SUMMARY OF THE RISK MANAGEMENT PLAN FOR CALQUENCE (ACALABRUTINIB)

This is a summary of the 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.

THE MEDICINE AND WHAT IT IS USED FOR

CALQUENCE has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. CALQUENCE contains acalabrutinib as the active substance and is given orally by a capsule.

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 EMA website, under the medicine's webpage

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 Benefit-Risk Evaluation Report (PBRER) 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.

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 (e.g., on the long-term use of the medicine).

Table - 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
Missing Information	Long-term safety Use in patients with moderate to severe cardiac impairment

Summary of Important Risks

Important Identified Risks

Important Identified Risk: Haemorrhage with or without association with thrombocytopenia	
Evidence for linking the risk to the medicine	BTK is present on platelets and is required for collagen- or shear stress-induced platelet aggregation and there is a correlation between the degree of BTK inhibition and the occurrence of clinical bleeding. Furthermore, analysis of the CALQUENCE Mono HemeMalig population showed that bleeding events were reported in 46.3% of the patients.

Important Identified Risks

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. Lower levels of von Willebrand factor activity, and factor VIII are also 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 preclinical evidence examining the role of BTK in XLA patients. Furthermore, the reported rates of infections (both any grade and Grade ≥3) for subjects in the CALQUENCE Mono HemMalig population were very common (per CIOMS-defined frequencies).
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, 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 haemorrhage. There is a plausible mechanism of action linking CALQUENCE and SPMs. The reported rates of SPM for subjects in the CALQUENCE Mono HemMalig population were very common (per CIOMS-defined frequencies). Results from two pivotal Phase 3 studies for CLL (ACE-CL-007 and ACE-CL-309) demonstrated higher incidence rates of SPM (skin and non-skin) in the CALQUENCE arm as compared to rates in the comparators arms. 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. Additionally, SPM has been described with other BTK inhibitors.
Risk factors and risk groups	**Patient factors** Age is a risk factor for secondary malignancy. Incidence of SPM in patients treated with BTK inhibitors for CLL was increased relative to the general population.

Important Identified Risks

	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 (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [oncovin], and prednisolone), 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.
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 two Phase 3 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 to the comparator arm. Furthermore, the reported rates of atrial fibrillation/flutter for subjects in the CALQUENCE Mono HemMalig population were common (per CIOMS-defined frequencies). 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. In recent years, increasing data have been reported supporting the notion that atrial fibrillation/flutter in the general population is heritable. 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 interleukin 2 (IL-2).
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8 **Additional risk minimisation measures**: None

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 acalabrutinib 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, ischemic heart disease, atrial fibrillation, and glucose intolerance, all increase the risk of stroke. Overall, atrial fibrillation (an important identified risk for acalabrutinib) may be associated with higher risk of cardiovascular events.
Risk minimisation measures	None

Missing Information

Missing Information: Long-term Safety	
Risk minimisation measures	**Routine risk minimisation measures**: None **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** D8220C00008 This utilisation will be further characterised from routine pharmacovigilance activities and from results of an ongoing Study D8220C00008, which is a Phase 3b, multicentre, open-label, single-arm study of CALQUENCE (ACP-196) in subjects with CLL. The primary objective of this study is to evaluate the safety and tolerability of CALQUENCE monotherapy in approximately 600 subjects with TN or R/R CLL who may receive CALQUENCE for 48 cycles of study treatment (28 days per cycle).

Missing Information: Use in Patients with Moderate to Severe Cardiac Impairment	
Risk minimisation measures	**Routine risk minimisation measures**: None **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** D8220C00008 This utilisation will be further characterised from routine pharmacovigilance activities and from results of a planned cohort in an ongoing Study D8220C00008, which is a Phase 3b, multicentre, open-label, single-arm study of CALQUENCE (ACP-196) in subjects with CLL. The primary objective of this study is to evaluate the safety and tolerability of CALQUENCE monotherapy in approximately 600 subjects with TN or R/R CLL who may receive CALQUENCE for 48 cycles of study treatment (28 days per cycle). The planned cohort to evaluate use in patients with moderate to severe cardiac impairment will have an inclusion and exclusion criteria specific to the cohort. A maximum of 30 subjects will be enrolled, beginning with 3 subjects, followed by a staggered expansion, pending no subjects have met pre-defined stopping criteria. Subjects will be carefully monitored for AEs and laboratory abnormalities, and will have routine assessments performed, which include ECGs, echocardiograms, and/or cardiac MRI.

Post-authorisation development plan

Studies Which are Conditions of the Marketing Authorisation

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

Other Studies in Post-authorisation Development Plan

D8220C00008 (ASSURE)

Study short name and title

Study D8220C00008: A Phase 3b, multicentre, open-label, single-arm study of CALQUENCE (ACP-196) in subjects with chronic lymphocytic leukaemia (ASSURE).

Purpose of the Study

Additional safety data are needed to further characterize less common AEs and management of common AEs for TN or R/R CLL patients treated with CALQUENCE. This study will provide data collected in a setting more reflective of real-world practice and it may further inform on patient management.

Study objectives

Primary objective: To evaluate the safety and tolerability of CALQUENCE monotherapy in subjects with TN or R/R CLL[a].

Secondary objective: To evaluate the investigator-assessed ORR, DOR, and PFS in subjects receiving CALQUENCE monotherapy.

[a]This includes Long Term Safety

Cohort to D8220C00008 (ASSURE)

Study short name and title

Cohort to Study D8220C00008: A Phase 3b, multicentre, open-label, single-arm study of CALQUENCE (ACP-196) in subjects with chronic lymphocytic leukaemia (ASSURE).

Purpose of the study

Additional safety data are needed to further characterize less common AEs and management of common AEs for TN or R/R CLL patients treated with CALQUENCE. This study will provide data collected in a setting more reflective of real-world practice and it may further inform on patient management.

In order to characterize the missing information on moderate to severe cardiac impairment in subjects treated with acalabrutinib this study will add a cohort to enrol subjects with pre-existing moderate to severe cardiac impairment with planned recruitment by Q4 2020

Study objectives

Primary objective: To evaluate the safety and tolerability of CALQUENCE monotherapy in subjects with TN or R/R CLL.

Secondary objective: To evaluate the investigator-assessed ORR, DOR, and PFS in subjects receiving CALQUENCE monotherapy.