date	Suspect medication?
							☐ Yes ☐ No
							☐ Yes ☐ No
							☐ Yes ☐ No
							☐ Yes ☐ No
							☐ Yes ☐ No
							☐ Yes ☐ No

5. Relevant Medical History *Please provide details of any other relevant medical history/concurrent diseases, including approximate dates of diagnosis and resolution if applicable.*

Medical history/concurrent diseases	Comments

6. Risk factors for transaminase elevations

Risk factor	History Current/Past	If yes, provide details
Alcohol use		

Hepatitis (any)		
Cirrhosis		
Gilbert's syndrome		
Hepatobiliary disorder		
Hyperlipidemia		
Heart failure		
Liver metastases		
Pancreatic disorder		
Other:		

7. Laboratory Results *Please provide details of the following relevant lab tests (attach test results if available)*

Test	**Reference Values** (provide units)	**Baseline Value (pre-treatment)** (dd/mm/yyyy)	**Event Onset Value** date (dd/mm/yyyy)	**Peak or Worst Value** (dd/mm/yyyy)	**Post-drug withdrawal Value** (dd/mm/yyyy)	**Return to Normal Value** (dd/mm/yyyy)
AST						
ALT						
Total bilirubin						
Direct bilirubin						
GGT						
ALP						
LDH						
PT/INR						
Others:						

8. Other Investigations

Other Investigations	Performed	Date	Results
Ultrasound	☐		
CT	☐		
MRI	☐		
MRCP	☐		
ERCP	☐		
Liver biopsy	☐		
Hepatologist consult	☐		
Toxicity screen	☐		

9. Serologies

Serology	Test Date	Result	Test performed and titer
Hepatitis A		☐ **Positive** ☐ **Negative**	
Hepatitis B		☐ **Positive** ☐ **Negative**	
Hepatitis C		☐ **Positive** ☐ **Negative**	
Hepatitis E		☐ **Positive** ☐ **Negative**	
Anti-EBV		☐ **Positive** ☐ **Negative**	
Anti-CMV		☐ **Positive** ☐ **Negative**	
Herpes		☐ **Positive** ☐ **Negative**	
Anti-ds DNA Ab		☐ **Positive** ☐ **Negative**	
Anti-smooth muscle Ab		☐ **Positive** ☐ **Negative**	
Anti-nuclear Ab		☐ **Positive** ☐ **Negative**	
IgG		☐ **Positive** ☐ **Negative**	
IgM		☐ **Positive** ☐ **Negative**	

Reporter Details

Reporter's name: Reporter's Address:	Is the reporter a healthcare professional (HCP)? No ☐ Yes ☐ If yes, please provide specialty:

Telephone#: Fax#/Email address:	If no, please confirm if we can contact the HCP? No ☐ Yes ☐ If yes, please provide contact information of the HCP

Thank you for completing this form.

VII.2 ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES – NOT APPLICABLE

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