27 March 2025
EMA/176133/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Calquence

International non-proprietary name: Acalabrutinib

Procedure No. EMEA/H/C/005299/II/0025

Note

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

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List of abbreviations

ABR	acalabrutinib, bendamustine, and rituximab
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCR	B-cell receptor
BID	twice daily
BR	bendamustine and rituximab
BTK	Bruton tyrosine kinase
BTKi	BTK inhibitor
CI	confidence interval
CLL	chronic lymphocytic leukaemia
COVID-19	coronavirus 2019-nCoV
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cutoff
DOR	duration of response
ECI	event of clinical interest
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio
IC50	50% inhibitory concentration
ICH	International Conference on Harmonisation

IDMC	Independent Data Monitoring Committee
IRC	Independent Review Committee
IV	intravenous
MCL	mantle cell lymphoma
MIPI	Mantle Cell Lymphoma International Prognostic Index
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NE	not estimable
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	overall response rate
OS	overall survival
PBR	placebo, bendamustine, rituximab
PD	progressive disease
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PPI	proton pump inhibitor
PR	partial response
PT	Preferred Term
RM	rituximab maintenance
RPSFT	Rank Preserving Structural Failure Time
R/R	relapsed/refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
SLL	small lymphocytic lymphoma
sMIPI	Simplified Mantle Cell Lymphoma International Prognostic Index
SOC	System Organ Class
TEAE	treatment-emergent adverse event

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 22 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 in combination with bendamustine and rituximab (BR) as treatment of adult patients with previously untreated Mantle Cell Lymphoma (MCL) based on interim results from study ACE-LY-308 (ECHO, D8220C00004); this is a Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Bendamustine and Rituximab (BR) Alone Versus in Combination with Acalabrutinib (ACP-196) in Subjects with Previously Untreated Mantle Cell Lymphoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6, succession 1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC. As part of the application the MAH requested a 1-year extension of the market protection.

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

During the evaluation of the procedure, the MAH withdrew this request.

Scientific advice

The MAH did not seek scientific advice from the CHMP.

International collaboration

The European Medicines Agency (EMA) was an observer of the review conducted under the Food and Drug Administration (FDA) project Orbis for this indication.

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	22 August 2024
Start of procedure:	14 September 2024
CHMP Rapporteur Assessment Report	8 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
CHMP Rapporteur Assessment Report	21 February 2025
PRAC Rapporteur Assessment Report	28 February 2025
PRAC members comments	5 March 2025
Updated PRAC Rapporteur Assessment Report	6 March 2025
PRAC Outcome	13 March 2025
CHMP members comments	17 March 2025
Updated CHMP Rapporteur Assessment Report	20 March 2025
Opinion	27 March 2025
The CHMP adopted a report on similarity of Calquence with Tecartus on (Appendix 1)	27 March 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Mantle cell lymphoma (MCL) is a relatively uncommon subtype of lymphoid malignancy and has been recognised as a distinct entity in the Revised European-American Lymphoma (REAL) classification since 1994.

State the claimed the therapeutic indication

"Calquence in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL)."

Epidemiology

MCL is a mature B-cell non-Hodgkin lymphoma (NHL) that accounts for 5%–7% of malignant lymphoma in Western Europe. The annual incidence of this disease has increased during recent decades to 1–2/100 000. The median age of patients at diagnosis is 68 years. Approximately three-quarters of patients with MCL are male.

Biologic features

MCL is a rare subtype of B-cell NHL associated with increased cellular proliferation, a reduced response to DNA damage, and enhanced cell survival caused by impaired apoptosis. MCL is characterised by chromosomal translocation t(11;14)(q13:q32) that juxtaposes the cyclin D1 locus with the immunoglobulin heavy chain gene locus. This results in overexpression of the cyclin D1 (CCDN1) gene and increased proliferation.

MCL is also characterised by disturbances in pathways and factors that regulate apoptosis. MCL cells avoid apoptosis through expression of BCL2, upregulation of the PI3 kinase (PI3K)/AKT pro-survival signalling pathway, activation of nuclear factor-kB (NF-kB), and loss-of-function TP53 mutations. More than 50% of MCL cases overexpresses BCL2.

Clinical presentation, diagnosis and stage

MCL is characterised by involvement of the lymph nodes, spleen, blood, and bone marrow with a short remission duration to standard therapies and a median overall survival of 4–5 years.

The diagnosis is made on a biopsy of a lymph node, tissue, bone marrow, or blood phenotype. Most tumours have a classic morphology of small-medium sized cells with irregular nuclei. Immunophenotyping is commonly used with the MCL cells being CD20+, CD5+, and positive for cyclin D1, whereas being negative for CD10 and Bcl6 5. The hallmark chromosomal translocation t(11:14)(q13;32) that causes overexpression of cyclin D1 can be shown in most cases.

Biologic features such as a high Ki-67 proliferation index or p53 mutations and p16 deletions are closely related to the more aggressive MCL subtypes whereas the absence of the transcription factor

SOX11 has been described as a characteristic of indolent MCL. In the rare cyclin D1-negative cases, detection of SOX11 may help to establish the diagnosis.

Prognosis of MCL is affected by the clinical presentation, disease stage, and pathologic features. The MCL international prognostic (MIPI) score prospectively divides patients into low-, intermediate-, and high-risk groups based on age, LDH, white blood cell count, and performance status. Blastoid and pleomorphic subtypes are associated with poorer survival. As in many other malignancies, mutated TP53 is an independent prognostic factor, and mutated cases have poor outcome.

Management

Newly diagnosed patients are considered for intensified chemotherapy (e.g., high-dose Ara-C [cytarabine]) and autologous stem cell transplant [ASCT]). However, most patients over 65 years do not qualify for dose-intensified regimens. According to the European Society for Medical Oncology (ESMO) guideline, rituximab (R) in combination with chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine (B) is recommended in this patient group. Although there is no globally accepted standard of care for patients over 65 years of age, BR followed by R maintenance has emerged as one standard treatment option based on results from large randomized controlled studies, ESMO and NCCN (National Comprehensive Cancer Network) guidelines.

Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisolone (VcR-CAP) is approved in the EU for first line treatment based on Study LYM-3002 where it was compared to rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). The ESMO recommended that first line treatments for elderly patients also include rituximab with bendamustine and cytarabine (R-BAC).

Given the activity of single agent Bruton Tyrosine Kinase inhibitor (BTKi) in relapsed MCL, several trials have incorporated BTKi into frontline therapy, in an effort to enhance the depth and duration of response after initial treatment. In frontline MCL, the addition of the BTKi ibrutinib to BR in older transplant-ineligible patients in the SHINE study (Wang et al 2022) resulted in superior PFS.

The role of R maintenance after initial treatment was evaluated in a randomized Phase 3 study comparing two different induction regimens (R-CHOP [n=239] vs. fludarabine, cyclophosphamide, and rituximab [FCR]; [n=246]) and two different maintenance regimens in elderly patients with MCL (rituximab [n=143] vs. interferon-α [131]) (Kluin-Nelemans, 2012). In patients who responded to induction therapy and were re-randomized to the maintenance phase, R maintenance demonstrated an improvement in median PFS when compared to interferon-α (77 months vs. 26 months (Kluin-Nelemans, 2012), respectively, as measured from the end of induction; HR=0.55, p=0.01) but resulted in an increase in low-grade infections (i.e., Grade 1-2) during the maintenance phase. Based on these results, R maintenance treatment has been incorporated into practice guidelines around the world (Dreyling 2017).

No curative treatment is available for MCL although intensive approaches (e.g. ASCT) can be beneficial to younger, fit patients. Furthermore, there is no single, globally accepted, and approved standard treatment regimen for patients with newly diagnosed MCL. Hence, there is an unmet medical need for more effective treatments with different mechanisms of action that provide alternative treatment options for patients with newly diagnosed MCL.

2.1.2. About the product

BTK is a non-receptor protein tyrosine kinase of the tec protein tyrosine kinase (TEC) family. BTK is expressed in cells of hematopoietic origin, excluding only T lymphocytes. BTK regulates multiple cellular processes including proliferation, apoptosis, differentiation, and cell migration in B-cells, myeloid cells, and platelets. In response to B-cell receptor (BCR) engagement, activated BTK translocates to the plasma membrane and transmits signals that play a significant role in proliferation and cell survival. BCR signalling via BTK has been demonstrated to be crucial for normal B-cell development and survival. Chronic activation of the BCR pathway has been implicated to play a key role in the pathogenesis of various B-cell malignancies.

Acalabrutinib (ACP-196), is a selective inhibitor of BTK. Binding of acalabrutinib, and its active metabolite, ACP-5862, to BTK permanently inactivates the enzyme and results in the inhibition of proliferation and survival signals in malignant B-cells.

Currently approved indications

- Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
- Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application.

2.2.1. Ecotoxicity/environmental risk assessment

The ERA from the initial marketing authorisation application (MAA) for Calquence was updated with regards to predicted environmental concentration (PEC) and resulting risk ratios.

The original ERA included a Phase II Tier B assessment of effects on sediment organisms. According to the original ERA, the $logD_{OW}$ values were <4.5 and thus no further screening for persistence, bioaccumulation, and toxicity was necessary. The values were 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 leukaemia 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.

Summary of main study results

Substance (INN/Invented Name): Acalabrutinib			
CAS-number (if available): 1420477-60-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log Kow	OECD107	log Dow = 1.29 at pH 5 log Dow = 1.96 at pH 7 log Dow = 1.99 at pH 9	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log Kow	1.99	not B
	BCF		B/not B
Persistence	$DT50_{total\ system}$ (12 °C) DT50sediment (12 °C)	59 d 203 d	vP
Toxicity	NOEC (Daphnia)	1.2 mg/L	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PECsurfacewater, refined with prevalence	0.054	µg/L	> 0.01 threshold: Y
Other concerns			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Sludge Sediment 1 (HOM) Sediment 2 (LOM) Soil 1 (HOM) Soil 2 (LOM)	OECD 106	 Koc, sludge = 5.05×10^2 L/kg Koc, sediment1=1.37×10^5 L/kg Koc, sediment2=1.20×10^5 L/kg Koc, soil 1 = 8.79×10^5 L/kg Koc, soil 2 = 1.84×10^6 L/kg	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems system I - Brandywine Creek system II – Choptank River	OECD 308	$DT_{50,\ water}$ = 3.5 d / 5.8 d $DT_{50,\ sediment}$ = 95 d / 53 d $DT_{50,\ whole\ system}$ = 12d / 18 d % shifting to sediment = 77.2 / 40 % CO_2 = 1.7 / 2.4 % NER = 58.4 / 43.2	I / II, 20 °C at d 14, parent + NER at test end at test end

		transformation products > 10%: TP-RT11.5min, 11.4%AR, d7			4-[(pyridin-2-yl)carbamoyl] benzoic acid
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOEC	2700	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	1200	µg/L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	3800	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	70000	µg/L	solubility limit, total respiration
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	244	mg/kg dw	o.c. 1.7%

2.2.2. Discussion on non-clinical aspects

An updated ERA was provided but no new non-clinical data were submitted in this application, which is considered acceptable given that the intended dose for the 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 calculated an updated $PEC_{SURFACEWATER-TOTAL}$ value (0.054 µg/L) for acalabrutinib based on the new indication combined with the authorised indication (chronic lymphocytic leukaemia). The risk ratios (PEC/PNEC) were subsequently re-calculated based on the updated $PEC_{SURFACEWATER-TOTAL}$ 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 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

Study No. of Sites Location	Randomization Dates DCO Total/Planned	Study Design Study Objective	Diagnosis	Study Treatments	Duration of Acalabrutinib Treatment, Median (Range)	Patients Enrolled/Treated/ Continuing Treatment Sex (M/F) Median Age (Range)	Efficacy Endpoints
Pivotal Study							
ACE-LY-308 (ECHO) 189 sites 26 countries	08 May 2017 to 27 March 2023 DCO: 15 Feb 2024 598/546[a]	Phase 3, multicentre, randomised, active comparator/placebo-controlled Efficacy and safety	Previously untreated MCL	Arm 1: Acalabrutinib 100 mg BID + bendamustine and rituximab Arm 2: Placebo + bendamustine and rituximab Crossover: Pts in Arm 2 could cross over to acalabrutinib 100 mg BID monotherapy	Arm 1: 28.6 months (0.13-80.07 months) Arm 2: 24.6 months (0.03-76.35 months) Crossover: 9.0 months (0.3-59.7 months)	Arm 1: 299/297/95 214 M/85 F 71 years (65-85 years) Arm 2: 299/297/77 209 M/90 F 71 years (65-86years)	Primary: IRC-assessed PFS Secondary: • INV-assessed PFS • ORR (IRC- and INV-assessed) • DOR • TTR • OS Exploratory: • Minimal residual disease

2.3.2. Pharmacokinetics

Study ACE-LY-308 included a PK sub-study in 36 patients with the following PK sampling of acalabrutinib and its main metabolite ACP-5862: Pre-dose and 0.5, 0.75, 1, 2, 3, 4, 6 hours post dose on Day 2 and Day 8 of Cycle 1 and Day 2 of Cycle 2. Additional sparse sampling was conducted at any timepoint between 0.5 to 4 hours post-dose on Cycle 1 Day 8 and on Cycle 1 Day 15 or 22.

The PK data from Study ACE-LY-308 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 second-line MCL patients (Study ACE-LY-004) are summarized in **Table 1** and **Table 2.**

The baseline characteristics/demographics between the studies included in the PK-comparison are summarized in **Table 3** and **Table 4**.

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

Analyte: Acalabrutinib	**Time (hours)**			
Study ID	**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: GeoCV, geometric coefficient of variation; h, hour; ID, identifier; PK, pharmacokinetics.

Table 2. Observed Plasma Concentrations versus Time (Steady State) Stratified by Population/Study for ACP-5862

Analyte: ACP-5862 **Study ID**		**Time (hours)**			
		1	**2**	**4**	**6**
ACE-CL-006	N	5	5	5	6
	GeoMean (GeoCV %)	350.97 (78.6%)	803.67 (24.2%)	520.58 (32.2%)	309.4 (35.5%)
	Median [range]	382.14 [132.9 - 789.2]	872.27 [529.6 - 957.4]	452.75 [359.3 - 751.8]	280.37 [224.3 - 537.9]
ACE-CL-007	N	248	251	249	-
	GeoMean (GeoCV %)	454.5 (153)	606.68 (86.4)	395.11 (58.3)	-
	Median [range]	622 [26.6 - 3390]	690 [37 - 2220]	401 [36.8 - 1730]	-
ACE-LY-308 (PK substudy)	N	35	36	36	36
	GeoMean (GeoCV %)	517.37 (107.6)	596.49 (66.1)	361.41 (44.6)	225.88 (41.9)
	Median [range]	701.97 [61.9 - 1503.6]	673.94 [108.4 - 1717.5]	362.41 [132.7 - 963.7]	227.41 [107.4 - 544.1]

Abbreviations: GeoCV, geometric coefficient of variation; h, hour; ID, identifier; PK, pharmacokinetics.

Table 3. 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 4. 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 (%)					

	ACE-LY-004 (N = 45)	ACE-CL-006 (N = 117)	ACE-CL-007 (N = 274)	ACE-LY-308 (N = 249)	Overall (N = 685)
Chronic lymphocytic leukemia	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)
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)
Eastasia, n (%)					
Non-Eastasian	45 (100)	117 (100)	271 (98.9)	216 (86.7)	649 (94.7)
Eastasian	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)
Acala+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 (%)					

	ACE-LY-004 (N = 45)	ACE-CL-006 (N = 117)	ACE-CL-007 (N = 274)	ACE-LY-308 (N = 249)	Overall (N = 685)
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)
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.

Population pharmacokinetic (PopPK) analysis

The applicant also provided a PopPK analysis to describe PK in the target population.

The pooled PopPK analysis dataset included 9691 acalabrutinib and 3743 ACP-5862 plasma concentrations and relevant covariates from 975 subjects for acalabrutinib and 580 subjects for ACP-5862 from studies ACE-CL-001, ACE-CL-003, ACE-CL-006, ACE-CL-007, ACE-LY-004, ACE-WM-001, ACE-LY-002, ACE-LY-003, ACE-MY-001, ACE-LY-106 (D8222C00001) and ACE-LY-308 (D8220C00004).

In this analysis, the previously developed population PK model (Report D8220C00009) was used as a starting point for the current model development.

The new base model was a 2-compartment model with a sequential zero-first order absorption and first order elimination on acalabrutinib and a 1 compartment model for ACP-5862 (simultaneously).

ECOG status (0 vs 1+) and treatment (acalabrutinib+BR, acalabrutinib only, other acalabrutinib combination) were not statistically significant on CL/F and were not included in the final model.

Indication was tested on the CL/F, there was no significant difference between CLL and MCL, but it was different from other pooled indications. The model was then further tested by pooling both MCL and CLL against other indications and was significant, however, the rest of the indication is less than 10% of the population, therefore, this covariate was not included in the final model.

Other covariates such as baseline body weight, hepatic impairment, renal impairment, sex, and age was tested on the parameters, but none were significant (**Table 5**).

Table 5. Covariate analysis in NONMEM (initial model without ECHO data)

Run number	OFV (ΔOFV)	degree of freedom	significant level	Description	Notes
Run301	10233	--	--	Starting base model	This model had PPI on F1 and ECOG1+ on CL/F
Run 303	10235 (2)	1	10.83	Add BWT on CL/F	Not significant as there is increase in Objective function value
Run304	10239 (6)	1	10.83	Add BWT on V1/F	Not significant as there is increase in Objective function value
Run305	10411 (178)	1	10.83	Add BWT on CLM/F	Not significant as there is increase in Objective function value
Run306	10429 (196)	1	10.83	Add Hepatic on CL/F	Not significant as there is increase in Objective function value
Run307	10249(16)	2	18.82	Add Renal on CL/F	Not significant as there is increase in Objective function value
Run308	10416 (183)	1	10.83	Add Sex on CL/F	Not significant as there is increase in Objective function value
Run310	10223 (10)	1	10.83	Add Age on CL/F	Not significant

Final parameter estimates are provided in **Table 6**.

Table 6. Parameter Estimates for Final Model

Run: run500, OFV: 13463.134					
Parameter	**Estimate**	**RSE (%)**	**Bootstrapb**	**Shrinkage (%)**	**Unit**
Population Parameter					
CL/F (parent)	147.70	1.44	147.83 [142.47; 154.49]	-	L/hr
V/F (parent)	77.28	3.15	81.20 [73.89; 104.92]	-	L
Q/F (parent)	18.99	3.99	19.04 [17.24; 21.30]	-	L/hr
VP/F (Parent)	156.30	3.19	157.50 [144.09; 177.15]	-	L
KA	1.07	1.97	1.07 [1.03; 1.13]	-	1/hr
D1	0.59	2.59	0.59 [0.54; 0.64]	-	hr

CLM/F (metabolite)	19.35	1.83	19.35 [18.69; 20.23]	-	L/hr
V/F (metabolite)	74.96	2.22	74.79 [70.33; 80.18]	-	L
Covariate					
PPI use on F1[a]	-0.23	8.51	-0.23 [-0.35; -0.07]	-	-
Between subject variability					
BSV CL/F (CV%)	32.83	7.24	32.83 [29.25; 36.53]	22.35	-
BSV V/F (parent) (CV%)	197.59	9.02	196.91 [185.32; 207.79]	23.66	-
BSV VP/F (parent) (CV%)	25.98	23.19	26.07 [9.95; 34.63]	70.02	-
BSV KA (CV%)	13.15	27.45	12.57 [2.43; 18.75]	65.52	-
BSV CLM/F (CV%)	23.19	18.82	23.19 [15.76; 30.59]	57.26	-
BSV on EPS (Parent) (CV%)	46.45	7.41	46.42 [42.60; 49.44]	2.71	-
Residual Variability					
Proportional component (Parent) (sd)	0.92	0.89	0.85 [0.81; 0.89]	1.94	-
Proportional component (Metabolite) (sd)	0.87	0.82	0.76 [0.73; 0.79]	2.84	-

a relative change (1+estimate)
b 50th [2.5th, 97.5th] percentiles, 1000 samples
Initial objective function used in the covariate search dropped by 3 points because of convergence run

The Goodness of Fit (GoF) plots and prediction-corrected visual predictive check (pcVPC) for ECHO are presented in **Figure 1** and **Figure 2** respectively.

Figure 1. Basic Goodness-of-Fit Plots for the Final Model – Observations Versus Predictions (ECHO Study)

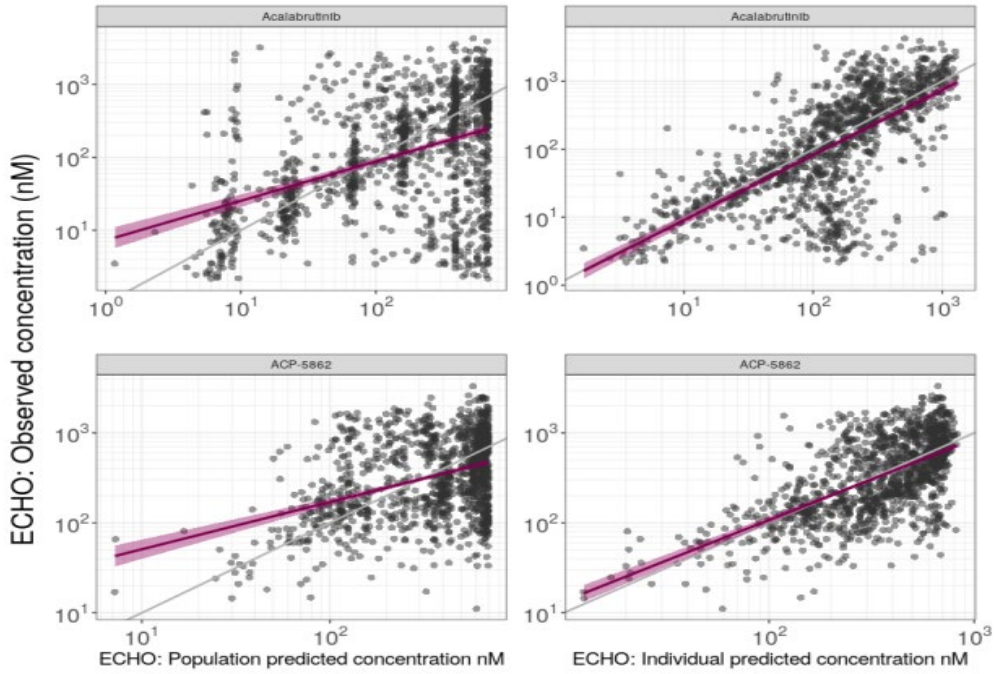
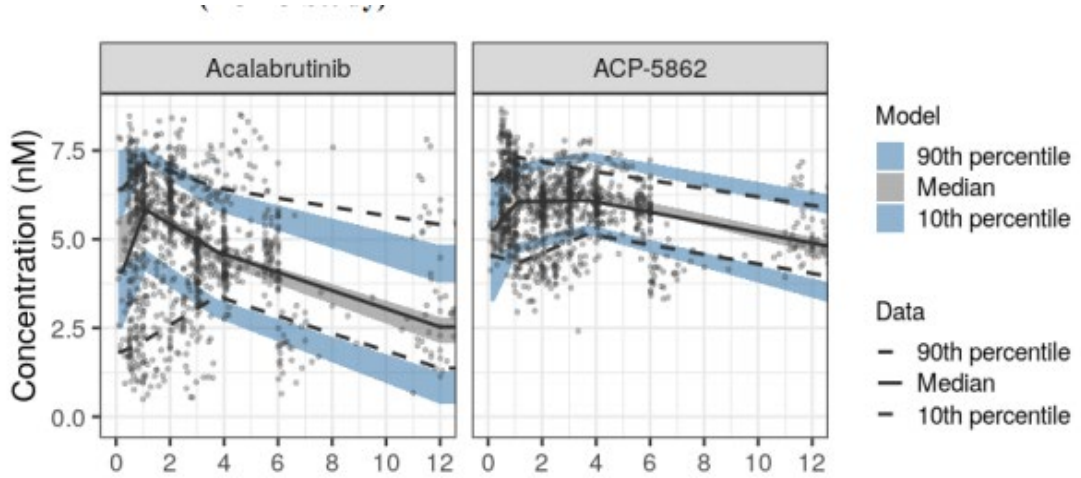


Figure 2. Prediction-corrected Visual Predictive Check for the Final Model in ECHO study patients for both acalabrutinib (left) and metabolite (right)



The solid and dashed lines are the median and the 5th and 95th percentiles of the observations. The shaded areas are the 90% CIs of the median and the 5th and 95th percentiles predicted by the model. Data was modelled on the log scale.

2.3.3. PK/PD modelling

The applicant provided exposure-response analyses of efficacy and safety endpoints which was included in the modelling report D8220C00004.

PK exposure was the individual predicted exposure metric (such as Cmax0-24hr, Cmaxss, AUC0-24h, AUCss) of acalabrutinib and ACP-5862, using empirical bayes estimates (EBE) from the updated PopPK model. To account for contribution of the major active metabolite (ACP-5862) to overall response, acalabrutinib and ACP-5862 molar concentrations was adjusted with respective potency and protein

binding (shown below) and was used to estimate total active AUC or Cmax (exposure metric for the total active moiety).

$$Total\ Active\ Concentration = C_{parent} \times f_{u_{parent}} + C_{metabolite} \times f_{u_{metabolite}} \times 0.5$$

Where Cparent and Cmetabolite are molar concentrations of acalabrutinib and ACP-5862, respectively; fuparent (free fraction of acalabrutinib) = 0.025; fumetabolite (free fraction of ACP-5862) = 0.013; and compared to acalabrutinib, ACP-5862 exhibits approximately 0.5-fold potency for inhibition.

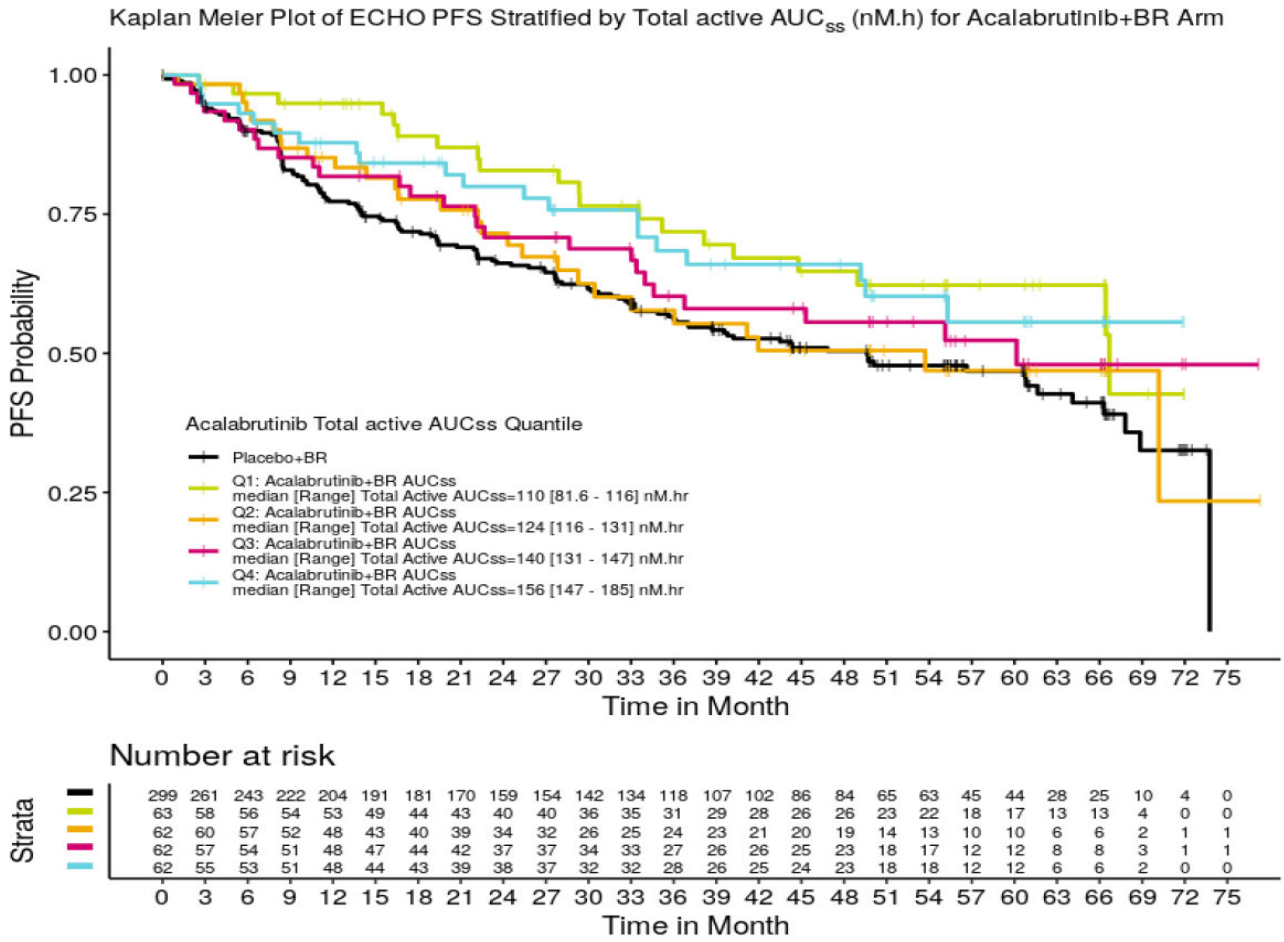
The exposure-response analysis included 598 subjects with 299 from the Placebo + BR arm and 299 in the acalabrutinib + BR arm. Of the 299 subjects in the Acalabrutinib + BR arm, 50 of them had no acalabrutinib (and ACP-5862) PK concentration. Hence, exposure response analysis was only performed on the 249 subjects with Acalabrutinib (and ACP-5862) PK concentration.

Exposure-efficacy analysis:

An exploratory Kaplan-Meier analysis evaluated the PFS (independent review committee [IRC]-assessed) as function of total active AUCss quartiles (

Figure 3).

Figure 3. Kaplan-Meier plot of ECHO stratified by Total Active AUCss



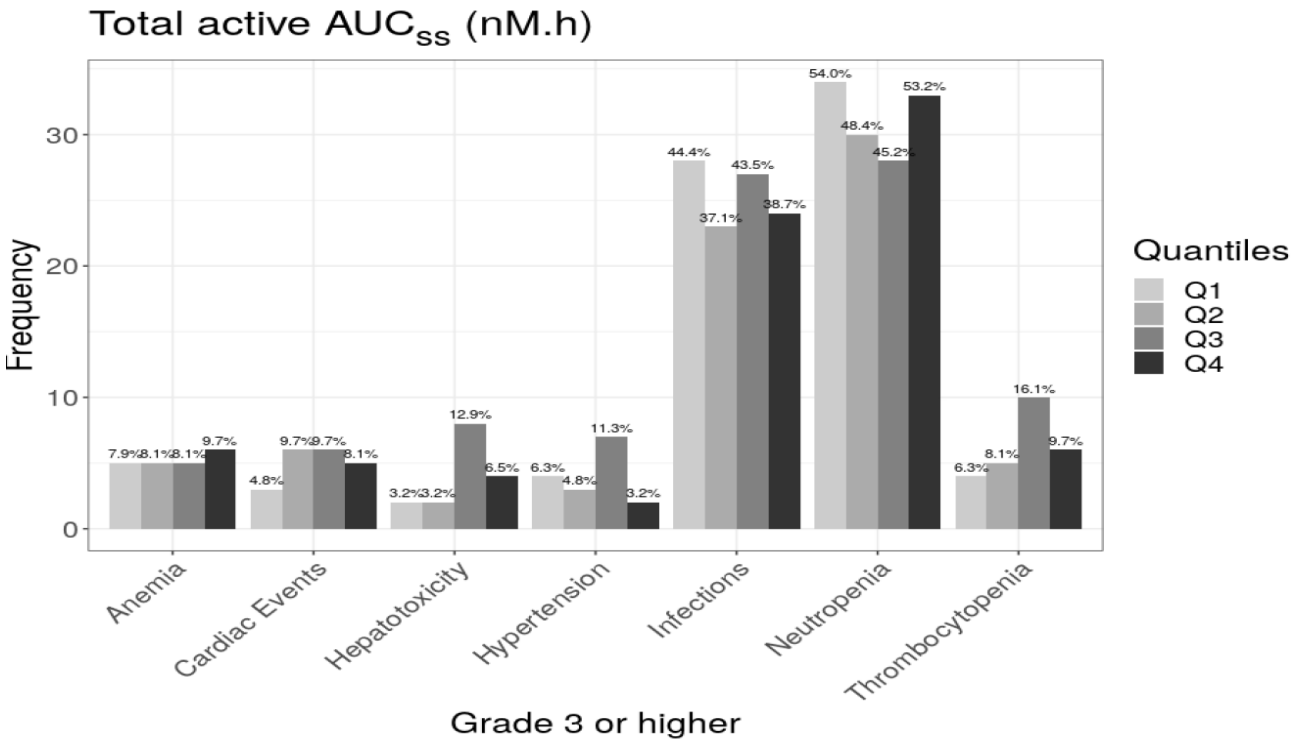
A Cox proportional hazard model did not identify a statistically significant exposure-response relationship for PFS (data not shown).

The exploratory graphical analyses using boxplots evaluated BOR (IRC-assessed) and ORR as a function of total active AUCss and indicated that median total active AUCss were similar across all response categories, suggesting a flat exposure-efficacy relationship.

Exposure-safety analysis:

The relationship between acalabrutinib exposure (total active AUC) versus the incidence of selected safety outcomes of clinical interest (Grade ≥3) acalabrutinib treated arm of ECHO are shown in **Figure 4**.

Figure 4. Bar Plot of Acalabrutinib total active AUCss Stratified by Selected Grade ≥3 AEs of Clinical Interest



2.3.4. Discussion on clinical pharmacology

The main clinical study (ECHO) supporting this application included collection of PK data.

The objective of the clinical pharmacology data package in the current variation was to describe PK in first-line MCL patients and to characterise potential PK differences between first-line MCL and CLL patients.

Pharmacokinetics

The PK data from ECHO was analysed using a PopPK approach which however had significant limitations.

Of note the applicant updated the PopPK model, which had been used during the initial marketing authorisation application for acalabrutinib, but the reasoning behind this update is unclear. A modelling analysis plan and model code would have been helpful for assessing the model structure but this was not provided nor was the model code in the documentation of this application.

The covariate analysis was carried out using a stepwise procedure. The Objective function value (OFV) increased for nearly all models in the stepwise covariate procedure which is a sign of issues with local minimum and/or suboptimal estimation properties of the model. Overall, the covariate analysis is not considered reliable.

The goodness-of-fit for the ECHO study based on the final PopPK model was suboptimal and there were signs of major model misspecifications of the observations vs typical predictions and CWRES plots.

Given these limitations, the PopPK model is not considered acceptable for describing PK in the target population and for characterising differences in PK compared between MCL and CLL patients.

Nevertheless, the PK in the target population was described using graphical and tabular descriptions of the observed PK observations from ECHO compared to Studies ACE-CL-006, ACE-CL-007 and ACE-LY-004. The results indicated that there are no clinically relevant PK-differences between the target population (first-line MCL patients) and approved indications (CLL patients in Studies ACE-CL-006 and ACE-CL-007) as well as second-line MCL patients (Study ACE-LY-004).

There were no clinically relevant differences between the baseline characteristics/demographics between the studies included in this comparison. Since there are no clinically relevant differences between populations, the Applicants' proposal to not update SmPC Section 5.2 is acceptable.

PKPD modelling

Exposure-response analyses of efficacy and safety endpoints were performed by the Applicant. No significant exposure-response trends were detected. However, the results from the exposure-response analyses should be interpreted with caution; the analyses were based only on patient data from ECHO where only a single dose level of acalabrutinib was utilised. This means that the exposure range were rather limited and does not allow adequate characterisation of the exposure-response relationship.

2.3.5. Conclusions on clinical pharmacology

Submitted data indicate 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

Not applicable.

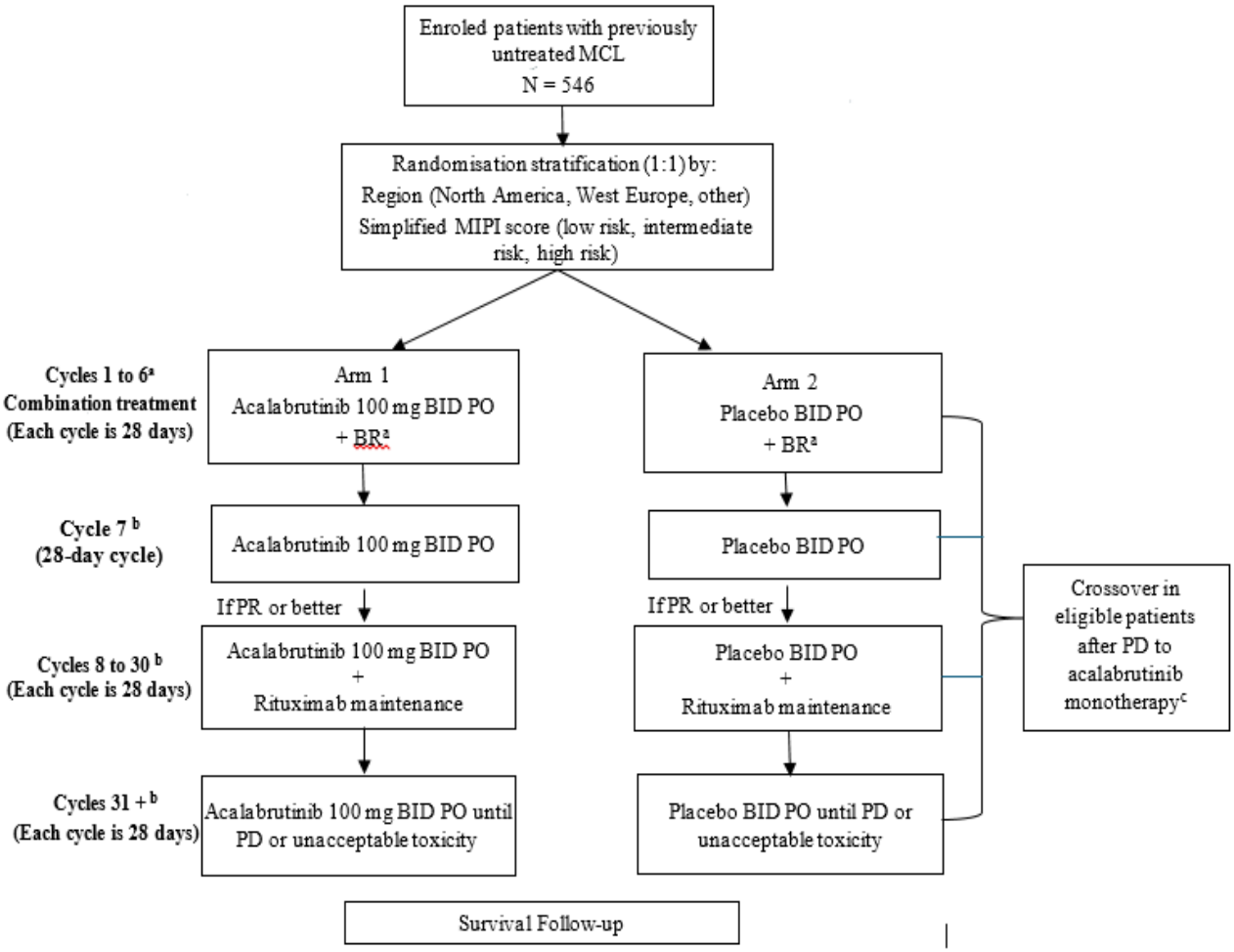
2.4.2. Main study

ACE-LY-308 (ECHO): A phase 3, randomized, double-blind, placebo-controlled, multicenter study of bendamustine and rituximab (BR) alone versus in combination with acalabrutinib (ACP-196) in subjects with previously untreated mantle cell lymphoma.

Methods

A diagrammatic representation of the study design is presented in **Figure 5**.

Figure 5. Study ACE-LY-308 (ECHO) design and the sequence of treatment periods.



[a] Bendamustine 90 mg/m^2 IV on Days 1 and 2 plus rituximab 375 mg/m^2 IV on Day 1 of each 28-day cycle. Every attempt was to be made to complete 6 cycles of BR. Thus, if a dose delay of up to 28 days resulted in omission of BR for that cycle, BR may have been given for an additional cycle.
[b] After 6 cycles of acalabrutinib or placebo in combination with BR, patients who were tolerating treatment and not progressing were to receive monotherapy acalabrutinib 100 mg BID or placebo BID. In addition, patients who have achieved a response (PR or greater) were to receive rituximab 375 mg/m^2 on Day 1 of every other cycle (starting on the next even-numbered cycle after completion of 6 cycles of BR) for a maximum of 12 additional doses (through no later than Cycle 30) (see Section 9.4.2, ECHO CSR for further details). Thereafter, patients continued to receive monotherapy acalabrutinib 100 mg BID or placebo BID (or last tolerated dose) until PD or unacceptable toxicity.
[c] Patients in the PBR arm who had PD at any time may have been eligible to cross over to receive acalabrutinib 100 mg BID monotherapy until PD or unacceptable toxicity.
Abbreviations: BID = twice daily; BR = bendamustine, rituximab; IV = intravenous; MCL=mantel cell lymphoma; MIPI = Mantel Cell Lymphoma International Prognostic Index; PD = progressive disease; PO = by mouth

Study participants

Inclusion criteria:

1. Men and women, ≥ 65 years of age.
2. Pathologically confirmed MCL, with documentation of chromosome translocation t(11;14)(q13;q32) and/or overexpression of cyclin D1 in association with other relevant markers (e.g. CD5, CD19, CD20, PAX5) (revised per Protocol Amendment 1.0).

3. Mantle cell lymphoma requiring treatment and for which no prior systemic anticancer therapies had been received.
4. Presence of radiologically measurable lymphadenopathy and/or extra-nodal lymphoid malignancy (revised per Protocol Amendment 1.0).
5. Eastern Cooperative Oncology Group performance status of ≤ 2.
6. Men who were sexually active and could beget children must have agreed to use highly effective forms of contraception during the study and for 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever was longest (revised per Protocol Amendment 1.0). See Protocol Amendment 4.0 (Global), Section 5.2, Appendix 16.1.1 for the definition of highly effective forms of contraception.
7. Men must have agreed to refrain from sperm donation during the study and for 6 months after the last dose of bendamustine or 12 months after the last dose of rituximab, whichever was longest (revised per Protocol Amendment 1.0).
8. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

Exclusion criteria:

1. History of prior malignancy except for the following:
    (a) Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and felt to be at low risk for recurrence by treating physician. Note: Provided they met other eligibility criteria, patients who are receiving hormonal therapy alone were allowed to enrol on study.
    (b) Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer.
    (c) Adequately treated carcinoma in situ without current evidence of disease.
2. Patients for whom the goal of therapy was tumour debulking before stem cell transplant.
3. Any history of CNS lymphoma or leptomeningeal disease.
4. Uncontrolled autoimmune haemolytic anaemia or idiopathic thrombocytopenic purpura.
5. Major surgical procedure within 28 days before first dose of study drug. Note: If a patient had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
6. Significant cardiovascular disease such as uncontrolled or untreated symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of first dose of study drug, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc > 480 msec (calculated using Friderica's formula: QT/RR0.33) at screening. Exception: Patients with controlled, asymptomatic atrial fibrillation during screening were allowed to enrol on study.
7. Absolute neutrophil count < 1.0×10^9/L or platelet count < 75×10^9/L; for patients with disease involvement in the bone marrow, ANC < 0.75×10^9/L or platelet count < 50×10^9/L.

Patients were only be considered eligible if peripheral blood counts could be maintained independent of growth factors or transfusions during the screening period.

8. Total bilirubin > 1.5 × ULN; or AST or ALT > 2.5 × ULN.
9. Estimated creatinine clearance of < 50 mL/min calculated using the formula of Cockcroft and Gault [(140-age) x mass (kg)/(72 × creatinine mg/dL) × 0.85 if female].
10. Prothrombin time/INR or aPTT (in the absence of a lupus anticoagulant) > 2.0 × ULN. Exception: Patients receiving warfarin were excluded; however, those receiving other anticoagulant therapy who had a higher INR/aPTT could be permitted to enrol to this study after discussion with the medical monitor.
11. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
12. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment), or intravenous anti-infective treatment within 2 weeks before first dose of study drug.
13. Known history of infection with HIV.
14. Ongoing immunosuppressive therapy, including systemic (e.g. IV or oral) corticosteroids within 2 weeks before the first dose of study drug. Note: Patients may have used topical or inhaled corticosteroids or low-dose steroids (≤ 20 mg prednisone equivalent/day for ≤ 2 weeks) as a therapy for comorbid conditions (revised per Protocol Amendment 1.0). During study participation, patients may have also received systemic (e.g. IV or oral) corticosteroids as needed for treatment-emergent comorbid conditions. Additional details on corticosteroids are provided in Section 9.4.6.
15. Known history of anaphylaxis or hypersensitivity to bendamustine, rituximab, or any of their components.
16. Serologic status reflecting active hepatitis B or C infection.
    (a) Patients who were anti-HBc positive and who were surface antigen negative needed to have a negative PCR result before randomisation. Those who were hepatitis B surface antigen positive or hepatitis B PCR positive were excluded.
    (b) Patients who were hepatitis C antibody positive needed to have a negative PCR result before randomisation. Those who were hepatitis C PCR positive were excluded.
17. Received a live virus vaccination within 28 days of first dose of study drug.
18. History of stroke or intracranial haemorrhage within 6 months of first dose of study drug.
19. History of bleeding diathesis (e.g. haemophilia or von Willebrand disease).
20. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before first dose of study drug.
21. Required or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon) within 7 days of first dose of study drug.
22. Required treatment with a strong CYP3A inhibitor/inducer.

23. Required treatment with proton pump inhibitors (e.g. omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Patients receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids were eligible for enrolment to this study.
24. Concurrent participation in another therapeutic clinical study.
25. Active CMV infection (active viremia as evidenced by positive PCR result for CMV DNA) (added per Protocol Amendment 1.0).
26. History of confirmed PML (added per Protocol Amendment 1.0).

Treatments

Patients were randomised to six 28-day cycles of acalabrutinib or placebo in combination with BR (induction therapy). During the induction therapy, the following doses were administered:

- Acalabrutinib or placebo (100 mg BID PO)
- Bendamustine (90 mg/m^2 IV) on Days 1 and 2 of each cycle
- Rituximab (375 mg/m^2 IV) on Day 1 of each cycle

Patients who were tolerating treatment and not progressing then received monotherapy acalabrutinib 100 mg BID or placebo BID (as per original randomisation) continuously until PD or unacceptable toxicity. In addition, patients who achieved a response (CR or PR) at end of induction therapy received maintenance rituximab (375 mg/m2 on Day 1 of every other cycle) for a maximum of 12 doses, up to Cycle 30.

From Cycle 31, patients continued to receive acalabrutinib monotherapy or placebo until PD or unacceptable toxicity. Patients randomised to placebo + BR, who had PD assessed by the investigator (confirmed by an unblinded physician external to the sponsor) could – if deemed eligible by the investigator - cross-over to receive acalabrutinib monotherapy (100 mg BID) until second PD or unacceptable toxicity.

Objectives

Primary objective

To evaluate the efficacy of acalabrutinib with bendamustine and rituximab (ABR) compared to placebo with bendamustine and rituximab (PBR) based on Independent review committee (IRC) assessment of Progression Free Survival (PFS) per the Lugano Classification for NHL (Cheson et al., 2014) in patients with previously untreated MCL.

Secondary objective

To evaluate ABR compared with PBR in terms of:

- IRC-assessed Objective Response Rate ORR (Complete Response (CR) + Partial Response (PR)) per the Lugano Classification for NHL
- Overall Survival (OS)
- Investigator-assessed PFS per the Lugano Classification for NHL
- Investigator-assessed ORR (CR + PR) per the Lugano Classification for NHL

- IRC-assessed and investigator-assessed Duration of Response (DOR) per the Lugano Classification for NHL
- IRC-assessed and investigator-assessed Time to Response (TTR) per the Lugano Classification for NHL

Outcomes/endpoints

Primary endpoint

PFS was defined as the time from the date of randomisation until PD or death from any cause, whichever occurred first. Kaplan-Meier curve was used to estimate the distribution of PFS.

Secondary endpoints

Best overall response was defined as the best response of CR, PR, stable disease, or PD as assessed by IRC per the Lugano Classification for NHL, at or before the initiation of subsequent anti-MCL therapy, whichever came first. ORR was defined as the proportion of patients achieving a best overall response of CR or PR and was based on the subset of patients with measurable disease at baseline.

OS was defined as the time from date of randomisation to date of death due to any cause regardless of whether the patient withdrew from randomised therapy or received another anti-MCL therapy.

DOR was defined as the time from the date of first documented response CR or PR until date of first documented PD (assessed by the IRC and investigator, respectively) or death due to any cause in the absence of PD, prior to the new anti-MCL therapy.

TTR was defined as the time from the date of randomisation until the date of first documented response CR or PR (assessed by the IRC and investigator, respectively) per the Lugano Classification for NHL, prior to the new anti-MCL therapy.

Sample size

The study was sized to achieve approximately 90% power at final analysis to detect a HR of 0.67 in IRC-assessed PFS which, under the model assumptions, translated into an improvement in median PFS from 52.9 months (Wang et al 2022) in the PBR arm to 79 months in the ABR arm with a 2-sided test at alpha level of 0.05.

With a 1:1 randomisation ratio, the study was expected to randomise 546 patients globally (273 patients per arm), with an additional enrolment in China of approximately 80 patients.

The targeted number of IRC-assessed PFS events for the primary analysis was 227 events (85% information fraction) for the interim analysis and 268 events for the final analysis. With consideration of potential COVID-19 death impact on the primary PFS analysis, the DCO date was determined to accrue approximately 10% more IRC-PFS events than protocol pre-specified 227 IRC-PFS events for interim analysis. Based on the DCO of 15 February 2024, the actual number of PFS events was 247.

Randomisation

Subjects were randomised in a 1:1 ratio into 2 arms to receive either acalabrutinib 100 mg BID plus BR (Arm 1) or placebo plus BR (Arm 2). The randomisation was performed stratified by geographic region (North America versus Western Europe versus Other) and simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score (low risk [0 to 3], versus intermediate risk [4 to 5], versus

high risk [6 to 11]). This study used an Interactive Voice/Web Response System (IXRS) for randomisation.

Blinding (masking)

This was a double-blind study.

The interim PFS analyses were performed by an external team of unblinded statisticians and programmers separate from the study team/independent of the sponsor reporting the final study results so that the study team was kept blinded.

Statistical methods

Analysis of primary endpoint

PFS were analysed using a 2-sided stratified log-rank test adjusting for the stratification factors Geographic region (North America; Western Europe; Other) and Simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score (low risk [0 to 3]; intermediate risk [4 to 5]; high risk [6 to 11]).

Additionally, a stratified Cox regression (proportional-hazards model) using Efron method adjusting for ties (Hertz-Picciotto 1997) were used to estimate PFS HR and the 2-sided 95% CI. Kaplan-Meier (KM) estimates of PFS (in month) and quartiles were presented for each treatment arm and the Brookmeyer-Crowley method was used (Brookmeyer and Crowley 1982) for the 95% CI.

A summary of PFS events (death and PD) and censoring reasons were provided by treatment arm. KM estimates of PFS probability and the corresponding 95% CI at selected time points were provided for each treatment arm. KM curves were presented by treatment arm.

The same analysis methods were used for the primary and the key secondary endpoints for PFS analysis using the IRC assessments or investigator assessments.

Analyses of secondary endpoints

Key secondary efficacy endpoints

ORR were compared between treatment arms (ABR versus PBR) for the main study period using the Stratified Cochran Mantel Haenszel (CMH) test adjusted for randomisation stratification factors as collected in the IXRS. The p-value from the CHM test was presented along with the stratified relative risk (ABR versus PBR) and common risk difference expressed as a percentage and corresponding 95% confidence intervals using the Miettinen-Nurminen (MN) method (Miettinen and Nurminen 1985).

Descriptive statistics were provided for best overall response of each subject by treatment arm. The number and proportion of subjects within each category of response were presented. The proportion were estimated by dividing the number of subjects within each category of response by total number of FAS subjects with measurable disease at baseline in each treatment arm. Each subject were counted within only one response group, with the best response during the main study period as the classification group.

Overall Survival

OS was calculated as: death date (or censoring date) – randomisation date + 1. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient

was known to be alive. Any patient recorded as alive or to have died after the DCO date was censored at the DCO date, as described in the SAP.

OS were analysed using identical statistical methods as outlined for PFS and adjusting for the same stratification factors. The HR for the treatment effect together with its 95% CI were presented.

Kaplan-Meier estimates and 95% CI for OS rates at selected time intervals were presented along with the median of OS (in month). The 95% CIs were based on the Brookmeyer-Crowley method for each treatment group.

In addition, the duration of follow-up was presented for censored subjects by treatment group, and for all subjects by treatment group.

Censoring rules

Censoring rules for PFS analyses

PFS events included death or first PD that occurred on or prior to the earliest of: data cutoff date, subsequent anti-MCL therapy start date, ≥2 consecutively missed response assessments, and study exit, including lost to follow-up or crossover.

Patients randomised to PBR who, at any time during the study, had PD assessed by the investigator and confirmed by an unblinded non-study team physician of the sponsor and were eligible to crossover, could have received treatment with acalabrutinib monotherapy at a dose of 100 mg BID until PD or unacceptable toxicity.

For analysis purposes, for subjects randomised to PBR and crossed over to receive single agent of acalabrutinib, the period from randomization to the day prior to the first dose of acalabrutinib, was defined as the main study period; the period from the first dose date of acalabrutinib to study exit was defined as the crossover period. For all other subjects (i.e., subjects randomised to ABR, and subjects randomized to PBR who did not cross over), there was only the main study period.

OS were analysed in the whole study period (main study period + crossover period) in the FAS.

Censoring Rules for OS analyses

Situation	**Date of Censoring**	**Outcome**
Death	Date of death	Event
Lost to follow-up immediately after randomisation	Randomisation date	Censored
Not known to have died at or prior to data cutoff date	Date last known alive before data cutoff date	Censored
Not known to have died at or prior to lost to follow-up or study exit	Date last known alive before lost to follow-up or study exit	Censored

Crossover was not censored in the OS analysis.

Missing data

In general, other than for partial dates, missing data were not imputed and were treated as missing. The algorithms for imputation of partial dates varied depending upon the parameter.

Sensitivity analyses

Sensitivity analysis of PFS

The following sensitivity analyses were planned for PFS as assessed by IRC between the ABR arm versus the PBR arm in support of the primary analysis

- Sensitivity analysis 1 - Unstratified analysis
- Sensitivity analysis 2 - Includes subsequent anti-MCL therapy
  A sensitivity analysis for PFS included the PFS events after starting subsequent anti-MCL therapy. Patients who did not have PFS events (PD/death) after starting subsequent anti-MCL therapy were censored at the last response assessment prior to the DCO.
- Sensitivity analysis 3 - Includes missing ≥ 2 consecutive response assessments
  A sensitivity analysis for PFS included the PFS events that occurred after the ≥ 2 consecutive missed response assessments. Patients who did not have PD/death after the ≥ 2 consecutive missed response assessments were censored at the last response assessment prior to the DCO.
- Sensitivity analysis 4 - Includes both subsequent anti-MCL therapy and missing ≥ 2 consecutive assessments
  A sensitivity analysis for PFS was conducted that did not censor subsequent anti-MCL therapy PFS events and did not censor PFS events after ≥ 2 consecutive missed response assessments. All other patients were censored at the last response assessment prior to the DCO if no PFS events were recorded. This sensitivity analysis evaluated the PFS results in a treatment policy setting, in which subsequent anti-MCL therapy and ≥ 2 consecutive missed response assessments were considered a part of the treatment regimen.
- Sensitivity analysis 5 - Per Protocol Population
  If > 10% of patients met the exclusion criterion in the Per Protocol Analysis Set, a 'deviation bias' sensitivity analysis may have been performed based on the Per Protocol Population.
- Sensitivity analysis 6 - Stratification according to eCRF
  If > 10% of patients had a discrepancy between the randomisation stratum as recorded in IXRS versus in EDC data from the eCRF, a sensitivity analysis was performed using the strata per EDC data from the eCRF for stratification. This analysis was not conducted as ≤ 10% of patients had a discrepancy between the IXRS-recorded and EDC-recorded stratification factors.
- Sensitivity analysis 7 - Censor COVID-19 death
  A sensitivity analysis was conducted to assess for the potential impact of COVID-19 deaths on PFS. This was assessed by repeating the PFS analysis except for censoring any patient who did not experience PD before death due to a fatal COVID-19 event

Sensitivity analysis of OS

Sensitivity analysis of OS (SAP) was performed for the following:

- Sensitivity analysis 1 - Censor the crossover patients
  Patients who crossed over to acalabrutinib monotherapy were censored at the date of first dose of acalabrutinib monotherapy.

- Sensitivity analysis 2 - Censor COVID-19 death
  A sensitivity analysis was conducted to assess for the potential impact of COVID-19 deaths on OS. This was assessed by repeating the OS analysis censoring any patient who died due to a fatal COVID-19 event.
- Sensitivity analysis 3 - Rank Preserving Structural Failure Time (RPSFT) Model for crossover and subsequent anti-MCL therapies
  The impact of crossover and subsequent anti-MCL therapies in PBR patients was evaluated by the RPSFT method.
  - Crossover from control arm to acalabrutinib monotherapy
    Crossover patients were those originally randomised to the control arm (PBR) and who crossed over to the acalabrutinib monotherapy after the investigator-confirmed PD assessment. The RPSFT method assumes that, for patients crossing over to acalabrutinib monotherapy, the survival time after crossover was adjusted accordingly.
  - Subsequent anti-MCL therapies
    The survival time for patients in the ABR arm after switching to subsequent anti-MCL therapies was not adjusted regardless of whether anti-MCL therapies were received. Only the survival time for PBR patients after switching to anti-MCL therapies was adjusted by the RPSFT model.

Subgroup analyses

Subgroup analyses were performed using potential prognostic variables at screening or baseline to investigate the consistency and robustness of PFS and OS between the ABR and PBR arms.

The hazard ratio (ABR arm and PBR arm) and its corresponding 95% CI for each subgroup were calculated based on an unstratified Cox regression model and displayed graphically in a forest plot.

Multiplicity

To control the overall type I error at a 2-sided 0.05 level, the Lan-DeMets alpha-spending function based on the O'Brien-Fleming boundaries was used to split α into α1 and α2 for interim and final analyses of IRC-assessed PFS, respectively. The nominal α1 and α2 levels were determined based on the actual number of IRC-assessed PFS events observed at the time of DCO. An alpha-exhaustive recycling strategy (Burman et al 2009) was utilized to adjust for multiplicity due to multiple endpoints.

With this approach, if the primary efficacy endpoint, IRC-assessed PFS in the ABR arm versus the PBR arm, achieved statistical significance at either the PFS IA (DCO1) or the PFS FA (DCO2), then the 5% alpha would be recycled to test the following secondary efficacy endpoints in a fixed sequential hierarchical manner: 1) IRC-assessed ORR and 2) OS.

Interim analysis

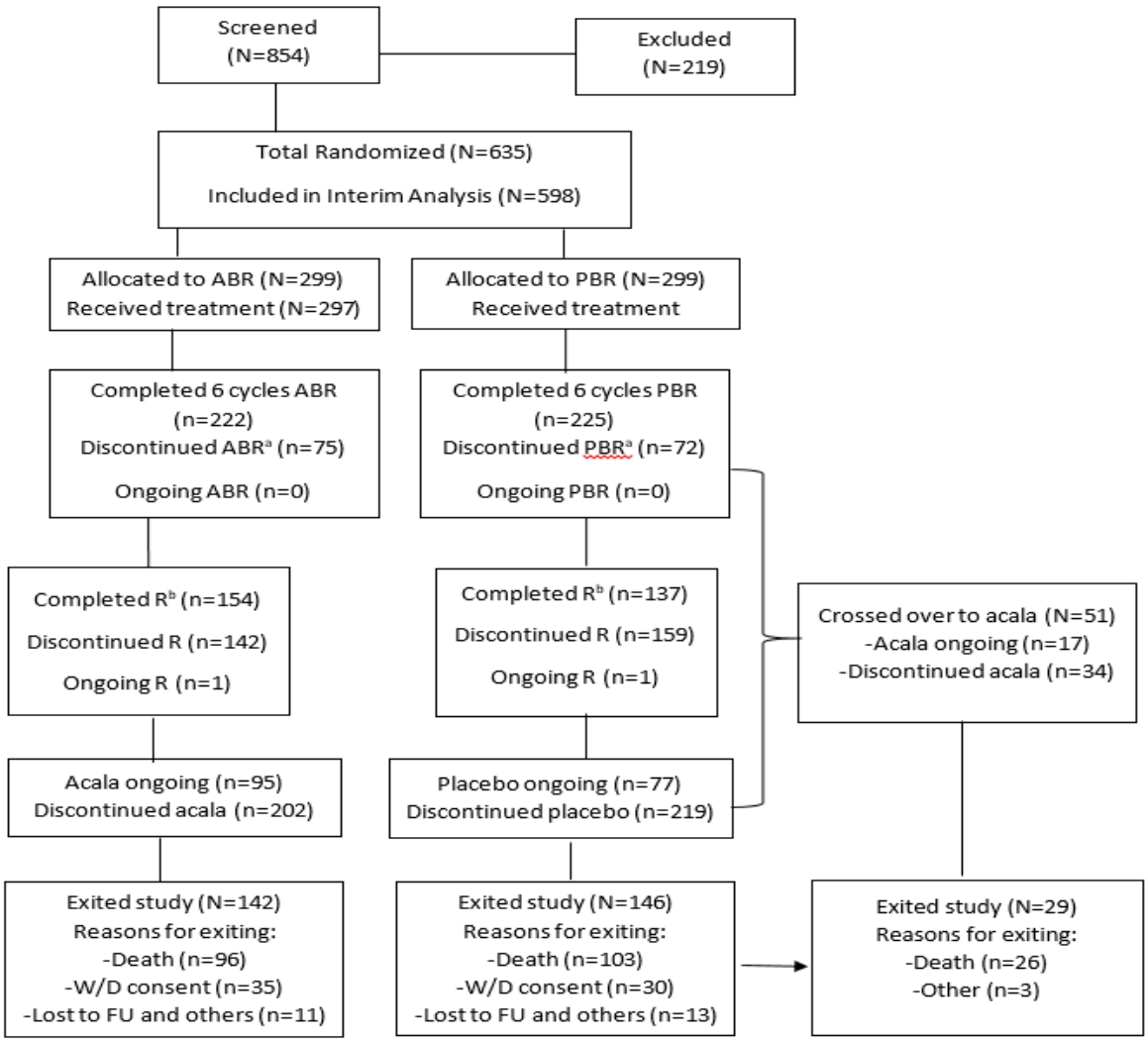
One interim analysis for PFS was planned for the study when approximately 227 IRC-assessed PFS events were observed. With consideration of potential COVID-19 death impact on the primary IRC-PFS analysis, the DCO date was determined to accrue approximately 10% more IRC-PFS events than protocol pre-specified 227 IRC-PFS events for interim analysis. The results of the interim analysis are presented in the interim CSR based on the DCO date of 15 February 2024. The final analysis was planned to occur when approximately 268 IRC-assessed PFS events have been observed.

If the criterion for early efficacy was met at the time of the IRC-PFS interim analysis, the DMC may have recommended to unblind the study in accordance with the terms of the DMC charter. Otherwise,

if the interim analysis results were not confirming the criteria for unblinding, then the plan was to continue the study to PFS final analysis with approximately 268 IRC-PFS events achieved.

Results

Participant flow



[a] *Discontinued any study drug.*
[b] *Patients who were reported by the investigator to have completed rituximab treatment per protocol.*

Abbreviations:ABR = acalabrutinib, bendamustine, rituximab; acala = acalabrutinib; FU = follow-up; W/D = withdrawn; PBR = placebo, bendamustine, rituximab

Recruitment

First patient was randomised on 08 May 2017 and last patient was randomised 27 March 2023.

The clinical cut-off date for presented data was 15 February 2024 (interim analysis).

Conduct of the study

Four protocol amendments were done during the study and amendments 3 and 4 are considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Summaries of the substantial amendments are presented below.

1. **Amendment 3.0 (08 June 2020):**

   The protocol was amended to remove the interim analysis that was planned to occur when approximately 152 IRC-assessed PFS events had been observed. Based on available external clinical trial information, it was determined that there was a low probability of a positive interim analysis outcome after 152 events in the present study. The study would proceed directly to the final analysis.

   This amendment also further defined the global intent-to-treat (ITT) population. Due to slower than anticipated enrolment in China, the global population was changed to include only 2-5 subjects from China. The study would close globally with approximately 546 subjects, including 2-5 subjects from China, and enrolment in China will continue until at least 80 subjects from China are randomised in addition to the approximately 546 subjects in the global population.

2. **Amendment 4.0 (06 June 2023):**

   The protocol was amended to re-introduce the interim analysis that was planned to occur when approximately 227 IRC-assessed PFS events had been observed and final analysis will occur when approximately 268 IRC-assessed PFS events have been observed. Covid-19 infections add an uncertain risk of impacting the study outcome. Adding in an IA and extending the FA to more PFS events helps mitigates the potential impact of Covid-19 on PFS events and the study primary endpoint. The extension of the FA also allows the study to collect more mature OS data and to have longer OS follow up.

Protocol deviations are summarised in **Table 7**.

Table 7. Summary of Important Protocol Deviations (Full Analysis Set (FAS), Study ACE-LY-308)

	No. (%) of patients		
	ABR (N = 299)	**PBR (N = 299)**	**Total (N=598)**
Patients with any important protocol deviations	43 (14.4%)	37 (12.4%)	80 (13.4%)
Laboratory	17 (5.7%)	15 (5.0%)	32 (5.4%)
Dosing	16 (5.4%)	12 (4.0%)	28 (4.7%)
Visit/procedure required	7 (2.3%)	6 (2.0%)	13 (2.2%)
Non-compliance	3 (1.0%)	2 (0.7%)	5 (0.8%)
Informed consent	0	2 (0.7%)	2 (0.3%)
Visit schedule	2 (0.7%)	0	2 (0.3%)
Concomitant medications	1 (0.3%)	0	1 (0.2%)
Enrolment criteria	0	1 (0.3%)	1 (0.2%)
Other	3 (1.0%)	3 (1.0%)	6 (1.0%)

Baseline data

Table 8. Patient demographics (FAS, ACE-LY-308)

	ABR (N = 299)	**PBR (N = 299)**	**Total (N = 598)**
Age (years)			
Mean (SD)	71.6 (4.73)	71.6 (4.60)	71.6 (4.66)
Median	71.0	71.0	71.0
Min, Max	65, 85	65, 86	65, 86
Age group, n (%)			
< 70	123 (41.1%)	117 (39.1%)	240 (40.1%)
≥ 70	176 (58.9%)	182 (60.9%)	358 (59.9%)
< 75	215 (71.9%)	222 (74.2%)	437 (73.1%)
≥ 75	84 (28.1%)	77 (25.8%)	161 (26.9%)
Sex, n (%)			
Male	214 (71.6%)	209 (69.9%)	423 (70.7%)
Female	85 (28.4%)	90 (30.1%)	175 (29.3%)
Race, n (%)			
White	233 (77.9%)	235 (78.6%)	468 (78.3%)
Asian	44 (14.7%)	49 (16.4%)	93 (15.6%)
American Indian or Alaska Native	2 (0.7%)	2 (0.7%)	4 (0.7%)
Black or African American	1 (0.3%)	2 (0.7%)	3 (0.5%)
Multiple	5 (1.7%)	0	5 (0.8%)
Not reported	14 (4.7%)	11 (3.7%)	25 (4.2%)
Ethnicity, n (%)			
Hispanic or Latino	34 (11.4%)	33 (11.0%)	67 (11.2%)
Not Hispanic or Latino	245 (81.9%)	252 (84.3%)	497 (83.1%)
Not reported	20 (6.7%)	14 (4.7%)	34 (5.7%)
Body mass index (BMI) (kg/m2)			
Mean (SD)	27.05 (4.702)	27.01 (4.729)	27.03 (4.712)
Median	26.40	26.30	26.35
Min, Max	16.2, 44.8	14.9, 41.8	14.9, 44.8
ECOG Performance Status, n (%)			
0	156 (52.2%)	140 (46.8%)	296 (49.5%)
1	129 (43.1%)	132 (44.1%)	261 (43.6%)
2	12 (4.0%)	23 (7.7%)	35 (5.9%)
3	0	2 (0.7%)	2 (0.3%)
Missing	2 (0.7%)	2 (0.7%)	4 (0.7%)

Table 9. Baseline disease characteristics (FAS, ACE-LY-308)

	ABR (N = 299)	**PBR (N = 299)**	**Total (N = 598)**
Histologically documented MCL, n (%)	299 (100.0%)	299 (100.0%)	598 (100.0%)
MCL type, n (%)			
Classic type	238 (79.6%)	243 (81.3%)	481 (80.4%)
Blastoid variant	26 (8.7%)	20 (6.7%)	46 (7.7%)
Pleomorphic variant	15 (5.0%)	18 (6.0%)	33 (5.5%)
Other	0	5 (1.7%)	5 (0.8%)
Unknown	19 (6.4%)	11 (3.7%)	30 (5.0%)
Not done	1 (0.3%)	2 (0.7%)	3 (0.5%)
Tumour bulk			
< 5 cm	187 (62.5%)	186 (62.2%)	373 (62.4%)
≥ 5 cm and < 10 cm	92 (30.8%)	92 (30.8%)	184 (30.8%)
≥ 10 cm	20 (6.7%)	21 (7.0%)	41 (6.9%)
Tumour burden[a]			
Mean (SD)	42.05 (46.847)	46.52 (70.791)	44.28 (60.016)
Median	25.70	27.28	26.32
Min, Max	1.0, 312.5	0.9, 898.5	0.9, 898.5
Ann Arbor staging for lymphoma, n (%)			
I	2 (0.7%)	1 (0.3%)	3 (0.5%)
II	15 (5.0%)	11 (3.7%)	26 (4.3%)
III	31 (10.4%)	24 (8.0%)	55 (9.2%)
IV	251 (83.9%)	263 (88.0%)	514 (86.0%)
Patients with extranodal disease, n (%)			
1 site	155 (51.8%)	155 (51.8%)	310 (51.8%)
2 or more sites	109 (36.5%)	122 (40.8%)	231 (38.6%)
Extranodal disease, n (%)			
No	35 (11.7%)	22 (7.4%)	57 (9.5%)
Yes	264 (88.3%)	277 (92.6%)	541 (90.5%)
Liver	7 (2.3%)	10 (3.3%)	17 (2.8%)
Lung	18 (6.0%)	30 (10.0%)	48 (8.0%)
Bone marrow	231 (77.3%)	239 (79.9%)	470 (78.6%)
Pleura	12 (4.0%)	9 (3.0%)	21 (3.5%)

Bone	8 (2.7%)	13 (4.3%)	21 (3.5%)
Skin	3 (1.0%)	4 (1.3%)	7 (1.2%)
Gastrointestinal	74 (24.7%)	75 (25.1%)	149 (24.9%)
Soft tissue	21 (7.0%)	24 (8.0%)	45 (7.5%)
Thyroid gland	4 (1.3%)	1 (0.3%)	5 (0.8%)
Other	22 (7.4%)	30 (10.0%)	52 (8.7%)
Involved	211 (70.6%)	218 (72.9%)	429 (71.7%)
Not Involved	82 (27.4%)	75 (25.1%)	157 (26.3%)
Indeterminant	1 (0.3%)	2 (0.7%)	3 (0.5%)
Missing	5 (1.7%)	4 (1.3%)	9 (1.5%)
Ki-67, n (%)			
< 30%	133 (44.5%)	126 (42.1%)	259 (43.3%)
≥ 30%	139 (46.5%)	147 (49.2%)	286 (47.8%)
< 50%	210 (70.2%)	199 (66.6%)	409 (68.4%)
≥ 50%	62 (20.7%)	74 (24.7%)	136 (22.7%)
Indetermined	4 (1.3%)	4 (1.3%)	8 (1.3%)
Missing	23 (7.7%)	22 (7.4%)	45 (7.5%)
TP53 Mutation Status			
Yes	22 (7.4%)	29 (9.7%)	51 (8.5%)
No	97 (32.4%)	83 (27.8%)	180 (30.1%)
Unknown	180 (60.2%)	187 (62.5%)	367 (61.4%)
Gastrointestinal disease, n (%)	74 (24.7%)	75 (25.1%)	149 (24.9%)
Simplified MIPI score			
Low risk [0-3]	99 (33.1%)	101 (33.8%)	200 (33.4%)
Intermediate risk [4-5]	128 (42.8%)	125 (41.8%)	253 (42.3%)
High risk [6-11]	72 (24.1%)	73 (24.4%)	145 (24.2%)
LDH > ULNc, n (%)			
Yes	52 (17.4%)	54 (18.1%)	106 (17.7%)
No	245 (81.9%)	241 (80.6%)	486 (81.3%)
Missing	2 (0.7%)	4 (1.3%)	6 (1.0%)
Haemoglobin concentration (g/dL)	N = 297	N = 297	N = 594
Mean (SD)	12.49 (1.857)	12.24 (1.987)	12.37 (1.925)
Median	12.70	12.30	12.50
Min, Max	7.2, 16.9	6.3, 17.2	6.3, 17.2
Platelet count[c] (10^9/L)	N =297	N =297	N =594
Mean (SD)	189.8 (83.32)	194.4 (83.62)	192.1 (83.43)
Median	180.0	189.0	183.0
Min, Max	51, 588	45, 477	45, 588
Absolute neutrophil count (10^9/L)	N = 296	N = 296	N = 592
Mean (SD)	5.54 (10.418)	5.54 (9.187)	5.54 (9.813)

Median	3.90	3.93	3.90
Min, Max	0.6, 117.9	0.7, 104.7	0.6, 117.9

Numbers analysed

Table 10. ACE-LY-308 analysis sets

	No. (%) of Patients		
	ABR (N=299)	**PBR (N=299)**	**Total (N=598)**
Full analysis set	299 (100%)	299 (100%)	598 (100%)
Safety analysis set	297 (99.3%)	297 (99.3%)	594 (99.3%)
Per-protocol analysis set	236 (78.9%)	252 (84.3%)	488 (81.6%)
Pharmacokinetic analysis set	187 (62.5%)	34 (11.4%)	221 (37.0%)
Biomarker analysis set	266 (89.0%)	252 (84.3%)	518 (86.6%)

Abbreviations: ABR = acalabrutinib, bendamustine, rituximab; No. = number; PBR = placebo, bendamustine, rituximab.

Outcomes and estimation

All results presented in this section are from the interim analysis with a clinical data cut-off of 15 February 2024 unless otherwise specified.

Primary endpoint

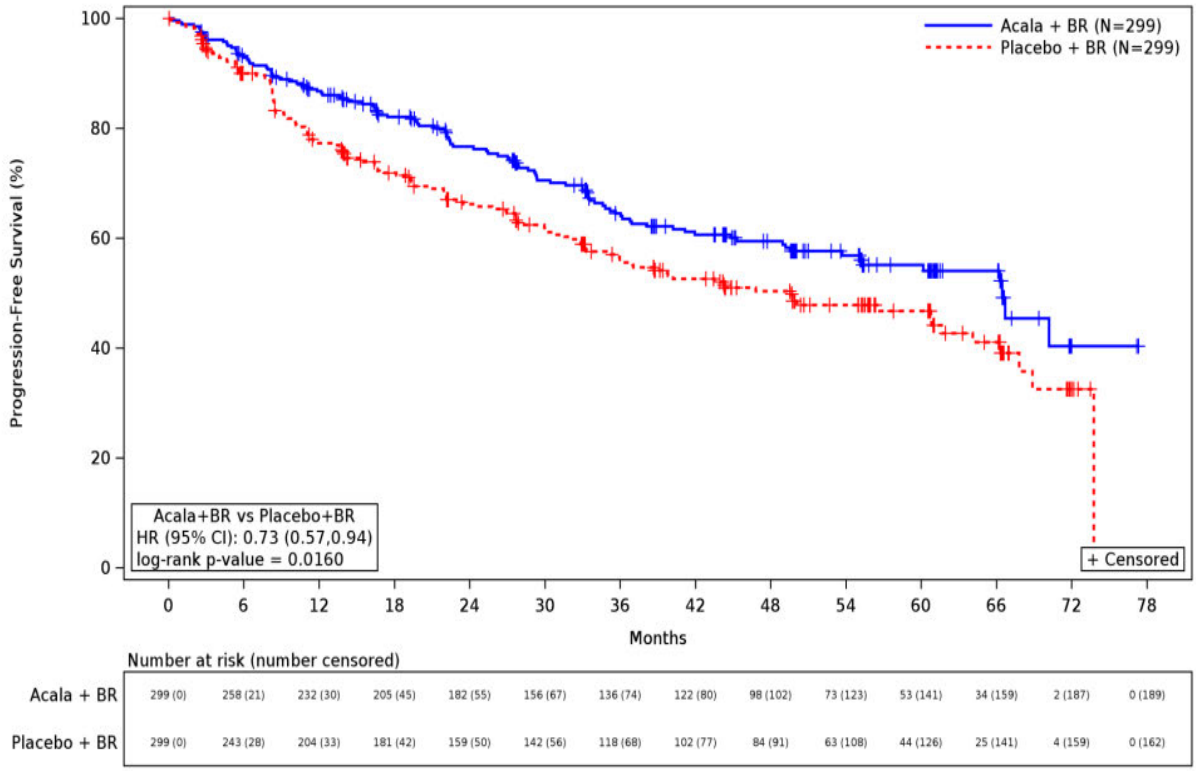
Table 11. Analysis of PFS by IRC Assessment (Full Analysis Set, ACE-LY-308)

	ABR (N = 299)	**PBR (N = 299)**
Patient status		
Events, n (%)	110 (36.8%)	137 (45.8%)
Death	53 (17.7%)	38 (12.7%)
Disease progression	57 (19.1%)	99 (33.1%)
Censored, n (%)	189 (63.2%)	162 (54.2%)
Data cutoff	126 (42.1%)	99 (33.1%)
Missing 2 or more consecutive response assessments	19 (6.4%)	14 (4.7%)
Start of subsequent anti-MCL therapy	8 (2.7%)	14 (4.7%)
Lost to follow-up or study exit or crossover	23 (7.7%)	24 (8.0%)
No response assessment post-randomisation	13 (4.3%)	11 (3.7%)
Progression-free survival (months)		
Median (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)

Min, Max	0.0+, 77.3+	0.0+, 73.8
Stratified analysis[a] (versus PBR)		
Hazard ratiob (95% CI)	0.73 (0.57, 0.94)	--
p-value[c]	0.0160	--
Unstratified analysis[a] (versus PBR)		
Hazard ratio[b] (95% CI)	0.72 (0.56, 0.93)	--
p-valuec	0.0112	--
KM estimates of PFSc probability by timepoint (%)		
24 months (95% CI), number by risk	76.7 (71.1, 81.3), 182	66.2 (60.1, 71.6), 159
36 months (95% CI), number by risk	64.5 (58.1, 70.2), 136	56.1 (49.7, 62.0), 118
48 months (95% CI), number by risk	59.5 (52.8, 65.5), 98	50.4 (43.8, 56.6), 84

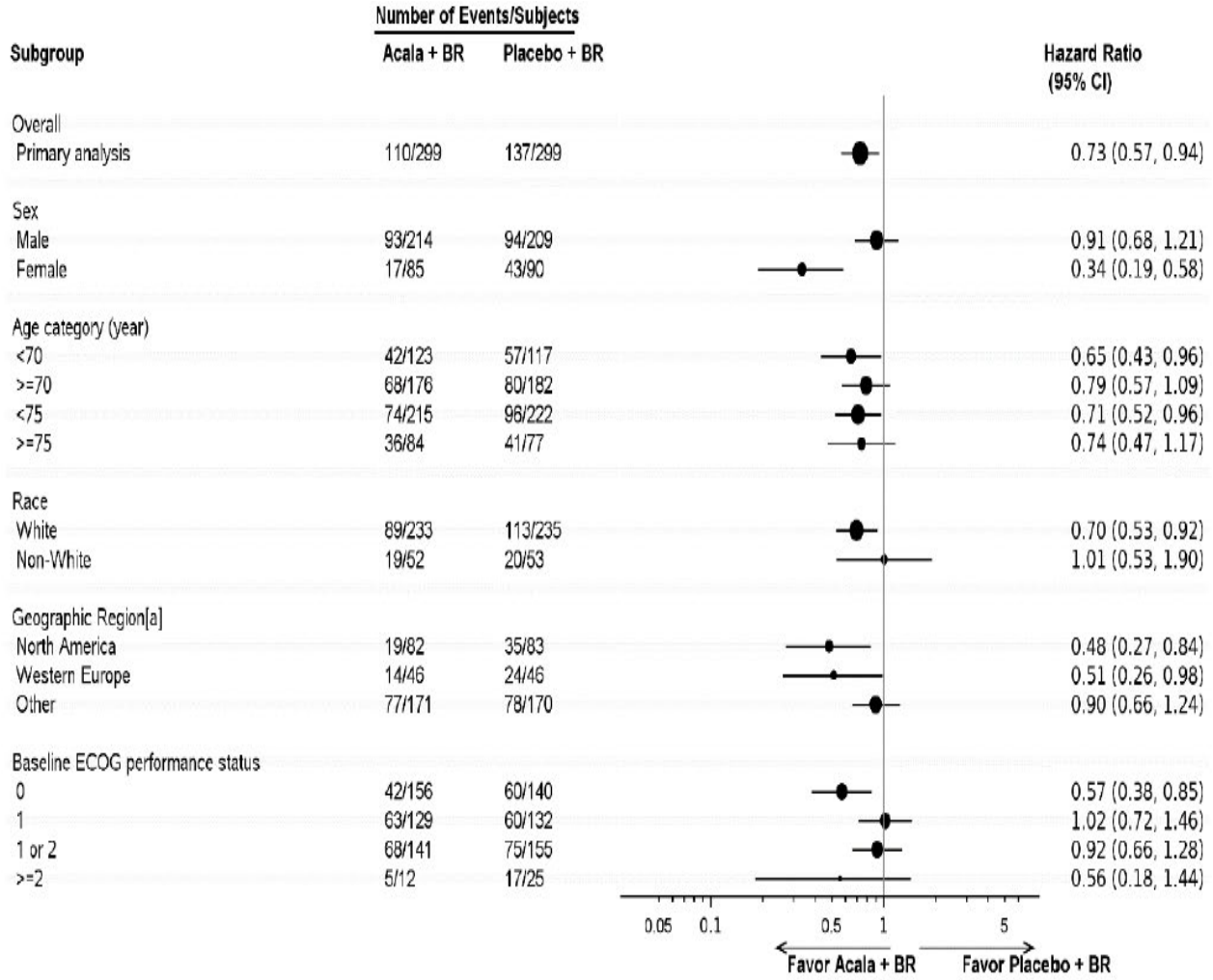
[a] Stratified/unstratified by randomisation stratification factors: Geographic Region (North America, Western Europe, Other) and simplified MIPI Score (Low Risk [0 to 3], Intermediate Risk [4 to 5], High Risk [6 to 11]) as collected via IXRS.
[b] Estimated based on stratified or unstratified Cox proportional hazards model for hazard ratio (95%CI), respectively.
[c] Estimated based on stratified or unstratified log-rank test for p-value, respectively.
Months are derived as days/30.4375.Time to event (or time to censor for censored patients) was calculated as date of disease progression or death (censoring date for censored patients) – randomisation date +1.
Abbreviations: "+" indicates a value from a censored patient; ABR = acalabrutinib, bendamustine, rituximab; CI = confidence interval; IRC = independent review committee; IXRS = Interactive Voice/Web Response System; KM = Kaplan-Meier; Max = maximum, MCL = mantle cell lymphoma; Min = minimum; MIPI = Mantle Cell Lymphoma International Prognostic Index; NE = not estimable; PBR = placebo, bendamustine, rituximab; PFS = progression-free survival.

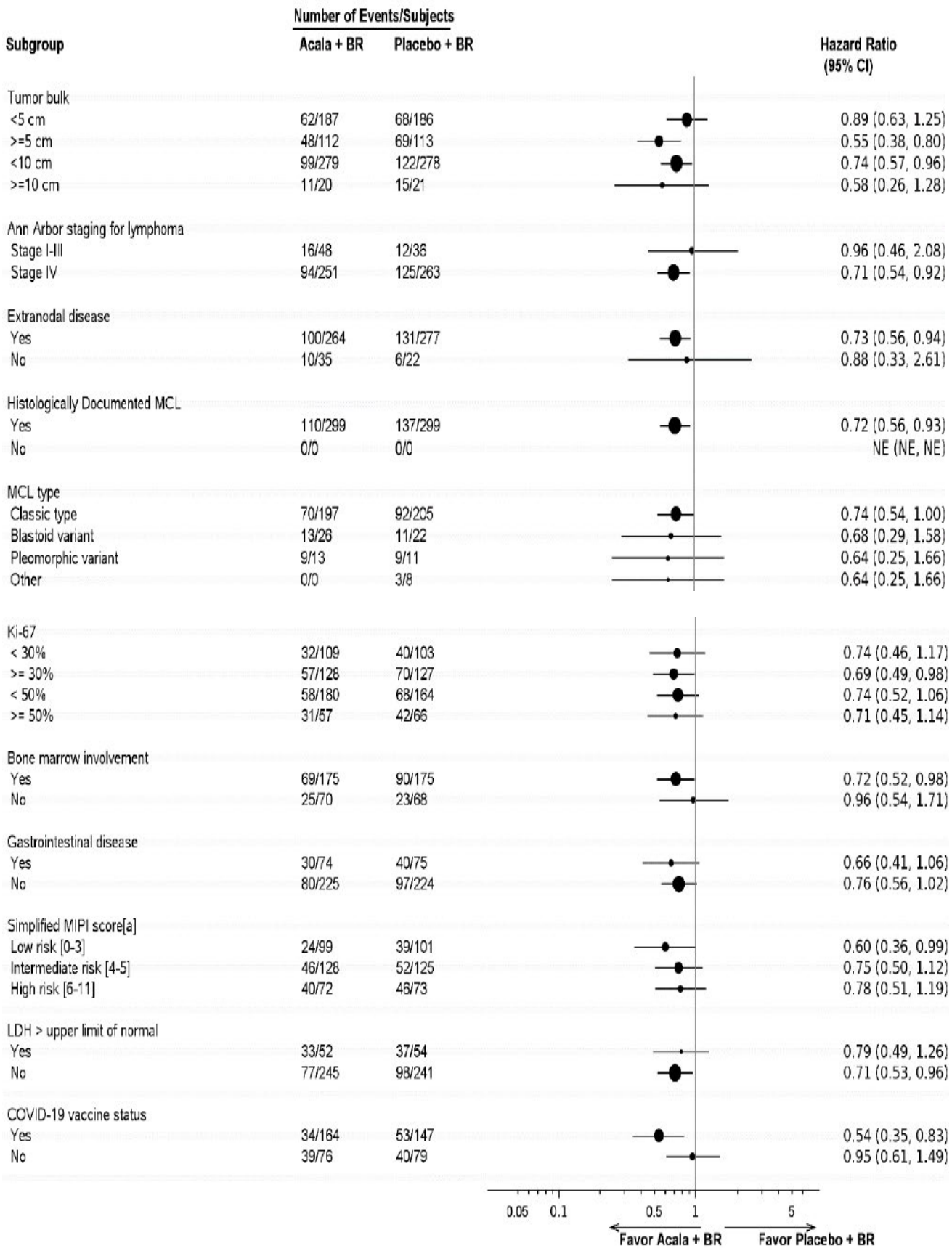
Figure 6. Kaplan-Meier Plot of IRC-Assessed Progression-Free Survival (FAS, ACE-LY-308)



Sub-group analysis of PFS

Figure 7. Forest Plot for Subgroup Analysis of PFS by IRC Assessment (FAS, ACE-LY-308)

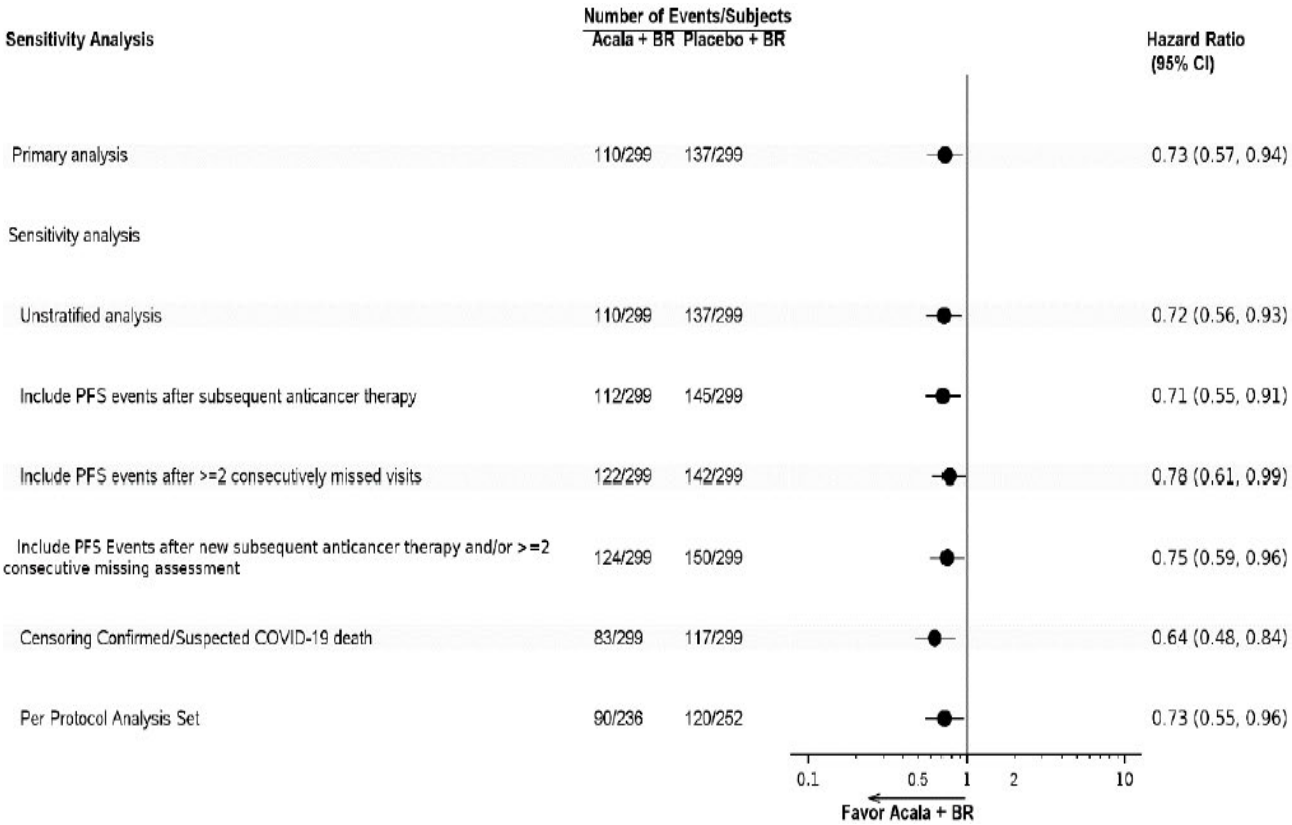

Number of Events/Subjects
Subgroup
Acala + BR
Placebo + BR
Hazard Ratio (95% CI)
Overall
Primary analysis 110/299 137/299 0.73 (0.57, 0.94)
Sex
Male 93/214 94/209 0.91 (0.68, 1.21)
Female 17/85 43/90 0.34 (0.19, 0.58)
Age category (year)
<70 42/123 57/117 0.65 (0.43, 0.96)
>=70 68/176 80/182 0.79 (0.57, 1.09)
<75 74/215 96/222 0.71 (0.52, 0.96)
>=75 36/84 41/77 0.74 (0.47, 1.17)
Race
White 89/233 113/235 0.70 (0.53, 0.92)
Non-White 19/52 20/53 1.01 (0.53, 1.90)
Geographic Region[a]
North America 19/82 35/83 0.48 (0.27, 0.84)
Western Europe 14/46 24/46 0.51 (0.26, 0.98)
Other 77/171 78/170 0.90 (0.66, 1.24)
Baseline ECOG performance status
0 42/156 60/140 0.57 (0.38, 0.85)
1 63/129 60/132 1.02 (0.72, 1.46)
1 or 2 68/141 75/155 0.92 (0.66, 1.28)
>=2 5/12 17/25 0.56 (0.18, 1.44)
0.05
0.1
0.5
1
5
Favor Acala + BR
Favor Placebo + BR



[a] Per IXRS record.

Sensitivity analysis of PFS

Figure 8. Forest Plot for Sensitivity Analysis of PFS by IRC Assessment (FAS, ACE-LY-308)



Anticancer refers to anti-MCL therapy.

Overall Survival

Table 12. Overall Survival (FAS, ACE-LY-308: Including Crossover Period, cut-off date 12 Aug 2024)

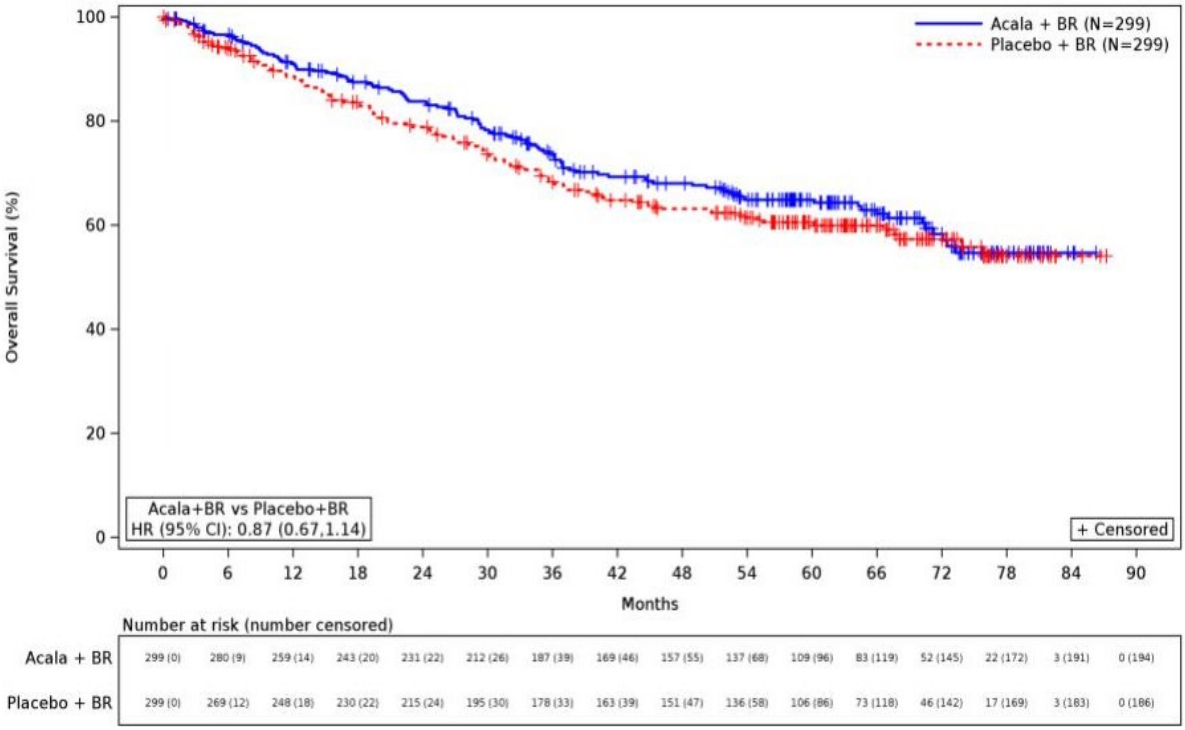
	A BR (N=299)	PBR (N=299)
Subject Status		
Events[a] – n (%)	105 (35.1%)	113 (37.8%)
Death	105 (35.1%)	113 (37.8%)
Censored – n (%)	194 (64.9%)	186 (62.2%)
Lost to follow-up immediately after randomization	2 (0.7%)	1 (0.3%)
Not known to have died at or prior to data cut-off date	146 (48.8%)	144 (48.2%)
Not known to have died at or prior to lost to follow-up or study exit	46 (15.4%)	41 (13.7%)
Overall Survival (months)		
Median (95% CI)	NE (72.1, NE)	NE (73.8, NE)
Min, Max	0.0+, 86.3+	0.0+, 87.2+
Stratified Analysis (vs. Arm 2: Placebo + BR)		
Hazard Ratio (95% CI)	0.87 (0.67, 1.14)	--
Unstratified Analysis[b] (vs. Arm 2: Placebo + BR)		
Hazard Ratio (95% CI)	0.88 (0.68, 1.15)	--
KM estimate of OS by timepoint (%)		
24 months OS rate (95% CI)	83.8 (79.0, 87.6)	78.8 (73.6, 83.2)
36 months OS rate (95% CI)	73.7 (68.1, 78.5)	68.3 (62.4, 73.4)
48 months OS rate (95% CI)	68.1 (62.1, 73.3)	63.2 (57.1, 68.6)

[a] *Death of any cause.*

Note: + designates value is from a censored patient.

Abbreviations: A+BR = acalabrutinib, bendamustine, rituximab; BR = bendamustine and rituximab; CI = confidence interval; IXRS = Interactive Voice/Web Response System; KM = Kaplan-Meier; Max = maximum; Min = minimum; n = number; MIPI = Mantle Cell Lymphoma International Prognostic Index; NE = not evaluable; OS = overall survival; P+BR = placebo, bendamustine, rituximab.

Figure 9. Kaplan-Meier Plot for OS (FAS, ACE-LY-308, cut-off date 12 Aug 2024)



PFS by investigator assessment

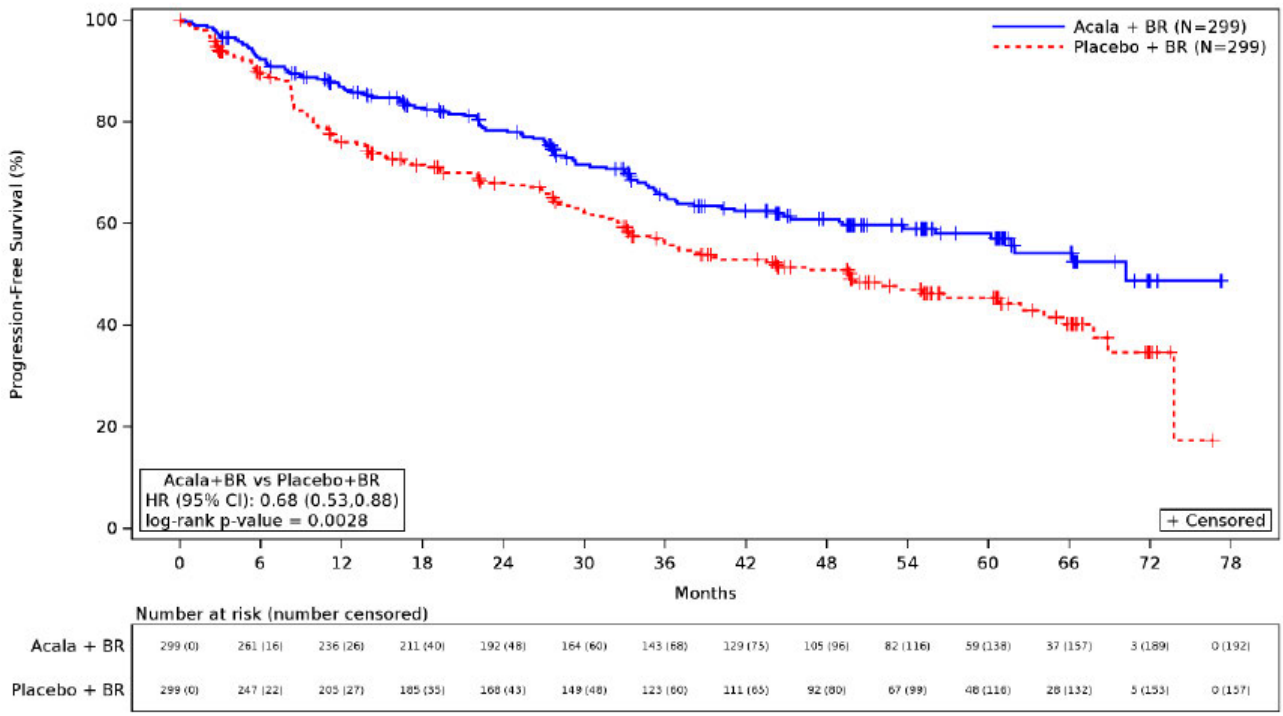
Table 13. Analysis of PFS by Investigator Assessment (FAS, ACE-LY-308)

	ABR (N=299)	**PBR (N=299)**
Patient status		
Events, n (%)	107 (35.8%)	142 (47.5%)
Death	51 (17.1%)	37 (12.4%)
Disease progression	56 (18.7%)	105 (35.1%)
Censored, n (%)	192 (64.2%)	157 (52.5%)
Data cutoff	130 (43.5%)	103 (34.4%)
Lost to follow-up or study exit	26 (8.7%)	21 (7.0%)
Missing 2 or more consecutive response Assessments	17 (5.7%)	15 (5.0%)
Start of subsequent anti-MCL therapy	8 (2.7%)	12 (4.0%)
No response assessment post-randomisation	11 (3.7%)	6 (2.0%)
Progression-free survival (months)		
Median (95% CI)	70.2 (61.7, NE)	49.7 (36.0, 62.4)
Min, Max	0.0+, 77.3+	0.0+, 76.7+

Stratified analysis[a] (versus PBR)		
Hazard ratio (95% CI)[b]	0.68 (0.53, 0.88)	--
p-value[c]	0.0028	--
Unstratified analysis (versus PBR)		
Hazard ratio (95% CI)[b]	0.68 (0.53, 0.87)	--
p-value[c]	0.0024	--
KM estimates of PFS probability by timepoint (%)		
24 months (95% CI), number by risk	78.3 (72.9, 82.8), 192	67.9 (62.0, 73.1), 168
36 months (95% CI), number by risk	65.7 (59.4, 71.2), 143	56.1 (49.8, 61.9), 123
48 months (95% CI), number by risk	60.8 (54.3, 66.7), 105	50.8 (44.4, 56.8), 92

[a] Stratified/unstratified by randomisation stratification factors: Geographic Region (North America, Western Europe, Other) and simplified MIPI Score (Low Risk [0 to 3], Intermediate Risk [4 to 5], High Risk [6 to 11]) as collected via IXRS.
[b] Estimated based on stratified or unstratified Cox proportional hazards model for hazard ratio (95% CI), respectively.
[c] Estimated based on stratified or unstratified log-rank test for p-value, respectively.
Months are derived as days/30.4375. Time to event (or time to censor for censored patients) is calculated as date of disease progression or death (censoring date for censored subjects)–randomisation date +1.
Source: Interim Clinical Study Report, Table 22.

Figure 10. Kaplan-Meier Plot for PFS by Investigator Assessment (FAS, ACE-LY-308)



The overall concordance rates between the IRC-assessed and investigator-assessed PD for ABR and PBR were 93.6% and 95.3%, respectively. The overall concordance rates between the IRC-assessed PFS and investigator-assessed PFS for ABR and PBR were 94.3% and 95.7%, respectively.

ORR by IRC assessment

Table 14. Best Overall Response by IRC Assessment (FAS, ACE-LY-308)

	IRC Assessment	
	ABR (N=299)	**PBR (N=299)**
Best overall response, n (%)		
CR	199 (66.6%)	160 (53.5%)
PR	73 (24.4%)	103 (34.4%)
Stable disease	3 (1.0%)	5 (1.7%)
PD	8 (2.7%)	13 (4.3%)
Unknown	1 (0.3%)	5 (1.7%)
Missing[a]	15 (5.0%)	13 (4.3%)
ORR (CR + PR), n (%)	272 (91.0%)	263 (88.0%)
95% CI[b]	(87.3%, 93.8%)	(83.9%, 91.3%)
ORR difference (versus PBR)	3.0%	--
95% CI[c]	(-2.0%, 8.1%)	--
p-value[d]	0.2196	--

ORR by investigator assessment

Table 15. Objective response rate by IRC Assessment (FAS, ACE-LY-308)

	Investigator Assessment	
	ABR (N=299)	**PBR (N=299)**
Best overall response, n (%)		
CR	223 (74.6%)	196 (65.6%)
PR	50 (16.7%)	70 (23.4%)
Stable disease	4 (1.3%)	7 (2.3%)
PD	7 (2.3%)	14 (4.7%)
Missing	15 (5.0%)	12 (4.0%)
ORR (CR + PR), n (%)	273 (91.3%)	266 (89.0%)
95% CI	(87.7%, 94.1%)	(85.0%, 92.2%)
ORR difference (versus PBR)	2.3%	--
95% CI	(-2.5%, 7.2%)	--
p-value	0.3239	--

The overall concordance rates between the IRC-assessed and investigator-assessed PD for ABR and PBR were 93.6% and 95.3%, respectively. The overall concordance rates between the IRC-assessed PFS and investigator-assessed PFS for ABR and PBR were 94.3% and 95.7%, respectively.

Duration of response by IRC

Table 16. Duration of Response by IRC Assessment (FAS, ACE-LY-308: Only for All Responding Patients [CR + PR])

	IRC Assessment	
	ABR (N = 272)	**PBR (N = 263)**
Patient status		
Events, n (%)	99 (36.4%)	117 (44.5%)
Death	52 (19.1%)	34 (12.9%)
Disease progression	47 (17.3%)	83 (31.6%)
Censored, n (%)	173 (63.6%)	146 (55.5%)
Data cutoff	126 (46.3%)	99 (37.6%)
Missing 2 or more consecutive response assessments	17 (6.3%)	13 (4.9%)
Start of subsequent anti-MCL therapy	7 (2.6%)	11 (4.2%)
Lost to follow-up or study exit or crossover	23 (8.5%)	23 (8.7%)
Duration of response (months)		
Median (95% CI)	63.5 (52.5, NE)	53.8 (37.6, 66.1)
Min, Max	0.0+, 74.5+	0.0+, 70.5+
KM estimates of DOR[a] probability by timepoint (%)		
24 months (95% CI), number at risk	77.1 (71.3, 81.8), 175	68.6 (62.3, 74.1), 151
36 months (95% CI), number at risk	64.6 (58.0, 70.4), 127	58.5 (51.8, 64.6), 112
48 months (95% CI), number at risk	59.9 (53.0, 66.1), 77	51.1 (44.0, 57.7), 64

[a] Kaplan-Meier estimate of the proportion of patients who were progression-free at the timepoint. Months are derived as days / 30.4375. Duration of response was calculated as date of disease progression or death (censoring date for censored patients) – (date of achieving the first CR or PR) + 1.

DOR by investigator assessment

Table 17. Duration of Response by Investigator Assessment (FAS, ACE-LY-308: Only for All Responding Patients [CR + PR])

	Investigator assessment	
	ABR (N=273)	**PBR (N=266)**
Patient status		
Events, n (%)	94 (34.4%)	121 (45.5%)
Death	49 (17.9%)	33 (12.4%)

Disease progression	45 (16.5%)	88 (33.1%)
Censored, n (%)	179 (65.6%)	145 (54.5%)
Data cutoff	130 (47.6%)	103 (38.7%)
Missing 2 or more consecutive response assessments	16 (5.9%)	14 (5.3%)
Start of subsequent anti-MCL therapy	7 (2.6%)	8 (3.0%)
Lost to follow-up or study exit or crossover	26 (9.5%)	20 (7.5%)
Duration of response (months)		
Median (95% CI)	NE (59.0, NE)	53.1 (40.7, 65.2)
Min, Max	0.0+, 74.5+	0.0+, 74.2+
KM estimates of DOR[a] probability by timepoint (%)		
24 months (95% CI), number at risk	79.8 (74.3, 84.3), 186	71.5 (65.5, 76.7), 163
36 months (95% CI), number at risk	66.4 (59.9, 72.1), 135	58.1 (51.4, 64.1), 116
48 months (95% CI), number at risk	62.4 (55.7, 68.5), 86	52.4 (45.5, 58.8), 73

[a] Kaplan-Meier estimate of the proportion of patients who were progression-free at the timepoint. Months are derived as days / 30.4375. Duration of response was calculated as date of disease progression or death (censoring date for censored patients) – (date of achieving the first CR or PR) + 1.

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 18. Summary of Efficacy for the ECHO Trial

Title: ACE-LY-308 (ECHO)	
Study identifier	Protocol Number: ACE-LY-308 (D8220C00004); EudraCT number: 2015-005220-26; ClinicalTrials.gov Identifier: NCT 2023-505707-23-00

<table>
<tr><td>Design</td><td colspan="2">ECHO is a Phase 3, randomised, double-blind, placebo-controlled, multicentre study evaluating the combination of acalabrutinib + BR (ABR) versus placebo + BR (PBR) in patients aged 65 years or older and with previously untreated MCL.
Patients were randomised 1:1 to either ABR or PBR and randomisation was stratified by:
• Geographic region (North America versus Western Europe versus Other)
• sMIPI score: (low risk [0 to 3], versus intermediate risk [4 to 5], versus high risk [6 to 11]))

Patients received six 28-day cycles of ABR or PBR as induction therapy. Patients who were tolerating treatment and not progressing at the end of induction then received acalabrutinib 100 mg BID or placebo BID (as per original randomisation) continuously until PD or unacceptable toxicity. In addition, patients who achieved a response (CR or PR) at the end of induction received maintenance rituximab for two years (one dose every other cycle for a maximum of 12 doses, up to Cycle 30).
Patients randomised to PBR and who, at any time during the study, had confirmed PD could cross over to receive acalabrutinib monotherapy as a subsequent line of therapy until the second PD or unacceptable toxicity (if meeting certain eligibility criteria). Patients in either treatment arm, who required subsequent therapy, were allowed to receive subsequent anti-MCL therapy at the investigator's discretion but needed to have discontinued acalabrutinib.
During treatment, regular CT scans were performed for response assessments every 12 weeks from Week 12 (± 7 days) through Week 96 and then every 6 months (24 weeks [± 7 days]) thereafter until PD. PET/CT scans were performed at Weeks 12 and 24 (± 7 days), and then only to confirm CR thereafter.</td></tr>
<tr><td></td><td>Duration of main phase:

Duration of Run-in phase:
Duration of Extension phase:</td><td>First patient randomised: 08 May 2017
Last patient randomised: 27 March 2023
Clinical cut-off date: 15 February 2024
not applicable
not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority. The ECHO study was designed to demonstrate superiority of addition of acalabrutinib to BR as compared with placebo + BR with approximately 90% power at final analysis to detect a HR of 0.67 in IRC-assessed PFS which, under the model assumptions, translated into a 49% improvement in median PFS from 52.9 months (Wang et al 2022) in the PBR arm to 79 months in the ABR arm with a 2-sided test at alpha level of 0.05.</td></tr>
<tr><td>Treatments groups</td><td>Acalabrutinib + BR</td><td>Cycle 1 to 6: Acalabrutinib + BR
Cycle 7: Acalabrutinib
Cycle 8 to 30: Acalabrutinib + rituximab maintenance (for patients who achieved PR or better on induction therapy)
Cycle 31+: Acalabrutinib until PD or unacceptable toxicity</td></tr>
<tr><td></td><td>Placebo + BR</td><td>Cycle 1 to 6: Placebo + BR
Cycle 7: Placebo
Cycle 8 to 30: Placebo + rituximab maintenance (for patients who achieved PR or better on induction therapy)
Cycle 31+: Placebo until PD or unacceptable toxicity</td></tr>
</table>

Endpoints and definitions	Primary endpoint	Progression-free survival (IRC-PFS)	Defined as the time from randomisation until PD or death from any cause, whichever occurred first as determined by IRC.
	Key secondary endpoint	Objective response rate (IRC-ORR)	Defined as the proportion of patients achieving a best overall response of CR or PR. Based on the subset of patients with measurable disease at baseline.
	Key secondary endpoint	Overall survival (OS)	Defined as the time from date of randomisation to date of death due to any cause regardless of whether the patient withdrew from randomised therapy or received another anti-MCL therapy.
Database lock	clinical cutoff date of 15 February 2024 (OS data cut-off 12 August 2024)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis set (FAS): includes all Global cohort patients who were randomised according to the study design and additional patients from China who were randomised for at least 24 months prior to the DCO of interim analysis.			
Descriptive statistics and estimate variability	Treatment group	Acalabrutinib + BR	Placebo + BR	Hazard Ratio / P-value Stratified
	Number of subject	299	299	-
	IRC-PFS (Events, n (%))	110 (36.8%)	137 (45.8%)	HR: 0.73 (0.57, 0.94), p=0.0160
	IRC-assessed ORR (CR+PR) (n, (%))	272 (91.0%)	263 (88.0%)	p=0.2196
	OS (Events, n (%))	97 (32.4%)	106 (35.5%)	HR: 0.87 (0.66, 1.15) p=0.3248
Notes	OS maturity rate 34% at DCO for the interim analysis.			

2.4.3. Discussion on clinical efficacy

To support the use of acalabrutinib in combination with bendamustine and rituximab in adult patients with previously untreated MCL, data from one study (ACE-LY-308, ECHO) were submitted.

ECHO is a Phase 3, randomised, double-blind, placebo-controlled, multicentre study evaluating the combination of ABR versus PBR in patients aged 65 years or older and with previously untreated MCL not intended for ASCT.

Bendamustine + rituximab (BR) and add-on acalabrutinib (ABR group) or placebo (PBR group) was given for 6 cycles as induction therapy. This was followed by continuous acalabrutinib or placebo until PD or unacceptable toxicity. In addition, responders to induction ABR or PBR (i.e. patients who achieved CR or PR) received a maximum of 12 cycles of rituximab maintenance. Patients randomised to placebo that had a confirmed PD could (if eligible) cross-over to receive acalabrutinib monotherapy. This is considered acceptable as approved treatments for R/R MCL includes targeted approaches such as BTKi. In the PBR arm,(29%) of patients received subsequent anti-MCL therapy. Of these, 76

patients (86%) received at least one BTKi. Two patients (one in each treatment arm) had ASCT as subsequent therapy.

The primary endpoint was PFS assessed by IRC. Secondary endpoints included IRC-assessed ORR and OS. Other secondary endpoints included PFS by INV assessment, IRC- and INV assessed DOR and INV assessed ORR. Type I error controlled secondary endpoints changed from INV-PFS and OS to IRC-ORR and OS in an early amendment, which is accepted.

The analysis methods are considered standard for oncology studies and acceptable. The overall type I error at a 2-sided 0.05 level was handled using the Lan-DeMets alpha-spending function based on the O'Brien-Fleming boundaries were α was split for interim and final analyses of IRC-assessed PFS. Further, the alpha was to be recycled to test the type I error controlled secondary efficacy endpoints in a fixed sequential hierarchical manner: IRC-assessed ORR and OS. The multiplicity handling strategies are accepted.

Four protocol amendments were claimed. Amendments 3 and 4 are considered substantial. Since the study is double-blinded and the reasons for the amendments seem to be based on information from external data, these changes are assumed to have minor impact on type I error and are hence accepted.

The calculation of the study sample size presented in the CSR was conducted to provide 90% power for the final analysis to detect a HR of 0.67 for IRC-assessed PFS for ABR compared to PBR. This sample size calculation was presented in protocol amendment 4.0. The original sample size calculation was performed assuming a median PFS time in the PBR arm of 48 months which was changed to 52.9 months. The power was changed from 85 to 90%. However, the HR remained unaltered.

A total number of 152 IRC-assessed PFS events in the ABR and PBR was initially planned for the interim analysis. According to the Applicant there was a low probability of a positive interim analysis outcome after 152 events, based on available external clinical trial information. The originally planned interim analysis was removed (protocol amendment 3.0) and replaced by a new interim analysis (protocol amendment 4.0) where the new targeted number of IRC-assessed PFS events for the primary analysis was 227 events. Approximately 10% more IRC-PFS events were included to avoid potential COVID-19 death impact, resulting in 247 PFS events.

In the interim analysis, on which the CSR is based, 598 (94.2%) of the 635 randomised patients were included as 37 patients (all from China) were excluded due to having < 2 years follow-up at the study DCO (data on file). This was specified in the protocol prior to unblinding and is accepted. The 598 patients constituted the FAS population for the analysis in the report.

Major protocol deviations were reported for 14.4% of subjects in the ABR group, and 12.4% of subjects in the PBR group. It is deemed unlikely that these deviations have had a major impact on the study outcomes.

Efficacy data and additional analyses

The FAS includes 598 of the 635 randomised patients. Demographics, baseline disease characteristics and extent of disease were balanced between study arms. Median age was 71 years which is reasonable considering the targeted population. Of the patients included in the ECHO trial, 90.4% had extra nodal disease. At study entry, 86.0% had stage IV, 9.2% had stage III, 4.3 had stage II and 0.5% had stage I disease.

Statistically significant IRC-assessed PFS was shown for the addition of acalabrutinib to BR, with HR of 0.73 (95% CI [0.57, 0.94]) and a median PFS difference of 16.8 months. A median PFS of 66.4 months and 49.6 months was recorded for ABR and PBR, respectively. In the ABR arm, 36.8% of the

patients had a PFS event, as compared with 45.8% in the PBR arm. It is noted that the proportion of deaths in the PFS analysis is higher in the ABR arm (17.7%) compared with the PBR arm (12.7%), whereas disease progression was a more frequently observed event among patients receiving PBR (33.1% as compared with 19.1% among patients in the ABR arm).

It is acknowledged that censoring in the PFS analysis is according to the FDA censoring recommendations. The potentially informative censoring appears balanced between arms in the FAS. The majority of crossover occurred during rituximab maintenance or monotherapy phases of the study. Only 3 patients crossed over during the induction period and were censored from the PFS analysis.

In sensitivity analysis of PFS, inclusion of events after subsequent anticancer therapy and/or after >2 consecutively missed visits resulted in a HR of 0.75 (0.59, 0.96) and was consistent with the primary analysis result. The sensitivity analyses performed are, overall, deemed adequate to evaluate the robustness of the primary analysis of PFS and are considered acceptable. The sensitivity analysis censoring for Covid-19 related deaths is of limited value since these are informative censorings.

The percentage of patients with an ORR by IRC assessment was similar between the two arms (91.0% for the ABR treatment arm and 88.0% for the PBR arm, p=0.2196).

Upon request, the MAH provided an updated OS analysis with DCO of 12 August 2024. At the time of the most recent analysis, OS maturity rate was 36% (218 of 598 target events) resulting in a HR of 0.87 (95% CI: 0.67, 1.14). With a median follow-up of 51 months in the ABR arm and 46 months in the PBR arm, 105 (35.1%) patients in the ABR arm and 113 (37.8%) patients in the PBR arm had died. Median OS was not met in either of the treatment groups.

OS is difficult to interpret due to cross-over and subsequent BTKi-therapy (29% of patients in the control arm). As BTKi is approved as second line treatment of MCL, this may be unavoidable. It is emphasised that the OS analysis is non-inferential as the IRC-ORR analysis was not statistically significant (and the study was not powered for OS) however the data so far are not indicative of a detrimental effect. The MAH has committed to submit the final OS results when these are available.

Analysis of PFS by INV assessment resulted in a nominally statistically significant difference between groups in favour of ABR (HR 0.68, CI [0.53, 0.87]). These results are consistent with the IRC-PFS analysis.

The estimated median DOR (IRC-assessed) for the ABR arm was 63.5 months (95% CI: 52.5, NE) and 53.8 months (95% CI: 37.6, 66.1) for the PBR arm. The estimated median investigator-assessed DOR for the ABR arm was not reached (95% CI: 59.0, NE) and for the PBR arm was 53.1 months.

Among patients with at least one evaluable MRD sample, most patients achieved MRD-negativity at some point during the study. MRD-negative rates at the end of 6 cycles of induction (24 weeks) were 70.7% (188/266) and 67.9% (171/252) with ABR and PBR, respectively. Relevant subgroup results are mainly consistent. When not evidently so, there is a lack of plausibility for effect modification (e.g. sex).

The backbone treatment is, according to the ESMO guideline, an option for elderly patients (defined as >65 years) not planned for dose-intensified immunochemotherapy followed by ASCT. In the ECHO study, age $\geq$ 65 years was used as a proxy for ineligibility for ASCT. In addition, patients for whom the therapy goal was debulking before ASCT were excluded. Thus, the CHMP requested that the indication claimed by the MAH should be amended for adult patients with previously untreated mantle cell MCL who are not eligible for ASCT. This was accepted by the MAH.

2.4.4. Conclusions on the clinical efficacy

Efficacy of acalabrutinib in combination with bendamustine and rituximab in the treatment of first line MCL has been established in the form of a clinically meaningful prolongation of PFS. Even though OS data are immature, there is no indication of a detrimental effect, as there is a trend in favour of the acalabrutinib treated patients. Final OS data are expected once available.

2.5. Clinical safety

Introduction

Acalabrutinib is a second generation BTKi. Common AEs associated with BTKi treatment include GI disturbances (diarrhoea, nausea, and vomiting), cytopenias, bleeding events, and infections. Other toxicities that have been associated with BTKi include atrial fibrillation and hypertension.

Patient exposure

The pivotal safety dataset supporting the proposed indication is based on the PFS interim analysis data (DCO 15 February 2024) from the ECHO study. A total of 635 patients were randomised, which included 85 patients from the China cohort (81 China mainland + 4 Taiwan). However, only 598 (299 in the ABR arm and 299 in the PBR arm) of the 635 patients were included in the primary analysis as 37 patients (all from China) were excluded due to having < 2 years follow up at the study DCO. A total of 594 patients received at least one dose of any study drug (297 in ABR arm and 297 in PBR arm).

The Safety Analysis Set (SAS) for the main study period consisted of all randomised patients who received any amount of study treatment during the main study period. If a patient incorrectly received acalabrutinib in any amount, the patient was analysed under the acalabrutinib arm, as a conservative approach. Exposure to acalabrutinib, bendamustine and rituximab is summarised in **Table 19**-**Table 21**.

Table 19. Acalabrutinib/Placebo treatment exposure, SAS, ACE-LY-308

Acalabrutinib/placebo treatment	ABR (N = 297)	PBR (N = 297)
Duration of exposure (months)[a], n	297	296[b]
Mean (SD)	32.461 (23.5280)	29.121 (23.0867)
Median	28.550	24.591
Min, Max	0.13, 80.07	0.03, 76.35
Actual cumulative dose (g), n	297	296
Mean (SD)	181.70 (139.546)	165.86 (135.120)
Median	154.10	131.50
Min, Max	0.8, 469.5	0.1, 464.7
Average daily dose (mg/day)[c], n	297	296
Mean (SD)	178.16 (32.134)	185.48 (24.902)
Median	192.65	194.67
Min, Max	72.4, 216.4	40.7, 244.1
Relative dose intensity (%)[d], n	297	296
Mean (SD)	89.08 (16.067)	92.74 (12.451)
Median	96.33	97.33
Min, Max	36.2, 108.2	20.4, 122.1
Patients receiving study treatment, n (%)	297 (100%)	296 (99.7%)
≤ 3 cycles	27 (9.1%)	27 (9.1%)
> 3 and ≤ 6 cycles	18 (6.1%)	24 (8.1%)
> 6 and ≤ 9 cycles	20 (6.7%)	21 (7.1%)
> 9 and ≤ 12 cycles	13 (4.4%)	26 (8.8%)
> 12 and ≤ 18 cycles	27 (9.1%)	26 (8.8%)
> 18 and ≤ 24 cycles	15 (5.1%)	16 (5.4%)
> 24 and ≤ 30 cycles	19 (6.4%)	19 (6.4%)
> 30 and ≤ 36 cycles	27 (9.1%)	19 (6.4%)
>36 and ≤ 42 cycles	14 (4.7%)	17 (5.7%)
>42 and ≤ 48 cycles	9 (3.0%)	13 (4.4%)
>48 and ≤ 54 cycles	13 (4.4%)	10 (3.4%)
>54 and ≤ 60 cycles	27 (9.1%)	22 (7.4%)
>60 and ≤ 66 cycles	17 (5.7%)	10 (3.4%)
>66 and ≤ 72 cycles	21 (7.1%)	23 (7.7%)
>72 and ≤ 78 cycles	19 (6.4%)	15 (5.1%)
>78 and ≤ 84 cycles	10 (3.4%)	8 (2.7%)
>84 and ≤ 90 cycles	1 (0.3%)	0

[a] Duration of exposure (months) for acalabrutinib/placebo is defined as (last dose date – first dose date + 1)/30.4375.

[b] Patient [redacted] did not have placebo exposure data.

[c] Average daily dose (mg/day) for acalabrutinib/placebo is defined as total cumulative dose received (mg) / duration of exposure (day).

[d] Relative dose intensity is the percentage of actual cumulative dose to the planned cumulative dose through the drug exposure period. Relative dose intensity for acalabrutinib/placebo was calculated as (total cumulative dose received [mg] / duration of exposure [days] × 100 [mg] × 2) × 100).

Abbreviations: ABR = acalabrutinib, bendamustine, rituximab; Max = maximum; Min = minimum; PBR = placebo, bendamustine, rituximab; SD = standard deviation.

Table 20. Bendamustine treatment exposure, SAS, ACE-LY-308

Bendamustine treatment	ABR (N = 297)	PBR (N = 297)
Duration of exposure (months)[a], n	297	296[b]
Mean (SD)	5.28 (1.315)	5.19 (1.193)
Median	5.55	5.55
Min, Max	0.9, 11.1	0.9, 7.4
Actual cumulative dose (g/m^2), n	297	296
Mean (SD)	0.933 (0.2410)	0.935 (0.2379)
Median	1.038	1.042
Min, Max	0.18, 1.66	0.09, 1.37
Relative dose intensity (%)[c], n	297	296
Mean (SD)	86.36 (22.319)	86.53 (22.027)
Median	96.11	96.44
Min, Max	16.3, 153.7	8.3, 126.9
Number of cycles administered, n	297	296
Mean (SD)	5.4 (1.27)	5.4 (1.24)
Median	6.0	6.0
Min, Max	1, 7	1, 6
Patients completed 6 cycles of bendamustine, n (%)	231 (77.8%)	235 (79.1%)
Patients receiving bendamustine, n (%)	297 (100%)	296 (99.7%)
≤ 3 cycles	32 (10.8%)	34 (11.4%)
> 3 and ≤ 6 cycles	264 (88.9%)	262 (88.2%)
> 6 cycles[d]	1 (0.3%)	0

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[a] Duration of exposure (months) was defined as (last dose date – first dose date + 28)/30.4375; the calculation of all variables is based on Cycle 1 to Cycle 6 for bendamustine.
[b] Patient [redacted] did not have placebo exposure data.
[c] Relative dose intensity is the percentage of actual cumulative dose to the planned cumulative dose through the drug exposure period. Relative dose intensity for bendamustine was calculated as (total cumulative dose received [mg/m^2] / total intended dose per protocol [90 mg/m^2] from Cycles 1 to 6 × 100).
[d] One patient in the ABR arm was noted as taking 8 cycles of BR and this was considered a major protocol deviation.

Abbreviations: ABR = acalabrutinib, bendamustine, rituximab; Max = maximum; Min = minimum; PBR = placebo, bendamustine, rituximab; SD = standard deviation.

The evaluation of the safety profile of ABR is additionally supported by safety and tolerability data of acalabrutinib monotherapy from an 11-study pool (Acalabrutinib Monotherapy Pool). This pooled safety dataset allows for characterization of the safety profile of acalabrutinib monotherapy in a larger patient population that includes patients across various haematological malignancies and stages of disease. Patients who crossed over from the ECHO study control arm (PBR) to receive at least 1 dose of acalabrutinib monotherapy during the crossover period were also included in the Acalabrutinib Monotherapy Pool.

A Combination Therapy Pool, which comprises data from three studies includes anti-cancer therapies from both ABR (acalabrutinib + BR) and AG (acalabrutinib + obinutuzumab) combination regimens. The backbone within these regimens (BR and G) have distinct safety profiles. The Combination Therapy Pool is presented in a side-by-side fashion in the safety tables, without direct comparison to ABR.

Table 21. Rituximab treatment exposure, SAS, ACE-LY-308

Rituximab treatment	ABR (N = 297)	PBR (N = 297)
Duration of exposure (months)[a], n	297	297
Mean (SD)	20.30 (9.504)	18.41 (10.192)
Median	27.47	23.92
Min, max	0.9, 28.6	0.9, 29.5
Duration of exposure (months) from Cycle 1 to 6[a], n	297	297
Mean (SD)	5.55 (1.337)	5.26 (1.305)
Median	5.52	5.52
Min, Max	0.9, 11.1	0.9, 9.2
Duration of exposure (months) from Cycle 8 to 30[a], n	245	230
Mean (SD)	16.97 (6.446)	16.03 (7.281)
Median	20.96	21.01
Min, Max	0.9, 22.9	0.9, 23.0
Actual cumulative dose (g/m^2), n	297	297
Mean (SD)	5.00 (2.050)	4.66 (2.231)
Median	6.03	5.63
Min, Max	0.4, 7.4	0.4, 10.1
Actual cumulative dose from Cycle 1 to 6 (g/m^2), n	297	297
Mean (SD)	2.09 (0.415)	2.05 (0.512)
Median	2.21	2.22
Min, Max	0.4, 2.6	0.4, 5.6
Actual cumulative dose from Cycle 8 to 30 (g/m^2), n	245	230
Mean (SD)	3.53 (1.306)	3.37 (1.482)
Median	4.16	4.13
Min, Max	0.3, 5.1	0.4, 5.2
Relative dose intensity[b], n	297	297
Mean (SD)	81.60 (23.186)	78.30 (25.571)
Median	92.82	90.47
Min, Max	16.3, 108.9	16.3, 149.3
Relative dose intensity from Cycle 1 to 6 (%)[b], n	297	297
Mean (SD)	92.81 (18.452)	91.04 (22.753)
Median	98.34	98.76
Min, Max	16.3, 114.1	16.3, 247.4
Relative dose intensity from Cycle 8 to 30 (%)[b], n	245	230
Mean (SD)	78.51 (29.033)	74.88 (32.930)
Median	92.50	91.71
Min, Max	7.3, 112.8	8.1, 115.7
Patients receiving rituximab up to Cycle 6, n (%)	297 (100%)	297 (100%)
Patients completed 6 doses of rituximab	260 (87.5%)	247 (83.2%)
Patients did not complete 6 doses of rituximab	37 (12.5%)	50 (16.8%)
Patients with CR or PR after completion of rituximab induction	250 (84.2%)	235 (79.1%)
Patients with CR or PR started rituximab maintenance	245 (82.5%)	230 (77.4%)
Patients with CR or PR who completed rituximab maintenance	114 (38.4%)	106 (35.7%)
Patients with CR or PR who did not complete rituximab maintenance	131 (44.1%)	124 (41.8%)

[a] Duration of exposure (months) was defined as (last dose date – first dose date + 28)/30.4375.

[b] Relative dose intensity is the percentage of actual cumulative dose to the planned cumulative dose through the drug exposure period. Relative dose intensity for rituximab was calculated as (total cumulative dose received [mg/m^2]/ total dose prescribed [375 mg/m^2] from dosed cycles × 100).

[b] Relative dose intensity for rituximab from Cycle 1 to 6 was calculated as (total cumulative dose received [mg/m^2] / total intended dose per protocol [375 mg/m^2] from Cycles 1 to 6 × 100). After the completion of 6 cycles of BR, patients who achieved a response (PR or greater) were to receive maintenance rituximab 375 mg/m^2 on Day 1 of every other cycle (starting on the next even-numbered cycle after completion of BR) for a maximum of 12 additional doses (through no later than Cycle 30).

Abbreviations: ABR = acalabrutinib, bendamustine, rituximab; BR = bendamustine and rituximab; CR = complete response; Max = maximum; Min = minimum; PBR = placebo, bendamustine, rituximab; PR = partial response; SD = standard deviation.

Adverse events

The MedDRA version 26.1 was used to code all AEs to a SOC and a PT. The severity of an AE in ECHO was assessed by NCI CTCAE version 5.0. Severities for studies in the pooled data were based on the version of NCI CTCAE used in each individual study at the time. Worst or maximum post-baseline grades were reported, unless specified otherwise.

TEAEs were defined as any AE with a start date on or after study treatment first dose date or any event that had started before treatment and worsened on or after study treatment first dose date, and up to 30 days post last dose of study treatment or until start of new anti-cancer therapy, whichever came first. Data displays summarise events that were treatment-emergent, unless indicated otherwise. Study drug-related TEAEs were those assessed by the investigator as related.

In studies that allowed patients to crossover from control arms to acalabrutinib monotherapy, only TEAEs experienced after the first dose date of acalabrutinib monotherapy were summarised for the Acalabrutinib Monotherapy Pool (**Table 22**).

Table 22. Overview of Treatment-emergent Adverse Events (Safety Population)

	Number (%) of patients			
	Pivotal ECHO data		**Pooled populations**	
	ABR (N = 297)	**PBR (N = 297)**	**Acalabrutinib monotherapy (N = 1478)**	**Combination therapy (N = 520)**
Any TEAEs				
Any grade	296 (99.7%)	294 (99.0%)	1446 (97.8%)	518 (99.6%)
Grade ≥ 3	264 (88.9%)	262 (88.2%)	988 (66.8%)	454 (87.3%)
Serious TEAEs				
Any grade	205 (69.0%)	184 (62.0%)	753 (50.9%)	328 (63.1%)
Grade ≥ 3	191 (64.3%)	166 (55.9%)	671 (45.4%)	304 (58.5%)
Fatal/Grade 5 TEAEs	36 (12.1%)	30 (10.1%)	125 (8.5%)	53 (10.2%)
Treatment-related TEAEs				
Any study drug	281 (94.6%)	274 (92.3%)	1103 (74.6%)	465 (89.4%)
Acalabrutinib/placebo-related[a]	262 (88.2%)	241 (81.1%)	1103 (74.6%)	435 (83.7%)
Treatment-related Grade ≥ 3 TEAEs				
Any study drug	223 (75.1%)	220 (74.1%)	451 (30.5%)	332 (63.8%)
Acalabrutinib/placebo-related[a]	197 (66.3%)	190 (64.0%)	451 (30.5%)	292 (56.2%)

	Number (%) of patients			
	Pivotal ECHO data		Pooled populations	
	ABR (N = 297)	PBR (N = 297)	Acalabrutinib monotherapy (N = 1478)	Combination therapy (N = 520)
TEAEs leading to study drug discontinuation				
Any study drug	150 (50.5%)	105 (35.4%)	234 (15.8%)	197 (37.9%)
Acalabrutinib/placebo	127 (42.8%)	92 (31.0%)	234 (15.8%)	174 (33.5%)
Bendamustine	46 (15.5%)	35 (11.8%)	0	46 (8.8%)
Rituximab	60 (20.2%)	60 (20.2%)	0	60 (11.5%)
Obinutuzumab	0	0	1 (0.1%)[b]	11 (2.1%)
TEAEs leading to study drug reduction				
Any study drug[c]	100 (33.7%)	81 (27.3%)	87 (5.9%)	120 (23.1%)
Acalabrutinib/placebo	30 (10.1%)	25 (8.4%)	87 (5.9%)	50 (9.6%)
TEAEs leading to study drug withholding				
Any study drug	242 (81.5%)	207 (69.7%)	724 (49.0%)	374 (71.9%)
Acalabrutinib/placebo	219 (73.7%)	179 (60.3%)	724 (49.0%)	351 (67.5%)
TEAE leading to infusion interruption (for infusion drug only)				
Any study drug	50 (16.8%)	81 (27.3%)	0	50 (9.6%)

A patient with multiple severity grades for the same preferred term is counted only once in most severe grade.
[a] Indicates investigator-assessed relationship to blinded treatment (i.e., acalabrutinib or placebo). Acalabrutinib/placebo at least 1 of the study drugs considered related by the investigator.
[b] Occurred in a patient from the ACE-CL-007 study who crossed over from obinutuzumab + chlorambucil treatment to acalabrutinib monotherapy.
[c] Combines dose reduced for acalabrutinib/placebo and bendamustine and infusion rate decreased for rituximab.
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; PBR = placebo + bendamustine + rituximab; TEAE = treatment-emergent adverse event.

Common Treatment-emergent Adverse Events

Table 23. Treatment-emergent Adverse Events Reported in ≥ 10% of Patients in Any Group by Preferred Term in Any Population (Safety Population)

	Number (%) of patients			
	Pivotal ECHO data		Pooled populations	
	ABR (N = 297)	PBR (N = 297)	Acalabrutinib monotherapy (N = 1478)	Combination therapy (N = 520)
Patients with ≥ 1 TEAE	296 (99.7%)	294 (99.0%)	1446 (97.8%)	518 (99.6%)
Nausea	127 (42.8%)	112 (37.7%)	322 (21.8%)	196 (37.7%)
Neutropenia	119 (40.1%)	123 (41.4%)	229 (15.5%)	180 (34.6%)
Diarrhoea	111 (37.4%)	83 (27.9%)	543 (36.7%)	221 (42.5%)
COVID-19	91 (30.6%)	62 (20.9%)	110 (7.4%)	136 (26.2%)
Headache	90 (30.3%)	42 (14.1%)	539 (36.5%)	187 (36.0%)
Fatigue	87 (29.3%)	72 (24.2%)	349 (23.6%)	162 (31.2%)
Pyrexia	86 (29.0%)	72 (24.2%)	262 (17.7%)	123 (23.7%)
Cough	80 (26.9%)	60 (20.2%)	373 (25.2%)	160 (30.8%)
Vomiting	76 (25.6%)	41 (13.8%)	207 (14.0%)	129 (24.8%)
Constipation	73 (24.6%)	75 (25.3%)	224 (15.2%)	127 (24.4%)
Anaemia	68 (22.9%)	60 (20.2%)	245 (16.6%)	98 (18.8%)
Rash	61 (20.5%)	48 (16.2%)	182 (12.3%)	92 (17.7%)
Upper respiratory tract infection	54 (18.2%)	44 (14.8%)	381 (25.8%)	139 (26.7%)
Neutrophil count decreased	53 (17.8%)	46 (15.5%)	38 (2.6%)	70 (13.5%)
Arthralgia	52 (17.5%)	49 (16.5%)	355 (24.0%)	145 (27.9%)
Back pain	48 (16.2%)	28 (9.4%)	191 (12.9%)	98 (18.8%)
Pneumonia	48 (16.2%)	39 (13.1%)	233 (15.8%)	80 (15.4%)
Pruritus	47 (15.8%)	40 (13.5%)	99 (6.7%)	69 (13.3%)
Rash maculo-papular	47 (15.8%)	19 (6.4%)	82 (5.5%)	88 (16.9%)
COVID-19 pneumonia	47 (15.8%)	37 (12.5%)	30 (2.0%)	58 (11.2%)
Dyspnoea	45 (15.2%)	28 (9.4%)	209 (14.1%)	79 (15.2%)

	Number (%) of patients			
	Pivotal ECHO data		Pooled populations	
	ABR (N = 297)	PBR (N = 297)	Acalabrutinib monotherapy (N = 1478)	Combination therapy (N = 520)
Oedema peripheral	44 (14.8%)	43 (14.5%)	176 (11.9%)	99 (19.0%)
Dizziness	43 (14.5%)	45 (15.2%)	206 (13.9%)	104 (20.0%)
Infusion related reaction	43 (14.5%)	65 (21.9%)	13 (0.9%)	88 (16.9%)
White blood cell count decreased	41 (13.8%)	31 (10.4%)	8 (0.5%)	41 (7.9%)
Decreased appetite	40 (13.5%)	40 (13.5%)	137 (9.3%)	76 (14.6%)
Myalgia	40 (13.5%)	29 (9.8%)	168 (11.4%)	75 (14.4%)
Thrombocytopenia	38 (12.8%)	34 (11.4%)	129 (8.7%)	64 (12.3%)
Hypertension	36 (12.1%)	47 (15.8%)	166 (11.2%)	75 (14.4%)
Contusion	33 (11.1%)	16 (5.4%)	298 (20.2%)	107 (20.6%)
Hypokalaemia	33 (11.1%)	32 (10.8%)	54 (3.7%)	51 (9.8%)
Urinary tract infection	33 (11.1%)	32 (10.8%)	146 (9.9%)	73 (14.0%)
Asthenia	31 (10.4%)	29 (9.8%)	103 (7.0%)	52 (10.0%)
Weight decreased	31 (10.4%)	19 (6.4%)	114 (7.7%)	50 (9.6%)
Platelet count decreased	30 (10.1%)	30 (10.1%)	46 (3.1%)	40 (7.7%)
Insomnia	30 (10.1%)	20 (6.7%)	153 (10.4%)	64 (12.3%)
Hyperuricaemia	29 (9.8%)	40 (13.5%)	56 (3.8%)	46 (8.8%)
Pain in extremity	29 (9.8%)	22 (7.4%)	147 (9.9%)	72 (13.8%)
Dyspepsia	27 (9.1%)	14 (4.7%)	98 (6.6%)	58 (11.2%)
Abdominal pain	23 (7.7%)	25 (8.4%)	134 (9.1%)	55 (10.6%)
Sinusitis	19 (6.4%)	6 (2.0%)	168 (11.4%)	58 (11.2%)
Skin lesion	18 (6.1%)	13 (4.4%)	80 (5.4%)	55 (10.6%)
Fall	17 (5.7%)	9 (3.0%)	131 (8.9%)	64 (12.3%)
Nasopharyngitis	16 (5.4%)	18 (6.1%)	123 (8.3%)	54 (10.4%)

A patient with multiple severity grades for the same preferred term is counted only once in most severe grade.
Preferred terms are listed in descending order of frequency for the ABR arm.
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; PBR = placebo + bendamustine + rituximab; TEAE = treatment-emergent adverse event

Grade ≥ 3 TEAEs

Table 24. TEAE Grade 3 or Higher AE Reported for ≥ 5% of Patients in Any Group by PT in Any Population (Safety Population)

	Number (%) of Patients			
	Pivotal ECHO data		Pooled Populations	
	ABR (N = 297)	PBR (N = 297)	Acalabrutinib Monotherapy (N = 1478)	Combination Therapy (N = 520)
Patients with ≥ 1 Grade ≥ 3 TEAE	264 (88.9%)	262 (88.2%)	988 (66.8%)	454 (87.3%)
Neutropenia	105 (35.4%)	110 (37.0%)	209 (14.1%)	160 (30.8%)
Neutrophil count decreased	46 (15.5%)	30 (10.1%)	31 (2.1%)	61 (11.7%)
COVID-19 pneumonia	40 (13.5%)	31 (10.4%)	28 (1.9%)	50 (9.6%)
White blood cell count decreased	30 (10.1%)	11 (3.7%)	5 (0.3%)	30 (5.8%)
Anaemia	28 (9.4%)	30 (10.1%)	140 (9.5%)	43 (8.3%)
COVID-19	26 (8.8%)	21 (7.1%)	29 (2.0%)	42 (8.1%)
Pneumonia	26 (8.8%)	19 (6.4%)	128 (8.7%)	42 (8.1%)
Rash maculo-papular	21 (7.1%)	2 (0.7%)	2 (0.1%)	23 (4.4%)
Lymphocyte count decreased	19 (6.4%)	29 (9.8%)	8 (0.5%)	20 (3.8%)
Thrombocytopenia	18 (6.1%)	16 (5.4%)	73 (4.9%)	33 (6.3%)
Leukopenia	17 (5.7%)	18 (6.1%)	5 (0.3%)	18 (3.5%)
Hypertension	16 (5.4%)	25 (8.4%)	70 (4.7%)	28 (5.4%)
Febrile neutropenia	15 (5.1%)	7 (2.4%)	25 (1.7%)	19 (3.7%)
Lymphopenia	8 (2.7%)	16 (5.4%)	0	8 (1.5%)

A patient with multiple severity grades for the same preferred term is counted only once in most severe grade.
Preferred terms are listed in descending order of frequency for the ABR arm.
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; PBR = placebo + bendamustine + rituximab.

Serious adverse event/deaths/other significant events

2.5.1.1. Serious adverse event

Table 25. SAE reported for >2% of patients in any group by PT (Safety Population)

	Number (%) of patients							
	Pivotal ECHO data				Pooled populations			
	ABR (N = 297)		PBR (N = 297)		Acalabrutinib monotherapy (N = 1478)		Combination therapy (N = 520)	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Patients with ≥ 1 serious TEAE	205 (69.0%)	191 (64.3%)	184 (62.0%)	166 (55.9%)	753 (50.9%)	671 (45.4%)	328 (63.1%)	304 (58.5%)
COVID-19 pneumonia	41 (13.8%)	39 (13.1%)	34 (11.4%)	30 (10.1%)	28 (1.9%)	27 (1.8%)	52 (10.0%)	49 (9.4%)
Pneumonia	28 (9.4%)	24 (8.1%)	21 (7.1%)	18 (6.1%)	122 (8.3%)	113 (7.6%)	46 (8.8%)	38 (7.3%)
COVID-19	26 (8.8%)	23 (7.7%)	19 (6.4%)	18 (6.1%)	33 (2.2%)	28 (1.9%)	40 (7.7%)	35 (6.7%)
Pyrexia	17 (5.7%)	7 (2.4%)	15 (5.1%)	4 (1.3%)	37 (2.5%)	17 (1.2%)	22 (4.2%)	9 (1.7%)
Febrile neutropenia	10 (3.4%)	10 (3.4%)	3 (1.0%)	3 (1.0%)	22 (1.5%)	21 (1.4%)	14 (2.7%)	14 (2.7%)
Atrial fibrillation	9 (3.0%)	6 (2.0%)	6 (2.0%)	4 (1.3%)	23 (1.6%)	19 (1.3%)	11 (2.1%)	8 (1.5%)
Sepsis	8 (2.7%)	8 (2.7%)	8 (2.7%)	8 (2.7%)	24 (1.6%)	22 (1.5%)	12 (2.3%)	12 (2.3%)
Anaemia	7 (2.4%)	7 (2.4%)	6 (2.0%)	6 (2.0%)	40 (2.7%)	36 (2.4%)	11 (2.1%)	11 (2.1%)
Neutropenia	5 (1.7%)	4 (1.3%)	6 (2.0%)	6 (2.0%)	6 (0.4%)	6 (0.4%)	5 (1.0%)	4 (0.8%)
Urinary tract infection	4 (1.3%)	4 (1.3%)	6 (2.0%)	5 (1.7%)	24 (1.6%)	21 (1.4%)	7 (1.3%)	6 (1.2%)
Pulmonary embolism	2 (0.7%)	2 (0.7%)	8 (2.7%)	8 (2.7%)	5 (0.3%)	3 (0.2%)	4 (0.8%)	4 (0.8%)
Infusion related reaction	2 (0.7%)	0	10 (3.4%)	5 (1.7%)	1 (0.1%)	0	6 (1.2%)	3 (0.6%)
Cellulitis	5 (1.7%)	5 (1.7%)	5 (1.7%)	4 (1.3%)	15 (1.0%)	13 (0.9%)	12 (2.3%)	12 (2.3%)

MedDRA version: 26.1
A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBR = placebo + bendamustine + rituximab; TEAE = treatment-emergent adverse event.
Source: see ISS Table 10, Module 5.3.5.3

Deaths

Table 26. Summary of All Deaths (Safety Population Including PBR Patients Who Crossed Over)

	Number (%) of patients			
	Pivotal ECHO data		**Pooled populations**	
	ABR (N = 297)	**PBR[a] (N = 297)**	**Acalabrutinib monotherapy (N = 1478)**	**Combination therapy (N = 520)**
Deaths	97 (32.7%)	105 (35.4%)	355 (24.0%)	133 (25.6%)
Primary cause of death				
Disease progression	30 (10.1%)	42 (14.1%)	127 (8.6%)	35 (6.7%)
Adverse event	46 (15.5%)	41 (13.8%)	142 (9.6%)	65 (12.5%)
Richter's Transformation	0	0	10 (0.7%)	2 (0.4%)
Other	14 (4.7%)	16 (5.4%)	37 (2.5%)	18 (3.5%)
Unknown	7 (2.4%)	6 (2.0%)	34 (2.3%)	13 (2.5%)
Within 30 days of last dose of study drug				

	Number (%) of patients			
	Pivotal ECHO data		Pooled populations	
	ABR (N = 297)	PBR[a] (N = 297)	Acalabrutinib monotherapy (N = 1478)	Combination therapy (N = 520)
Deaths	37 (12.5%)	48 (16.2%)	182 (12.3%)	52 (10.0%)
Primary cause of death				
Disease progression	9 (3.0%)	17 (5.7%)	54 (3.7%)	9 (1.7%)
Adverse event	27 (9.1%)	27 (9.1%)	108 (7.3%)	40 (7.7%)
Richter's Transformation	0	0	6 (0.4%)	0
Other	0	3 (1.0%)	9 (0.6%)	1 (0.2%)
Unknown	1 (0.3%)	1 (0.3%)	5 (0.3%)	2 (0.4%)
More than 30 days after last dose of study drug				
Deaths	60 (20.2%)	57 (19.2%)	173 (11.7%)	81 (15.6%)
Primary cause of death				
Disease progression	21 (7.1%)	25 (8.4%)	73 (4.9%)	26 (5.0%)
Adverse event	19 (6.4%)	14 (4.7%)	34 (2.3%)	25 (4.8%)
Richter's Transformation	0	0	4 (0.3%)	2 (0.4%)
Other	14 (4.7%)	13 (4.4%)	28 (1.9%)	17 (3.3%)
Unknown	6 (2.0%)	5 (1.7%)	29 (2.0%)	11 (2.1%)

[a] *Includes deaths in PBR arm during the main study period and after crossover to acalabrutinib monotherapy (ad hoc analysis, data on file).*
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; PBR = placebo + bendamustine + rituximab.

Table 27. TEAE with a Fatal Outcome Reported for 2 or More Patients (CTCAE Grade 5) in Any Group (Safety Population)

	Number (%) of patients			
	Pivotal ECHO data		Pooled populations	
	ABR (N = 297)	PBR (N = 297)	Acalabrutinib monotherapy (N = 1478)	Combination therapy (N = 520)
Patients with a Grade 5 TEAE	36 (12.1%)	30 (10.1%)	125 (8.5%)	53 (10.2%)
COVID-19 pneumonia	15 (5.1%)	10 (3.4%)	5 (0.3%)	18 (3.5%)
COVID-19	8 (2.7%)	6 (2.0%)	12 (0.8%)	11 (2.1%)
Pneumonia	3 (1.0%)	0	16 (1.1%)	5 (1.0%)
Sepsis	1 (0.3%)	2 (0.7%)	5 (0.3%)	4 (0.8%)
Pulmonary embolism	0	2 (0.7%)	1 (0.1%)	0
Septic shock	0	0	8 (0.5%)	0
Cerebrovascular accident	0	0	4 (0.3%)	1 (0.2%)

	Number (%) of patients			
	Pivotal ECHO data		Pooled populations	
	ABR (N = 297)	PBR (N = 297)	Acalabrutinib monotherapy (N = 1478)	Combination therapy (N = 520)
Respiratory failure	0	1 (0.3%)	4 (0.3%)	0
Acute myeloid leukaemia	0	0	2 (0.1%)	0
Aspergillus infection	0	0	2 (0.1%)	0
Cardiac arrest	0	1 (0.3%)	3 (0.2%)	0
Cardio-respiratory arrest	0	0	2 (0.1%)	0
Multiple organ dysfunction syndrome	0	0	2 (0.1%)	0
Pneumonia viral	0	0	2 (0.1%)	0
Pyrexia	0	0	2 (0.1%)	0
Brain abscess	0	0	2 (0.1%)	0

A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Preferred terms are listed in descending order of frequency for the ABR arm.
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; CTCAE = Common Terminology Criteria for Adverse Events; PBR = placebo + bendamustine + rituximab; TEAE = treatment-emergent adverse event

Events of clinical interest (ECI)

Events of clinical interest for acalabrutinib were selected based on nonclinical findings, emerging data from clinical studies of acalabrutinib, and pharmacological effects of approved BTK inhibitors. ECIs identified for acalabrutinib were: cardiac events, cytopenias, haemorrhages, hepatotoxicity, hypertension, infections, Interstitial lung disease (ILD)/pneumonitis, Second Primary Malignancies (SPMs), and Tumour Lysis Syndrome (TLS).

Cardiac events

Table 28. Treatment-emergent Events of Clinical Interest. Cardiac Events (Safety Population)

	Number (%) of patients							
	Pivotal ECHO data				Pooled populations			
ECI category ECI subcategory	ABR (N = 297)		PBR (N = 297)		Acalabrutinib monotherapy (N = 1478)		Combination therapy (N = 520)	
Preferred term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Cardiac events	71 (23.9%)	23 (7.7%)	55 (18.5%)	18 (6.1%)[a]	332 (22.5%)	112 (7.6%)	145 (27.9%)	48 (9.2%)
Atrial fibrillation	20 (6.7%)	12 (4.0%)	13 (4.4%)	5 (1.7%)	109 (7.4%)	34 (2.3%)	37 (7.1%)	16 (3.1%)
Atrial fibrillation	18 (6.1%)	11 (3.7%)	13 (4.4%)	5 (1.7%)	102 (6.9%)	32 (2.2%)	35 (6.7%)	15 (2.9%)
Atrial flutter	3 (1.0%)	1 (0.3%)	0	0	7 (0.5%)	2 (0.1%)	5 (1.0%)	1 (0.2%)
Ventricular tachyarrhythmias	7 (2.4%)	0	7 (2.4%)	0	10 (0.7%)	2 (0.1%)	10 (1.9%)	0
Ventricular extrasystoles	4 (1.3%)	0	4 (1.3%)	0	7 (0.5%)	0	7 (1.3%)	0
Ventricular arrhythmias	2 (0.7%)	0	2 (0.7%)	0	1 (0.1%)	0	2 (0.1%)	0
Ventricular fibrillation	0	0	0	0	2 (0.1%)	2 (0.1%)	0	0
Ventricular tachycardia	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	0	1 (0.2%)	0
Other cardiac events	53 (17.8%)	12 (4.0%)	45 (15.2%)	13 (4.4%)	275 (18.6%)	83 (5.6%)	120 (23.1%)	34 (6.5%)
Other cardiac events with ≥ 2% incidence in any group								
Palpitations	10 (3.4%)	0	3 (1.0%)	0	55 (3.7%)	0	25 (4.8%)	0
Angina pectoris	6 (2.0%)	0	4 (1.3%)	1 (0.3%)	29 (2.0%)	6 (0.4%)	16 (3.1%)	4 (0.8%)
Tachycardia	6 (2.0%)	1 (0.3%)	7 (2.4%)	0	34 (2.3%)	0	11 (2.1%)	1 (0.2%)
Cardiac failure	3 (1.0%)	2 (0.7%)	6 (2.0%)	2 (0.7%)	20 (1.4%)	15 (1.0%)	6 (1.2%)	2 (0.4%)

MedDRA v26.1
A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; ECI = event of interest; MedDRA = Medical Dictionary for Regulatory Activities; PBR = placebo + bendamustine + rituximab; PT = preferred term; TEAE = treatment-emergent adverse event.

There were no fatal cardiac event in the ABR arm. In the PBR arm, there were 3 (1.0%) patients with fatal events one each of myocardial infarction, cardiac arrest, and cardiopulmonary failure.

Events of atrial fibrillation (based on the PTs of atrial fibrillation and atrial flutter), were reported in 6.7% and 4.4% of patients in the ABR and PBR arms, respectively, and Grade ≥ 3 atrial fibrillation events in 4.0% and 1.7% of patients. No patients in either arm had fatal atrial fibrillation events. Median time from first dose of study drug to onset of the ECI atrial fibrillation in the ABR and PBR arms was 343 days (range: 7 to 2080) and 231 days (range: 5 to 2152), respectively.

Cytopenias

Table 29. Treatment-emergent Events of Clinical Interest. Cytopenia in ≥10% patients in any group (Safety Population)

ECI Category ECI Subcategory	Number (%) of patients							
	Pivotal ECHO data				Pooled populations			
	ABR (N = 297)		PBR (N = 297)		Acalabrutinib monotherapy (N = 1478)		Combination therapy (N = 520)	
Preferred term	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Anaemia	72 (24.2%)	28 (9.4%)	62 (20.9%)	30 (10.1%)	253 (17.1%)	140 (9.5%)	105 (20.2%)	44 (8.5%)
Anaemia	68 (22.9%)	28 (9.4%)	60 (20.2%)	30 (10.1%)	245 (16.6%)	140 (9.5%)	98 (18.8%)	43 (8.3%)
Leukopenia	175 (58.9%)	158 (53.2%)	182 (61.3%)	162 (54.5%)	308 (20.8%)	269 (18.2%)	253 (48.7%)	229 (44.0%)
Neutropenia	163 (54.9%)	149 (50.2%)	166 (55.9%)	138 (46.5%)	286 (19.4%)	259 (17.5%)	239 (46.0%)	219 (42.1%)
Neutropenia	119 (40.1%)	105 (35.4%)	123 (41.4%)	110 (37.0%)	229 (15.5%)	209 (14.1%)	180 (34.6%)	160 (30.8%)
Neutrophil count decreased	53 (17.8%)	46 (15.5%)	46 (15.5%)	30 (10.1%)	38 (2.6%)	31 (2.1%)	70 (13.5%)	61 (11.7%)
Other leukopenia	74 (24.9%)	62 (20.9%)	75 (25.3%)	60 (20.2%)	36 (2.4%)	17 (1.2%)	77 (14.8%)	64 (12.3%)
White blood cell count decreased	41 (13.8%)	30 (10.1%)	31 (10.4%)	11 (3.7%)	8 (0.5%)	5 (0.3%)	41 (7.9%)	30 (5.8%)
Thrombocytopenia	68 (22.9%)	29 (9.8%)	61 (20.5%)	24 (8.1%)	170 (11.5%)	92 (6.2%)	103 (19.8%)	49 (9.4%)
Thrombocytopenia	38 (12.8%)	18 (6.1%)	34 (11.4%)	16 (5.4%)	129 (8.7%)	73 (4.9%)	64 (12.3%)	33 (6.3%)
Platelet count deceased	30 (10.1%)	11 (3.7%)	30 (10.1%)	8 (2.7%)	46 (3.1%)	21 (1.4%)	40 (7.7%)	17 (3.3%)

MedDRA v26.1
A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; ECI = event of clinical interest; MedDRA = Medical Dictionary for Regulatory Activities; PBR = placebo + bendamustine + rituximab; TEAE = treatment-emergent adverse event.

Haemorrhages

Table 30. Treatment-emergent Events of Clinical Interest. Haemorrhages in ≥2% patients in any group (Safety Population)

ECI subcategory	Number (%) of patients							
	Pivotal ECHO data				Pooled populations			
	ABR (N = 297)		PBR (N = 297)		Acalabrutinib monotherapy (N = 1478)		Combination therapy (N = 520)	
PT	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Haemorrhage	84 (28.3%)	6 (2.0%)	51 (17.2%)	10 (3.4%)	681 (46.1%)	67 (4.5%)	215 (41.3%)	21 (4.0%)
Contusion	33 (11.1%)	0	16 (5.4%)	0	298 (20.2%)	0	107 (20.6%)	0
Haematuria	12 (4.0%)	2 (0.7%)	2 (0.7%)	1 (0.3%)	61 (4.1%)	6 (0.4%)	21 (4.0%)	4 (0.8%)
Haematoma	11 (3.7%)	1 (0.3%)	4 (1.3%)	0	87 (5.9%)	7 (0.5%)	27 (5.2%)	1 (0.2%)
Conjunctival haemorrhage	9 (3.0%)	0	0	0	24 (1.6%)	0	18 (3.5%)	0
Ecchymosis	9 (3.0%)	1 (0.3%)	4 (1.3%)	0	84 (5.7%)	0	16 (3.1%)	1 (0.2%)
Epistaxis	8 (2.7%)	0	4 (1.3%)	0	118 (8.0%)	4 (0.3%)	33 (6.3%)	0
Purpura	7 (2.4%)	0	2 (0.7%)	0	26 (1.8%)	0	9 (1.7%)	0
Petechiae	6 (2.0%)	0	1 (0.3%)	0	131 (8.9%)	0	32 (6.2%)	0
Increased tendency to bruise	2 (0.7%)	0	4 (1.3%)	0	65 (4.4%)	0	11 (2.1%)	0
Rectal haemorrhage	5 (1.7%)	0	1 (0.3%)	0	25 (1.7%)	2 (0.1%)	11 (2.1%)	0
Major haemorrhage	7 (2.4%)	6 (2.0%)	16 (5.4%)	10 (3.4%)	81 (5.5%)	67 (4.5%)	27 (5.2%)	21 (4.0%)

MedDRA version 26.1
A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Major haemorrhage was defined as any haemorrhagic event that was serious or Grade ≥ 3 in severity, or that was a central nervous system haemorrhage (any severity grade).
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; ECI = event of clinical interest; MedDRA = Medical Dictionary for Regulatory Activities; PBR = placebo + bendamustine + rituximab; PT = preferred term; TEAE = treatment-emergent adverse event.

There was one fatal haemorrhage event (aortic aneurysm rupture) in the PBR arm. No patient in the ABR arm had a fatal haemorrhage event.

In the ECHO study, most patients with haemorrhage events in the ABR (N = 84) and PBR (N = 51) arms did not have concomitant thrombocytopenia (81.0% and 90.2%, respectively). Few patients in either arm had concomitant Grade ≥ 3 thrombocytopenia (3.6% and 2.0%, respectively). Major haemorrhage events with concomitant Grade ≥ 3 thrombocytopenia were uncommon, occurring in 1 patient in the ABR arm and no patients in the PBR arm.

Hepatotoxicity

Events of any grade hepatotoxicity were reported in 14.1% and 12.8% of patients in the ABR and PBR arms, respectively. Grade 3 to 4 hepatotoxicity events were reported in 6.7% and 2.0% of patients, respectively. There were no fatal events in either arm.

The most frequently reported Grade 3 to 4 hepatotoxicity events in the ABR and PBR arms, respectively, were ALT increased (4.4% and 0.3%), AST increased (3.0% and 0.3%), and gamma-glutamyl transferase increased (1.7% and 0.7%). Following expert medical review by the sponsor of the ECHO study data, an imbalance was noted between arms for transaminase elevations (ALT/AST increased), notably Grade ≥3 events, and after review of the data causality to the ABR combination could not be excluded.

Most transaminase elevations were transient, mild to moderate in severity, non-serious, and resolved spontaneously. Grade 3 or higher events were managed with dose interruption. Very few events resulted in dose reduction or acalabrutinib discontinuation. These transaminase elevations were not accompanied by symptoms and signs of liver injury or clinically significant increases of serum bilirubin.

The review of liver enzymes levels for AST and ALT alongside bilirubin levels following the criteria for potential Hy's Law resulted in the identification of 7 patients in ECHO, 2 in the ABR arm and 5 in the PBR arm. A comprehensive evaluation of these patients did not identify any confirmed Hy's Law cases.

Hypertension

The incidence of hypertension events of any grade was lower in the ABR arm than in the PBR arm (12.5% versus 16.2%, respectively). Grade ≥ 3 events were reported in 5.7% and 8.4% of patients, respectively. No fatal event related to hypertension was reported.

Median time from first dose of study drug to onset of hypertension of any grade was 309 days (range: 2 to 1329) and 311 days (range: 1 to 1342) in the ABR and PBR arms, respectively.

Infections

Infections of any grade occurred in 78.1% and 71.0% of patients in the ABR and PBR arms, respectively. Grade ≥ 3 infections occurred in 41.1% and 34.0% of patients in the ABR and PBR arms, respectively, including Grade 5 (fatal) infections in 10.4% and 6.1% of patients, respectively. The most frequently reported infections (in ≥ 10% of patients) were COVID-19 (30.6% and 20.9%), upper respiratory tract infection (18.2% and 14.8%), pneumonia (16.2% and 13.1%), COVID 19 pneumonia (15.8% and 12.5%), and urinary tract infection (11.1% and 10.8%) in the ABR and PBR arms, respectively.

Serious infections of any grade were reported for 40.4% and 33.0% of patients in the ABR and PBR arms, respectively. Grade 5 infection was higher in the ABR arm than in the PBR arms (10.4% and

6.1%, respectively). The Grade 5 infections were due to COVID-19 pneumonia (5.1% and 3.4%), COVID-19 (2.7% and 2.0%), pneumonia (1.0% and 0 patients), post-acute COVID-19 (0.3% and 0), sepsis (0.3% and 0.7%), urosepsis (0.7% and 0), clostridium difficile colitis (0.3% and 0), and pneumonia cytomegaloviral (0.3% and 0).

Interstitial lung disease /pneumonitis

Interstitial lung disease/pneumonitis of any grade occurred in 10 (3.4%) patients in both the ABR and PBR arms, and Grade ≥ 3 events in 2 (0.7%) and 4 (1.3%) patients in the ABR and PBR arms, respectively.

One (0.3%) patient had a fatal interstitial lung disease/pneumonitis event (pneumonitis) in the ABR arm.

The incidence of ILD/pneumonitis events in the ABR arm in ECHO was similar to that in the Acalabrutinib Monotherapy Pool.

Second Primary malignancies (SPMs)

Table 31. Treatment-emergent Events of Clinical Interest. Second Primary malignancies in >1 (0.3%) patient in either arm (Safety Analysis set)

ECI subcategory Preferred term	No. (%) of patients							
	ABR (N = 297)				PBR (N = 297)			
	Any grade	Grade 3-4	Grade 5	Grade ≥ 3	Any grade	Grade 3-4	Grade 5	Grade ≥ 3
Second primary malignancies	53 (17.8%)	20 (6.7%)	2 (0.7%)	22 (7.4%)	43 (14.5%)	20 (6.7%)	2 (0.7%	22 (7.4%)
Squamous cell carcinoma of skin	18 (6.1%)	4 (1.3%)	0	4 (1.3%)	9 (3.0%)	5 (1.7%)	0	5 (1.7%)
Basal cell carcinoma	14 (4.7%)	2 (0.7%)	0	2 (0.7%)	12 (4.0%)	3 (1.0%)	0	3 (1.0%)
Bowen's disease	8 (2.7%)	1 (0.3%)	0	1 (0.3%)	3 (1.0%)	0	0	0
Squamous cell carcinoma	6 (2.0%)	2 (0.7%)	0	2 (0.7%)	7 (2.4%)	2 (0.7%)	0	2 (0.7%)
Skin cancer	3 (1.0%)	0	0	0	1 (0.3%)	0	0	0
Malignant melanoma	2 (0.7%)	1 (0.3%)	0	1 (0.3%)	3 (1.0%)	3 (1.0%)	1 (0.3%)	3 (1.0%)
Colorectal adenocarcinoma	2 (0.7%)	1 (0.3%)	0	1 (0.3%)	0	0	0	0
Keratoacanthoma	2 (0.7%)	0	0	0	0	0	0	0
Myelodysplastic syndrome	2 (0.7%)	2 (0.7%)	0	2 (0.7%)	0	0	0	0
Prostate cancer	1 (0.3%)	0	0	0	4 (1.3%)	0	0	0
Renal cell carcinoma	0	0	0	0	2 (0.7%)	2 (0.7%)	0	2 (0.7%)
Transitional cell carcinoma	0	0	0	0	2 (0.7%)	0	1 (0.3%)	1 (0.3%)
Second primary malignancies, excluding non-melanoma skin	29 (9.8%)	14 (4.7%)	2 (0.7%)	16 (5.4%)	32 (10.8%)	18 (6.1%)	2 (0.7%)	20 (6.7%)
Squamous cell carcinoma[a]	6 (2.0%)	2 (0.7%)	0	2 (0.7%)	7 (2.4%)	2 (0.7%)	0	2 (0.7%)
Colorectal adenocarcinoma	2 (0.7%)	1 (0.3%)	0	1 (0.3%)	0	0	0	0
Malignant melanoma	2 (0.7%)	1 (0.3%)	0	1 (0.3%)	3 (1.0%)	2 (0.7%)	1 (0.3%)	3 (1.0%)
Prostate cancer	1 (0.3%)	0	0	0	4 (1.3%)	0	0	0
Renal cell carcinoma	0	0	0	0	2 (0.7%)	2 (0.7%)	0	2 (0.7%)
Transitional cell carcinoma	0	0	0	0	2 (0.7%)	0	1 (0.3%)	1 (0.3%)

[a] Included here based on the verbatim term used for coding of these events.
MedDRA version 26.1
Patients were counted only once for each preferred term using the highest grade.
Preferred terms are listed in descending order of frequency (any grade) for the ABR arm.
Abbreviations: ABR = acalabrutinib, bendamustine, rituximab; ECI = event of clinical interest; MedDRA = Medical Dictionary for Regulatory Activities; PBR = placebo, bendamustine, rituximab.

Four patients had Grade 5 SPMs, 2 (0.7%) patients in the ABR arm (intestinal adenocarcinoma [onset Study Day 842] and neuroendocrine carcinoma [onset Study Day 871]), and 2 (0.7%) patients in the PBR arm (transitional cell carcinoma [onset Study Day 764]) and malignant melanoma [onset Study Day 39]).

The incidence of SPMs, excluding non-melanoma skin, of any grade was similar in the ABR and PBR arms (9.8% and 10.8%). Grade ≥ 3 events of SPMs, excluding non-melanoma skin, were reported in 5.4% and 6.7% of patients in the ABR and PBR arms, respectively.

The median time from first dose of study drug to onset of first SPM was 485 days (range: 64 to 2206) and 590 days (range: 39 to 1758 days), respectively. The median time from first dose of study drug to onset of first SPM, excluding non-melanoma skin was 506 days (range: 90 to 2144) and 686 days (range: 39 to 1866).

Tumour Lysis Syndrome (TLS)

In the ABR and PBR arms, TLS of any grade was reported in 4 (1.3%) and 6 (2.0%) patients, respectively, and all of the TLS events were Grade ≥ 3.

Two patients had fatal TLS (1 (0.3%) patient in each arm). The investigators considered the case in the ABR arm as related to bendamustine and rituximab, and the case in the PBR arm as related to rituximab.

All TLS events occurred in the context of disease progression.

The incidence of TLS events in the ABR arm in ECHO was similar to that in the Acalabrutinib Monotherapy Pool.

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, March 2024. Additionally, "suspected transmission of an infectious agent via product" is an AESI for study treatments containing biologic products (e.g., rituximab) and therefore applies to the ECHO study as rituximab is a constituent of the ABR and PBR regimens.

The AESI ventricular arrythmias is defined by the same PTs as the ECI ventricular tachyarrhythmias and were similar between the two arms.

No suspected transmission of an infectious agent via product was reported in the ECHO arms or the Combination Therapy Pool.

Adverse Drug Reactions

Analyses were conducted to identify any new ADRs for acalabrutinib that were observed from patients in the ABR arm in ECHO. This included analysis of AEs by frequency, severity, causal relationship, AEs leading to discontinuation, SAEs, AEs with a fatal outcome, and AESIs/ECIs. Where applicable, further evaluation was conducted on individual case/case series review and analysis including time to onset, temporal relationship, challenge/rechallenge, outcome, and plausibility (

Table 32). Acalabrutinib-related haematologic adverse drug reactions are summarised in **Table 33**.

Table 32. Frequency and CTCAE Grades of acalabrutinib-related adverse drug reactions (Safety Population)

ADR System Organ Class/ ADR Term	Number (%) of patients							
	ECHO Study Arms				Acalabrutinib Monotherapy Pool (N = 1478)		Combination Therapy Pool (N = 520)	
	ABR (N = 297)		PBR (N = 297)					
	All grades	Grade ≥ 3[a]	All grades	Grade ≥ 3[a]	All grades	Grade ≥ 3[a]	All grades	Grade ≥ 3[a]
Blood and lymphatic system disorders								
Leukopenia[b]	175 (58.9%)	158 (53.2%)	182 (61.3%)	162 (54.5%)	308 (20.8%)	269 (18.2%)	253 (48.7%)	229 (44.0%)
Neutropenia[b]	163 (54.9%)	149 (50.2%)	166 (55.9%)	138 (46.5%)	286 (19.4%)	259 (17.5%)	239 (46.0%)	219 (42.1%)
Anaemia[b]	72 (24.2%)	28 (9.4%)	62 (20.9%)	30 (10.1%)	253 (17.1%)	140 (9.5%)	105 (20.2%)	44 (8.5%)
Thrombocytopenia[b]	68 (22.9%)	29 (9.8%)	61 (20.5%)	24 (8.1%)	170 (11.5%)	92 (6.2%)	103 (19.8%)	49 (9.4%)
Cardiac disorders								
Atrial fibrillation/flutter[b]	20 (6.7%)	12 (4.0%)	13 (4.4%)	5 (1.7%)	109 (7.4%)	34 (2.3%)	37 (7.1%)	16 (3.1%)
Nervous system disorders								
Headache	90 (30.3%)	4 (1.3%)	42 (14.1%)	2 (0.7%)	539 (36.5%)	17 (1.2%)	187 (36.0%)	7 (1.3%)
Dizziness	43 (14.5%)	2 (0.7%)	45 (15.2%)	1 (0.3%)	206 (13.9%)	2 (0.1%)	104 (20.0%)	4 (0.8%)
Respiratory, thoracic and mediastinal disorders								
Epistaxis	8 (2.7%)	0	4 (1.3%)	0	118 (8.0%)	4 (0.3%)	33 (6.3%)	0
Gastrointestinal disorders								
Diarrhoea	111 (37.4%)	9 (3.0%)	83 (27.9%)	7 (2.4%)	543 (36.7%)	39 (2.6%)	221 (42.5%)	24 (4.6%)
Nausea	127 (42.8%)	4 (1.3%)	112 (37.7%)	4 (1.3%)	322 (21.8%)	12 (0.8%)	196 (37.7%)	4 (0.8%)
Constipation	73 (24.6%)	3 (1.0%)	75 (25.3%)	1 (0.3%)	224 (15.2%)	1 (0.1%)	127 (24.4%)	3 (0.6%)
Abdominal pain[b]	36 (12.1%)	6 (2.0%)	37 (12.5%)	3 (1.0%)	215 (14.5%)	18 (1.2%)	83 (16.0%)	11 (2.1%)
Vomiting	76 (25.6%)	2 (0.7%)	41 (13.8%)	3 (1.0%)	207 (14.0%)	11 (0.7%)	129 (24.8%)	5 (1.0%)
General disorders and administration site conditions								
Fatigue	87 (29.3%)	8 (2.7%)	72 (24.2%)	11 (3.7%)	349 (23.6%)	30 (2.0%)	162 (31.2%)	13 (2.5%)
Asthenia	31 (10.4%)	3 (1.0%)	29 (9.8%)	2 (0.7%)	103 (7.0%)	13 (0.9%)	52 (10.0%)	4 (0.8%)

Table 33. Frequency and CTCAE Grades of acalabrutinib-related haematologic adverse drug reactions (Safety Population)

Hematologic Adverse Reactions	Number (%) of patients							
	ECHO Study Arms				Acalabrutinib Monotherapy Pool (N = 1478)		Combination Therapy Pool (N = 520)	
	ABR (N = 297)		PBR (N = 297)					
	All grades	Grade ≥ 3[a]	All grades	Grade ≥ 3[a]	All grades	Grade ≥ 3[a]	All grades	Grade ≥ 3[a]
Absolute neutrophil count decreased[b]	228 (76.8%)	168 (56.6%)	229 (77.1%)	149 (50.2%)	649 (43.9%)	355 (24.0%)	363 (69.8%)	252 (48.5%)
Haemoglobin decreased[b]	236 (79.5%)	32 (10.8%)	193 (65.0%)	34 (11.4%)	700 (47.4%)	160 (10.8%)	347 (66.7%)	55 (10.6%)
Platelets decreased[b]	206 (69.4%)	53 (17.8%)	178 (59.9%)	48 (16.2%)	545 (36.9%)	140 (9.5%)	313 (60.2%)	81 (15.6%)

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

[b] Represents the incidence of laboratory findings, not of reported adverse events.

Abbreviations: A = acalabrutinib; B = bendamustine; P = placebo; R = Rituximab; SPM = second primary malignancy

Laboratory findings

Haematology

The incidence of patients experiencing any grade treatment-emergent abnormal values was similar in both arms in the ECHO study. The largest difference in any grade values between the ABR and PBR arms, respectively, were decreased haemoglobin (79.5% and 65.0%) and decreased platelets (69.4% and 59.9%). The incidences of Grade 3 to 4 decreased haemoglobin and decreased platelets were similar in both arms. There were a higher incidence of Grade 4 decreased ANC in the ABR arm (35.7% and 28.6%, respectively).

Median times from first dose of study drug to onset of Grade ≥ 3 cytopenia were similar in the ABR and PBR arms, respectively, for neutropenia (113.5 and 113.0 days) and thrombocytopenia (28.0 and 11.5 days), and longer in the ABR arm for anaemia (151.5 and 29.5 days). Median durations were similar for neutropenia (13.0 and 12.0 days), thrombocytopenia (8.0 and 7.0 days), and anaemia (15.0 and 8.0 days).

Clinical Chemistry

Clinical chemistry parameters with the largest difference in any grade values between the arms were decreased calcium (50.8% and 41.4% in ABR and PBR arms respectively), sodium increased (46.8% and 38.7%), increased creatinine (36.7% and 28.3%), albumin decreased (38.0% and 31.6%), phosphate decreased (36.0% and 29.3%), and increased total bilirubin (18.9% and 12.5%).

The incidence of Grade 3 to 4 abnormalities in the analysed chemistry parameters was generally comparable between the 2 arms, except for a slightly higher incidence (≥ 5% difference between arms) of increased ALT levels in 20 (6.7%) patients compared to 7 (2.4%) patients, and urate levels in 134 (45.1%) patients compared to 119 (40.1%) patients in the ABR and PBR arms, respectively.

Overall shifts in mean clinical chemistry grades over time were similar in the ABR and PBR arms. The majority of patients had values that remained at Grade 0 or shifted to Grade 1 postbaseline, and the lowest percentages were for shifts from Grade 0 to Grade 3 or Grade 4. With the exception of elevated transaminases (ALT and AST increased) during ABR treatment, no new safety signal was observed.

A higher incidence was observed in the shifts in ALT toxicity grades from baseline to the maximum postbaseline values between the ABR and PBR arms. A total of 284 (95.6%) patients in the ABR arm and 286 (96.9%) patients in the PBR arm had Grade 0 ALT values at baseline; 158 (53.2%) and 165 (55.9%) patients, respectively, had values that remained at Grade 0 postbaseline. In the ABR arm, 17 (5.7%) patients had ALT values that shifted from Grade 0 to Grade 3, which was slightly higher compared with the PBR arm where 6 (2.0%) patients experienced this shift. Both arms documented shifts from Grade 0 to Grade 4 in 1 (0.3%) patient each.

A higher incidence was observed in the shifts in AST toxicity grades from baseline to the maximum postbaseline values between ABR and PBR arms. A total of 284 (95.6%) patients in the ABR arm and 274 (92.9%) patients in the PBR arm had Grade 0 AST values at baseline; 130 (43.8%) and 135 (45.8%) patients, respectively, had values that remained at Grade 0 postbaseline, 128 (43.1%) and 123 (41.7%) patients had values that shifted from Grade 0 to Grade 1. Shifts from Grade 0 at baseline to Grade 3 were observed in 12 (4.0%) and 6 (2.0%) patients, respectively. Shifts from Grade 0 at baseline to Grade 4 postbaseline were observed in 1 (0.3%) patient in each arm.

Serum immunoglobulin and T/B/NK/monocyte cell counts

There were no clinically important changes in serum immunoglobulin values (IgG, IgA, IgM) from baseline to last post-baseline values for all patients and no clinically meaningful differences between treatment groups.

There were no clinically important changes in T/B/NK/monocyte cell counts (CD4, CD8, CD19, NK cell counts) from baseline to last post-baseline values for all patients, and no clinically meaningful differences between treatment groups.

Safety in special populations

There were no clinically meaningful differences in the safety profiles of ABR compared to PBR with respect to age, sex, race, hepatic impairment, and renal impairment.

Discontinuation due to adverse events

Table 34. Treatment-emergent Adverse Events Leading to Discontinuation of Acalabrutinib by Preferred Term in ≥1% of Patients in Any Group

	Number (%) of patients			
	Pivotal ECHO data		**Pooled populations**	
	ABR (N = 297)	**PBR (N = 297)**	**Acalabrutinib monotherapy (N = 1478)**	**Combination therapy (N = 520)**
Patients with ≥ 1 TEAE leading to treatment discontinuation	127 (42.8%)	92 (31.0%)	234 (15.8%)	174 (33.5%)
COVID-19	14 (4.7%)	9 (3.0%)	9 (0.6%)	17 (3.3%)
COVID-19 pneumonia	13 (4.4%)	8 (2.7%)	8 (0.5%)	15 (2.9%)
Neutropenia	12 (4.0%)	10 (3.4%)	5 (0.3%)	12 (2.3%)
Pneumonia	5 (1.7%)	1 (0.3%)	12 (0.8%)	6 (1.2%)
Hepatitis B reactivation	4 (1.3%)	5 (1.7%)	5 (0.3%)	6 (1.2%)
Sepsis	1 (0.3%)	3 (1.0%)	3 (0.2%)	3 (0.6%)

Preferred terms are listed in descending order of frequency (any grade) for the ABR arm.
Abbreviations: ABR = acalabrutinib + bendamustine + rituximab; AG = acalabrutinib +obinutuzumab; PBR = placebo + bendamustine + rituximab; TEAE = treatment-emergent adverse events

2.5.2. Discussion on clinical safety

Acalabrutinib, is a selective BTKi (Bruton Tyrosine Kinase inhibitor). Other approved BTKi's are Imbruvica, Brukinsa and Jaypirca. The safety profile of this class of drugs is by now well characterised. Class related concerns include GI disturbances (diarrhoea, nausea, and vomiting), cytopenias, bleeding events, and infections. Other toxicities that have been associated with BTKi include atrial fibrillation and hypertension.

ECHO Study

A total of 594 patients received at least one dose of any study drug (297 in ABR arm and 297 in PBR arm).

The evaluation of the safety profile of ABR is additionally supported by safety and tolerability data of acalabrutinib monotherapy from 1478 patients in an 11-study pool (*Acalabrutinib Monotherapy Pool*) and 520 patients in a *Combination Therapy Pool*, with data from 3 studies, including ABR (acalabrutinib + BR) and AG (acalabrutinib + obinutuzumab) combination regimens.

Exposure

The median duration of exposure of acalabrutinib was 4 months longer for patients in the ABR arm compared to the exposure to placebo in the PBR arm (28.6 versus 24.6 months, respectively). Also, median duration of exposure to rituximab was 3.6 months longer for patients in the ABR arm compared to that in the PBR arm (27.5 and 23.9 months). However, there were no difference in median rituximab exposure during cycle 1 to 6 (both 5.52 months) and, equal median exposure for cycle 8 to 30 (20.96 vs 21.01 for the ABR and PBR arms). The median duration of exposure of bendamustine was the same for patients in both arms (5.6 and 5.6 months). At the DCO, 231 (77.8%) and 232 (78.1%) patients in the ABR and PBR arms, respectively, completed 6 cycles of BR, and 222 (74.7%) and 225 (75.8%) patients completed 6 cycles of acalabrutinib/placebo plus BR.

Disposition

Almost half of the patients had discontinued the study at the DCO with similar rate in ABR and PBR arms 47.1% and 48.5%, respectively. The main reason was death, 32.3% in ABR and 34.3% in PBR arm.

There was a substantial rate of discontinuation of treatment (acalabrutinib/placebo) due to 'Adverse Event' in both arms, but clearly higher in the ABR arm, 43.3% vs 31.6% in the PBR-arm.

Adverse Events and Deaths

Grade ≥ 3 TEAEs (ABR 88.9% and PBR 88.2%) are comparable between the treatment arms. However, a higher proportion of patients in the ABR arm compared to the PBR arm had Grade ≥ 3 serious TEAEs (64.3% vs. 55.9%).

The TEAEs by PT with difference of ≥ 5 percentage points in the ABR arm compared to the PBR arm, were: headache (30.3% and 14.1%), vomiting (25.6% and 13.8%), COVID-19 (30.6% and 20.9%), diarrhoea (37.4% and 27.9%), rash maculo-papular (15.8% and 6.4%), back pain (16.2% and 9.4%), cough (26.9% and 20.2%), dyspnoea (15.2% and 9.4%), nausea (42.8% and 37.7%), fatigue (29.3% and 24.2%) and contusion (11.1% and 5.4%) however no difference in thrombocytopenia (12.8% and 11.4%).

The incidences of most Grade ≥3 TEAEs in the ABR arm were generally similar to the PBR arm, with the exception of a higher rate in ABR arm of; neutrophil count decreased (15.5% and 10.1%), WBC count decreased (10.1% and 3.7%), COVID-19 pneumonia (13.5% and 10.4%), rash maculo-papular (7.1% and 0.7%), and febrile neutropenia (5.1% and 2.4%). These TEAEs are consistent with the established safety profile of acalabrutinib and can all be expected adverse drug reactions to study drugs.

The incidence of grade >3 pneumonia irrespective of infective agent was 22.3% in the ABR arm vs 16.8% in PBR arm. If adding COVID-19 infections the incidence difference increased to 7.2% (i.e. 31.1% in ABR arm vs 23.9% in PBR arm).

Grade ≥ 3 SAEs occurred in 64.3% and 55.9% of patients, this difference was primarily due to the SAEs in the infections and infestations SOC (40.4% and 33.0%). Grade ≥3 SAEs reported in ≥5% of

patients in the ABR and PBR arms, respectively, were COVID-19 pneumonia (13.1% and 10.1%), pneumonia (8.1% and 6.1%), and COVID-19 (7.7% and 6.1%).

Deaths: At the DCO, 97 (32.7%) patients had died in the ABR arm, and 105 (35.4%) patients had died in the PBR arm. Death due to AEs were similar between arms with 46 (15.5%) in ABR and 41 (13.8%) patients in PBR. Grade 5 TEAE are reported in similar frequency, 36 (12.1%) and 30 (10.1%) patients in the ABR and PBR arms, respectively. However, there was a difference in the number of fatal TEAE that were reported in the SOC infections/ infestations, 31 cases in the ABR-arm and 18 cases in the PBR-arm, which seems to be driven by more frequent COVID-19 infections. There were no fatal TEAEs of cardiac disorders or vascular disorders in the ABR-arm.

The majority of AEs that are higher in the ABR arm are infections and cytopenia. The current SmPC includes guidance on dose modifications in relation to grade 3 or 4 neutropenia, thrombocytopenia and other haematological grade 4 or unmanageable grade 3 toxicities. Additional warnings are included in SmPC section 4.4 in relation to infections and cytopenias. The haematological and infectious ADR frequencies are also included in SmPC section 4.8. It is considered that data from the ECHO study do not warrant any updates in relation to these risks.

Haemorrhages of any grade were more frequent in the ABR arm, 28.3% and 17.2% of patients the ABR and PBR arms, respectively. This was mostly low-grade contusions, haematuria and haematomas. The Grade >3 any haemorrhages and Grade >3 Major haemorrhage events were similar between arms. No clear relation was found with concomitant thrombocytopenia. Haemorrhage is a known ADR for acalabrutinib and the SmPC contains dose reduction advice in section 4.2, and additional warnings in section 4.4 including mitigation recommendations. The haemorrhage events data from the ECHO study give no rise to concern on the tolerability of acalabrutinib as add-on to the BR regimen. The current warnings in the SmPC are considered sufficient to manage this risk.

Grade 3 to 4 hepatotoxicity were reported in 6.7% and 2.0% of patients in ABR and PBR, respectively. No fatal events in either arm. ALT increased, and AST increased were included as ADRs for the ABR combination. There were no confirmed Hy's Law cases. Presently, there is no evidence that these transaminase elevations are associated with overt liver injury.

Cardiac events of any grade were more frequent in the ABR arm (23.9%) than in the PBR arm (18.5%). However, the incidences of cardiac events, including atrial fibrillation, in the ABR arm were generally consistent with the Acalabrutinib Monotherapy Pool. Atrial fibrillation/flutter is included in the ADR table in SmPC section 4.8 and there is additionally warnings in section 4.4 which is considered sufficient.

The incidence and severity of hypertension events were lower in the ABR arm than in PBR arm in the ECHO study. Hypertension is included among the ADR in section 4.8 of the SmPC, which is considered sufficient.

Interstitial lung disease (ILD)/pneumonitis of any grade occurred in 10 (3.4%) patients in both the ABR and PBR arms and there were 2.4% with PT pneumonitis in the ABR arm compared to 1.3% in the PBR arm. One patient had a fatal pneumonitis in the ABR arm. As the reported events are reasonably likely to be caused by the ABR treatment regimen, pneumonitis has been included as an ADR for the combination treatment in the SmPC section 4.8 with a frequency of common. In addition, prescribers are advised in section 4.4 to monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. cough, dyspnoea or hypoxia) and manage ILD/pneumonitis as clinically indicated.

In the ECHO study Second primary malignancies (SMPs) are common in both arms, with similar frequency in the ABR and PBR arms (9.8% and 10.8%). SPMs are a known ADR of acalabrutinib and

therefore listed in SmPC section 4.8, together with information in section 4.4, this is considered sufficient for prescribers.

TLS of any grade was reported in 4 (1.3%) and 6 (2.0%) patients in the ABR and PBR arms, respectively. One patient in each arm had fatal TLS.

TLS is already listed as an ADR in Calquence SmPC section 4.8 in both the monotherapy and the combination therapy tables. TLS is a severe and life-threatening side-effect of treatment and prescribers need to be aware of the importance of a mitigation strategy. Therefore, a warning is now included in the SmPC that patients considered at risk for TLS (e.g., presence of bulky disease at baseline) should be assessed for possible risk of TLS and closely monitored as clinically indicated.

2.5.3. Conclusions on clinical safety

The addition of acalabrutinib to BR results in a clinically relevant increase in toxicity, particularly with respect to the risks of cytopenias and infection. However, these risks are already known from the overall safety profile of acalabrutinib and can be managed with the warnings in the product information. In addition, new warnings with regards to the risks of tumour lysis syndrome and interstitial lung disease/pneumonitis have been added to the product information Overall, the safety profile of the proposed combination treatment in the first line setting of MCL has been sufficiently characterised.

2.5.4. 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 an updated RMP version 6.2 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 6.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6.2 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 [a]
			Final Report	Q4 2029

Risk minimisation measures

Safety concern	**Risk minimisation measures**
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

Safety concern	Risk minimisation measures
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, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, new warnings with regard to the risks of tumour lysis syndrome and interstitial lung disease/pneumonitis have been added to the product information. The Package Leaflet (PL) 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

Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphomas (NHL) that accounts for 5%–7% of malignant lymphoma in Western Europe. The annual incidence of this disease has increased during recent decades to 1–2/100 000.

MCL is associated with increased cellular proliferation, a reduced response to DNA damage, and enhanced cell survival caused by impaired apoptosis. MCL is characterised by chromosomal translocation t(11;14)(q13:q32) causing overexpression of the cyclin D1 (CCDN1) gene.

The presently sought indication is: "Calquence in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT).

3.1.2. Available therapies and unmet medical need

Newly diagnosed patients with MCL are considered for autologous stem cell transplant (ASCT). However, Most patients over 65 years do not qualify for such dose-intensified regimens. According to the ESMO guideline, rituximab (R) in combination with chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine (B) is recommended in this patient group.

There is an unmet medical need for patients with newly diagnosed MCL as no curative treatment is available.

3.1.3. Main clinical studies

Study ACE-LY-308 or ECHO study is a Phase 3, randomised, double-blind, placebo-controlled, multicentre study evaluating the add-on of acalabrutinib or placebo until progression, on top of a standard regimen of bendamustine and rituximab in patients aged 65 years or older with previously untreated MCL, and that are not eligible for ASCT.

In the ECHO study, bendamustine + rituximab (BR) and add-on acalabrutinib (ABR group) or placebo (PBR group) was given for 6 cycles as induction therapy. This was followed by continuous acalabrutinib or placebo until PD or unacceptable toxicity. In addition, responders to induction ABR or PBR (i.e. patients who achieved CR or PR) received a maximum of 12 cycles of rituximab maintenance. Patients randomised to placebo that had a confirmed PD could (if eligible) cross-over to receive acalabrutinib monotherapy.

The primary endpoint was PFS assessed by IRC. Secondary endpoints were alpha protected in a fixed hierarchical manner beginning with IRC assessed ORR and followed by OS.

3.2. Favourable effects

In the primary analysis 36.8% of the patients in the ABR arm had a PFS event, as compared with 45.8% in the PBR arm. Statistically significant IRC-assessed PFS was shown for the addition of acalabrutinib to BR, with HR of 0.73 (95% CI [0.57, 0.94]) and a median PFS difference of 16.8 months. A median PFS of 66.4 months and 49.6 months was recorded for ABR and PBR, respectively.

ORR by IRC assessment was the subsequent endpoint in the test hierarchy. The percentage of patients with an ORR as assessed by the IRC was similar between the two arms (91.0% for the ABR treatment arm and 88.0% for the PBR arm, p=0.2196).

In the most recent OS analysis (cutoff date of 12 August 2024, OS maturity rate 36%), the median follow-up was 51 months in the ABR arm and 46 months in the PBR arm. With a total of 218 deaths (105 [35.1%] patients in the ABR arm and 113 [37.8%] patients in the PBR arm) the HR was 0.87; 95% CI: 0.67, 1.14).

3.3. Uncertainties and limitations about favourable effects

No effect on OS has been established and will not be established with statistical confidence due to lack of statistical power as well as, after the ORR outcome, lack of multiplicity control. Moreover, cross-over and subsequent BTKi-therapy (29% of patients in the control arm) complicates the interpretation of OS. Nevertheless, the MAH will provide the final OS results when available to rule out the possibility of

a detrimental effect of the addition of acalabrutinib to the backbone of bendamustine and rituximab in survival.

The study design does not allow for the isolation of the effect of maintenance acalabrutinib treatment after induction in combination with chemoimmunotherapy.

3.4. Unfavourable effects

The main Safety Analysis Set (SAS) included a total of 594 patients that received at least one dose of any study drug (297 in ABR arm and 297 in PBR arm). At the DCO (15 February 2024), the median time on follow-up was 46.2 months in the ABR arm and 36.6 months in the PBR arm.

The most frequently reported (≥ 20% of patients in either treatment arm) TEAEs in the ABR and PBR arms, respectively, were nausea (42.8% and 37.7%), neutropenia (40.1% and 41.4%), diarrhoea (37.4% and 27.9%), COVID-19 (30.6% and 20.9%), headache (30.3% and 14.1%), fatigue (29.3% and 24.2%), pyrexia (29.0% and 24.2%), cough (26.9% and 20.2%), vomiting (25.6% and 13.8%), constipation (24.6% and 25.3%), anaemia (22.9% and 20.2%), rash (20.5% and 16.2%), and infusion-related reaction (14.5% and 21.9%).

TEAEs of any grade and Grade ≥ 3 are comparable between the treatment arms. An overall higher incidence of serious TEAE Grade ≥3 was observed in the ABR arm compared with the PBR arm for (64.3% vs. 55.9%).

Amongst the identified events of clinical or special interest, a higher rate of Grade ≥3 TEAEs in the ABR arm compared to the BR was observed for neutropenia (50.2% vs 46.5%), infections (41.1% vs 34.0%), hepatotoxicity (6.7% vs 2.0%) and atrial fibrillation (4.0% vs 17%).

Fatal TEAEs occurred in 36 (12.1%) and 30 (10.1%) patients in the ABR and PBR arms, respectively. When evaluated by SOC, 31 of the total 36 fatal TEAEs (86.1%) were in the infection and infestations SOC in the ABR arm compared to 18 of the total 30 (60.0%) fatal TEAEs in the PBR arm.

The incidence of any grade TEAEs that led to discontinuation of acalabrutinib/placebo was higher in the ABR arm than in the PBR arm (42.8% and 31.0%, respectively). This high incidence of TEAEs was mainly in the infections and infestations SOC (17.8% and 11.8%).

3.5. Uncertainties and limitations about unfavourable effects

Patients with significant risk factors for cardiovascular disease and bleeding were excluded from the study and thus the reported incidence of these type of events might underestimate the true magnitude of these risks.

3.6. Effects Table

Table 35. Effects Table for Calquence in combination with bendamustine and rituximab for the treatment of adult patients with previously untreated mantle cell lymphoma. data cut-off: 12 Aug 2024

Effect	Short description	Unit	ABR N=299	BR N=299	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	ABR N=299	BR N=299	Uncertainties / Strength of evidence	References
PFS	Time from randomisation until disease progression (according to the Lugano Classification for NHL) or death-IRC assessed	N (%)	110 (36.8%)	137 (45.8%)	SoE: HR: 0.73; 95% CI: (0.57, 0.94), p-value: 0.0160 Unc: OS data immature and non inferentiel but do not seem to indicate a detrimental effect: HR: 0.87; 95% CI: (0.67, 1.14)	ACE-LY-308
Unfavourable Effects			**N=297**	**N=297**		
Grade 3/4 TEAE	Incidence: Any Infections Neutropenia Hepatotoxicity Atrial fibrillation	%	 88.9 41.1 50.2 6.7 4.0	 88.2 34.0 46.5 2.0 1.7	SoE: Data from adequately sized RCT Equal (few) patients withdraw consent or were lost to follow-up. Unc: Exclusion of patients at high risk for CV disease and bleeding	ACE-LY-308
Grade 5 TEAE		% (n)	12.1 (36)	10.1 (30)		
Discontinuation	TEAE leading to discontinuation of acalabrutinib or placebo	%	42.8	31		

Abbreviations: *ABR: Acalabrutinib, Bendamustine and Rituximab; BR: Bendamustine and Rituximab, PFS: Progression Free Survival; NHL: Non-Hodgkins Lymphoma; IRC: Independent Review Committee; HR: Hazard Ratio; CI: Confidence Interval; OS: Overall Survival; TEAE: Treatment Emergent Adverse Event.*

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The addition of acalabrutinib to a standard BR regimen resulted in a clinically relevant prolongation of PFS.

The addition of acalabrutinib to BR therapy increases toxicity, mainly due to infections and cytopenias. As patients at higher risk for cardiovascular and haemorrhage side effects were excluded, the number of patients who are unsuitable for ASCT but still fit enough to tolerate the addition of acalabrutinib on top of BR could be small. However, overall toxicity appears acceptable. While OS data are immature, this being an indolent lymphoma, the trend is reassuring and the level of uncertainty acceptable as there is no indication of a detrimental effect on OS.

3.7.2. Balance of benefits and risks

The clinical benefit of the increased PFS of acalabrutinib when added to the backbone of bendamustine and rituximab is deemed to outweigh the increased toxicity of the triple combination 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 previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant 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 in combination with bendamustine and rituximab (BR) as treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT) based on interim results from study ACE-LY-308 (ECHO, D8220C00004); this is a Phase III, randomized, double-blind, placebo-controlled, multicenter study of BR alone versus in combination with acalabrutinib (ACP-196) in subjects with previously untreated MCL. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6, succession 2 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

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.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR

module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘‘Calquence-EMEA/H/C/005299/II/25’