27 February 2025
EMA/CHMP/50170/2025
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Calquence

International non-proprietary name: Acalabrutinib

Procedure No. EMEA/H/C/005299/II/0026

Marketing authorisation holder (MAH) AstraZeneca AB

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ASCT	autologous stem cell transplant
ATP	adenosine triphosphate
$AUC_{24h,ss}$	area under the drug concentration-time curve through 24 hours post-dosing at steady state
BCR	B-cell receptor
bd	twice daily
BR	bendamustine plus rituximab
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor(s)
CAR-T	chimeric antigen receptor T cell
CHOP	cyclophosphamide/doxorubicin/vincristine/prednisone
CI	confidence interval
CLL	chronic lymphocytic leukaemia
$C_{max,ss}$	maximum drug concentration at steady state
CNS	central nervous system
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GI	gastrointestinal
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRC	independent review committee
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	mantle cell lymphoma international prognostic index
NHL	non-Hodgkin lymphoma
NK	natural killer
NSCLC	non-small cell lung cancer

ORR	overall response rate
OS	overall survival
PD	Pharmacodynamic or progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
popPK	population pharmacokinetic(s)
PR	partial response
RM	rituximab maintenance
R/R	relapsed/refractory
SAE	serious adverse event
SLL	small lymphocytic lymphoma
sMIPI	simplified mantle cell lymphoma international prognostic index
SmPC	Summary of Product Characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
TEC	tec protein tyrosine kinase
TLS	tumour lysis syndrome
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 26 August 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include CALQUENCE as monotherapy for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy based on final results from study ACE-LY-004 (D8225C00002); this is an open-label, phase 2 study of ACP-196 in subjects with Mantle Cell Lymphoma. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial and formatting changes to the PI.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0111/2023 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH received Scientific Advice from the CHMP on 14 December 2017 (EMEA/H/SA/3090/3/2017/PA/III). The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	26 August 2024
Start of procedure:	14 September 2024
CHMP Rapporteur Assessment Report	11 November 2024
PRAC Rapporteur Assessment Report	15 November 2024
PRAC members comments	20 November 2024
PRAC Outcome	28 November 2024
CHMP members comments	2 December 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	5 December 2024
Request for supplementary information (RSI)	12 December 2024
PRAC Rapporteur Assessment Report	3 February 2025
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
CHMP Rapporteur Assessment Report	12 February 2025
PRAC Outcome	13 February 2025
CHMP members comments	17 February 2025
Updated CHMP Rapporteur Assessment Report	24 February 2025
Opinion	27 February 2025

2. Scientific discussion

2.1. Introduction

Mantle Cell Lymphoma (MCL)

MCL is a rare subtype of B-cell non-Hodgkin lymphoma (NHL) that accounts for approximately 7% of adult NHLs in the United States (US) and Europe. MCL occurs more frequently in older adults, with a median age at diagnosis of 68 years. Approximately three-quarters of patients with MCL are male, and white individuals are affected almost twice as frequently as black individuals (Armitage and Longo 2022, Swerdlow et al 2017, Teras et al 2016). MCL has distinct morphologic and molecular features. The primary cell of origin of MCL is thought to be a naive B-cell of pre-germinal centre origin within the mantle zone of the lymph node. MCL is characterized by the overexpression of cyclin D1, a protein that stimulates cell growth and dysregulation of the cell cycle, as a result of the translocation t(11;14)(q13;q32) (Bertoni et al 2006).

Prognosis is variable but MCL typically has an aggressive disease course and a high rate of relapse. During the last decade, in addition to the clinical 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 features. MCL remains largely incurable and associated with poor outcomes. With standard chemotherapy, the median duration of remission according to most studies is 1.5 to 3 years and the median survival is 3 to 6 years (Leukemia and Lymphoma Society 2021). In the United Kingdom, the 5-year net survival (survival adjusted for the background population mortality rate) has been estimated to be 47.3% (Lamb et al 2024). Some patients succumb to their disease in less than 6 months, whereas others (~8%) survive more than 10 years. For the more aggressive blastoid and pleomorphic variants, median overall survival (OS) is 29 months (Hoster et al 2016). All patients eventually relapse after frontline therapy. Management of R/R MCL is particularly difficult, and options are limited. In this setting, monotherapies with BTK inhibitors (BTKi) have become the preferred salvage treatments, based on superior efficacy compared with conventional chemotherapy or other targeted therapies (Dreyling et al 2017).

Claimed therapeutic indication

Calquence as monotherapy is indicated for the treatment of adult patients with (MCL) who have received at least one prior therapy.

Management

Frontline MCL treatment involves dichotomising patients based on autologous stem cell transplant (ASCT) eligibility. Patients deemed transplant eligible typically receive chemo-immunotherapy, consolidative ASCT in first remission, and rituximab maintenance (RM).

For patients who are not fit for dose-intensified regimens, bendamustine plus rituximab (BR) is a frontline standard, along with options like VR-CAP and R-CHOP. RM is an option. There is data to support the use of covalent BTK inhibitors both in fit and less fit patients in the frontline setting, as well as in maintenance.

Ibrutinib is an approved standard therapy in the R/R MCL setting and are common second- and third-line regimens. After failing treatment with a BTKi, options for patients for later line treatments are very

limited and outcomes are poor. Potential treatment options include non-covalent BTKi such as pirtobrutinib, which have demonstrated efficacy in patients previously treated with a covalent-BTK, rituximab and lenalidomide, bortezomib-based regimens, temsirolimus-based regimens (suboptimal outcomes compared to BTKi), further cancer immunotherapy, or, for fitter patients, chimeric antigen receptor T cell (CAR-T) therapy and allogeneic transplantation. An unmet need for improved therapy and treatment options remains in relapsed and refractory mantle cell lymphoma.

2.1.1. About the product

Acalabrutinib (ACP-196), is an orally bioavailable, covalent inhibitor of BTK. Acalabrutinib forms a covalent bond with Cys481 in the BTK adenosine triphosphate (ATP) pocket, inactivating the enzyme and resulting in the inhibition of proliferation and survival signals in malignant B cells.

Acalabrutinib has been granted marketing approval in the European Union [EU], for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) previously untreated or those who have received at least one prior therapy.

2.1.2. The development programme/compliance with CHMP guidance/scientific advice

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The original ERA includes a Phase II Tier B assessment of effects on sediment organisms. According to the original ERA, the $logD_{OW}$ values are <4.5 and thus no further screening for persistence, bioaccumulation, and toxicity was necessary. The values are also <3 and thus not triggering a bioconcentration study. Acalabrutinib is however very persistent in sediment according to the OECD 308 study.

Phase I: Updated predicted environmental concentration

The maximum daily dose for the indication MCL is 200 mg/day, resulting in $PEC_{SURFACEWATER}$ value of 0.006 µg/L. For the indication chronic lymphocytic leukemia with the maximum daily dose of 200 mg/day, the $PEC_{SURFACEWATER}$ value was 0.048 µg/L, using a refined Fpen based on prevalence data as defined in the orphan drug designation. Combining both indications, an updated $PEC_{SURFACEWATER-TOTAL}$ was calculated to 0.054 µg/L.

Phase II Tier A and B: Updated risk ratios (PEC/PNEC)

New phase II risk ratios are based on the updated $PEC_{SURFACEWATER-TOTAL}$ (0.054 µg/L) and the PNEC (predicted no-effect concentration) values that were presented for the original ERA submitted for the MAA. The updated risk ratios are presented below.

Phase II Tier A

Compartment	PEC	PNEC	PEC/PNEC (action limit)

Surface water	0.054 µg/L	120 µg/L	4.5×10^{-4} (<1)
Groundwater	0.014 µg/L	120 µg/L	1.1×10^{-4} (<1)
Microorganism	0.054 µg/L	100000 µg/L	5.4×10^{-7} (<0.1)

Phase II Tier B

Compartment	PEC	PNEC	PEC/PNEC (action limit)
Sediment	697 µg/kg	14 400 µg/kg	0.048 (<1)

The updated risk ratios remain below the action limits. Therefore, the clinical use of acalabrutinib considered in the present report for the indications chronic lymphocytic leukaemia and MCL is not expected to pose a risk for the environment.

2.2.2. Discussion on non-clinical aspects

An updated ERA is provided but no new non-clinical data have been submitted in this application, which is considered acceptable given that the clinical dose intended for treatment of the new indication (MCL) is the same as for the previously authorised indication. No changes in SmPC sections 4.6 or 5.3 are proposed or required.

The MAH has calculated an updated PECSURFACEWATER-TOTAL value (0.054 µg/L) for acalabrutinib based on the new indication MCL combined with the authorised indication (chronic lymphocytic leukaemia). The risk ratios (PEC/PNEC) were subsequently re-calculated based on the updated PECSURFACEWATER-TOTAL and the PNEC values that were presented for the original ERA submitted for the MAA. The resulting risk ratios remain below the action limits. Therefore, it is agreed that the use of acalabrutinib for the indications considered in the present report (MCL and chronic lymphocytic leukaemia) is not expected to pose a risk for the environment.

2.2.3. Conclusion on the non-clinical aspects

Considering the above data, acalabrutinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	Patients Enrolled/Treated/ Continuing Treatment Sex (M/F) Median Age (Range)	Healthy subjects or diagnosis of patients	Duration of acalabrutinib treatment, Median (range)	Study status; type of report
Uncontrolled Clinical Studies									
Efficacy	ACE-LY-004	Module 5.3.5.2	Response, safety, PK, PD	Phase 2, open label	Acalabrutinib 100 mg bd Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity	124/0 99M/25F 68 years (42-90 years)	Relapsed/ refractory mantle cell lymphoma	17.5 months (0.1-65.3 months)	Complete (primary efficacy endpoint achieved) Final CSR(s) (v1.0; v2.0, 24-Month Follow-up Update; Addendum to v2.0, 54-Month Close-Out Analysis)

2.3.2. Pharmacokinetics

No new PK data in the target population from Study ACE-LY-004 were submitted in the current procedure. PK data from ACE-LY-004 were submitted in the initial MAA (EMEA/H/C/005299/0000). A selection of PK results from Study ACE-LY-004 including comparisons to other patient populations are included in the this section of this report.

Study ACE-LY-004 was an open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma (see further details about the study design in Sections 2.4 and 2.5 of this report.

The primary objective was not related to PK but a secondary objective of the study was to characterize the PK profile of ACT-196.

PK analysis was evaluated on 45 patients with histologically documented MCL, who have relapsed prior treatment regimens following a single dose of 100 mg BID ACP-196 on Day 1 and Day 8.

Plasma samples for PK analysis of acalabrutnib were taken pre-dose and at 0.5, 0.75, 1, 2, 4, and 6 hours post-dose for analysis on Days 1 and 8 of dosing. On Days 15, 22, and 28 plasma samples were taken at pre-dose and 1-hour post-dose administration.

In Study ACE-LY-004, pharmacokinetic analyses were performed on Day 1 and Day 8 ACP-196 plasma concentration versus time data from 45 patients with histologically documented MCL.

The PK data from Study ACE-LY-004 vs time since most recent dose at steady-state compared to approved indications (CLL patients in Studies ACE-CL-006 and ACE-CL-007) as well as first-line MCL patients (Study ACE-LY-308) are summarised in **Table 1** and **Figure 1**. The baseline characteristics/demographics between the studies included in the PK-comparison are summarized in **Table 2** and **Table 3**.

Table 1. Observed Plasma Concentrations Versus Time (Steady State) Stratified by Population/Study for Acalabrutinib.

Analyte: Acalabrutinib **Study ID**		**Time (hours)**			
		1	**2**	**4**	**6**
ACE-CL-006	N	99	102	102	99
	GeoMean (GeoCV %)	343.27 (235.3%);	290.67 (97%)	69.01 (114.8%)	29.85 (124.1%)
	Median [range]	558.54 [4.1 - 2341.6]	310.42 [18 - 1465.1]	67.99 [8.6 - 794.8]	31.36 [4.6 - 476.9]
ACE-CL-007	N	243	249	248	-
	GeoMean (GeoCV %)	406.47 (266.8)	296.07 (113.8)	83.61 (121.9)	-
	Median [range]	604 [3.3 - 5220]	322 [3.7 - 2170]	72.85 [4.6 - 1620]	-
ACE-LY-004	N	44	39	40	40
	GeoMean (GeoCV %)	790.28 (131.8)	333.09 (70.6)	66.54 (98.9)	25.64 (77.7)
	Median [range]	978.5 [14.9 - 4380]	290 [81.6 - 1930]	61.15 [22.8 - 2070]	25.1 [7.8 - 126]
ACE-LY-308 (PK substudy)	N	35	36	36	36
	GeoMean (GeoCV %)	409.85 (189.8)	285.53 (99.8)	70.12 (104.4)	28.9 (91.8)
	Median [range]	530.61 [3.6 - 2111.7]	355.53 [26.4 - 1510.2]	56.18 [12.8 - 513.4]	27.71 [8.9 - 219.1]

Abbreviations: CV, coefficient of variation; Geo, geometric; h, hour; ID, identifier; PK, pharmacokinetic.

Figure 1. Overlay of Observed Plasma Concentrations Versus Time (Steady State) Stratified by Population/Study for Acalabrutinib. Note: X-axis represents actual time of the PK sample collection at steady state**.**

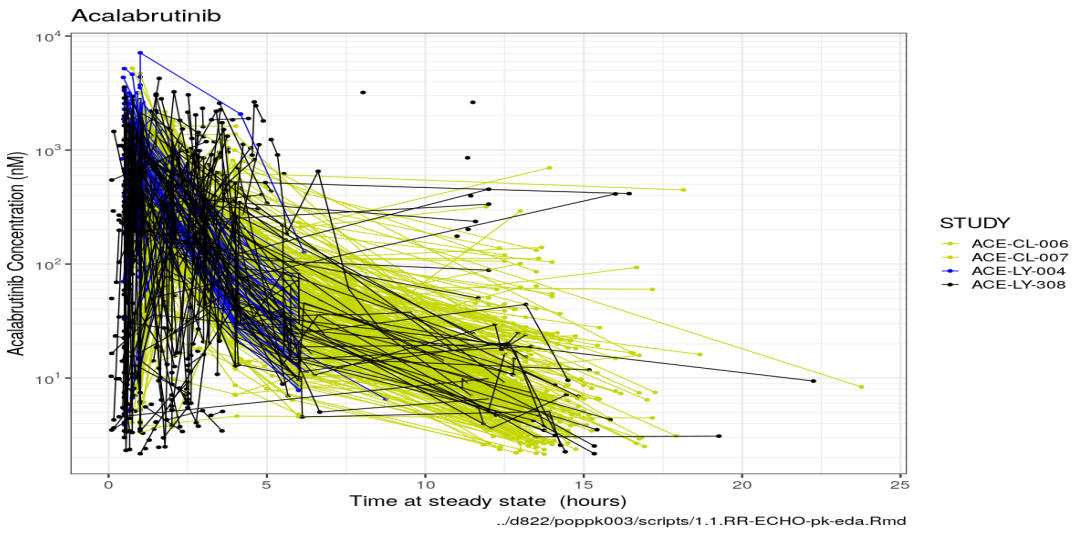


Table 2. Comparison of the Distribution of Relevant Continuous Covariates/Patient Demographics Between the Populations/Studies

	ACE-LY-004 (N = 45)	ACE-CL-006 (N = 117)	ACE-CL-007 (N = 274)	ACE-LY-308 (N = 249)	Overall (N = 685)
Baseline age (year)					
Mean (SD)	66.2 (11.4)	65.2 (10.1)	69.5 (7.81)	71.6 (4.77)	69.3 (7.99)
Median [Min, Max]	68.0 [44.0, 90.0]	66.0 [41.0, 87.0]	70.0 [41.0, 88.0]	71.0 [65.0, 85.0]	70.0 [41.0, 90.0]
Baseline weight (kg)					
Mean (SD)	83.6 (17.1)	80.0 (17.3)	80.4 (18.4)	77.6 (16.8)	79.5 (17.6)
Median [Min, Max]	83.9 [49.0, 140]	79.0 [45.6, 157]	78.5 [44.0, 149]	76.4 [40.0, 132]	78.0 [40.0, 157]
Missing, n (%)	1 (2.2)	1 (0.9)	0 (0)	0 (0)	2 (0.3)
Baseline eGFR (mL/min/1.73 m^2)					
Mean (SD)	75.0 (18.4)	79.1 (24.8)	74.8 (21.6)	83.9 (23.3)	78.9 (22.9)
Median [Min, Max]	74.5 [39.6, 123]	76.6 [27.8, 168]	73.5 [27.5, 162]	80.7 [34.6, 175]	74.8 [27.5, 175]
Missing, n (%)	0 (0)	0 (0)	8 (2.9)	1 (0.4)	9 (1.3)
Baseline Alanine Aminotransferase (U/L)					
Mean (SD)	20.8 (8.93)	19.5 (12.0)	19.9 (18.0)	17.6 (10.2)	19.0 (14.0)
Median [Min, Max]	18.0 [7.00, 45.0]	17.0 [5.00, 96.0]	16.0 [5.00, 241]	15.0 [5.00, 75.0]	16.0 [5.00, 241]
Missing, n (%)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.1)
Baseline Aspartate Aminotransferase (U/L)					
Mean (SD)	21.3 (6.21)	22.3 (8.92)	22.9 (12.3)	22.7 (10.0)	22.6 (10.6)
Median [Min, Max]	20.0 [13.0, 38.0]	21.0 [6.00, 73.0]	21.0 [8.00, 164]	20.0 [5.00, 77.0]	21.0 [5.00, 164]
Baseline Bilirubin (µmol/L)					
Mean (SD)	8.30 (3.83)	9.10 (5.24)	8.90 (6.19)	8.17 (4.46)	8.63 (5.32)
Median [Min, Max]	7.00 [3.00, 22.0]	7.90 [2.90, 28.2]	7.40 [2.60, 67.4]	7.00 [2.60, 29.1]	7.20 [2.60, 67.4]
Missing, n (%)	2 (4.4)	0 (0)	3 (1.1)	0 (0)	5 (0.7)

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation

Table 3. Comparison of the Distribution of Relevant Categorical Covariates/Patient Demographics Between the Populations/Studies.

	ACE-LY-004 (N = 45)	ACE-CL-006 (N = 117)	ACE-CL-007 (N = 274)	ACE-LY-308 (N = 249)	Overall (N = 685)
Disease Indication, n (%)					
Chronic lymphocytic leukaemia	0 (0)	117 (100)	274 (100)	0 (0)	391 (57.1)
Mantle cell lymphoma	45 (100)	0 (0)	0 (0)	249 (100)	294 (42.9)

	ACE-LY-004 (N = 45)	ACE-CL-006 (N = 117)	ACE-CL-007 (N = 274)	ACE-LY-308 (N = 249)	Overall (N = 685)
Sex, n (%)					
Female	8 (17.8)	35 (29.9)	104 (38.0)	72 (28.9)	219 (32.0)
Male	37 (82.2)	82 (70.1)	170 (62.0)	177 (71.1)	466 (68.0)
Race, n (%)					
White	34 (75.6)	110 (94.0)	254 (92.7)	194 (77.9)	592 (86.4)
Black/African American	1 (2.2)	3 (2.6)	9 (3.3)	0 (0)	13 (1.9)
Asian	0 (0)	0 (0)	3 (1.1)	37 (14.9)	40 (5.8)
American Indian or Alaska Natives	0 (0)	0 (0)	0 (0)	2 (0.8)	2 (0.3)
Other	0 (0)	4 (3.4)	0 (0)	15 (6.0)	19 (2.8)
Missing	10 (22.2)	0 (0)	8 (2.9)	1 (0.4)	19 (2.8)
East Asia, n (%)					
Non-East Asian	45 (100)	117 (100)	271 (98.9)	216 (86.7)	649 (94.7)
East Asian	0 (0)	0 (0)	3 (1.1)	33 (13.3)	36 (5.3)
Ethnicity, n (%)					
Hispanic/Latino	1 (2.2)	2 (1.7)	11 (4.0)	26 (10.4)	40 (5.8)
Not Hispanic/Latino	33 (73.3)	100 (85.5)	248 (90.5)	209 (83.9)	590 (86.1)
Not reported	0 (0)	15 (12.8)	15 (5.5)	14 (5.6)	44 (6.4)
Unknown	11 (24.4)	0 (0)	0 (0)	0 (0)	11 (1.6)
Combination, n (%)					
Monotherapy	45 (100)	117 (100)	274 (100)	0 (0)	436 (63.6)
Acalabrutinib + BR	0 (0)	0 (0)	0 (0)	249 (100)	249 (36.4)
Hepatic Impairment Status, n (%)					
Normal	41 (91.1)	104 (88.9)	254 (92.7)	228 (91.6)	627 (91.5)
Mild	2 (4.4)	13 (11.1)	13 (4.7)	20 (8.0)	48 (7.0)
Moderate	0 (0)	0 (0)	3 (1.1)	1 (0.4)	4 (0.6)
Severe	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.1)
Missing	2 (4.4)	0 (0)	3 (1.1)	0 (0)	5 (0.7)
Renal Impairment Status, n (%)					
Normal	7 (15.6)	38 (32.5)	58 (21.2)	94 (37.8)	197 (28.8)
Mild	30 (66.7)	62 (53.0)	170 (62.0)	137 (55.0)	399 (58.2)
Moderate	8 (17.8)	16 (13.7)	45 (16.4)	18 (7.2)	87 (12.7)
Severe	0 (0)	1 (0.9)	1 (0.4)	0 (0)	2 (0.3)
End stage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ECOG Performance Status, n (%)					
Fully active	24 (53.3)	60 (51.3)	141 (51.5)	123 (49.4)	348 (50.8)
Ambulatory	18 (40.0)	52 (44.4)	117 (42.7)	115 (46.2)	302 (44.1)

	ACE-LY-004 (N = 45)	ACE-CL-006 (N = 117)	ACE-CL-007 (N = 274)	ACE-LY-308 (N = 249)	Overall (N = 685)
Ambulatory but no work	2 (4.4)	5 (4.3)	16 (5.8)	11 (4.4)	34 (5.0)
Limited self-care	1 (2.2)	0 (0)	0 (0)	0 (0)	1 (0.1)
Completely disabled	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dead	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Use of PPI, n (%)					
Not present	41 (91.1)	105 (89.7)	262 (95.6)	228 (91.6)	636 (92.8)
Present	4 (8.9)	12 (10.3)	12 (4.4)	21 (8.4)	49 (7.2)
Imputed present	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: BR, bendamustine and rituximab; ECOG, Eastern Cooperative Oncology Group; PPI, proton pump inhibitor.

2.3.3. Pharmacodynamics

Acalabrutinib (ACP-196) is an orally bioavailable, covalent inhibitor of BTK. Acalabrutinib forms a covalent bond with Cys481 in the BTK adenosine triphosphate (ATP) pocket, inactivating the enzyme and resulting in the inhibition of proliferation and survival signals in malignant B cells. Acalabrutinib has an active metabolite, ACP-5862, that is also a covalent inhibitor of BTK. The biochemical profiling indicates that the pharmacological activity and kinase selectivity profile for ACP-5862 was comparable to that of acalabrutinib.

Primary and secondary pharmacology

New studies were not submitted in support of this extension of indication application. Data from the initial MAA submission demonstrated that acalabrutinib is highly selective for BTK; among all other kinases tested, only the structurally related kinases bone marrow kinase on chromosome X on-receptor tyrosine kinase, erb-b2 receptor tyrosine kinase 4 and TEC were inhibited with 50% inhibitory concentration (IC50) values <150 nM, compared with an IC50 of 5.1 nM for BTK (Byrd et al 2016).

2.3.4. PK/PD modelling

Exposure-response analyses including data from Study ACE-LY-004 were submitted in the initial MAA (EMEA/H/C/005299/0000). No new exposure-response data were submitted by the Applicant.

2.3.5. Discussion on clinical pharmacology

The initial MAA for Calquence sought approval in a target population (CLL) different to the population studied in ACE-LY-004 (second-line MCL). Hence, the PK data from ACE-LY-004 are more important for the overall assessment of the clinical pharmacology data in the current procedure.

Pharmacokinetics

There were no clinically relevant differences between the baseline characteristics/demographics between the studies included in this comparison.

The MAH provided graphical and tabular summaries of the observed acalabrutinib PK data which confirmed that there are no clinically relevant PK-differences between second-line MCL patients and the approved Calquence indications (CLL patients in Studies ACE-CL-006 and ACE-CL-007) as well as first-line MCL patients (Study ACE-LY-308). Since there are no clinically relevant differences between populations, the MAH's proposal not to update SmPC Section 5.2 is acceptable.

Of note, the median acalabrutinib concentrations at 1 hour following the most recent dose were higher for Study ACE-LY-004 than for the other studies but were within the distribution of PK concentrations at 1 hour time-point for the other studies. Apart from the 1-hour sample, the concentrations were comparable between all studies. Scatter plots of concentrations vs time since the most recent dose also confirmed that the PK-profiles for the target population (ACE-LY-004) were comparable to the other studies.

PK/PD modelling

No new exposure-response analyses have been submitted which was considered acceptable in the current variation.

2.3.6. Conclusions on clinical pharmacology

The presentation of acalabrutinib PK data is acceptable and indicated that there are no clinically relevant PK-differences between second-line MCL patients and CLL patients. No updates in the SmPC section 5.2 have been proposed which is acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study

The acalabrutinib dose of 100 mg bd used in the ACE-LY-004 study is the currently approved dose globally for patients with CLL.

This dose was established based on assessment of PK and pharmacodynamic (PD) characteristics of acalabrutinib and the active metabolite, ACP-5862, in addition to *in vitro* drug metabolism, PK profiling and in vivo drug-drug interaction studies, the details of which were described in the initial marketing authorisation application for Calquence.

2.4.2. Main study

ACE-LY-004: An Open-label, uncontrolled Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma

Methods

Study participants

Inclusion criteria

1. Men and women ≥18 years of age.

2. Pathologically confirmed MCL, with documentation of monoclonal B cells that had a chromosome translocation t(11;14)(q13;q32) and/or overexpressed cyclin D1.

3. Disease had relapsed after or been refractory to ≥1 prior therapy for MCL and now required further treatment.

4. Documented failure to achieve at least partial response (PR) with, or documented disease progression after, the most recent treatment regimen.

5. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 lesion that measured ≥2.0 cm in the longest dimension and ≥1.0 cm in the longest perpendicular dimension as assessed by computed tomography scan).

6. At least 1, but no more than 5, prior treatment regimens for MCL. (Note: Subjects who had received ≥2 cycles of prior treatment with bortezomib, either as single agent or as part of a combination therapy regimen, were considered to be bortezomib exposed).

7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.

8. Women who were sexually active and could bear children must have agreed to use highly effective forms of contraception during the study and for 2 days after the last dose of study treatment. This criterion was changed from "90 to 2 days after last dose" per protocol amendment 8.0, dated 22 November 2017

9. Men who were sexually active and could beget children must have agreed to use highly effective forms of contraception, and to refrain from sperm donation, during the study and for 90 days after the last dose of study treatment.

Exclusion criteria

1. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject had been disease free for ≥2 years or which would not have limited survival to <2 years.

2. A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could have compromised the subject's safety, interfered with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk.

3. 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 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) >480 msec.

4. Malabsorption syndrome, disease significantly affecting gastrointestinal (GI) function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

5. Any immunotherapy within 4 weeks of first dose of study treatment.

6. The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study treatment was <5 times the half-life of the previously administered agent(s).

7. Prior exposure to a BCR inhibitor (e.g., BTK, phosphoinositide-3 kinase [PI3K], or SYK inhibitors) or BCL-2 inhibitor (e.g., ABT-199).

8. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of MCL or other conditions. Note: Subjects may have used topical or inhaled corticosteroids or low-dose steroids (≤10 mg of prednisone or equivalent per day) as therapy for comorbid conditions. During study participation, subjects may also have received systemic or enteric corticosteroids as needed for treatment-emergent comorbid conditions.

9. Grade ≥2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.

10. Known history of human immunodeficiency virus or active infection with hepatitis C virus or hepatitis B virus (HBV) or any uncontrolled active systemic infection.

11. Major surgery within 4 weeks before first dose of study treatment.

12. Uncontrolled autoimmune haemolytic anaemia or idiopathic thrombocytopenia purpura.

13. Known history of a bleeding diathesis (eg, haemophilia, von Willebrand disease).

14. History of stroke or intracranial haemorrhage within 6 months before the first dose of study treatment.

15. Required or received anticoagulation with warfarin or equivalent vitamin K antagonist (e.g., phenprocoumon) within 7 days of first dose of study treatment.

16. Required treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).

17. Absolute neutrophil count (ANC) <0.75 x 109/L or platelet count <50 x 109/L; for subjects with disease involvement in the bone marrow, ANC <0.50 x 109/L or platelet count <30 x 109/L.

18. Creatinine >2.5 x institutional upper limit of normal (ULN); total bilirubin >2.5 x ULN; and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3.0 x ULN.

19. Breastfeeding or pregnant.

20. Concurrent participation in another therapeutic clinical trial.

21. Known central nervous system lymphoma or leptomeningeal disease.

22. Required treatment with a strong cytochrome P450 (CYP) 3A inhibitor/inducer.

23. Presence of a GI ulcer diagnosed by endoscopy within 3 months prior to screening.

Treatments

Acalabrutinib (ACP-196) capsules, 100 mg bid continuously in repeated 28-day cycles.

No comparator treatment was used in this study.

Subjects received study treatment until disease progression, or an unacceptable treatment-related toxicity occurred.

Objectives

Primary objective

• To determine the activity of acalabrutinib in subjects with R/R MCL as measured primarily by response rate. In addition, activity of acalabrutinib was evaluated using Duration of Response (DOR), Progression Free Survival (PFS) and Overall Survival (OS).

Secondary objectives

- To characterise the safety profile of acalabrutinib
- To characterise the pharmacokinetic (PK) profile of acalabrutinib
- To evaluate the pharmacodynamic effects of acalabrutinib

Outcomes/endpoints

Primary endpoint

Investigator-assessed Objective response rate (ORR) according to the Lugano classification for Non-Hodgkin Lymphoma (NHL).

Secondary endpoints

Investigator-assessed DOR and PFS according to the Lugano classification;

OS.

Sample size

This study was planned to enrol approximately 117 subjects.

A one-sample Chi-square test with a 0.025 one-sided significance level had more than 99% power to test the null hypothesis that ORR was ≤20% (not considered clinically compelling) versus the alternative hypothesis that ORR was ≥40%. The sample size also provided adequate estimation utility for safety and other secondary analyses. In particular, with a sample size of 117 subjects, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% was 69.1%, 90.6%, or 99.8%, respectively. This provided reasonable assurance that events occurring at ≥1% frequency could be identified in this Phase 2 study.

Randomisation and blinding (masking)

This was an open label study.

Statistical methods

Timing of analysis

The final analysis of primary and secondary efficacy endpoints occurred approximately 14 months (Cycle 15) after the last subject had been enrolled. A follow-up analysis was performed when all subjects had completed their study participation.

Primary endpoint

The primary analysis of ORR was conducted on the All-treated Population, defined as all enrolled subjects who received ≥1 dose of study treatment. ORR and the corresponding 95% 2-sided CI calculated using the exact binomial distribution were presented. Subgroup analyses were provided.

The order of overall response category was CR > PR > stable disease (SD) > PD. Descriptive statistics were provided for best overall response. The number and proportion of subjects within each category of response as well as the associated 95% CIs were presented. The proportion was estimated by

dividing the number of subjects within each category of response by the total number of subjects in the analysis population. Each subject was counted within only 1 response group, with the best response during the study as the classification group.

Secondary endpoints

Duration of response (DOR)

DOR was defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of objective MCL disease progression or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date were censored. Subjects who had the event after the start of subsequent anticancer therapy were censored at the last adequate disease assessment on or before the start of subsequent anticancer therapy and data cutoff time. Subjects with no adequate postbaseline disease assessment were censored on first dose date.

Progression-free survival (PFS)

PFS was defined as the interval from the start of study treatment to the first documentation of objective MCL disease progression per investigator assessment or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date were censored. Subjects who had the event after the start of subsequent anticancer therapy were censored at the time of their last adequate disease assessment on or before the start of subsequent anticancer therapy or data cutoff. Subjects with no adequate postbaseline disease assessment were censored on first dose date.

A sensitivity analysis of PFS was performed where all subjects who progressed or died (including those after the start of subsequent therapy) were considered as events.

Overall survival (OS)

The duration of OS was measured from the time of first study treatment administration until the date of death from any cause. Subjects who were known to be alive as of their last known status were censored at their last date known to be alive.

Endpoints assessed by Independent Review Committee (IRC)

ORR, DOR, and PFS were assessed by the IRC according to the Lugano classification were defined and analysed similarly as those assessed by the investigator.

Analysis of secondary endpoints

The analysis of DOR was conducted on the subset of the All-treated Population who achieved CR or PR as their best overall response.

The analysis of PFS and OS was conducted on the All-treated Population. The analysis of DOR, PFS, and OS was estimated using the Kaplan-Meier (KM) method. KM estimates with 95% CIs were calculated for event time quartiles and event-free rates were calculated at selected timepoints. In addition, the reason for censoring was summarized for DOR, PFS, and OS.

The same analysis methods for investigator-assessed ORR were applied to IRC-assessed ORR. The discordant responses assessed by the investigator and IRC using the Lugano classification were provided.

Interim analysis

An interim analysis for futility based on response rate was performed in September 2015 per Protocol Amendment 3, dated 17 July 2015. In this interim analysis, within the first 28 subjects enrolled to bortezomib-naive cohort, the required response rate for continuation was exceeded (≥8/28

responders). Within the first 12 subjects enrolled to the bortezomib-exposed cohort, the required response rate for continuation was also exceeded ≥3/12 responders). Based on this interim analysis, enrolment to both study cohorts was allowed to continue without interruption.

Results

Participant flow

Table 4. Subject Disposition: 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

	All Subjects N = 124 n (%)
Subjects who discontinued acalabrutinib	124 (100.0%)[b]
Disease progression	77 (62.1%)
Study terminated by sponsor	18 (14.5%)[b]
Adverse event	15 (12.1%)
Subject started alternative cancer therapy	6 (4.8%)
Investigator's discretion not related to AE/SAE	3 (2.4%)
Withdrawal of consent	2 (1.6%)
Death	1 (0.8%)
Lost to follow-up	1 (0.8%)
Other	1 (0.8%)
Subjects discontinued from study	124 (100.0%)
Death	59 (47.6%)
Study terminated by sponsor	51 (41.1%)
Withdrawal of consent	10 (8.1%)
Lost to follow-up	3 (2.4%)
Other	1 (0.8%)
Time on study (months) [a]	
N	124
Mean (SD)	39.1 (22.96)
Median	38.1
Min, Max	0.3, 68.8

a Time on study = [(Earlier of study exit date or data cutoff date) – (First dose date) + 1]/30.4375.
b At the time of study closure 106 subjects discontinued study treatment in the main study; 18 subjects (14.5%) were still on treatment in the extension phase and the reason for treatment discontinuation in these subjects is 'study terminated by sponsor'.

Recruitment

Study start date: 02 March 2015 (First subject consented)

Data cutoff date: 28 February 2017

Conduct of the study

The protocol was amended 6 times, and enrolment started under protocol amendment 1.0.

Summary of main protocol amendments after the start of subject recruitment

Amendment 2 (16 March 2015)

Provided updated background information on ACP-196 and to assure consistency in eligibility criteria and other study requirements across studies.

Amendment 3 (17 July 2015)

The frequency of urine pregnancy tests was increased and the frequency of PET/CT scans during treatment was decreased. In addition, the protocol has been clarified to state that subjects with confirmed CR are not required to undergo PET/CT scans unless there is suspicion of PD.

Amendment 4 (14 November 2015)

The study consisted of 2 parallel cohorts (bortezomib naive and the bortezomib exposed) each based on a Simon's 2-stage design. Subjects who received at least 2 cycles of other commercially available proteasome inhibitors were enrolled into the bortezomib-exposed cohort. The protocol was amended based on emerging data that supported the merging of the 2 cohorts by prior bortezomib exposure. The Phase 2 study of ibrutinib in R/R MCL reported similar ORRs in the bortezomib naive and bortezomib-exposed subjects (68% and 67%, respectively) (Wang et al 2013), indicating that prior bortezomib exposure does not appear to influence response to BTK inhibitor therapy. This was further supported by emerging data from this study (ACE-LY-004). The study retained the original planned sample size of 117 subjects to obtain adequate safety and exposure data with acalabrutinib in this patient population.

Amendment 5 (5 January 2016)

PET/CTs requirements changed to the end of Cycle 2 and Cycle 6 and at any time to confirm a complete response (CR) or as clinically indicated.

Amendment 6 (19 July 2016)

Revised the imaging window for computed tomography (CT) and positron emission tomography (PET)/CT scans to 21 days before and up to 7 days after the scheduled study visit date for Cycles ≥ 6.

In addition, the final analysis changed from 6 months after the last subject had been enrolled to approximately 14 months after the last subject has been enrolled.

Important protocol deviations are summarised in **Table *5***.

Table 5. Important Protocol Deviations; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects) (All Treated Subjects)

Important Protocol Deviation	**All Subjects (N = 124) n (%)**
Subjects with at least 1 important protocol deviation	20 (16.1%)
Assessments or procedures deviations; SAE not reported within 24 hours	9 (7.3%)
Assessments or procedures deviations; safety assessments not completed	2 (1.6%)
Assessments or procedures deviations; endpoint out of statistical window	1 (0.08)
Eligibility	1 (0.8%)[a]

ICF & general GCP non-compliance	4 (3.2%)
Study medication compliance	4 (3.2%)

a One subject had squamous cell carcinoma prior to study entry that was removed a few days after starting study treatment

Baseline data

Table 6. Demographics, Study ACE-LY-004 (All Treated Subjects) (All Treated Subjects)

	All Subjects N = 124 n (%)
Age (years)	
Mean (SD)	67.1 (10.5)
Median	68
Min, max	42, 90
Age group	
< 65 years	44 (35.5%)
³ 65 years	80 (64.5%)
< 75 years	92 (74.2%)
³ 75 years	32 (25.8%)
Sex	
Male	99 (79.8%)
Female	25 (20.2%)
Race	
Black or African American	3 (2.4%)
White	92 (74.2%)
Not reported	29 (23.4%)
Ethnicity	
Hispanic or Latino	4 (3.2%)
Not Hispanic or Latino	90 (72.6%)
Missing	30 (24.2%)
Region	
US	45 (36.3%)
Ex-US	79 (63.7%)

Table 7. Baseline and Disease Characteristics, Study ACE-LY-004 (All Treated Subjects)

	All Subjects N = 124 n (%)
ECOG, n (%)	
0	71 (57.3%)
1	44 (35.5%)
2	8 (6.5%)

	All Subjects N = 124 n (%)
3	1 (0.8%)
Time (months) from initial diagnosis to first dose	
Mean (SD)	55.2 (39.2)
Median	46.3
Min, max	2.5, 170.1
Tumor burden (cm^2)	
Mean (SD)	34.1 (43.7)
Median	20.4
Min, max	2.6, 299.0
Simplified MIPI score [a]	
Low risk [0-3]	48 (38.7%)
Intermediate risk [4-5]	54 (43.5%)
High risk [6-11]	21 (16.9%)
Missing	1 (0.8%)
Tumor bulk	
< 5 cm	78 (62.9%)
≥ 5 and < 10 cm	36 (29.0%)
≥ 10 cm	10 (8.1%)
Ann Arbor staging for lymphoma	
I	2 (1.6%)
II	7 (5.6%)
III	22 (17.7%)
IV	93 (75.0%)
Refractory disease at baseline [b]	
Yes	30 (24.2%)
No	94 (75.8%)
LDH > upper limit normal	
Yes	33 (26.6%)
No	90 (72.6%)
Missing	1 (0.8%)
Bone marrow aspiration and biopsy result [c]	
Involved	62 (50.0%)
Not involved	60 (48.4%)
Indeterminate	1 (0.8%)
Other [d]	1 (0.8%)
Number of subjects with extranodal disease	89 (71.8%)
Bone marrow	63 (50.8%)
Gastrointestinal	13 (10.5%)
Pulmonary/lung	12 (9.7%)

	All Subjects N = 124 n (%)
Skin/dermis	8 (6.5%)
Pleura	7 (5.6%)
Soft tissue	7 (5.6%)
Osseous/bone	5 (4.0%)
Hepatic/liver	2 (1.6%)
Unknown	2 (1.6%)

a *The simplified MIPI score was derived with the use of the 4 prognostic factors of age, ECOG score, LDH level, and white blood cell count at baseline. The MIPI score range depended on the range of these characteristics. The MIPI classifies subjects as having low-, intermediate-, or high-risk disease, as defined by scores of 0 to 3, 4 or 5, and 6 to 11, respectively.*

b Refractory disease was defined as a lack of at least a PR to the last therapy before study entry

c The basis for determining bone marrow involvement was not specified in the protocol and could be based on histology, immunohistochemistry, or flow cytometry.

d Not enough cells.

Table 8. Select Prior Therapies for Mantle Cell Lymphoma, Study ACE-LY-004 (All Treated Subjects)

	All Subjects N = 124 n (%)
Number of prior therapy regimens for MCL	
Mean (SD)	1.9 (1.1)
Median	2
Min, max	1, 5
1	59 (47.6%)
2	37 (29.8%)
≥ 3	28 (22.6%)
Select prior therapy regimens for MCL	
Rituximab as single agent or part of a regimen	118 (95.2%)
CHOP based regimen	64 (51.6%)
ARA-C based regimen	42 (33.9%)
Bendamustine and rituximab based regimen	27 (21.8%)
Hyper-CVAD	26 (21.0%)
Bortezomib/carfilzomib	24 (19.4%)
DHAP	24 (19.4%)
Stem cell transplant	22 (17.7%)
Other chemotherapy [a]	12 (9.7%)
BEAM	9 (7.3%)
Lenalidomide	8 (6.5%)
FC	8 (6.5%)
mTOR inhibitor	6 (4.8%)
Other [b]	3 (2.4%)

a Includes melphalan, mitoxanthrone, gemcitabine, vincristine, cladarabine, cisplatin, oxaliplatin, chlorambucil, cyclophosphamide, iphosphamide, epirubicin, and etoposide as single agents or in

combination.
b Includes alemtuzumab and ibritumomab tiuxetan.

Numbers analysed

The primary efficacy and safety analyses were performed on the All-treated Population, defined as all enrolled subjects who received ≥1 dose of study treatment. All 124 enrolled subjects received at least 1 dose of study treatment. The analyses of DOR time to best response, and time to CR) were conducted on the subset of the All-treated Population who achieved CR or PR as their best overall response.

Outcomes and estimation

Objective response rate by investigator

Table 9. Overall Response Rate and Best Overall Response by Investigator Assessment, Study ACE-LY-004 (All Treated Subjects) at the 12-Month Analysis, the 24-Month Update, and the 54-month Final Analysis

	All Subjects (N = 124)					
	12-month analysis		24-Month Update		54-Month Final Analysis	
	n (%)	95% CI [a]	n (%)	95% CI [a]	n (%)	95% CI [a]
ORR (CR + PR)	100 (80.6%)	(72.6%, 87.2%)	—	—	101 (81.5%)	(73.5%, 87.9%)
Best response						
CR	49 (39.5%)	(30.9%, 48.7%)	53 (42.7%)	(33.9%, 51.9%)	59 (47.6%)	(38.5%, 56.7%)
PR	51 (41.1%)	(32.4%, 50.3%)	47 (37.9%)	(29.3%, 47.1%)	42 (33.9%)	(25.6%, 42.9%)
SD	11 (8.9%)	(4.5%, 15.3%)	—	—	10 (8.1%)	(3.9%, 14.3%)
PD	10 (8.1%)	(3.9%, 14.3%)	—	—	—	—
NE [b]	3 (2.4%)	(0.5%, 6.9%)	—	—	—	—

a 95% exact binomial CI.
b Included subjects without any adequate postbaseline disease assessment.
Note: The 12-month analysis data cutoff date was 28 February 2017. The 24-month update data cutoff date was 12 February 2018. The 54-month final analysis data cutoff date was 04 December 2020.
Note: Data that have not changed since the 12-month analysis data cutoff date are indicated by a dash and are not repeated in the update columns.

Duration of response

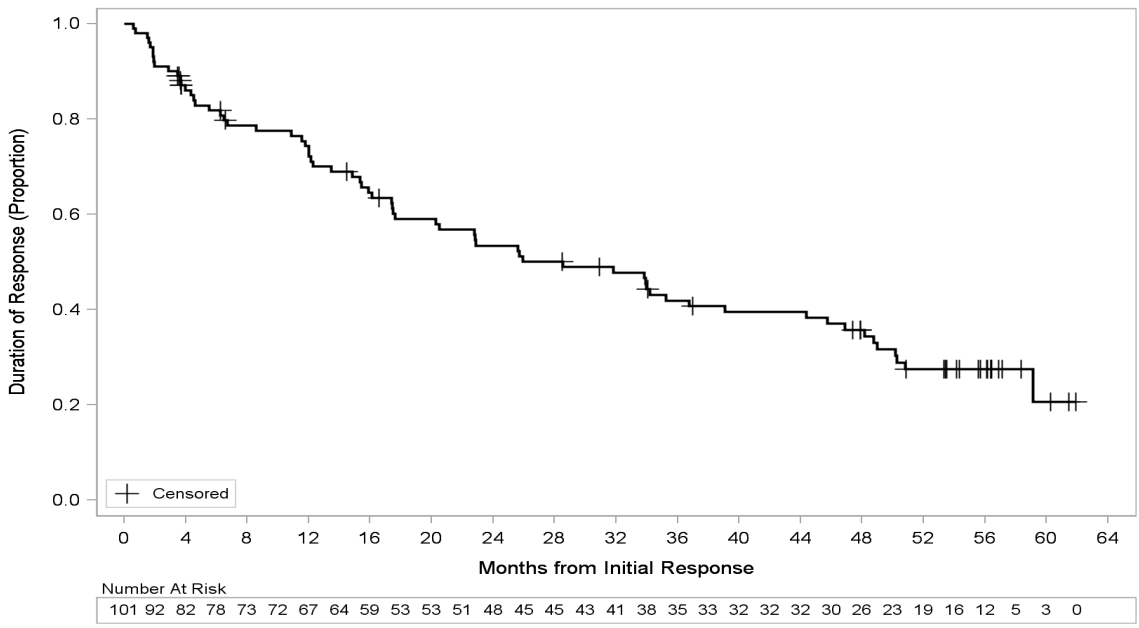
Table 10. Duration of Response by Investigator Assessment; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects Who Achieved Partial or Complete Response)

	All Subjects N = 101
DOR, n (%)	
Events [a]	66 (65.3%)
Disease progression	61 (60.4%)

	All Subjects N = 101
Death	5 (5.0%)
Censored [b]	35 (34.7%)
Data cutoff	21 (20.8%)
Subsequent anticancer therapy	11 (10.9%)
Lost to follow-up	2 (2.0%)
Withdrew consent	1 (1.0%)
DOR [c] (months) based on KM estimates	
Median (95% CI)	28.6 (17.5, 39.1)
Min, Max	0.59, 61.90+

a Events were the number of subjects who progressed according to the Lugano classification or died. PDs and deaths occurring after initiation of subsequent anticancer therapy were censored at the last adequate disease assessment before initiation of subsequent anticancer therapy.
b Subjects alive without progression according to the Lugano classification by the analysis data cutoff date were censored at their last adequate disease assessment date before the data cutoff date.
c DOR was calculated as the number of months from first documented response to the date of the first event (PD or death) or censoring before the data cutoff date.
N = number of all treated subjects who achieved CR or PR; + indicates censored observations

Table 11. Kaplan-Meier Plot for Duration of Response by Investigator Assessment Study ACE-LY-004; 54-Month Final Analysis (All Treated Subjects Who Achieved Partial or Complete **Response)**



Objective response rate by IRC

The ORR was 79.8% (95% CI 71.7%, 86.5%) and the CR rate was 39.5% (95% CI 30.9%, 48.7%) based on IRC assessment according to the Lugano classification.

The overall concordance rates between the investigator- and IRC-assessed responses for ORR and CR were 91.1% and 93.5%, respectively.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12. Summary of Efficacy for trial ACE-LY-004

Title: An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma			
Study identifier	Study code: ACE-LY-004 (D8225C00002) EU CTR: 2023-509352-34-00 NCT Number: NCT02213926		
Design	ACE-LY-004 is a single-arm, Phase II, multicentre, open-label study in subjects with histologically documented mantle cell lymphoma (MCL) who had failed to ≥ 1 (but not > 5) prior treatment regimens. This study was designed to determine the activity of acalabrutinib in subjects with relapsed or refractory MCL (R/R MCL) as measured primarily by objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).		
	Duration of study:		02 March 2015 (first subject enrolled) to 04 December 2020 (54-month final data cutoff date for the final analysis)
Hypothesis	Study ACE-LY-004 planned to enrol approximately 117 subjects. For efficacy, a one-sample Chi-square test with a 0.025 one-sided significance level had more than 99% power to test the null hypothesis that ORR was ≤20% (not considered clinically compelling) versus the alternative hypothesis that ORR was ≥40%. For safety, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% was 69.1%, 90.6%, or 99.8%, respectively. This provided reasonable assurance that events occurring at ≥1% frequency could be identified. Based on the above, the applicant set the statistical power to ensure an adequate number of subjects not only for efficacy but also from the safety perspective.		
Treatments groups	Acalabrutinib		Acalabrutinib 100 mg twice daily (bd) orally (124 subjects were enrolled)
Endpoints and definitions	Primary endpoint	ORR based on investigator assessment according to the Lugano classification	ORR was defined as the proportion of subjects who achieved either a complete response (CR) or partial response (PR) as best overall response based on investigator assessment according to the Lugano classification for non-Hodgkin lymphoma (hereafter referred to as Lugano classification)
	Key Secondary endpoints	DOR based on investigator assessment according to the Lugano classification	DOR was defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of objective MCL disease progression or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date were censored. Subjects who had the event after the start of subsequent anticancer therapy were censored at the last adequate disease assessment on or before the start of subsequent anticancer therapy and data cutoff time. Subjects with no adequate postbaseline disease assessment were censored on first dose date.

		PFS based on investigator assessment according to the Lugano classification	PFS was defined as the interval from the start of study treatment to the first documentation of objective MCL disease progression per investigator assessment or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date were censored. Subjects who had the event after the start of subsequent anticancer therapy were censored at the time of their last adequate disease assessment on or before the start of subsequent anticancer therapy or data cutoff. Subjects with no adequate postbaseline disease assessment were censored on first dose date.
		OS	The duration of OS was measured from the time of first study treatment administration until the date of death from any cause. Subjects who were known to be alive as of their last known status were censored at their last date known to be alive.
Final Data cutoff date	04 December 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis of ORR was conducted on the All-treated Population at the cutoff date of 04 December 2020 (54-month final analysis). ORR and the corresponding 95% 2-sided confidence interval (CI) calculated using the exact binomial distribution are presented. The All-treated population is defined as all enrolled subjects who received ≥ 1 dose of study treatment.		
Descriptive statistics and estimate variability		54-Month-Final Analysis N=124 subjects	
		n (%)	95% CI
	ORR (CR + PR)	101 (81.5%)	(73.5%, 87.9%)
	Best overall response		
	CR	59 (47.6%)	(38.5%, 56.7%)
	PR	42 (33.9%)	(25.6%, 42.9%)
	SD	10 (8.1%)	(3.9%, 14.3%)
	PD	10 (8.1%)	(3.9%, 14.3%)
	Non evaluable (NE)	3 (2.4%)	(0.5%, 6.9%)
Effect estimate per comparison	Not applicable		

Analysis description	**Secondary analysis**	
Analysis population and time point description	The analysis of DOR was conducted on the subset of the All-treated Population who achieved CR or PR as their best overall response. The analysis of PFS and OS was conducted on the All-treated Population. The analysis of DOR, PFS, and OS was estimated using the Kaplan-Meier (KM) method. KM estimates with 95% CIs were calculated for event time quartiles and event-free rates were calculated at selected timepoints.	
Descriptive statistics and estimate variability		54-Month Final Analysis N=101
	DOR (months) based on KM estimates	
	Median (95% CI)	28.6 (17.5, 39.1)
	Min, Max	0.59, 61.90+
	KM point estimate DOR [a] (%)	
	36 Months	41.9 (31.7, 51.8)
	48 Months	35.8 (25.9, 45.7)
	[a] DOR was calculated as the number of months from first documented response to the date of the first event (PD or death) or censoring before the data cutoff of 04 December 2020 (54-month final analysis).	
		54-Month Final Analysis N=124
	PFS (months) based on KM estimates	
	Median (95% CI)	22.0 (16.6, 33.3)
	Min, Max	0.03+, 63.61+
	KM point estimate for PFS [b] (%)	
	24 Months (95% CI)	49.6 (40.1, 58.4)
	48 Months (95% CI)	31.1 (22.5, 39.9)
	[b] PFS was calculated as the number of months from first dose date to the date of first event (PD or death) or censoring prior to the data cutoff of 04 December 2020 (54-month final analysis).	
		54-Month Final Analysis N=124
	OS (months) based on KM estimates	
	Median (95% CI)	59.2 (36.5, NE)
	Min, Max	0.26, 68.83+
	KM point estimate for OS [c] (%)	
	24 Months (95% CI)	72.4 (63.5, 79.5)
	48 Months (95% CI)	52.4 (42.9, 61.0)
	[c] Survival was calculated as the number of months from the first dose date to the date of death or censoring	

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH conducted a single-arm, phase 2 Study to evaluate the efficacy of acalabrutinib in the treatment of mantle cell lymphoma.

The MAH has not followed CHMP's advice to conduct a randomised trial (EMA/CHMP/SAWP/795386/2017). However, as the pivotal trial ACE-LY-004 already has extensive follow-up, randomised data in CLL is the basis for acalabrutinib's current full approval, and further data in 1st line mantle cell lymphoma are currently under assessment (procedure EMEA/H/C/005299/II/0025), the totality of data is considered sufficient to support the current application.

Sample size

The study adhered to the initial target sample size of 117 patients. Only 7 additional patients were enrolled, making a total of 124 patients.

The study was originally powered to demonstrate an ORR exceeding 20% in bortezomib-naïve patients and exceeding 15% in bortezomib-experienced patients. However, no such success criterion was planned for the efficacy analysis, which was a simple descriptive analysis of the ORR (and the 95% confidence interval for ORR) in the 124 enrolled patients, all of whom received at least one dose of treatment.

Statistical methods

A follow-up analysis was conducted 24 months after the last patient had been enrolled, and a close-out analysis was conducted when all patients had exited the study (54 months after the last patient had been enrolled).

The trial had one futility interim analysis, which was conducted under Amendment 3.0, when patients were being stratified by bortezomib status upon enrolment (stratification by bortezomib status ended under Amendment 4.0 because other studies had indicated that efficacy would be similar). Based on patients' bortezomib status, different stopping criteria were used (<8/28 responders in the bortezomib-naïve subgroup; <3/12 responders in the bortezomib-exposed subgroup). Neither of these stopping criteria was met, so the study continued.

In the analyses of DOR and PFS, the protocol initially stated that patients who progressed or died after missing 2 or more missing tumour assessments would be censored. According to EMA guidance (EMA/CHMP/27994/2008/Rev 1), such patients should be counted as cases. From protocol amendment 4.0, the censoring rules were removed from the protocol and deferred to the statistical analysis plan, (dated 15-March-2017) which contained no rule to censor patients after missing 2 or more assessments. Therefore, the censoring rules used in this trial are appropriate for EMA.

Conduct of the study

The protocol was amended 6 times, and enrolment started under protocol amendment 1.0.

Efficacy data and additional analyses

At the 54-month analysis, the overall response was 81.5% with a CR rate of 47.6% by investigator assessment per Lugano classification. Responses were durable with a median DOR of 28.6 months. The evaluation of efficacy of acalabrutinib in r/r MCL is based on non-randomised data, and effects of

acalabrutinib on standard endpoints like PFS and OS cannot be inferred. Although the ORR seen in the pivotal trial is unmistakeably a drug effect, there is principally a need to conclude that the benefit conferred by tumour shrinkage outweighs any adverse effects. As this is a same-class drug as the predecessor ibrutinib, where high ORR with durable responses was considered to outweigh adverse effects, the same conclusion is possible for acalabrutinib, based on numerically improved ORR and DoR and a safety profile that is qualitatively not inferior.

The initially applied for indication by the MAH was for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

The inclusion criteria of study ACE-LY-004 stipulated that patients had to have disease which had relapsed or been refractory after ≥1 prior therapy for MCL and requiring further treatment as well as documented failure to achieve at least partial response (PR) with, or documented disease progression after, the most recent treatment regimen. In addition, patients were required to have received at least 1, but no more than 5, prior treatment regimens for MCL. Taken together, a population relapsed or refractory to ≥1 prior therapy for MCL, was enrolled.

However, the CHMP noted that patients with prior exposure to BTK inhibitors were specifically excluded from the ACE-LY-OO4 trial.

The MAH's updated proposal for the treatment of adult patients with MCL who have received at least one prior therapy and who did not previously progress on treatment with a BTK inhibitor was also not accepted by the CHMP. The pivotal study population did not include patients who were previously treated with a BTK inhibitor but did not progress on treatment. It is not clear if acalabrutinib is effective in this population, as patients might have developed resistance (e.g. resistance mutations) but stopped treatment before progression was shown. Moreover, the CHMP considered that in the clinical scenario where a patient has previously been treated with a BTK inhibitor for MCL but without progressing, it would be normal practice to reintroduce the same prior BTK inhibitor. Therefore the CHMP requested that the final indication should be modified to "treatment of adult patients with relapsed or refractory MCL who have received at least one prior therapy not previously treated with a BTK inhibitor", to better reflect the studied population. This proposal was accepted by the MAH.

2.4.4. Conclusions on the clinical efficacy

The clinical efficacy data submitted in this extension of indication application support the benefit of acalarbrutinib in the final agreed indication.

2.5. Clinical safety

Introduction

The most common ADRs previously established for acalabrutinib monotherapy include those related to infections, bone marrow suppression, headache, diarrhoea, bruising, musculoskeletal pain, nausea, fatigue, cough and rash.

Patient exposure

The key safety data in support of this application derive from the final long-term follow-up analysis (54-month analysis) of the phase II study (ACE-LY-004) in subjects with R/R MCL, with data cutoff 04 December 2020, and a median follow-up of 38.1 months (**Table 13**).

At the time of final data cutoff, 51 of the 124 subjects (41.1%) were continuing in study ACE LY 004.

Table 13. Exposure to Study Treatment; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

	All Subjects N=124
Duration of exposure (months)[a]	
Mean (SD)	25.3 (21.90)
Median	17.5
Min, Max	0.1, 65.3
Duration of exposure, n (%)	
≤3 Months	16 (12.9%)
>3 to ≤6 Months	17 (13.7%)
>6 to ≤12 Months	17 (13.7%)
>12 to ≤24 Months	20 (16.1%)
>24 to ≤36 Months	17 (13.7%)
>36 to ≤48 Months	8 (6.5%)
>48 to ≤60 Months	15 (12.1%)
>60 Months	14 (11.3%)
Actual cumulative dose (g) [b]	
Mean (SD)	149.0 (129.85)
Median	103.2
Min, Max	0.6, 396.2
Average daily dose (mg) [c]	
Mean (SD)	192.2 (18.94)
Median	197.0
Min, Max	54.2, 200.0
Relative dose intensity [d]	
Mean (SD)	96.1 (9.47)
Median	98.6
Min, Max	27.1, 100.0

a Duration of exposure is the interval between first dose date and the last dose date.
b Actual cumulative dose is the total dose administered during the drug exposure period.
c Average daily dose is the ratio of actual cumulative dose and duration of exposure.
d Relative dose intensity was the ratio of the actual cumulative dose to the planned cumulative dose through the treatment exposure period.

Adverse events

Adverse events presented in this section were coded using MedDRA Version 21.1. A subject with multiple severity grades for a given adverse event was counted only once under the maximum severity.

Table 14. Overview of Treatment-Emergent Adverse Events; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

	All Subjects N = 124 n (%)
TEAE	
Any grade	123 (99.2%)
Grade 1-2	41 (33.1%)
Grade 3-4	78 (62.9%)
Study drug-related adverse event	
Any grade	99 (79.8%)
Grade 3-4	41 (33.1%)
Treatment-emergent Serious adverse event	
Any grade	62 (50.0%)
Grade 3-4	57 (46.0%)
Study drug-related serious adverse event	
Any grade	22 (17.7%)
Grade 3-4	20 (16.1%)
Fatal/Grade 5 TEAE	4 (3.2%)
Adverse event leading to study drug discontinuation	15 (12.1%)

Common adverse events by preferred term

Table 15. Treatment-Emergent Adverse Events Reported in ≥ 5% of Subjects; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

Preferred Term	**All Subjects N = 124 n (%)**
Headache	48 (38.7%)
Diarrhoea	47 (37.9%)
Fatigue	37 (29.8%)
Cough	29 (23.4%)
Myalgia	27 (21.8%)
Nausea	27 (21.8%)
Asthenia	22 (17.7%)
Constipation	20 (16.1%)
Upper respiratory tract infection	20 (16.1%)
Dyspnoea	19 (15.3%)
Pyrexia	19 (15.3%)

Vomiting	19 (15.3%)
Anaemia	18 (14.5%)
Dizziness	18 (14.5%)
Rash	18 (14.5%)
Contusion	16 (12.9%)
Sinusitis	16 (12.9%)
Abdominal pain	15 (12.1%)
Pneumonia	15 (12.1%)
Back pain	14 (11.3%)
Neutropenia	14 (11.3%)
Arthralgia	13 (10.5%)
Bronchitis	11 (8.9%)
Musculoskeletal pain	11 (8.9%)
Oedema peripheral	11 (8.9%)
Petechiae	11 (8.9%)
Abdominal pain upper	10 (8.1%)
Herpes zoster	10 (8.1%)
Nasopharyngitis	10 (8.1%)
Paraesthesia	10 (8.1%)
Decreased appetite	9 (7.3%)
Epistaxis	9 (7.3%)
Insomnia	9 (7.3%)
Memory impairment	9 (7.3%)
Muscle spasms	9 (7.3%)
Stomatitis	9 (7.3%)
Haematoma	8 (6.5%)
Pain in extremity	8 (6.5%)
Vision blurred	8 (6.5%)
Erythema	7 (5.6%)
Fall	7 (5.6%)
Hypoaesthesia	7 (5.6%)
Hypotension	7 (5.6%)
Influenza	7 (5.6%)
Lacrimation increased	7 (5.6%)
Peripheral swelling	7 (5.6%)
Thrombocytopaenia	7 (5.6%)

Grade 3 or Higher Adverse Events

Table 16. Grade 3 or Grade 4 Treatment-Emergent Adverse Events; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects) Reported in ≥ 2 Subjects

Preferred Term	All Subjects N = 124 n (%)
At least 1 Grade 3 or 4 TEAE	78 (62.9%)
Anaemia	14 (11.3%)
Neutropenia	14 (11.3%)
Pneumonia	9 (7.3%)
Diarrhoea	5 (4.0%)
Thrombocytopaenia	5 (4.0%)
General physical health deterioration	4 (3.2%)
Neutrophil count decreased	4 (3.2%)
Dyspnoea	3 (2.4%)
Hyperuricaemia	3 (2.4%)
Tumour lysis syndrome	3 (2.4%)
Urinary tract infection	3 (2.4%)
Vomiting	3 (2.4%)
Abdominal pain	2 (1.6%)
Asthenia	2 (1.6%)
Cataract	2 (1.6%)
Colitis	2 (1.6%)
Decreased appetite	2 (1.6%)
Fatigue	2 (1.6%)
Gastrointestinal haemorrhage	2 (1.6%)
Headache	2 (1.6%)
Hypertension	2 (1.6%)
Inguinal hernia	2 (1.6%)
Myalgia	2 (1.6%)
Nausea	2 (1.6%)
Oedema peripheral	2 (1.6%)
Rash	2 (1.6%)
Sepsis	2 (1.6%)
Syncope	2 (1.6%)
Upper respiratory tract infection	2 (1.6%)

Serious adverse event/deaths/other significant events

Serious adverse events

Table 17. Treatment-Emergent Serious Adverse Events; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects) Reported in ≥ 2 Subjects

Preferred Term	All Subjects N = 124 n (%)
Any treatment-emergent SAE	62 (50.0%)
Pneumonia	8 (6.5%)
Anaemia	6 (4.8%)
General physical health deterioration	4 (3.2%)
Colitis	2 (1.6%)
Gastrointestinal haemorrhage	2 (1.6%)
Pyrexia	2 (1.6%)
Sepsis	2 (1.6%)
Tumour lysis syndrome	2 (1.6%)
Upper respiratory tract infection	2 (1.6%)
Vomiting	2 (1.6%)

Deaths

Table 18. Summary of All Deaths; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

	All Subjects N = 124 n (%)
Death	59 (47.6%)
Disease progression	40 (32.3%)
Adverse event	6 (4.8%)
Other	6 (4.8%)
Unknown	7 (5.6%)
Within 30 days of last dose	8 (6.5%)
More than 30 days after last dose	51 (41.1%)

Adverse events of special interest (AESI)

The only AESI category for acalabrutinib is ventricular arrythmias, as defined in the Acalabrutinib Investigator's Brochure, 13th Edition. There were no reports of AESIs in the ACE-LY-004 study.

Selected TEAEs of Clinical Interest (ECIs)

Selected TEAEs for additional analyses (ECIs) were identified based on nonclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved BTK inhibitors. The following events are considered ECIs: cardiac events; cytopenias (anaemia, leukopenia [neutropenia and other leukopenia] and thrombocytopaenia); haemorrhage events; hepatic events; hypertension; infection; ILD/pneumonitis; second primary malignancies (including and excluding skin malignancies); and TLS.

Cardiac Events

Table 19. Treatment-Emergent Events of Clinical Interest: Cardiac Events; 54 Month Final Analysis (All Treated Subjects), Study ACE-LY-004 (All Treated Subjects)

ECI Category	All Subjects N = 124 n (%)		
Preferred Term	Any Grade	Grade 3 or 4	Grade 5
Cardiac events	16 (12.9%)	6 (4.8%)	0
Atrial fibrillation	3 (2.4%)	0	0
Mitral valve incompetence	2 (1.6%)	0	0
Tachycardia	2 (1.6%)	0	0
Acute coronary syndrome	1 (0.8%)	1 (0.8%)	0
Acute myocardial infarction	1 (0.8%)	1 (0.8%)	0
Angina pectoris	1 (0.8%)	0	0
Aortic valve incompetence	1 (0.8%)	0	0
Atrioventricular block complete	1 (0.8%)	1 (0.8%)	0
Bradycardia	1 (0.8%)	0	0
Cardiac failure	1 (0.8%)	1 (0.8%)	0
Cardio-respiratory arrest	1 (0.8%)	1 (0.8%)	0
Coronary artery disease	1 (0.8%)	1 (0.8%)	0
Extrasystoles	1 (0.8%)	0	0
Pericardial effusion	1 (0.8%)	0	0
Right ventricular enlargement	1 (0.8%)	0	0
Sinus arrest	1 (0.8%)	1 (0.8%)	0
Sinus tachycardia	1 (0.8%)	0	0
Tricuspid valve incompetence	1 (0.8%)	0	0
Ventricular extrasystoles	1 (0.8%)	0	0

Cardiac events were based on the System organ class (SOC) Cardiac disorders.

Five subjects had Grade 3 events, including 1 event considered related to study treatment (SAE of acute coronary syndrome). One subject had a Grade 4 cardiac event (SAE of Cardiorespiratory arrest) which was considered not related to study treatment. There were no Grade 5 cardiac events.

Five subjects had serious cardiac events (acute myocardial infarction, coronary artery disease, cardio-respiratory arrest, acute coronary syndrome and cardiac failure). Among those 5 subjects, 3 had a medical history of cardiovascular disease: 1 subject with coronary artery disease had a medical history of mild arteriosclerosis and coronary artery bypass; 1 subject with acute coronary syndrome (considered treatment-related by the investigator) had a medical history of ischaemic stroke; and 1 subject with cardiac failure (that resolved within 4 days) had a medical history that included coronary artery disease, angioplasty, coronary arterial stent insertion, and moderate hypercholesterolaemia.

Cytopenias

Table 20. Treatment-Emergent Events of Clinical Interest: Cytopenia Events; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

ECI Category ECI Subcategory Preferred Term	All Subjects N = 124 n (%)		
	Any Grade	Grade 3 or 4	Grade 5
Anaemia	18 (14.5%)	14 (11.3%)	0
Anaemia	18 (14.5%)	14 (11.3%)	0
Leukopenia	18 (14.5%)	18 (14.5%)	0
Neutropenia	18 (14.5%)	18 (14.5%)	0
Neutropenia	14 (11.3%)	14 (11.3%)	0
Neutrophil count decreased	4 (3.2%)	4 (3.2%)	0
Febrile neutropenia	1 (0.8%)	1 (0.8%)	0
Other leukopenia	1 (0.8%)	1 (0.8%)	0
Leukopenia	1 (0.8%)	1 (0.8%)	0
Thrombocytopaenia	9 (7.3%)	6 (4.8%)	0
Thrombocytopaenia	7 (5.6%)	5 (4.0%)	0
Platelet count decreased	3 (2.4%)	1 (0.8%)	0

Leukopenia events were based on the SMQ Haematopoietic leukopenia [narrow + broad]. Anaemia events were based on the SMQ Haematopoietic erythropenia [narrow + broad]. Thrombocytopaenia events were based on the SMQ Haematopoietic thrombocytopaenia [narrow + broad].

Haemorrhage

Table 21. Treatment-Emergent Events of Clinical Interest: Haemorrhage and Major Haemorrhage; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

ECI Category Preferred Term	All Subjects N = 124 n (%)		
	Any Grade	Grade 3 or 4	Grade 5
Haemorrhage	46 (37.1%)	5 (4.0%)	0
Contusion	16 (12.9%)	0	0
Petechiae	11 (8.9%)	0	0
Epistaxis	9 (7.3%)	0	0
Haematoma	8 (6.5%)	1 (0.8%)	0
Purpura	6 (4.8%)	0	0
Ecchymosis	4 (3.2%)	0	0
Increased tendency to bruise	3 (2.4%)	0	0
Gastrointestinal haemorrhage	2 (1.6%)	2 (1.6%)	0
Haematuria	2 (1.6%)	1 (0.8%)	0
Blood blister	1 (0.8%)	0	0
Conjunctival haemorrhage	1 (0.8%)	0	0
Haematochezia	1 (0.8%)	0	0
Haemorrhagic diathesis	1 (0.8%)	0	0

ECI Category Preferred Term	All Subjects N = 124 n (%)		
	Any Grade	**Grade 3 or 4**	**Grade 5**
Periorbital haematoma	1 (0.8%)	0	0
Post-procedural haemorrhage	1 (0.8%)	0	0
Rectal haemorrhage	1 (0.8%)	0	0
Subdural haematoma	1 (0.8%)	1 (0.8%)	0
Vessel puncture site haematoma	1 (0.8%)	0	0
Major haemorrhage	5 (4.0%)	5 (4.0%)	0
Gastrointestinal haemorrhage	2 (1.6%)	2 (1.6%)	0
Haematoma	1 (0.8%)	1 (0.8%)	0
Haematuria	1 (0.8%)	1 (0.8%)	0
Subdural haematoma	1 (0.8%)	1 (0.8%)	0

Haemorrhage events were based on SMQ Haemorrhage terms (excluding laboratory terms). Major haemorrhage events were further defined with criteria of Grade ≥ 3, serious, or any grade or seriousness CNS haemorrhage.

Hepatic Events

Table 22. Treatment-Emergent Events of Clinical Interest: Hepatotoxicity; 54 Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

ECI Category Preferred Term	All Subjects N = 124 n (%)		
	Any Grade	**Grade 3 or 4**	**Grade 5**
Hepatotoxicity	7 (5.6%)	3 (2.4%)	0
Blood bilirubin increased	2 (1.6%)	0	0
Alanine aminotransferase increased	1 (0.8%)	1 (0.8%)	0
Drug-induced liver injury	1 (0.8%)	1 (0.8%)	0
Hepatic steatosis	1 (0.8%)	0	0
Hepatotoxicity	1 (0.8%)	1 (0.8%)	0
Transaminases increased	1 (0.8%)	0	0

Hepatotoxicity events were based on SMQ [narrow] Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions, SMQ [narrow] Liver related investigations signs, and SMQ [narrow] Hepatitis, non-infectious.

Three subjects had Grade 3 hepatotoxicity events, including 1 event of hepatotoxicity (related to study treatment) and 1 event of drug-induced liver injury (verbatim term: cytolytic hepatitis due to concomitant medication, considered related to piperacillin/tazobactam per the investigator and considered not related to study treatment), and 1 event of ALT increased (not related to study treatment). All these events resolved.

One subject met biochemical criteria for Hy's law, associated with SAEs of Grade 4 jaundice (cholestatic) and hydronephrosis, considered not related to study treatment.

Hypertension

Table 23. Treatment-Emergent Events of Clinical Interest: Hypertension; 54 Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

ECI Category Preferred Term	All Subjects N = 124 n (%)		
	Any Grade	Grade 3 or 4	Grade 5
Hypertension	5 (4.0%)	2 (1.6%)	0
Hypertension	4 (3.2%)	2 (1.6%)	0
Blood pressure increased	1 (0.8%)	0	0

Hypertension events were based on SMQ Hypertension [narrow].

Infections

Table 24. Treatment-Emergent Events of Clinical Interest: Infections; 54 Month Final Analysis, Study ACE-LY-004 (All Treated Subjects) Reported in ≥ 2 Subjects

ECI Category Preferred Term	All Subjects N = 124 n (%)		
	Any Grade	Grade 3 or 4	Grade 5
Infections	84 (67.7%)	21 (16.9%)	0
Upper respiratory tract infection	20 (16.1%)	2 (1.6%)	0
Sinusitis	16 (12.9%)	0	0
Pneumonia	15 (12.1%)	9 (7.3%)	0
Bronchitis	11 (8.9%)	0	0
Herpes zoster	10 (8.1%)	1 (0.8%)	0
Nasopharyngitis	10 (8.1%)	0	0
Influenza	7 (5.6%)	0	0
Lower respiratory tract infection	6 (4.8%)	1 (0.8%)	0
Rhinitis	6 (4.8%)	0	0
Urinary tract infection	5 (4.0%)	3 (2.4%)	0
Conjunctivitis	4 (3.2%)	0	0
Laryngitis	4 (3.2%)	0	0
Respiratory tract infection	4 (3.2%)	1 (0.8%)	0
Localised infection	3 (2.4%)	0	0
Oral herpes	3 (2.4%)	0	0
Pharyngitis	3 (2.4%)	1 (0.8%)	0
Cellulitis	2 (1.6%)	0	0
Chronic sinusitis	2 (1.6%)	0	0
Eye infection	2 (1.6%)	0	0
Fungal infection	2 (1.6%)	0	0
Sepsis	2 (1.6%)	2 (1.6%)	0
Tracheitis	2 (1.6%)	0	0
Viral infection	2 (1.6%)	0	0

Grade 3 and Grade 4 infections were reported in 21 subjects (16.9%). Four subjects had Grade 4 infections, including 2 events considered related to study treatment (urosepsis and sepsis). All Grade 4 infections were reported as serious, and all resolved. There were no Grade 5 infections.

Seventeen subjects had treatment-emergent SAEs of infection. The most frequently reported serious infection was pneumonia, reported in 8 subjects (6.5%). No events of infection led to study treatment discontinuation in any subjects.

Interstitial Lung Disease/Pneumonitis

Table 25. Treatment-Emergent Events of Clinical Interest: Interstitial Lung Disease/Pneumonitis; 54 Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

ECI Category Preferred Term	All Subjects N = 124 n (%)		
	Any Grade	Grade 3 or 4	Grade 5
Interstitial lung disease	3 (2.4%)	1 (0.8%)	0
Interstitial lung disease	2 (1.6%)	1 (0.8%)	0
Pulmonary fibrosis	1 (0.8%)	0	0

Events of ILD/pneumonitis were based on the SMQ [narrow] ILD.

Second Primary Malignancies

Table 26. Treatment-Emergent Events of Clinical Interest: Second Primary Malignancies; 54 Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

ECI Category Preferred Term	All Subjects N = 124 n (%)		
	Any Grade	Grade 3 or 4	Grade 5
Second primary malignancies (skin neoplasms, malignant and unspecified)	16 (12.9%)	6 (4.8%)	1 (0.8%)
Basal cell carcinoma	6 (4.8%)	0	0
Squamous cell carcinoma of skin	3 (2.4%)	1 (0.8%)	0
Malignant melanoma	2 (1.6%)	1 (0.8%)	0
Diffuse large B-cell lymphoma	1 (0.8%)	1 (0.8%)	0
Hodgkin's disease	1 (0.8%)	1 (0.8%)	0
Invasive ductal breast carcinoma	1 (0.8%)	1 (0.8%)	0
Metastases to meninges	1 (0.8%)	1 (0.8%)	0
Myelodysplastic syndrome	1 (0.8%)	1 (0.8%)	0
Non-small cell lung cancer	1 (0.8%)	0	1 (0.8%)
Squamous cell carcinoma	1 (0.8%) [a]	0	0

[a] *This subject had SCC in situ of chest, which was excised. This event is therefore considered as skin SPM.*

Second primary malignancies were based on the SMQ Malignant tumours (including Haematological malignant tumours SMQ and Non-haematological malignant tumours SMQ), SMQ Malignant lymphomas [narrow], and SMQ Myelodysplastic syndrome [narrow].

In addition to the cases presented in **Table 26**, there were 2 additional SPMs that occurred beyond the treatment-emergent reporting period and were reported to be the cause of death in these 2 patients; 1 patient had Grade 5 myelodysplastic syndrome diagnosed 56 days after the last dose of study treatment in a patient who had previously discontinued due to thrombocytopaenia and the second patient died of secondary acute myeloid leukaemia diagnosed at 253 days after treatment discontinuation.

Tumour Lysis Syndrome

Events of TLS were based on the PT of TLS. Three subjects (2.4%) had TLS.

Laboratory findings

Haematology

Table 27. Treatment-Emergent Laboratory haematological abnormalities; 54 Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

Laboratory Analyte (abnormal direction)	N	All Subjects N = 124 n (%)		
		Any Grade	Grade 3	Grade 4
Absolute lymphocyte count (decreased)	123	48 (39.0%)	18 (14.6%)	2 (1.6%)
Absolute lymphocyte count (increased)	123	36 (29.3%)	13 (10.6%)	0
Absolute neutrophil count (decreased)	123	46 (37.4%)	9 (7.3%)	9 (7.3%)
Haemoglobin (decreased)	123	57 (46.3%)	10 (8.1%)	0
Leukocytes (decreased)	123	49 (39.8%)	5 (4.1%)	4 (3.3%)
Platelets (decreased)	120	64 (53.3%)	11 (9.2%)	4 (3.3%)

The maximum toxicity grade experienced after first dose of study treatment up to 30 days after the last dose was considered for each subject.

N = Total number of subjects with baseline and at least 1 postbaseline record in the analysis population.

n = Number of subjects in the category with worst postbaseline grade higher than their baseline grade and percentage (%) was calculated relative to the number of all subjects in the analysis set (N).

CTCAE version 4.03 was used for severity grading.

Lymphocytosis

In the 54-month final analysis, lymphocytosis occurred in 43 (35.0%) of 123 subjects (95% CI: 26.6%, 44.1%), with a median time to first postbaseline ALC meeting the lymphocytosis criteria of 1.1 weeks (range: 0.7 to 228.0 weeks). Lymphocytosis resolved in 34 (79.1%) of 43 subjects. Median duration of lymphocytosis was 6.7 weeks (range: 0.1 to 180.1 weeks). Lymphocytosis was not resolved (censored) for 9 (20.9%) of 43 subjects.

Clinical Chemistry

Table 28. Treatment-Emergent Laboratory Abnormalities in Clinical Chemistry; 54 Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

Laboratory Analyte (abnormal direction)	N	All Subjects N = 124 n (%)		
		Any Grade	Grade 3	Grade 4
ALT (increased)	123	36 (29.3%)	4 (3.3%)	0
Albumin (decreased)	123	20 (16.3%)	1 (0.8%)	0
ALP (increased)	123	32 (26.0%)	2 (1.6%)	0
AST (increased)	123	40 (32.5%)	1 (0.8%)	0
Bilirubin (increased)	123	12 (9.8%)	2 (1.6%)	0
Calcium (increased) [a]	123	3 (2.4%)	0	0
Calcium (decreased) [a]	123	19 (15.4%)	2 (1.6%)	3 (2.4%)
Creatinine (increased)	123	114 (92.7%)	0	0
Glucose (increased) [b]	123	73 (59.3%)	4 (3.3%)	0
Glucose (decreased) [b]	123	19 (15.4%)	0	0
Magnesium (increased)	123	8 (6.5%)	0	0
Magnesium (decreased)	123	9 (7.3%)	0	0
Phosphate (decreased)	123	34 (27.6%)	6 (4.9%)	0
Potassium (increased)	123	11 (8.9%)	1 (0.8%)	2 (1.6%)
Potassium (decreased)	123	17 (13.8%)	1 (0.8%)	0
Sodium (increased)	123	15 (12.2%)	0	0
Sodium (decreased)	123	33 (26.8%)	6 (4.9%)	1 (0.8%)
Uric acid (increased) [c]	123	35 (28.5%)	23 (18.7%)	12 9.8%)

a Based on uncorrected serum calcium.

b Based on non-fasting state.

c Based on laboratory only.

Treatment-emergent laboratory abnormality is defined as the event when postbaseline laboratory value with grade worse than baseline grade was observed in specified direction.

The maximum toxicity grade experienced after first dose of study treatment up to 30 days after the last dose was considered for each subject.

N = Total number of subjects with baseline and at least 1 postbaseline record in the analysis population.

n = Number of subjects with observations in the category and percentage (%) was calculated relative to the number of all subjects in the analysis set (N).

CTCAE version 4.03 was used for severity grading.

Hepatitis B Virus Reactivation

Five subjects had any kind of hepatitis (A, B, or C) at screening. This included the following: 1 subject with hepatitis; 1 subject with hepatitis A and hepatitis B core antibody; 2 subjects with hepatitis B, and 1 subject with hepatitis C antibody positive. Of these 5 subjects, 3 hepatitis B virus patients were confirmed by medical history data.

As of the 54-month final analysis, 2 of these subjects had discontinued the study due to 'death (progressive disease)' and 3 subjects discontinued due to 'study terminated by sponsor'. No subject in

this study had clinical or laboratory evidence of hepatitis B virus reactivation except for 1 subject, who was reactive at Study Day 519 only, but not reactive at subsequent visits through Study Day 1595.

Vital Signs and physical findings

There were no clinically important differences in mean systolic and diastolic blood pressure, respiratory rate, heart rate, temperature, and body weight from baseline to last postbaseline values in the 54-month final analysis.

For individual shifts in toxicity grade for blood pressure (systolic and diastolic) from baseline to maximum postbaseline grade. Three subjects (2.4%) shifted from normal systolic blood pressure at baseline to Grade 3, and 2 subjects (1.6%) shifted from normal diastolic blood pressure at baseline to Grade 3.

ECOG Performance Status

For maximum shift from baseline in ECOG score in the 54-month final analysis. The subjects who maintained their ECOG score were 46.3% of subjects. The percentages of subjects who had a 1-, 2-, or 3-score worsening in maximum postbaseline ECOG score were 39.8%, 10.6%, and 0.8%, respectively.

Electrocardiogram Data

ECG data were collected at screening only. Two subjects had baseline ECG results that were classified as abnormal clinically significant (1 subject had sinus tachycardia and 1 subject had left bundle branch block); however, both subjects were asymptomatic and therefore eligible for study entry. Two subjects (1.6%) had a QTc value of > 480 msec at baseline; these subjects were deemed eligible for study entry.

Discontinuation due to adverse events

Adverse events leading to discontinuation

Table 29. Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects)

Preferred Term	**All Subjects N = 124 n (%)**
Subjects with at least 1 TEAE that led to study treatment discontinuation	15 (12.1%)
Aortic stenosis	1 (0.8%)
Atrial fibrillation	1 (0.8%)
Autoimmune encephalopathy	1 (0.8%)
Blood blister	1 (0.8%)
Diffuse large B-cell lymphoma	1 (0.8%)
Dyspnoea	1 (0.8%)
Hodgkin's disease	1 (0.8%)
Leukostasis syndrome	1 (0.8%)
Malignant melanoma	1 (0.8%)

Myelodysplastic syndrome	1 (0.8%)
Non-cardiac chest pain	1 (0.8%)
Non-small cell lung cancer	1 (0.8%)
Petechiae	1 (0.8%)
Pulmonary embolism	1 (0.8%)
Pulmonary fibrosis	1 (0.8%)
Rash	1 (0.8%)
Subdural haematoma	1 (0.8%)
Thrombocytopaenia	1 (0.8%)

Adverse events leading to dose withholding

Table 30. Treatment-Emergent Adverse Events Leading to Dose withholding; 54-Month Final Analysis, Study ACE-LY-004 (All Treated Subjects) Reported in ≥ 2 Subjects

Preferred Term	**All Subjects N = 124 n (%)**
Subjects with at least 1 TEAE that led to study treatment dose delay	51 (41.1%)
Herpes zoster	8 (6.5%)
Pneumonia	6 (4.8%)
Vomiting	6 (4.8%)
Nausea	5 (4.0%)
Anaemia	4 (3.2%)
Neutropenia	4 (3.2%)
Rash	3 (2.4%)
Urinary tract infection	3 (2.4%)
Cataract	2 (1.6%)
Diarrhoea	2 (1.6%)
Gastrointestinal haemorrhage	2 (1.6%)
Headache	2 (1.6%)
Intestinal obstruction	2 (1.6%)
Neutrophil count decreased	2 (1.6%)

Adverse events leading to dose adjustment

In 3 subjects (2.4%), at least 1 TEAEs resulted in dose reduction. These are fatigue, haematuria and sinusitis.

Post marketing experience

As of 30 October 2023, the cumulative overall global post-marketing patient exposure to acalabrutinib was estimated to be approximately 62,179 patient-years, including exposure to acalabrutinib (100 mg) capsule, estimated to be approximately 48,107 patient-years and for acalabrutinib (100 mg) tablet estimated to be 14,072 patient-years. No new safety concern was identified based on the post-marketing safety reports.

2.5.1. Discussion on clinical safety

The most common ADRs previously established for acalabrutinib monotherapy include those related to infections, bone marrow suppression, headache, diarrhoea, bruising, musculoskeletal pain, nausea, fatigue, cough and rash.

To support the safety assessment of the R/R MCL indication, the applicant has submitted data from the pivotal, Phase 2 ACE-LY-004 study, a single arm trial on 124 subjects with R/R MCL, who were treated with 100 mg acalabrutinib bd.

Although the pivotal study is a single-arm trial, the safety database provided is considered to be of acceptable size, and sufficiently comprehensive given the known safety profile of acalabrutinib in B-cell malignancies.

The median duration on treatment was 17.5 months (range: 0.1 to 65.3) and median time on study 38.1 months (range: 0.3 to 68.8 months).

In the ACE-LY-004 study, the most common adverse events of all grades, by PT, were headache (38.7%), diarrhoea (37.9%), fatigue (29.8%), cough (23.4%), myalgia and nausea (21.8% each), consistent with the previously established ADRs of acalabrutinib.

In terms of AEs by severity, Grade 3-4 events were reported in 78 subjects (62.9%), among which the most common were anaemia [11.3%], neutropenia [11.3%], pneumonia [7.3%], diarrhoea [4.0%] and thrombocytopenia [4.0%]). SAEs were reported in 62 subjects (50.0%), with the most common being Pneumonia [6.5%], anaemia [4.8%] and general physical health deterioration [3.2%].

A total of 59 (47.6) patients died during the study. The main cause of death was disease progression and AE; 2 fatal AEs occurred within 30 days from last acalabrutinib dose (PTs suicide attempt and pulmonary embolism) and four >30 days from last acalabrutinib dose (PTs: aortic stenosis, non-small cell lung cancer, MDS, pneumonia).

Events of Clinical Interest (ECIs)

The most observed ECIs (with incidences ≥ 10%) were events of infections (67.7%), haemorrhage (37.1%), anaemia and leukopenia (14.5%, each), cardiac events and second primary malignancies (12.9%, each).

The most common Grade 3/4 of the ECIs were infections (16.9%), followed by leukopenia (14.5%) and anaemia (11.3%). There was one death (0.8%) reported related to second primary malignancies excluding skin. These ECIs are already listed in the 4.8. ADR Table in the SmPC or listed as safety specifications in the RMP. Overall, no new concerns have been identified in relation to the ECIs.

2.5.2. Conclusions on clinical safety

The safety profile as characterised in the pivotal study is in line with what has previously been established for acalabrutinib monotherapy. No new safety concerns have been identified based on the submitted data and therefore no changes have been introduced to the undesirable effects section

Overall, the safety profile of acalabrutinib is considered acceptable and can be managed with the currently proposed warnings in the product information.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 7.2 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 7.2 with the following content:

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

Pharmacovigilance plan

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
			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 with treatment-naïve or R/R CLL and moderate to severe cardiac impairment.	Safety in patients with pre-existing moderate to severe cardiac impairment	Protocol Submission	Apr2024
			Final Report	Q4 2029

Risk minimisation measures

Safety concern	**Risk minimisation measure**
Haemorrhage with or without association with thrombocytopenia	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8
Serious infections with or without association with neutropenia	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8
Second primary malignancy	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8
Atrial fibrillation/flutter	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8
Cerebrovascular events	None
Hepatotoxicity	**Routine risk communication:** SmPC section 4.2
Long-term safety	None
Use in patients with moderate to severe cardiac impairment	**Routine risk communication:** SmPC section 4.2

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the proposed changes are limited and not considered to significantly affect the readability of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for acalabrutinib is for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) not previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

The incidence of MCL is approximately 1 to 2 per 100,000 in Europe and the US. Prognosis for patients with MCL is poor, with OS of 3 to 5 years at diagnosis.

3.1.2. Available therapies and unmet medical need

Frontline MCL treatment is based on patients' autologous stem cell transplant (ASCT) eligibility. Patients deemed transplant eligible typically receive chemo-immunotherapy, consolidative ASCT in first remission, and rituximab maintenance (RM).

For patients who are not fit for dose-intensified regimens, bendamustine plus rituximab (BR) is a frontline standard, along with options like VR-CAP and R-CHOP.

BTK inhibitors have become standard therapy in the R/R MCL setting and are common second- and third-line regimens. After failing treatment with a BTKi, options for patients for later line treatments are very limited and outcomes are poor. Potential treatment options include non-covalent BTKi such as pirtobrutinib, which have demonstrated efficacy in patients previously treated with a covalent-BTK, rituximab and lenalidomide, bortezomib-based regimens, temsirolimus-based regimens further cancer immunotherapy, or, for fitter patients, chimeric antigen receptor T cell (CAR-T) therapy and allogeneic transplantation.

MCL remains uncurable and thus an unmet need for improved therapy and treatment options remains in relapsed and refractory mantle cell lymphoma.

3.1.3. Main clinical studies

The efficacy of acalabrutinib for the treatment of patients with R/R MCL is based on the pivotal study, ACE-LY-004, conducted in the intended target population (R/R MCL) and using the intended therapeutic regimen (100 mg bd as monotherapy).

Study ACE-LY-004 was a Phase 2, multicentre, open-label study in patients with histologically documented MCL, who had relapsed after or been refractory to ≥ 1 (but not > 5) prior treatment regimens. This study was designed to determine the activity of acalabrutinib in patients with R/R MCL as measured by response rate. Duration of response (DOR), PFS, and OS were also assessed.

124 patients with R/R MCL were enrolled in study ACE LY-004 and data were presented from the final cutoff date for this study, 04 December 2020.

At the time of the data cutoff date, all 123 patients enrolled were included in the All-treated population analysis set which was defined as all enrolled subjects who had received ≥1 dose of study treatment.

3.2. Favourable effects

The Objective response rate (ORR) by investigator assessment per Lugano classification was 81.5 (95% CI: 73.5, 87.9).

With a median follow-up of 38.1 months the median DOR was 28.6 months.

3.3. Uncertainties and limitations about favourable effects

The evaluation of efficacy of acalabrutinib in r/r MCL is based on non-randomised data, and effects of acalabrutinib on standard endpoints like PFS and OS cannot be inferred.

3.4. Unfavourable effects

Grade 3/4 TEAEs were reported in 78 subjects (62.9%). The most commonly reported events were anaemia (11.3%), neutropenia (11.3%), pneumonia (7.3%), diarrhoea (4%) and thrombocytopenia (4%).

Events of Clinical Interest (ECIs) were reported with a relatively high frequency; the most common were infections (67.7%), haemorrhage (37.1%), anaemia and leukopenia (14.5%, each), cardiac events and second primary malignancies (12.9%, each).

All of the above events are amongst the most commonly reported events in previous trials with acalabrutinib. This confirms that the safety profile of acalabrutinib in the new indication is consistent with what is already from its use in different patient populations.

Almost half of the enrolled patients had died by the time of the final clinical cut-off date, most commonly due to disease progression.

AEs leading to study treatment discontinuation were reported in 15 subjects (12.1%); five subjects discontinued treatment due to secondary primary malignancy and two due to bleeding events.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainty regarding the association of acalabrutinib in the observed adverse events arises from the uncontrolled, single-arm nature of the submitted trial. However, the observed reported events appear to be in line with acalabrutinib's known safety profile derived from RCT data.

3.6. Effects Table

Table 31. Effects Table for Calquence for the treatment of adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor (data cut-off: 04 December 2020)

Effect	Short description	Unit	Calquence	Uncertainties / Strength of evidence	References
Favourable Effects					
ORR	Percentage of participants with a partial response or better according to the Lugano classification by investigator	% 95% CI	81.5 (73.5, 87.9)	Single arm trial CR: 47.6, 95% CI (38.5, 56.7)	ACE-LY-004
Median DoR	Interval from the first documentation of CR or PR to the earlier of the first documentation of objective MCL disease progression or death from any cause.	Months	28.6 (17.5 39.1)		
Unfavourable Effects					
Grade 3/4 AE	Incidence: Any Anaemia Neutropenia Pneumonia Diarrhoea	%	 62.9 11.3 11.3 7.3 4.0	Absence of control arm Observed data consistent with	ACE-LY-004

Effect	Short description	Unit	Calquence	Uncertainties / Strength of evidence	References
	Thrombocytopenia		4.0	known safety profile of acalabrutinib	
Deaths	All deaths Due to PD AEs Other	%	47.6 32.3 4.8 4.8		

Abbreviations: ORR: objective response rate; CI = Confidence Interval, CR: Complete response; DoR: Duration of response; AE: adverse event; PD: progressive disease

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The overall and complete response rates are high, and the responses are considered durable and clinically relevant.

The safety database has an acceptable follow-up for describing the long-term safety profile of acalabrutinib monotherapy in the sought indication. Due to the uncontrolled data generated by the single-arm, ACE-LY-004 study, the effects of acalabrutinib are not exhaustively characterised in the claimed indication. Nevertheless, the safety data of acalabrutinib in the R/R MCL population is largely consistent with the established safety profile of acalabrutinib monotherapy conducted in other clinical settings.

3.7.2. Balance of benefits and risks

Despite the absence of a comparative trial, it can be concluded that efficacy for acalabrutinib in the claimed indication has been demonstrated. The clinical benefit of acalabrutinib in the intended target population is considered to outweigh the risks associated with its use, which can be managed with the risk minimisation measures as reflected in the product information.

3.8. Conclusions

The overall B/R of Calquence for the treatment of adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include CALQUENCE as monotherapy for the treatment of adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor based on final results from study ACE-LY-004 (D8225C00002); this is an open-label, phase 2 study of ACP-196 in subjects with Mantle Cell Lymphoma. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial and formatting changes to the PI.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Calquence is not similar to Tecartus within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.