25 April 2025
EMA/CHMP/124570/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Calquence

International non-proprietary name: Acalabrutinib

Procedure No. EMEA/H/C/005299/II/0028

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

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AV	acalabrutinib and venetoclax
AVG	acalabrutinib, venetoclax, and obinutuzumab
BCL2	B-cell leukaemia/lymphoma 2 protein
BCR	B-cell receptor
BID	twice daily
BM	bone marrow
BOR	best overall response
BR	bendamustine and rituximab
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
CI	confidence interval
CLL	chronic lymphocytic leukaemia
COVID-19	coronavirus disease 2019
CR	complete response/remission
CRi	complete response/remission with incomplete bone marrow recovery
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cutoff date
DDI	drug/drug interaction
DoR	duration of response
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer

EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FCR	fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
HR	hazard ratio
IGHV	Immunoglobulin heavy-chain variable region gene
ILD	interstitial lung disease
IPTW	Inverse probability of treatment weighting
IRC	independent review committee
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
KM	Kaplan-Meier
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary of Regulatory Activities
MoA	Mechanism of action
NE	Not estimated
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PB	peripheral blood
PD	progressive disease
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
PO	by mouth
PopPK	population pharmacokinetics
PRO	patient reported outcome
PT	preferred term
QD	once daily
R/R	relapsed or refractory
SAE	serious adverse event

SD	standard deviation
SLL	small lymphocytic lymphoma
SMQ	standardized MedDRA query
SOC	system organ class
SoC	standard of care
SPM	second primary malignancy
sBR	structured benefit risk
TEAE	treatment-emergent adverse event
TLS	tumour lysis syndrome
TN	treatment naïve (previously untreated)
ULN	upper limit of normal
uMRD	undetectable minimal residual disease
VAS	visual analogue scale

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 7 October 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 venetoclax with or without obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), based on interim results from study AMPLIFY (D8221C00001). This is a Randomized, Multicenter, Open-Label, Phase 3 Study to Compare the Efficacy and Safety of Acalabrutinib in Combination with Venetoclax with and without Obinutuzumab Compared to Investigator's Choice of Chemoimmunotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia Without del(17p) or TP53 Mutation (AMPLIFY). 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 8 of the RMP has also been submitted.

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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received scientific advice from the CHMP on 20 September 2018 (EMEA/H/SA/3090/4/2018/PA/III). The Scientific advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: <N/A>

Timetable	Actual dates
Submission date	7 October 2024
Start of procedure:	2 November 2024
CHMP Rapporteur Assessment Report	20 December 2024
PRAC Rapporteur Assessment Report	6 January 2025
PRAC members comments	8 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 January 2025
Request for supplementary information (RSI)	30 January 2025
CHMP Rapporteur Assessment Report	21 March 2025
PRAC Rapporteur Assessment Report	28 March 2025
PRAC members comments	2 April 2025
Updated PRAC Rapporteur Assessment Report	Not applicable
PRAC Outcome	10 April 2025
CHMP members comments	14 April 2025
Updated CHMP Rapporteur Assessment Report	16 April 2025
Opinion	25 April 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Chronic lymphocytic leukaemia (CLL) is the most prevalent form of adult leukaemia, with an age adjusted incidence of 3.3–6.4 per 100000 person-years and a median age at diagnosis of 70 years.

Claimed therapeutic indication

Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Clinical presentation, diagnosis and stage/prognosis

The diagnosis of CLL is established using peripheral blood counts and immunophenotyping that demonstrates a minimum of 5 x 109 monoclonal B cells that co-express the surface antigens CD5,

CD19, CD20, and CD23. The clonality of the circulating B lymphocytes needs to be confirmed by demonstrating light chain restriction using flow cytometry.

Treatment of CLL is initiated once there is evidence for progressive or symptomatic/active disease as defined by IWCLL guidelines. While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias. Treatment of CLL is therefore often deferred in asymptomatic patients with early-stage disease.

Despite the relatively long-life expectancy for early-stage disease with the recent advent of multiple treatment options including Bruton tyrosine kinase (BTK) and B-cell leukaemia/lymphoma 2 protein (BCL2) inhibitors, CLL remains an incurable disease. The goals of therapy are to improve quality of life and to prolong survival.

Management

The choice of frontline treatment options for CLL depends on patient characteristics, such as patient's age and overall health, and disease characteristics, including the presence of certain chromosomal abnormalities and mutations. For asymptomatic patients, watchful waiting (observation) remains an option, specifically closely monitoring a patient's condition without giving any treatment until signs or symptoms appear or change.

The development of novel molecularly targeted agents, particularly BTK inhibitors (acalabrutinib and ibrutinib) and the apoptosis regulator BCL2 antagonist venetoclax, has transformed the treatment paradigm for patients with CLL, particularly for those with high-risk disease who have inferior outcomes with chemotherapy-based regimens. Targeted treatment (BTKi or venetoclax) with or without anti-CD20 mAbs are the therapy of choice in most front-line CLL settings regardless of mutational status. However, fludarabine, cyclophosphamide, and rituximab (FCR) is also indicated in young and fit patients with mutated IGHV.

Randomised clinical studies had previously established the FCR combination as frontline therapy in a younger, fitter population with few comorbidities. In a head-to-head comparison (CLL10 study) of previously untreated fit patients who received bendamustine and rituximab (BR) versus FCR, the results showed a median Progression Free Survival (PFS) of 42.3 months in BR versus 57.6 months for FCR treated patients. No notable differences were observed in OS benefit between BR and FCR. This study established the combination of FCR as a Standard of Care (SoC) option for front-line therapy in fit patients with CLL. For patients with moderate renal dysfunction, BR is preferred over FCR. Moreover, for patients ≥ 65 years of age, if chemoimmunotherapy is deemed appropriate, BR is a choice of treatment.

In the Phase III ELEVATE TN study, previously untreated CLL patients inclusive of those with high-risk cytogenetics such as 17p deletion, unmutated IGHV or TP53 mutation were randomised to receive acalabrutinib and obinutuzumab, acalabrutinib monotherapy, and obinutuzumab and chlorambucil in 1:1:1 ratio.

After a median follow-up of 28.3 months, the primary analysis showed acalabrutinib + obinutuzumab demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with a 90% reduction in risk of disease progression or death (HR = 0.10 [95% CI: 0.06, 0.17]; p < 0.0001). Acalabrutinib monotherapy also demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with an 80% reduction in risk of disease progression or death (HR = 0.20 [95% CI: 0.13, 0.30]; p value < 0.0001).

The combination of acalabrutinib + obinutuzumab as well as acalabrutinib alone, when compared to obinutuzumab + chlorambucil, demonstrated a survival benefit based on the OS HR of 0·47, (95% CI: 0.21, 1.06; p-value = 0.06) and OS HR of 0·60; (95% CI: 0.28, 1.27; p-value = 0·16), respectively. The data from the ELEVATE-TN study supported the approval of acalabrutinib with or without obinutuzumab for the treatment of CLL.

Studies evaluating another second generation BTKi, zanubrutinib, as a monotherapy led to its approval for use in treatment naïve and R/R CLL/SLL patients. SEQUOIA was a randomised Phase III study in previously untreated CLL/SLL patients who were elderly and/or adults with comorbidities which precluded use of FCR. Patients with del(17p) received zanubrutinib as monotherapy and those without del(17p) were randomised to either zanubrutinib alone or BR. At a median follow-up of 26.2 months, in patients without 17p deletion, treatment with zanubrutinib showed improved PFS versus BR (HR = 0.42; 95% CI: 0.28, 0.63; p-value < 0.0001).

In the ALPINE study, patients with R/R CLL/SLL were randomised 1:1 to receive zanubrutinib or ibrutinib. At a median follow-up of 29.6 months, zanubrutinib demonstrated superiority over ibrutinib with PFS that was significantly longer (p-value = 0.002), with a HR of 0.65 (95% CI: 0.49, 0.86). Median PFS for zanubrutinib was not reached and was 34.2 months in the ibrutinib group (95% CI: 33.3 to NE). Based on results from the SEQUOIA and ALPINE studies, zanubrutinib was approved for the treatment of CLL/SLL.

In the EU and other countries outside of the US, ibrutinib in combination with venetoclax is approved as a fixed duration therapy in previously untreated CLL. Ibrutinib plus venetoclax demonstrated superior IRC-assessed PFS compared to obinutuzumab plus chlorambucil in older CLL patients and/or those with comorbidities, but no difference in OS was observed at the GLOW primary analysis.

2.1.2. About the product

Acalabrutinib (ACP-196), is a second generation, selective inhibitor of Bruton tyrosine kinase (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.

2.1.3. The development programme/scientific advice

CHMP Scientific advice was received on the following topics:

- The proposed toxicology package
- It was recommended to power the study for evaluation of both control regimens or perform 2 different studies.
- The Standard of Care (SoC) in the comparator arms were considered acceptable.
- PFS as primary endpoint supported by EFS/DFS (e.g. at 4 years) would need to be provided to

support regulatory decision making.

- The contribution of acalabrutinib and venetoclax in the regimen would need to be established at time of submission.
- MRD collection and analyses was also supported.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided a revised ERA in accordance with the updated EMA Guidance on the environmental risk assessment of medicinal products for human use (CHMP 2024) in support of this application.

The calculation of the PEC of acalabrutinib, uses a refined Fpen based on European disease prevalence data and the maximum daily dose in the PEC calculation. The resulting estimation of the PEC and environmental risk (PEC:PNEC ratios) are considered conservative.

Phase I:

The maximum daily dose for the indication MCL is 200 mg/day, resulting in PECSURFACEWATER value of 0.006 µg/L. For the indication chronic lymphocytic leukaemia with the maximum daily dose of 200 mg/day, the PECSURFACEWATER 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 PECSURFACEWATER-TOTAL was calculated to 0.054 µg/L.

Phase II Tier A: updated risk ratios (PEC/PNEC)

New phase II risk ratios are based on the guideline on environmental risk assessment from 2024 and 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	12 µg/L	1.1×10^{-3} (<1)
Microorganism	0.54 µg/L	100000 µg/L	5.4 × 10-6 (<0.1)
Sediment	740 µg/kg	14 400 µg/kg	0.051 (<1)

Summary of main study results

Substance (INN/Invented Name): Acalabrutinib					
CAS-number (if available): 1420477-60-6					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log Dow	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 D_{OW}	< 3 at pH 5, 7 and 9			not B
Persistence	DT50total system (12 °C) DT50sediment (12 °C)	216 d 203 d			vP
Toxicity	NOEC or CMR	1.2 mg/L STOT, Category 2 (H373)			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**
Dissociation constant, pKa		3.5 (pyridine), 5.8 (imidazopyrazine), 12.1 (benzamide)			
Water solubility		70 mg/L at pH 6.8 and 25°C			Not readily biodegradable
Activated sludge die away	OECD 314B	DT50 (parent) = 0.711 days 3.58% mineralisation over 28 days			Not readily biodegradable
Adsorption-Desorption Soil 1 = Silty clay loam soil Soil 2 = Loamy sand soil Sediment 1 = Loam sediment Sediment 2 = Sand sediment Sludge [mean, n=2]	OECD 106	$K_{oc,\ sludge}$ = 5.05 x 10^2 L/kg $K_{oc,\ sediment}$1=1.37 x 10^5 L/kg $K_{oc,\ sediment2}$=1.20 x 10^5 L/kg $K_{oc,\ soil\ 1}$ = 8.79 x 10^5 L/kg $K_{oc,\ soil\ 2}$ = 1.84 x 10^6 L/kg			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC EC10 EC50 EC50	2700 26000 >41000 29000	µg/L µg/L µg/L µg/L	 Growth rate Growth rate Yield
Daphnia sp. Reproduction Test	OECD 211	NOEC LOEC	1200 2700	µg/L µg/L	rate of first brood generation
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC LOEC	3800 >3000	µg/L µg/L	No significant effects observed
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	70000	µg/L	solubility limit, total respiration
Sediment dwelling organism/Chironomus riparius	OECD 218	NOEC LOEC	244 461	mg/kg dw mg/kg dw	Emergence ratio and development rate
Phase IIb Studies					

Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = Brandywine Creek (HOC) Sediment 2 = Choptank River (LOC)	OECD 308	$DT_{50, water}$ = 3.5 d / 5.8 d $DT_{50, sediment}$ = 95 d / 53 d $DT_{50, whole\ system}$ = 101 d / 54.4 d % shifting to sediment = 77.2 / 40 % CO_2 = 1.7 / 2.4 % NER = 58.4 / 43.2 transformation products > 10%: TP-RT11.5min, 11.4%AR, d7	I / II, 20 °C at d 14, parent + NER at test end at test end 4-[(pyridin-2-yl)carbamoyl]benzoic acid

2.2.2. Discussion on non-clinical aspects

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

The MAH has calculated an updated $PEC_{SURFACEWATER-TOTAL}$ value (0.054 µg/L) based on the use of acalabrutinib for the treatment of chronic lymphocytic leukaemia. The risk ratios (PEC/PNEC) were subsequently re-calculated based on considerations in the new ERA guideline implemented 01 September 2024 and the updated PECSURFACEWATER-TOTAL and the PNEC values that were presented for the original ERA submitted for the MAA. The resulting risk ratios remain below the action limits. Therefore, the use of acalabrutinib for the indications considered in the present report (MCL and chronic lymphocytic leukaemia) is not expected to pose a risk for the environment.

2.2.3. Conclusion on the non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

The AMPLIFY study (also referred to as ACE-CL-311) was designed to assess the efficacy and safety of a fixed-duration therapy of acalabrutinib in combination with venetoclax with or without obinutuzumab for the treatment of patients with previously untreated CLL versus investigator's choice of chemoimmunotherapy.

Efficacy data in support of this application, presented in this section, are from the primary PFS analysis (DCO 30 April 2024), unless otherwise stated.

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 European Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study CSR Location	Study Design	Subjects (N; type, ethnicity; age, body weight: median [range])	Treatments (dose, dosage form, route)
AMPLIFY Study ACE-CL-311 (D8221C00001), Randomized, Multicenter, Open-Label, Phase III Study to Compare the Efficacy and Safety of Acalabrutinib in Combination with Venetoclax (AV) with and without Obinutuzumab (AVG) Compared to Investigator's Choice of Chemoimmunotherapy (Chemo) in Subjects with Previously Untreated Chronic Lymphocytic Leukemia Without del(17p) or TP53 Mutation CSR location: Module 5.3.5.1	Randomized, open-label, multicenter study	Patients with previously untreated CLL; N = 867 Randomized: AV = 291; AVG = 286; Chemo = 290 Sex: Male = 559, Female = 308; Age: median (range) 61 yrs (26-86); Race: White = 765 (88.2%), Asian = 31 (3.6%), Black or African American = 21 (2.4%)	Acalabrutinib 100 mg, administered twice daily, provided as hard gelatin capsules for oral administration. Venetoclax, administered orally, will begin at Cycle 3 and continue following a 5-week ramp-up at a fixed daily dose until the end of Cycle 14. Obinutuzumab will be administered by intravenous (IV) infusion as an absolute (flat) dose of 1000 mg, starting at Cycle 2 and continue through Cycle 7.

2.3.2. Pharmacokinetics

Study ACE-CL-311 (AMPLIFY) included PK sampling at pre-dose and 1- and 4-hours post-dose on Day 1 of Cycles 1, 5, and 7 (28-day cycle). Acalabrutinib and the active metabolite ACP-5862 were quantified.

The MAH provided graphical and tabular summaries of observed PK data from ACE-CL-311, including comparisons to studies in other populations (**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 (nM) versus time (Steady State) stratified by population/study for acalabrutinib

Analyte: Acalabrutinib Study ID		**Time (hours)**			
		1 h	**2 h**	**4 h**	**6 h**
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)
	N	243	249	248	-

ACE-CL-007	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-CL-311	N	531	-	525	-
	GeoMean (GeoCV %)	266.45 (390.6)	-	96.29 (133.3)	-
	Median (range)	486.47 (2.4 – 4003.9)	-	97.98 (2.6 – 1472.9)	-

Abbreviations: GeoMean, geometric mean; GeoCV, geometric coefficient of variation; h, hour; ID, identifier

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

Analyte: ACP-5862 Study ID		**Time (hours)**			
		1 h	**2 h**	**4 h**	**6 h**
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-CL-311	N	532	-	526	-
	GeoMean (GeoCV %)	350.7 (152.3)	-	406.07 (60)	-
	Median (range)	483.66 (14.3 – 2203.8)	-	428.95 (21.6 – 1709.3)	-

Abbreviations: GeoMean, geometric mean; GeoCV, geometric coefficient of variation; h, hour; ID, identifier

Table 3. Comparison of relevant continuous covariates/patient demographics between the populations/ studies

Parameter	**ACE-CL-006 (N = 117)**	**ACE-CL-007 (N = 274)**	**ACE-CL-311 (N = 571)**	**Overall (N = 962)**
Baseline age (year)				
Mean (SD)	65.2 (10.1)	69.5 (7.81)	60.0 (9.43)	63.3 (10.0)

Median (Min, Max)	66.0 (41.0, 87.0)	70.0 (41.0,88.0)	61.0 (29.0, 84.0)	64.0 (29.0, 88.0)
Baseline weight (kg)				
Mean (SD)	79.9 (17.2)	80.4 (18.4)	80.2 (16.3)	80.2 (17.0)
Median (Min, Max)	79.0 (45.6, 157)	78.5 (44.0, 149)	79.0 (43.0, 140)	79.0 (43.0, 157)
Baseline height (cm)				
Mean (SD)	171 (10.6)	169 (9.14)	172 (9.97)	171 (9.87)
Median (Min, Max)	172 (142, 196)	169 (143, 193)	172 (143, 196)	170 (142, 196)
Missing	0	0	2 (0.4%)	2 (0.2%)
Baseline body mass index (kg/m^2)				
Mean (SD)	27.0 (4.59)	27.9 (5.40)	27.2 (4.78)	27.4 (4.95)
Median (Min, Max)	26.6 (17.9, 48.3)	27.1 (17.6, 50.5)	26.6 (17.2, 52.6)	26.7 (17.2, 52.6)
Missing	0	0	2 (0.4%)	2 (0.2%)
Baseline body surface area (m^2)				
Mean (SD)	1.92 (0.229)	1.90 (0.228)	1.92 (0.221)	1.92 (0.224)
Median (Min, Max)	1.92 (1.42, 2.67)	1.90 (1.38, 2.55)	1.91 (1.32, 2.57)	1.91 (1.32, 2.67)
Missing	0	0	2 (0.4%)	2 (0.2%)
Baseline creatinine clearance (mL/min)				
Mean (SD)	89.7 (37.2)	81.2 (29.5)	89.2 (27.3)	87.0 (29.5)
Median (Min, Max)	87.5 (27.2, 264)	77.9 (29.0, 249)	85.2 (36.6, 249)	83.3 (27.2, 264)
Missing	0	0	1 (0.2%)	1 (0.1%)
Baseline eGFR (mL/min/1.73 m^2)				
Mean (SD)	79.1 (24.8)	74.8 (21.3)	74.3 (16.3)	75.0 (19.1)
Median (Min, Max)	76.6 (27.8, 168)	73.7 (27.5, 162)	73.1 (26.5, 136)	73.6 (26.5, 168)
Missing	0	0	1 (0.2%)	1 (0.1%)
Baseline alanine aminotransferase (U/L)				
Mean (SD)	19.5 (12.0)	19.9 (17.9)	18.8 (9.48)	19.2 (12.7)
Median (Min, Max)	17.0 (5.00, 96.0)	16.0 (5.00, 241)	17.0 (5.00, 76.0)	17.0 (5.00, 241)
Missing	0	0	2 (0.4%)	2 (0.2%)
Baseline aspartate aminotransferase (U/L)				
Mean (SD)	22.3 (8.92)	22.9 (12.3)	22.2 (8.47)	22.4 (9.75)
Median (Min, Max)	21.0 (6.00, 73.0)	21.0 (8.00, 164)	21.0 (7.00, 91.0)	21.0 (6.00, 164)
Missing	0	0	1 (0.2%)	1 (0.1%)
Baseline bilirubin (µmol/L)				

Mean (SD)	9.10 (5.24)	8.89 (6.16)	9.12 (5.10)	9.05 (5.44)
Median (Min, Max)	7.90 (2.90, 28.2)	7.45 (2.60, 67.4)	8.00 (3.00, 44.0)	7.80 (2.60, 67.4)
Missing	0	0	14 (2.5%)	14 (1.5%)

Abbreviations: eGFR, estimated glomerular filtration rate; Max, maximum; Min, minimum; SD, standard deviation.

Table 4. Comparison of relevant continuous covariates/patient demographics between the populations/ studies

Parameter	**ACE-CL-006 (N = 117)**	**ACE-CL-007 (N = 274)**	**ACE-CL-311 (N = 571)**	**Overall (N = 962)**
Sex				
Female	35 (29.9%)	104 (38.0%)	198 (34.7%)	337 (35.0%)
Male	82 (70.1%)	170 (62.0%)	373 (65.3%)	625 (65.0%)
Race				
White	110 (94.0%)	262 (95.6%)	508 (89.0%)	880 (91.5%)
Black/African American	3 (2.6%)	9 (3.3%)	14 (2.5%)	26 (2.7%)
Asian	0	3 (1.1%)	12 (2.1%)	15 (1.6%)
American Indian or Alaska Natives	0	0	1 (0.2%)	1 (0.1%)
Other	4 (3.4%)	0	2 (0.4%)	6 (0.6%)
Missing	0	0	34 (6.0%)	34 (3.5%)
East asia				
Non-East asian	117 (100%)	271 (98.9%)	562 (98.4%)	950 (98.8%)
East asian	0	3 (1.1%)	9 (1.6%)	12 (1.2%)
Ethnicity				
Hispanic/Latino	2 (1.7%)	11 (4.0%)	36 (6.3%)	49 (5.1%)
Not Hispanic/Latino	100 (85.5%)	248 (90.5%)	490 (85.8%)	838 (87.1%)
Not reported	15 (12.8%)	15 (5.5%)	45 (7.9%)	75 (7.8%)
Unknown	0	0	0	0
Combination				
Monotherapy	117 (100%)	274 (100%)	0	391 (40.6%)
Acala + V	0	0	289 (50.6%)	289 (30.0%)
Acala + VG	0	0	282 (49.4%)	282 (29.3%)
Hepatic impairment status				
Normal (bilirubin ≤ ULN, and AST ≤ ULN)	104 (88.9%)	257 (93.8%)	508 (89.0%)	869 (90.3%)
Mild (bilirubin ≤ ULN, and AST > ULN or bilirubin >1.0 × ULN to ≤ 1.5 × ULN, and AST of any value)	13 (11.1%)	13 (4.7%)	46 (8.1%)	72 (7.5%)
Moderate (bilirubin > 1.5 × ULN to ≤ 3 × ULN, and AST of any value)	0	3 (1.1%)	3 (0.5%)	6 (0.6%)
Severe (bilirubin >3.0 × ULN, and AST of any value)	0	1 (0.4%)	0	1 (0.1%)
Missing	0	0	14 (2.5%)	14 (1.5%)

Renal impairment status				
Normal (eGFR ≥ 90 mL/min/1.73 m2)	38 (32.5%)	58 (21.2%)	84 (14.7%)	180 (18.7%)
Mild (eGFR 60–89 mL/min/1.73 m2)	62 (53.0%)	170 (62.0%)	385 (67.4%)	617 (64.1%)
Moderate (eGFR 30–59 mL/min/1.73 m2)	16 (13.7%)	45 (16.4%)	100 (17.5%)	161 (16.7%)
Severe (eGFR 15–29 mL/min/1.73 m2)	1 (0.9%)	1 (0.4%)	1 (0.2%)	3 (0.3%)
End stage (eGFR < 15 mL/min/ 1.73 m2 / on dialysis)	0	0	1 (0.2%)	1 (0.1%)
ECOG performance status				
Fully active	60 (51.3%)	141 (51.5%)	312 (54.6%)	513 (53.3%)
Ambulatory	52 (44.4%)	117 (42.7%)	216 (37.8%)	385 (40.0%)
Ambulatory but no work	5 (4.3%)	16 (5.8%)	42 (7.4%)	63 (6.5%)
Limited self-care	0	0	0	0
Completely disabled	0	0	0	0
Dead	0	0	0	0
Missing	0	0	1 (0.2%)	1 (0.1%)
Use of PPI				
Not present	108 (92.3%)	262 (95.6%)	525 (91.9%)	895 (93.0%)
Present	9 (7.7%)	12 (4.4%)	45 (7.9%)	66 (6.9%)
Imputed present	0	0	1 (0.2%)	1 (0.1%)

Abbreviations: Acala + VG, acalabrutinib + venetoclax + obinutuzumab; Acala +V, acalabrutinib + venetoclax; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; NA, not available; PPI, proton pump inhibitor; ULN, upper limit of normal.

Population pharmacokinetic (PopPK) analysis

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

The pooled PopPK analysis dataset included 13290 acalabrutinib and 7902 ACP-5862 plasma concentrations and relevant covariates from 1569 subjects for acalabrutinib and 1174 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).

The PopPK dataset included 4039 acalabrutinib observations and 7902 ACP-5862 observations from 571 patients from AMPLIFY.

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

The structural PK model remained, i.e. 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). The previously reported covariate PPI use on relative bioavailability was kept. Indication nor combination were statistically significant covariates using a corresponding $p<0.001$ threshold.

Final parameter estimates are provided in **Table 5**.

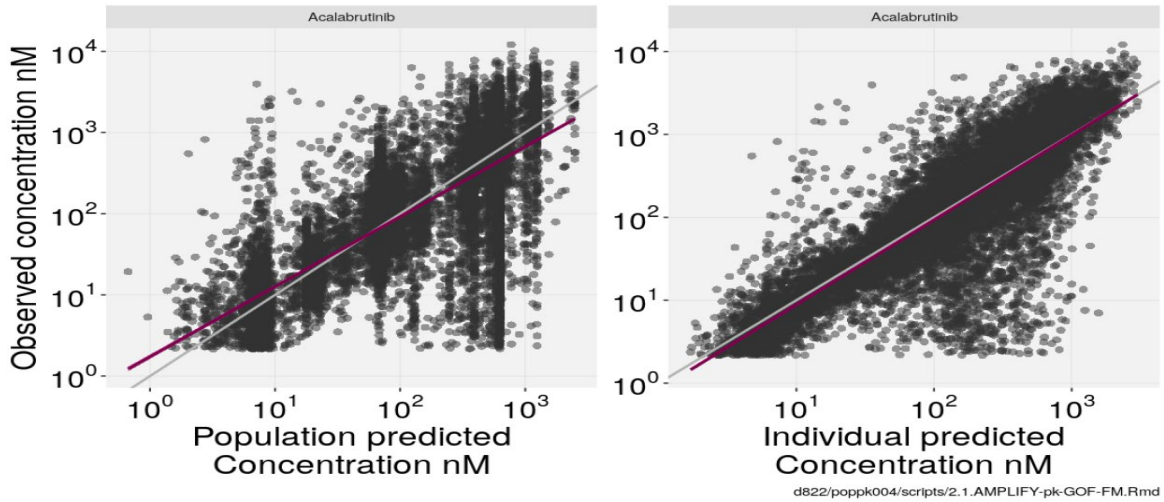
Table 5. Parameter estimates for final model

	Estimate	RSE (%)	95% CI	Unit
Population Parameter				
CL/F (Parent)	154	1.13	[150; 157]	L/hr
V/F central (Parent)	79.9	3.58	[74.3; 85.5]	L
Q/F (Parent)	19.4	3.93	[17.9; 20.9]	L/hr
VP/F peripheral (Parent)	186	3.30	[174; 198]	L
KA	0.991	1.38	[0.964; 1.02]	1/hr
D1	0.522	2.88	[0.493; 0.552]	hr
CLM/F (Metabolite)	19.9	1.15	[19.5; 20.4]	L/hr
VCM/F (Metabolite)	78.5	1.57	[76.1; 80.9]	L
Covariate				
PPI use on F1 [a]	-0.159	10.6	[-0.192; -0.126]	-
Interindividual Variability				
BSV CL/F (Parent) (CV%)	28.3	3.14	[28.3; 28.3]	-
BSV V/F (Parent) (CV%)	184	3.63	[184; 185]	-
BSV VP/F (Parent) (CV%)	31.4	9.70	[31.3; 31.4]	-
BSV KA (CV%)	12.7	10.6	[12.7; 12.8]	-
BSV CLM/F (Metabolite) (CV%)	19.6	6.05	[19.6; 19.7]	-
BSV on EPS (Parent) (CV%)	43.8	3.01	[43.8; 43.8]	-
Residual Variability				
Proportional component (Parent) (sd)	87.1	1.55	[87.1; 87.2]	-
Proportional component (Metabolite) (sd)	76.0	0.406	[76.0; 76.0]	-

[a]relative change (1+estimate)

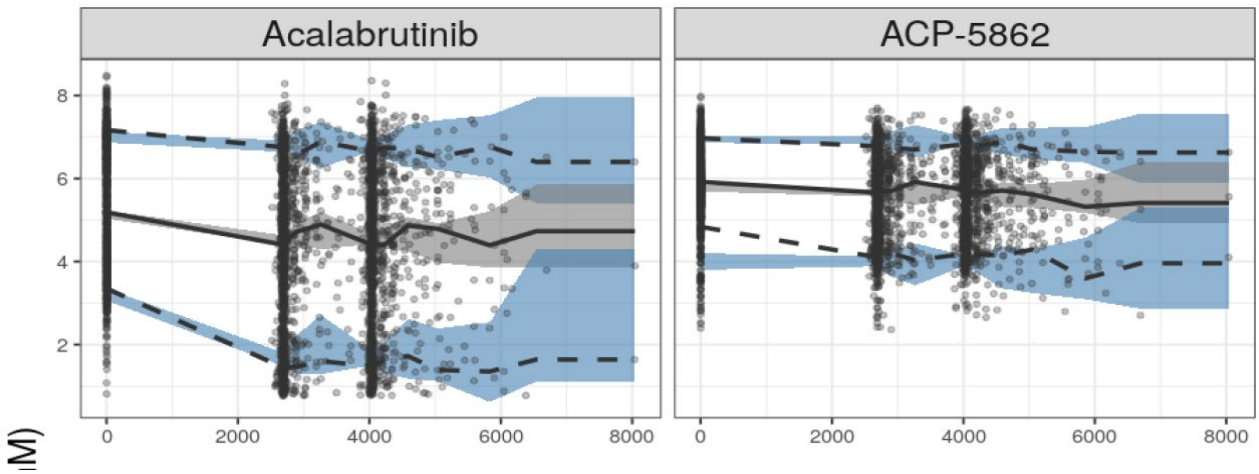
The Goodness of Fit (GoF) plots and prediction-corrected visual predictive check (pcVPC) for AMPIFLY are presented in **Figure 1** and **Figure 2** respectively.

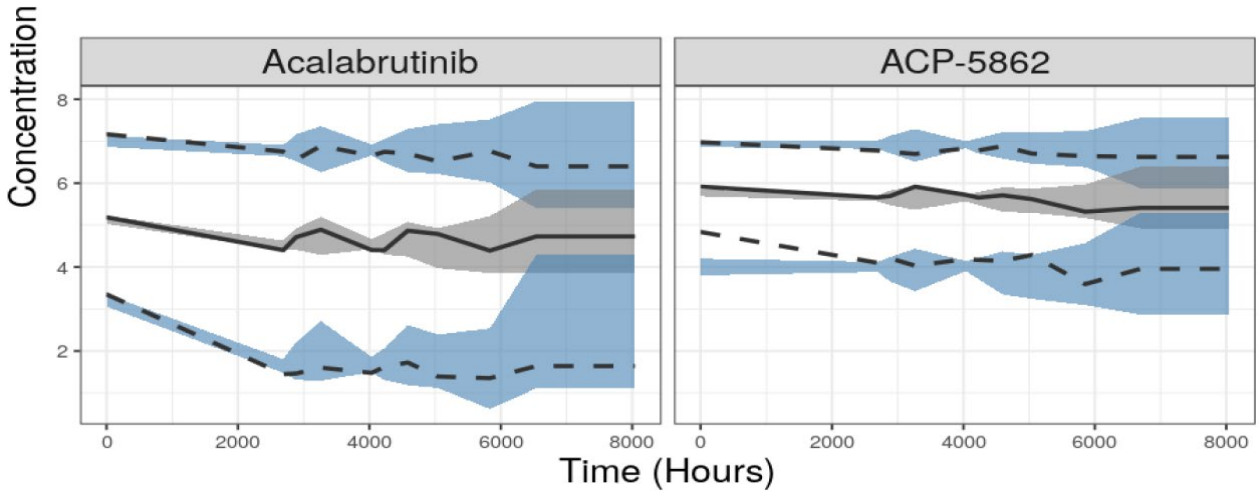
Figure 1. Basic Goodness-of-Fit Plots for the Final Model – Observations Versus Predictions (AMPLIFY; Acalabrutinib)



Grey line is the line of unit. Red line is the linear model smother with 95% CI (shaded area)
DV vs PRED on left and DV vs IPRED on right

Figure 2. Prediction-Corrected Visual Predictive Check for the Final Model in AMPLIFY Study Patients for Both Acalabrutinib (left) and Metabolite (right) with (top) and without (bottom) Overlaying Observed Data





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 has provided exposure-response analyses of efficacy and safety endpoints which was included in the modelling report D8221C00001.

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 were 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).

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

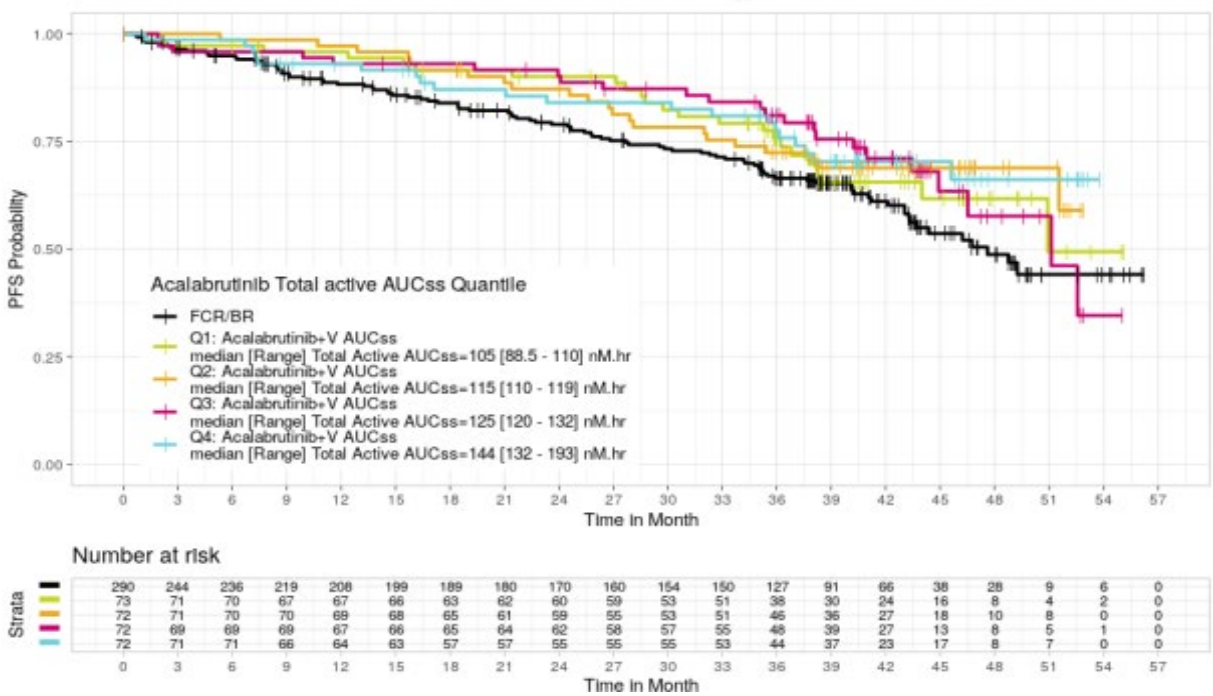
Where Cparent and Cmetabolite are molar concentrations of acalabrutinib and ACP-5862, respectively; fuparent (free fraction of acalabrutinib) = 0.025; fumetabolite (free fraction of ACP-5862) = 0.013; and compared to acalabrutinib, ACP-5862 exhibits approximately 0.5-fold potency for inhibition.

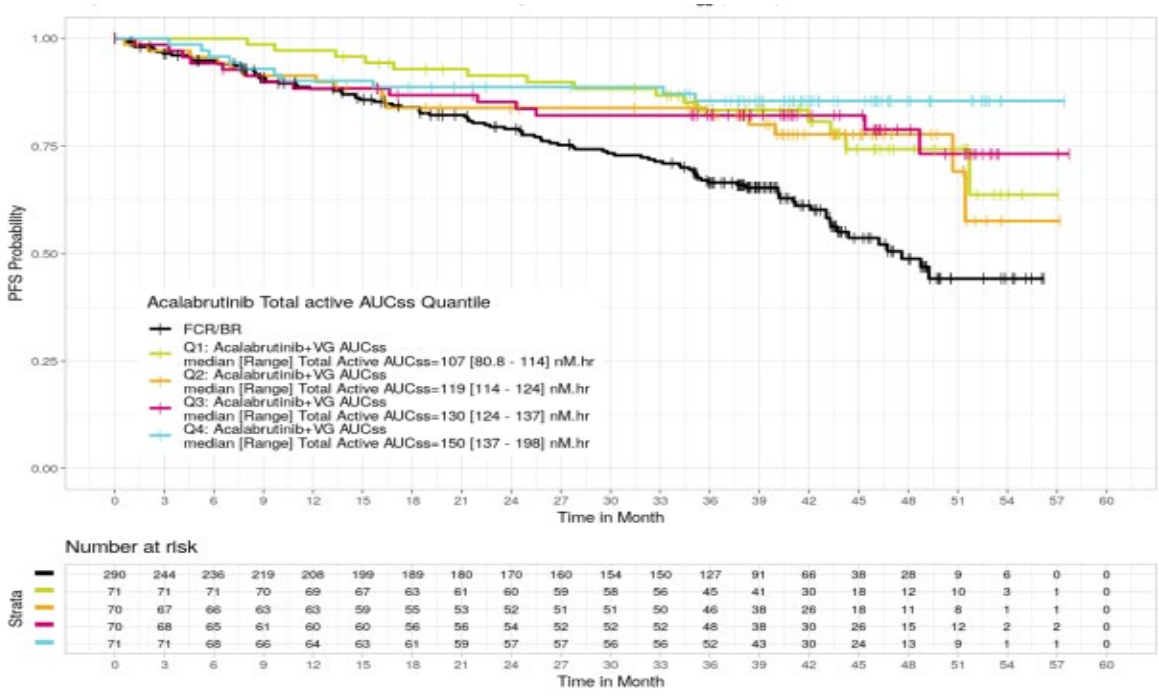
Following exclusions, the exposure-response analysis included 571 subjects treated with acalabrutinib (289 in the acalabrutinib+venetoclax arm and 282 in the acalabrutinib+venetoclax+obinutuzumab arm). Regarding exclusions, of the subjects that received acalabrutinib, 6 of them had no acalabrutinib (and ACP-5862) PK concentrations and were not included in the analysis. Data from 290 patients in the reference arm were generally not included in the exposure-response analysis but were used in certain plots for comparison purpose only.

Exposure-efficacy analysis:

An exploratory Kaplan-Meier analysis evaluated the PFS as function of total active AUCs quartiles (**Figure 3**) suggest that there is no clear trend in the relationship between PFS and total active AUCss as indicated by the overlap in the Kaplan-Meier curves for all four exposure quartiles over the duration of the assessment.

Figure 3. Kaplan-Meier plot of AMPLIFY stratified by Total Active AUCss- (Top Panel: AV Arm, Bottom Panel: AVG Arm)





AV: Acalabrutinib + Venetoclax; AVG: Acalabrutinib + Venetoclax + Obinutuzumab; FCR: Fludarabine, cyclophosphamide, and rituximab; BR: Bendamustine and rituximab; Total active AUCss: total active moiety of the area under the plasma concentration-time curve from time 0 to 24 hours (2 dosing intervals) at steady state. The table below the Kaplan-Meier curves represents the number of patients available for the analyses (i.e., not censored or discontinued).

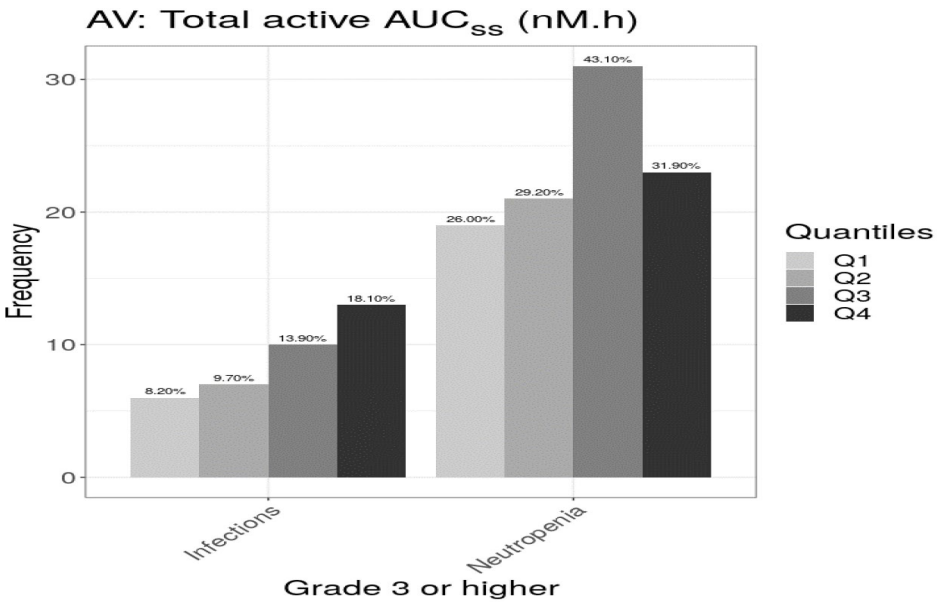
A Cox proportional hazard model did not identify a statistically significant exposure-response relationship for PFS (data not shown).

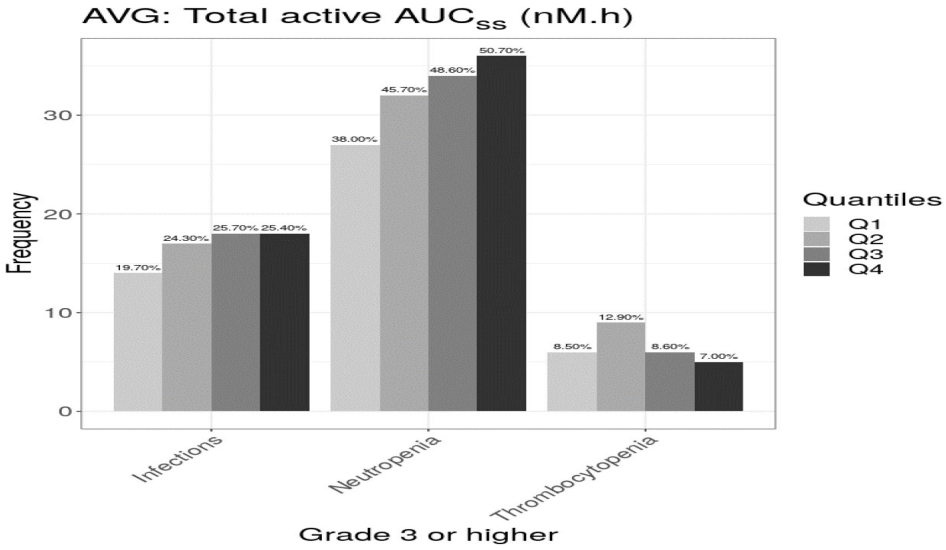
The exploratory graphical analysis using boxplot evaluated the association between total active exposure and ORR and indicated that median total active exposure were similar across all response categories, suggesting a flat relationship in ORR.

Exposure-safety analysis:

The relationship between acalabrutinib exposure (total active AUC) versus the incidence of any AEs (Grade ≥3) and selected safety outcomes of clinical interest (i.e., percentage of subjects with a specific AE) acalabrutinib treated arm of AMPLIFY is shown in **Figure 4**. Acalabrutinib exposure (AUCss, and total active AUC) was generally similar regardless of whether the selected safety outcomes of clinical interest were present or absent (data not shown).

Figure 4. Bar Plot of Acalabrutinib Total Active AUCss Stratified by Quartile and Selected Grade ≥3 AEs of Clinical Interest.





AV: Acalabrutinib + Venetoclax; AVG: Acalabrutinib + Venetoclax + Obinutuzumab; Total active AUCss: total active moiety of the area under the plasma concentration-time curve from time 0 to 24 hours (2 dosing intervals) at steady state. The shaded bars represent the 4 quantiles (quartiles) of total active AUCss with Q1 = first quartile, Q2 = second quartile, Q3 = third quartile, and Q4 = fourth quartile. The numbers on top of the bar plots are the respective percentage of subjects with AEs within each quantile of acalabrutinib exposure.

2.3.4. Discussion on clinical pharmacology

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

The objective of the clinical pharmacology data package in the current variation is to describe acalabrutinib PK in first-line CLL patients co-treated with venetoclax (the target population) and to characterise potential PK differences between first-line CLL patients not co-treated with venetoclax.

Pharmacokinetics

The PK data from AMPLIFY were also analysed using a PopPK approach which however had significant limitations.

From the provided PopPK report, it was unclear which covariates were explored, and which results were used to arrive to the final PK model. A modelling analysis plan and model code would have been helpful for better assessing the covariate model. However, covariate evaluation of indication and combination treatment on CL/F was described and reported. Combination treatment with venetoclax is considered the most important covariate to explore within this procedure. Acalabrutinib is a P-gP substrate *in vitro* and venetoclax is a P-gP inhibitor *in vitro*, thus, a potential PK DDI cannot be excluded. Combination treatment was explored on CL/F which was considered reasonable. However, it would have been relevant to explore combination treatment as a covariate also on the absorption related parameters KA, D1 and F1 (i.e. relative bioavailability). This is because P-gP is known to be present in the gut which means that a PK DDI involving P-gP may affect rate and extent of absorption.

The goodness-of-fit for the AMPLIFY study based on the final PopPK model is suboptimal. There were signs of major model misspecifications according to the observations vs typical predictions plot for the metabolite ACP-5862. There were also model misspecifications according to CWRES plots for ACP-5862. No major model misspecifications were noted for acalabrutinib. The pcVPC did not indicate any obvious model misspecification for neither compound.

Given these limitations, the PopPK model is not considered acceptable for describing PK in the target population. Nevertheless, an updated PopPK model is not requested since reasonable graphical and tabular summaries of the observed PK data were provided.

The PK in the target population as observed in the AMPLIFY study was compared to previously conducted studies with acalabrutinib in other populations. The results indicated that there are no clinically relevant PK-differences between the target population (CLL patients co-treated with venetoclax) and the currently approved indications of acalabrutinib (CLL patients in Studies ACE-CL-006 and ACE-CL-007) as well as second-line MCL patients (Study ACE-LY-004).

The applicants' proposal not to update SmPC Section 5.2 was therefore considered acceptable.

Exposure-response

Exposure-response analyses of efficacy and safety endpoints were performed by the applicant. No clinically significant exposure-response trends were detected, however, a numerical increase in some safety endpoints such as infections and neutropenia at increasing exposures were noted. The results from the exposure-response analyses should be interpreted with caution; The analyses were based only on patient data from AMPLIFY where only a single dose level of acalabrutinib was explored. This means that the exposure range will be rather limited which 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 first-line CLL patients co-treated with venetoclax and CLL patients without co-treatment with venetoclax. No updates in the SmPC section 5.2 have been proposed which is acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study

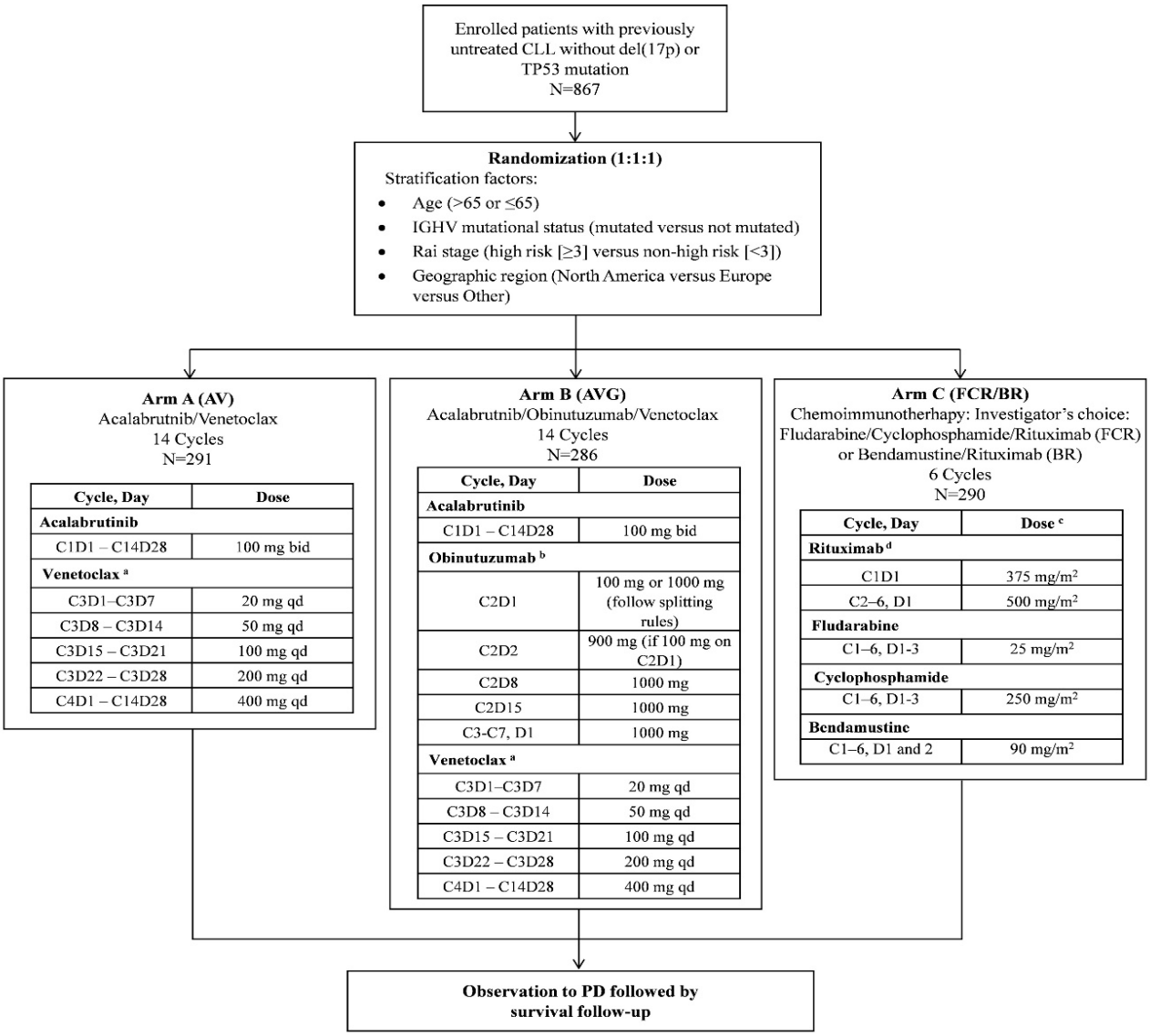
Not applicable.

2.4.2. Main study

ACE-CL-311 (AMPLIFY): a randomised, multicentre, open-label, Phase III study to compare the efficacy and safety of acalabrutinib in combination with venetoclax with and without obinutuzumab compared to investigator's choice of chemoimmunotherapy in patients with previously untreated CLL without del(17p) or TP53 mutation.

Figure 5 shows the design of the study, the sequence of treatment periods, and the treatment regimens.

Figure 5. Flowchart of study ACE-CL-311 design



Cycle, Day	Dose
Acalabrutinib	
C1D1 – C14D28	100 mg bid
Venetoclax [a]	
C3D1–C3D7	20 mg qd
C3D8 – C3D14	50 mg qd
C3D15 – C3D21	100 mg qd
C3D22 – C3D28	200 mg qd
C4D1 – C14D28	400 mg qd

Cycle, Day	Dose
Acalabrutinib	
C1D1 – C14D28	100 mg bid
Obinutuzumab [b]	
C2D1	100 mg or 1000 mg (follow splitting rules)
C2D2	900 mg (if 100 mg on C2D1)
C2D8	1000 mg
C2D15	1000 mg
C3-C7, D1	1000 mg
Venetoclax [a]	
C3D1–C3D7	20 mg qd
C3D8 – C3D14	50 mg qd
C3D15 – C3D21	100 mg qd
C3D22 – C3D28	200 mg qd
C4D1 – C14D28	400 mg qd

Cycle, Day	Dose [c]
Rituximab [d]	
C1D1	375 mg/m^2
C2–6, D1	500 mg/m^2
Fludarabine	
C1–6, D1-3	25 mg/m^2
Cyclophosphamide	
C1–6, D1-3	250 mg/m^2
Bendamustine	
C1–6, D1 and 2	90 mg/m^2

[a] The 20-mg and 50-mg doses of venetoclax were administered in the hospital for patients who were at high-risk of tumour lysis syndrome (TLS), or if they were indicated to hospitalise, and thereafter at home daily for 7 days. The dose then increased every 7 days to the target dose of 400 mg, and venetoclax was to be administered at home unless a patient was indicated to hospitalise.
[b] Only the first dose (1000 mg) of obinutuzumab administration was allowed to be split over 2 days.
[c] Patients received either FCR or BR.
[d] The first dose could have been given over 2 days at investigator discretion per standard of care.

Methods

Study participants

Key inclusion criteria

1. Men and women ≥18 years of age.
2. ECOG performance status of 0–2.
3. Diagnosis of CLL that meets published diagnostic criteria (Hallek et al 2018):
    (a) Monoclonal B cells (either kappa or lambda light chain restricted) that are clonally co-expressing B-cell marker (CD19, CD20, and CD23) and CD5.
    (b) Prolymphocytes may comprise < 55% of blood lymphocytes.
    (c) Presence of ≥ 5x109 B lymphocytes/L (5000/μL) in the peripheral blood (at any point since the initial diagnosis).
4. Active disease per IWCLL 2018 criteria that requires treatment
5. Meet the following laboratory parameters:
    (a) Adequate bone marrow function independent of growth factor or transfusion support within 1 week of Screening, as follows:
        (i) ANC ≥750 cells/μL (0.75x109/L); ANC ≥ 500 cells/μL (0.50x109/L) in patients with documented bone marrow involvement of CLL
        (ii) Platelet count ≥ 50,000 cells/μL (50x109/L); platelet count ≥ 30,000 cells/μL (30x109/L) in patients with documented bone marrow involvement of CLL
    (b) Serum AST and ALT ≤ 2.5 x upper limit of normal (ULN)
    (c) Total bilirubin ≤ 2 x ULN, unless directly attributable to Gilbert's syndrome
    (d) Estimated creatinine clearance of ≥ 50 mL/min, calculated using the Cockcroft and Gault equation (if male, [140-Age] x Mass [kg] / [72 x creatinine mg/dL]; multiply by 0.85 if female); estimated creatinine clearance of ≥ 70 mL/min for patients selected by investigator to receive FCR in Arm C.

Key exclusion criteria

1. Any prior CLL-specific therapies (except corticosteroid treatment administered due to necessary immediate intervention; within the last 10 days before start of study treatment, only dose equivalents up to 20 mg prednisone daily were permitted).
2. Detected del(17p) or TP53 mutation.
3. Transformation of CLL to aggressive non-Hodgkin lymphoma (e.g., Richter's transformation, PLL, or diffuse large B-cell lymphoma) or CNS involvement by leukaemia.
4. Any comorbidity or organ system impairment rated with a single CIRS-G score of 4 (excluding the eyes/ears/nose/throat/larynx organ system and disease under study) or a total CIRS-G score of > 6.
5. Significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification at Screening. Note: Patients with controlled, asymptomatic atrial fibrillation were allowed to enrol on study.
6. Known history of infection with HIV.

7. Any active significant infection (e.g., bacterial, viral or fungal, including patients with positive cytomegalovirus DNA PCR).
8. Serologic status reflecting active hepatitis B or C infection.
    (a) Patients who were hepatitis B core antibody positive and who were hepatitis B surface antigen negative will need to have a negative PCR result before randomisation and must be willing to undergo DNA PCR testing during the study. Those who were H hepatitis B surface antigen-positive or hepatitis B PCR positive will be excluded.
    (b) Patients who were hepatitis C antibody positive will need to have a negative PCR result before randomisation. Those who were hepatitis C PCR positive will be excluded.
9. History of bleeding diathesis (e.g., haemophilia, von Willebrand disease).
10. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists.
11. Requires treatment with a strong CYP3A inhibitor. The use of strong or moderate CYP3A inhibitors or inducers within 7 days of the first dose of study drug is prohibited.
12. Breastfeeding or pregnant.

Treatments

Arm A (acalabrutinib+venetoclax; AV)

Acalabrutinib 100 mg capsules were orally administered from Cycle 1 at a fixed twice daily (BID) dose for 14 cycles; venetoclax oral dosing was to begin at Cycle 3 and continued following a 5-week ramp-up at a fixed daily dose of 400 mg until the end of Cycle 14, or until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurred first.

Arm B (acalabrutinib+venetoclax+obinutuzumab; AVG)

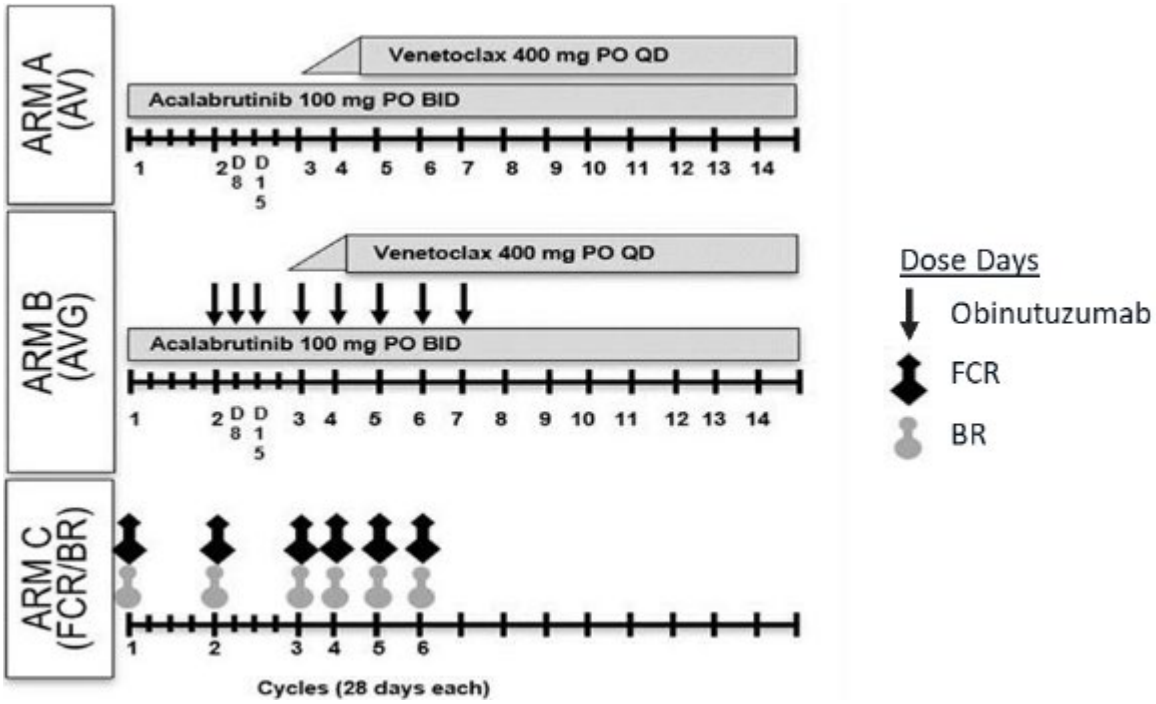
Acalabrutinib (100 mg capsules) were orally administered from Cycle 1 at a fixed BID dose for 14 cycles; obinutuzumab administered as IV infusion at an absolute (flat) dose of 1000 mg and was to begin at Cycle 2 and continued through Cycle 7; venetoclax dosing was to begin at Cycle 3 and continue following a 5-week ramp-up at a fixed daily dose of 400 mg until the end of Cycle 14, or until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurred first.

Arm C (chemoimmunotherapy; investigator's choice of fludarabine+cyclophosphamide+rituximab or bendamustine+rituximab; FCR/BR)

All patients who were randomised to standard chemoimmunotherapy were to receive up to 6 cycles of either FCR or BR as IV infusions, according to standard institutional practice. Patients ≤ 65 years of age with a creatinine clearance of ≥ 70 mL/min were restricted to FCR.

Treatment regimens in ACE-CL-311 are depicted in **Figure 6**.

Figure 6. Treatment Regimens in ACE-CL-311



Objectives

The AMPLIFY study was designed to evaluate whether the finite duration of acalabrutinib in combination with venetoclax with or without obinutuzumab as a first-line treatment setting could improve long-term treatment outcomes in patients with previously untreated CLL without del(17p) or TP53 mutation.

Outcomes/endpoints

Primary endpoint

- PFS assessed by IRC (Arm A vs Arm C)

Key secondary endpoints

- PFS assessed by IRC (Arm B vs Arm C)
- MRD negativity rate (Arm A vs Arm C and Arm B vs Arm C)
- Overall survival (OS, Arm A vs Arm C and Arm B vs Arm C)

Other secondary endpoints (all investigated in Arm A vs Arm C and Arm B vs Arm C)

- PFS by investigator assessment.
- Event-free survival (EFS, IRC and INV)
- Objective response rate (ORR, IRC and INV)
- Duration of response (DoR, IRC and INV)
- Time to next treatment (TTNT)

Exploratory endpoints

- PROs by EORTC-QLQ-C30, IL27, FACIT-Fatigue, PGIC, PGIS and EQ-5 D-5 L

Sample size

According to SAP version 4.0 dated 28 Feb 2024, the study was expected to randomise approximately 260 subjects per arm. With a 1:1:1 randomisation ratio, the study would randomise 780 subjects in total.

Under the exponential model assumptions, the study was sized to achieve approximately 90% power to detect a hazard ratio of 0.62 in PFS at the 2-sided significance level of 0.05 based on 188 events at final analysis, which translates into a 61% improvement in median PFS from 44.7 months in Arm C (FCR/BR) to 72.1 months in Arm A (AV). The hazard ratio of 0.62 was based on the GAIA- CLL13 interim analysis of PFS for venetoclax-obinutuzumab-ibrutinib versus chemoimmunotherapy, in which the upper bound of the 97.5% confidence interval (CI) for the hazard ratio was 0.54 (Eichhorst et al. 2023).

Given that this study was anticipated to have a higher proportion of death due to Coronavirus disease 2019 (COVID-19) than GAIA-CLL13 (at least 24% and 18% of PFS events at interim and final analysis in 3 arms combined, respectively), a more conservative hazard ratio of 0.62 was assumed, which translates to a median PFS of 72.1 months in Arm A (AV) under the exponential distribution and under median PFS of 44.7 months in Arm C (FCR/BR).

Randomisation

Subjects were randomised in a 1:1:1 ratio to

- Arm A: Acalabrutinib/venetoclax [AV]
- Arm B: Acalabrutinib/venetoclax/obinutuzumab [AVG]
- Arm C: Chemoimmunotherapy - Investigator's choice of fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab (BR) – [FCR/BR].

All subjects were planned to be centrally assigned to randomised study treatment using an Interactive Voice/Web Response System (IxRS).

After approximately 780 subjects had been randomised into the study, enrolment outside of China (i.e., global enrolment) was planned to be closed and additional Chinese subjects would be recruited into the China extension cohort until approximately 117 Chinese subjects had been randomised (in both the global cohort and the China extension cohort).

For Arm C, approximately 50% of subjects were planned to be treated with FCR and 50% treated with BR per investigator's choice. The investigator must had declared the choice of FCR or BR for a subject before randomisation. When the number of subjects randomised to Arm C with one of the investigator-chosen regimens (FCR or BR) approached 130, future subjects with the same investigator's choice for Arm C would not be eligible to participate in the study. The IxRS was planned to be used to balance the allocation of FCR and BR by region.

Blinding (masking)

This was an open-label study.

Statistical methods

Analysis of primary endpoint

The primary efficacy endpoint IRC-assessed PFS was defined as the time from the date of randomisation until disease progression (assessed per IWCLL 2018 criteria) or death from any cause, whichever occurred first. PFS was planned to be calculated as date of first disease progression or death (censoring date for censored subjects) - randomisation date + 1.

The primary efficacy analysis was planned to be performed on the FAS to compare IRC-assessed PFS between Arms A (AV) and C (FCR/BR) using a stratified 2-sided log rank test and a method that corresponds to the Breslow approach for handling ties (Breslow, 1974). The estimate of the hazard ratio (HR) and its corresponding 95% CI was planned to be computed using a stratified Cox proportional hazards model with Efron's method for ties and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach.

The four randomisation stratification factors were planned to be used for the stratified analyses: age (>65 or ≤65), immunoglobulin heavy-chain variable region gene (IGHV) mutational status (mutated versus unmutated), Rai stage (high risk [≥3] versus non-high risk [<3]), and geographic region (North America versus Europe versus Other).

If there was at least one stratum that had fewer than two events in either treatment arm or fewer than 10 events across both treatment arms (where a stratum was defined as stratification factor 1 * stratification factor 2 * stratification factor 3 * stratification factor 4), stratification factors would be collapsed until all strata had at minimum two events per treatment arm and 10 events across both treatment arms for the primary endpoint. More details regarding the order in which the stratification factors were planned to be collapsed in the following order: 1. Geographic region (North America versus Europe versus Other) 2. Age (>65 or ≤65) 3. Rai stage (high risk [≥3] versus non-high risk.

The distribution of IRC-assessed PFS was planned to be summarized for each treatment arm using median and its corresponding 95% CI based on Kaplan-Meier (KM) estimates and the Brookmeyer-Crowley method for the CI. The proportion of subjects who were progression free and associated 95% CI would be estimated based on KM method at selected timepoints by treatment arm.

Analyses of secondary endpoints

The same analysis method was planned to be used when analysing key secondary endpoint PFS compared between Arms B and C, where PFS was assessed by IRC review per IWCLL 2018 criteria.

Timing of Interim and final analysis

According to Protocol version 7 and latest version of the SAP, one interim analysis would be conducted to assess early efficacy of Arm A (AV) versus Arm C (FCR/BR) with respect to the primary efficacy endpoint, IRC-assessed PFS. The interim analysis would occur when approximately 141 IRC-assessed PFS events (75% of the 188 events required for final analysis) in Arm A (AV) and Arm C (FCR/BR) combined had been observed. The interim analysis was anticipated to occur approximately 40 months after the first subject had been randomised (i.e., 14 months after the last subject had been randomised).

The final analysis would be conducted when approximately 188 IRC-assessed PFS events in Arm A (AV) and Arm C (FCR/BR) combined had been observed. The final analysis was anticipated to occur approximately 52 months after the first subject was randomised (i.e., 26 months after the last subject was randomised).

The crossing boundaries (nominal alpha levels) for the event-driven interim analysis and final analysis for IRC-assessed PFS were 0.019 and 0.044, respectively. The actual crossing boundaries (nominal alpha levels) for the interim and final analyses would be determined based on the actual number of IRC-assessed PFS events observed at the time of data cutoff.

If the criterion for early efficacy was met at the time of the interim analysis, the DMC could recommend stopping the study in accordance with the terms of the DMC charter. At the time of the final analysis for PFS, an interim futility analysis for OS s planned be performed to exclude harm and support the risk-benefit determination. OS is planned to be tested for futility using a non-binding boundary and control for Type I error rate at a 2-sided 0.05 level.

Multiplicity

For both the interim and final analyses, if the primary endpoint achieved statistical significance, then secondary endpoints (selected secondary endpoints for the interim analysis) were planned to be tested in a manner that would preserve the overall Type I error rate at the 2-sided significance level of 0.05.

To control the overall Type I error, the Lan-DeMets alpha-spending function based on the O'Brien-Fleming boundaries was planned to be used to split α into α1 and α2 for interim and final analyses of IRC-assessed PFS, respectively.

An alpha-exhaustive recycling strategy (Burman et al 2009) was planned to be utilized to adjust for multiplicity due to multiple endpoints.

If the primary efficacy endpoint, IRC-assessed PFS in Arm A (AV) versus Arm C (FCR/BR), achieved statistical significance at either the PFS IA or PFS FA, then the 5% alpha would be recycled to test the following secondary efficacy endpoints in a fixed sequential hierarchical manner:

1. PFS as assessed by IRC between Arms B (AVG) and C (FCR/BR)
2. MRD negativity rate measured in the peripheral blood by flow cytometry (10^{-4}) between Arm A (AV) at Cycle 9 and Arm C (FCR/BR) at 12 weeks after the start of Cycle 6
3. MRD negativity rate measured in the peripheral blood by flow cytometry (10^{-4}) between Arm B (AVG) at Cycle 10 and Arm C (FCR/BR) at 12 weeks after the start of Cycle 6
4. OS between Arms A (AV) and C (FCR/BR)
5. OS between Arms B (AVG) and C (FCR/BR)

The hypotheses were planned to be tested using alpha (test mass) recycling, where the test mass that becomes available after each rejected hypothesis is recycled to the secondary hypotheses not yet rejected. This testing procedure stops when the entire test mass is allocated to non-rejected hypotheses.

If the testing procedure stops, the p-value for subsequent tests would be presented as descriptive. If the primary efficacy endpoint, IRC-assessed PFS in Arms A (AV) versus C (FCR/BR), does not cross boundary at the interim analysis, the trial was planned to continue, and the final analysis would be conducted.

Censoring rules and handling of missing data

Subjects who withdrew from the study or were considered lost to follow-up without prior

documentation of disease progression were planned to be censored on the date of the last adequate response assessment.

Subjects who started new anticancer therapy would be censored on the date of the last response assessment before start of subsequent anti-CLL therapy.

Subjects who had 2 or more consecutively missed response assessments (without PD or death prior), regardless of whether there is a PD or death afterward would be censored at date of last response assessment before 2 or more consecutively missed response assessments.

For subjects without an adequate post-baseline disease assessment, PFS would be censored on the date of randomisation.

Sensitivity analyses

According to the SAP, the following sensitivity analyses were planned to be performed for primary endpoint PFS as assessed by IRC between Arms A versus C and Arms B versus C in support of primary and key secondary efficacy analyses:

- Unstratified analysis
- The PFS was planned to be analysed as the time from date of randomization to the date of first disease progression or death due to any cause, whichever came first, regardless of the use of subsequent anticancer therapy, i.e., subjects would not be censored at the last adequate disease assessment prior to the subsequent anticancer therapy. If a subject had neither PD nor death after the initiation of subsequent anticancer therapy prior to data cutoff, the subject would be censored at the last adequate disease assessment prior to data cutoff regardless of initiation of subsequent anticancer therapy.
- Subjects with PFS events after 2 or more consecutively missed visits would not be censored at the last adequate assessment. In particular, PD or death after 2 or more consecutively missed visits will be included as a PFS event.
- To assess for the potential impact of Coronavirus disease 2019 (COVID-19) deaths on PFS, subjects with death related to COVID-19 infection (and without progression prior to death) were planned to be censored at their last evaluable assessment prior to their COVID-19 related death date.
- If >10% of subjects had a discrepancy between the randomization stratum as recorded in IxRS versus in EDC/laboratory data, a sensitivity analysis was planned to be performed using the strata per IxRS for stratification.
- Due to the high number of expected deaths due to COVID-19, a sensitivity analysis may be performed on all randomized subjects in the global cohort plus the China extension cohort (note: the primary analysis is performed on the global cohort only; the global cohort includes the approximately 780 subjects randomized globally.
- If >10% of subjects in any treatment group did not receive any randomised therapy, a "deviation bias" sensitivity analysis may be performed based on the per-protocol population, defined in Section 2.1 in the SAP.

Subgroup analyses

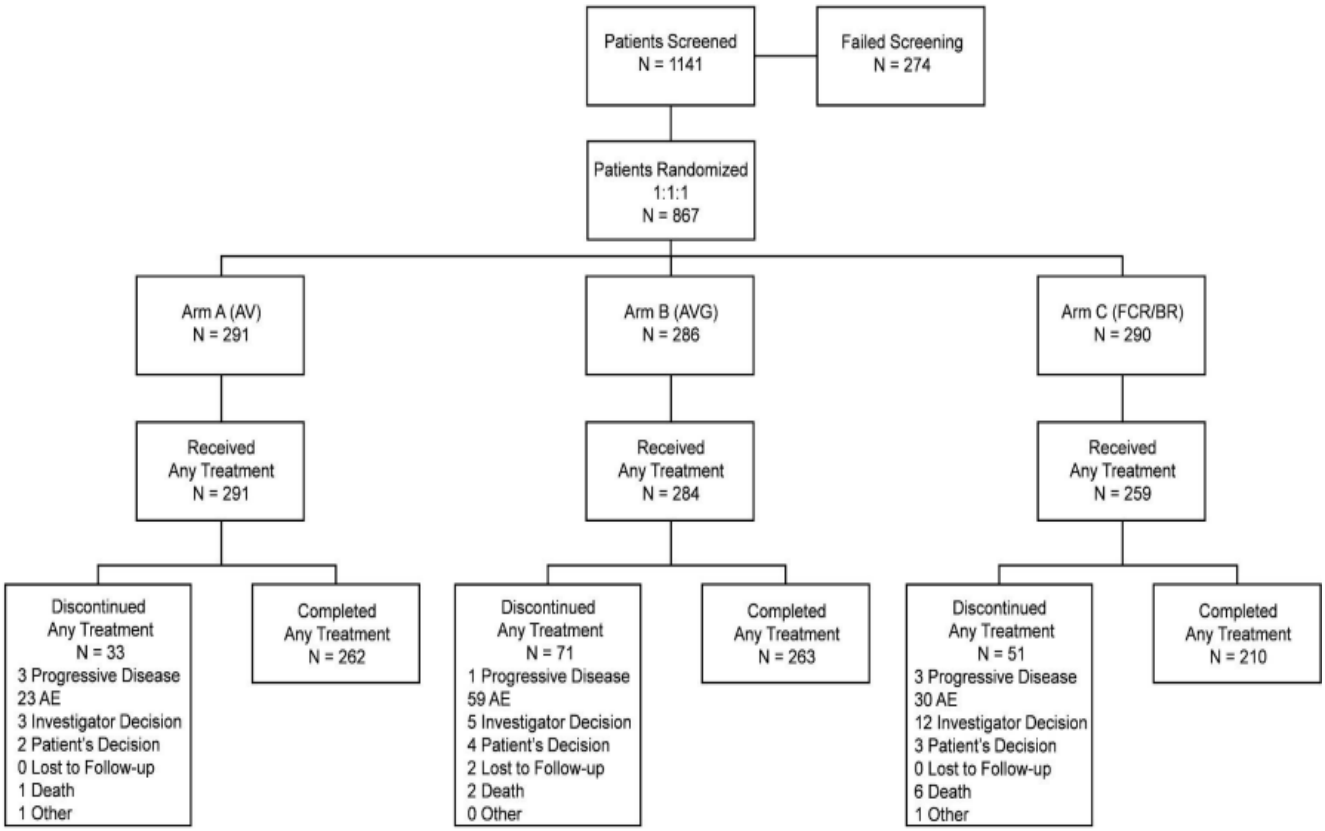
Subgroup analyses were planned to be performed using potential prognostic variables at screening or baseline listed below to investigate the consistency and robustness of PFS as assessed by IRC between Arms A versus C and Arms B versus C:

- Randomisation stratification factors per EDC/lab data recording. Randomisation stratification factors as presented in the randomisation section.
- Sex (male versus female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino) · ECOG Performance Status (2, ≤1)
- Complex karyotype (yes, no)
- CD38 expression (yes, no)
- ZAP-70 expression (yes, no)
- 11q deletion mutation (yes, no)

No adjustment to the significance level for testing was planned to be made since all the subgroup analyses were to be considered exploratory and may only be supportive of the primary analysis of PFS.

Results

Participant flow



Recruitment

First patient enrolled: 25 February 2019.

Last patient was randomised: 21 September 2023.

The clinical cut-off date for presented data was 30 April 2024.

Conduct of the study

Seven protocol amendments were done during the study and amendments 1, 5 and 6 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.

- **Amendment 1, Version 2.0, 11 July 2019**

  The protocol was amended to change the treatment duration for acalabrutinib to 14 cycles and venetoclax to 12 cycles. This amendment was introduced to address the evolving treatment landscape for CLL, which is moving towards a fixed duration treatment regimen as opposed to the current treatment paradigm of BTKi treatment to progression. Continued treatment is thought to lead to selection for resistant clones and result in disease progression.

  Ongoing studies of BTKi in combination with venetoclax have shown high complete response rates and MRD negativity in contrast to BTKi monotherapy. In view of such deep responses, it is unclear if continuing BTKi therapy beyond completion of combination treatment will yield incremental benefit, acalabrutinib treatment will be completed at the same time as venetoclax.

Required bone marrow biopsies were reduced to two time points as a result of the shortened combination treatment duration. These will occur at Cycle 9/10 to allow for comparison to the control Arm and at 12 weeks after completion of the experimental combination treatments.

- **Amendment 5.0 Version 6.0/ 22 March 2023**

  The protocol was amended to extend the timeframe to detect both early and late onset mechanisms for resistance.

- **Amendment 6.0, Version 7.0, 12 October 2023**

  The primary rationale for this protocol amendment was to include a change to the hazard ratio for the primary endpoint, IRC-assessed PFS of Arm A (AV) versus Arm C (FCR/BR). The PFS hazard ratio was changed from 0.65 to 0.62 based on the results of the GAIA-CLL13 interim analysis and accounting for the high proportion of deaths due to COVID-19 (at least 24% and 18% of PFS events in 3 arms combined at interim and final analysis, respectively) observed in this study. As such, the interim analysis will occur when 141 IRC-assessed PFS events in Arms A (AV) and C (FCR/BR) have been observed, and the final analysis will be conducted when approximately 188 IRC-assessed PFS events in Arm A (AV) and Arm C (FCR/BR) have been observed.

  A futility analysis for OS was added at the time of the final analysis for the primary endpoint.

Protocol deviations

Table 6. Summary of Important Protocol Deviations (FAS), study ACE-CL-311

	Arm A (AV) (N = 291) n (%)	Arm B (AVG) (N = 286) n (%)	Arm C (FCR/BR) (N = 290) n (%)	Total (N = 867) n (%)
Patients with at least one important protocol deviation	66 (22.7)	49 (17.1)	72 (24.8)	187 (21.6)
Inclusion criteria	3 (1.0)	0	1 (0.3)	4 (0.5)
Exclusion criteria	7 (2.4)	3 (1.0)	5 (1.7)	15 (1.7)
Investigational product deviation	4 (1.4)	5 (1.7)	16 (5.5)	25 (2.9)
Excluded medications taken	1 (0.3)	4 (1.4)	2 (0.7)	7 (0.8)
Deviations related to study procedure	11 (3.8)	17 (5.9)	17 (5.9)	45 (5.2)
Other important protocol deviations	42 (14.4)	23 (8.0)	37 (12.8)	102 (11.8)
Patients with at least one important protocol deviation related to COVID-19	0	2 (0.7)	1 (0.3)	3 (0.3)
Investigational product deviation	0	1 (0.3)	1 (0.3)	2 (0.2)
Deviations related to study procedure	0	1 (0.3)	0	1 (0.1)

The important protocol deviations category "Other" included deviations related to informed consent not obtained properly, and incorrect stratification of patients.

Baseline data

Table 7. Demographic Characteristics (FAS), study ACE-CL-311

	Arm A (AV) (N = 291)	Arm B (AVG) (N= 286)	Arm C (FCR/BR) (N = 290)	Total (N = 867)
Age (years)				
Mean (SD)	59.9 (9.4)	60.1 (9.5)	59.8 (9.7)	59.9 (9.5)
Median	61.0	61.0	61.0	61.0
Min, Max	31, 84	29, 81	26, 86	26, 86

	Arm A (AV) (N = 291)	Arm B (AVG) (N= 286)	Arm C (FCR/BR) (N = 290)	Total (N = 867)
Age group, n (%)				
≤ 65	212 (72.9)	210 (73.4)	213 (73.4)	635 (73.2)
> 65	79 (27.1)	76 (26.6)	77 (26.6)	232 (26.8)
≤ 75	282 (96.9)	274 (95.8)	280 (96.6)	836 (96.4)
> 75	9 (3.1)	12 (4.2)	10 (3.4)	31 (3.6)
Sex, n (%)				
Male	178 (61.2)	198 (69.2)	183 (63.1)	559 (64.5)
Female	113 (38.8)	88 (30.8)	107 (36.9)	308 (35.5)
Race, n (%)				
American Indian or Alaska Native	1 (0.3)	0	1 (0.3)	2 (0.2)
Asian	4 (1.4)	9 (3.1)	18 (6.2)	31 (3.6)
Black or African American	3 (1.0)	11 (3.8)	7 (2.4)	21 (2.4)
Native Hawaiian or Other Pacific Islander	0	0	2 (0.7)	2 (0.2)
White	265 (91.1)	248 (86.7)	252 (86.9)	765 (88.2)
Multiple	0	2 (0.7)	0	2 (0.2)
Not reported	18 (6.2)	16 (5.6)	10 (3.4)	44 (5.1)
Ethnicity, n (%)				
Hispanic or Latino	21 (7.2)	15 (5.2)	19 (6.6)	55 (6.3)
Not Hispanic or Latino	246 (84.5)	250 (87.4)	256 (88.3)	752 (86.7)
Not reported	24 (8.2)	21 (7.3)	15 (5.2)	60 (6.9)

Table 8. Baseline disease characteristics (FAS), study ACE-CL-311

	Arm A (AV) (N = 291)	Arm B (AVG) (N =286)	Arm C (FCR/BR) (N = 290)	Total (N = 867)
ECOG performance status, n (%)				
≤ 1	262 (90.0)	272 (95.1)	262 (90.3)	796 (91.8)
2	28 (9.6)	14 (4.9)	26 (9.0)	68 (7.8)
Missing	1 (0.3)	0	2 (0.7)	3 (0.3)
Time from initial diagnosis to randomisation (months)				
Mean (SD)	42.58 (43.09)	41.76 (46.89)	41.67 (46.97)	42.00 (45.63)
Median	28.52	26.10	29.55	27.53
Min, Max	0.8,236.9	0.6,234.7	0.5,317.1	0.5,317.1
Bulky disease, n (%)				

	Arm A (AV) (N = 291)	Arm B (AVG) (N =286)	Arm C (FCR/BR) (N = 290)	Total (N = 867)
< 5 cm	178 (61.2)	186 (65.0)	166 (57.2)	530 (61.1)
≥ 5 cm	113 (38.8)	100 (35.0)	124 (42.8)	337 (38.9)
< 10 cm	271 (93.1)	267 (93.4)	269 (92.8)	807 (93.1)
≥ 10 cm	20 (6.9)	19 (6.6)	21 (7.2)	60 (6.9)
CIRS-G total score				
Mean (SD)	2.7 (2.1)	2.8 (2.1)	2.7 (2.0)	2.7 (2.0)
Median	2.0	3.0	2.0	2.0
Min, Max	0,9	0,17	0,8	0,17
CIRS-G total score category, n (%)				
0	48 (16.5)	44 (15.4)	52 (17.9)	144 (16.6)
1-6	237 (81.4)	241 (84.3)	235 (81.0)	713 (82.2)
> 6	6 (2.1)	1 (0.3)	3 (1.0)	10 (1.2)
CIRS3+a, n (%)				
Yes	24 (8.2)	24 (8.4)	26 (9.0)	74 (8.5)
No	267 (91.8)	262 (91.6)	264 (91.0)	793 (91.5)
CIRS-G category by age group b, n (%)				
Age group ≤ 65 years, n	212	210	213	635
≤ 6	208 (98.1)	210 (100)	212 (99.5)	630 (99.2)
> 6	4 (1.9)	0	1 (0.5)	5 (0.8)
Age group > 65 years, n	79	76	77	232
≤ 6	77 (97.5)	75 (98.7)	75 (97.4)	227 (97.8)
> 6	2 (2.5)	1 (1.3)	2 (2.6)	5 (2.2)
Age group ≤ 75 years, n	282	274	280	836
≤ 6	276 (97.9)	273 (99.6)	278 (99.3)	827 (98.9)
> 6	6 (2.1)	1 (0.4)	2 (0.7)	9 (1.1)
Age group > 75 years, n	9	12	10	31
≤ 6	9 (100)	12 (100)	9 (90.0)	30 (96.8)
> 6	0	0	1 (10.0)	1 (3.2)
Rai stage, n (%)				
0	3 (1.0)	1 (0.3)	4 (1.4)	8 (0.9)
I	47 (16.2)	61 (21.3)	62 (21.4)	170 (19.6)
II	104 (35.7)	108 (37.8)	97 (33.4)	309 (35.6)
III	69 (23.7)	51 (17.8)	59 (20.3)	179 (20.6)
IV	68 (23.4)	65 (22.7)	68 (23.4)	201 (23.2)
11q deletion mutation, n (%)				
Yes	51 (17.5)	56 (19.6)	46 (15.9)	153 (17.6)

	Arm A (AV) (N = 291)	Arm B (AVG) (N =286)	Arm C (FCR/BR) (N = 290)	Total (N = 867)
No	238 (81.8)	230 (80.4)	242 (83.4)	710 (81.9)
Missing	2 (0.7)	0	2 (0.7)	4 (0.5)
IGHV mutation, n (%)				
Mutated	124 (42.6)	117 (40.9)	118 (40.7)	359 (41.4)
Unmutated	167 (57.4)	169 (59.1)	172 (59.3)	508 (58.6)
Complex karyotype, n (%)				
Yes	45 (15.5)	46 (16.1)	42 (14.5)	133 (15.3)
Low (3 aberrations)	21 (7.2)	14 (4.9)	22 (7.6)	57 (6.6)
Medium (4 aberrations)	11 (3.8)	11 (3.8)	7 (2.4)	29 (3.3)
High (≥ 5 aberrations)	13 (4.5)	21 (7.3)	13 (4.5)	47 (5.4)
No	230 (79.0)	223 (78.0)	217 (74.8)	670 (77.3)
Missing	16 (5.5)	17 (5.9)	31 (10.7)	64 (7.4)
CD38 expression, n (%)				
Yes	67 (23.0)	70 (24.5)	60 (20.7)	197 (22.7)
No	123 (42.3)	116 (40.6)	132 (45.5)	371 (42.8)
Missing	101 (34.7)	100 (35.0)	98 (33.8)	299 (34.5)
Zap-70 expression, n (%)				
Yes	95 (32.6)	92 (32.2)	89 (30.7)	276 (31.8)
No	95 (32.6)	93 (32.5)	102 (35.2)	290 (33.4)
Missing	101 (34.7)	101 (35.3)	99 (34.1)	301 (34.7)
B2-microglobulin (mg/L), n (%)				
≤ 3.5	103 (35.4)	122 (42.7)	107 (36.9)	332 (38.3)
> 3.5	169 (58.1)	151 (52.8)	143 (49.3)	463 (53.4)
Missing	19 (6.5)	13 (4.5)	40 (13.8)	72 (8.3)
Creatine clearance < 60 mL/min, n (%)				
Yes	38 (13.1)	39 (13.6)	30 (10.3)	107 (12.3)
No	253 (86.9)	245 (85.7)	260 (89.7)	758 (87.4)
Missing	0	2 (0.7)	0	2 (0.2)
Cytopenia, n (%)				
Neutropenia – ANC ≤ $1.5x10^9$/L				
Yes	20 (6.9)	25 (8.7)	20 (6.9)	65 (7.5)
No	271 (93.1)	261 (91.3)	269 (92.8)	801 (92.4)
Missing	0	0	1 (0.3)	1 (0.1)
Anaemia – haemoglobin < 11 g/dL				

	Arm A (AV) (N = 291)	Arm B (AVG) (N =286)	Arm C (FCR/BR) (N = 290)	Total (N = 867)
Yes	103 (35.4)	85 (29.7)	94 (32.4)	282 (32.5)
No	188 (64.6)	201 (70.3)	195 (67.2)	584 (67.4)
Missing	0	0	1 (0.3)	1 (0.1)
Thrombocytopenia – platelets < $100x10^9$/L				
Yes	66 (22.7)	68 (23.8)	58 (20.0)	192 (22.1)
No	225 (77.3)	218 (76.2)	231 (79.7)	674 (77.7)
Missing	0	0	1 (0.3)	1 (0.1)
All of the above	5 (1.7)	7 (2.4)	6 (2.1)	18 (2.1)
Any of the above	148 (50.9)	128 (44.8)	130 (44.8)	406 (46.8)
Prior red blood cell transfusion in 28 days prior to randomisation, n (%)				
Yes	7 (2.4)	3 (1.0)	4 (1.4)	14 (1.6)
No	284 (97.6)	283 (99.0)	286 (98.6)	853 (98.4)
Prior platelet transfusion in 28 days prior to randomization, n (%)				
Yes	1 (0.3)	0	0	1 (0.1)
No	290 (99.7)	286 (100)	290 (100)	866 (99.9)
B-symptoms, n (%)				
Weight loss	37 (12.7)	22 (7.7)	22 (7.6)	81 (9.3)
Fever	3 (1.0)	4 (1.4)	4 (1.4)	11 (1.3)
Night sweats	122 (41.9)	119 (41.6)	120 (41.4)	361 (41.6)
All of the above	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.3)
Any of the above	131 (45.0)	125 (43.7)	129 (44.5)	385 (44.4)
ALC (10^9/L)				
Mean (SD)	94.503 (78.514)	86.905 (83.669)	93.191 (89.445)	91.556 (83.952)
Median	71.920	66.285	70.640	70.366
Min, Max	1.09,397.08	1.63,553.39	1.11,556.11	1.09,556.11
ANC (10^9/L)				
Mean (SD)	5.204 (3.165)	5.647 (9.268)	5.408 (4.136)	5.418 (6.115)
Median	4.520	4.645	4.390	4.535
Min, Max	0.00,18.48	0.10,152.80	0.00,40.11	0.00,152.80
Platelets (10^9/L)				
Mean (SD)	149.4 (67.7)	150.8 (65.0)	154.6 (69.4)	151.6 (67.4)
Median	140.0	142.5	146.0	143.0

	Arm A (AV) (N = 291)	Arm B (AVG) (N =286)	Arm C (FCR/BR) (N = 290)	Total (N = 867)
Min, Max	22,546	37,482	9,698	9,698
Haemoglobin (g/dL)				
Mean (SD)	11.70 (2.08)	12.16 (2.09)	11.85 (2.12)	11.90 (2.10)
Median	11.80	12.40	11.90	12.00
Min, Max	5.8,16.5	5.8,17.0	5.9,17.3	5.8,17.3
Current smoker, n (%)				
Yes	33 (11.3)	27 (9.4)	31 (10.7)	91 (10.5)
No	68 (23.4)	72 (25.2)	75 (25.9)	215 (24.8)
Never smoked	180 (61.9)	174 (60.8)	175 (60.3)	529 (61.0)
Missing	10 (3.4)	13 (4.5)	9 (3.1)	32 (3.7)

a. CIRS3+ is defined as CIRS-G score of 3 or 4 in any single organ system.
b. Percentages are based on the number of patients in the age group.

Numbers analysed

Table 9. Description of analysis sets, study ACE-CL-311

Analysis Set	
Full Analysis Set (FAS)	All randomized patients regardless of the treatment actually received. Patients were analysed according to the Arm to which they were randomised, following the 'intent-to-treat' principle. FAS was the primary analysis set used for all efficacy analyses. Additionally, demographic and patient characteristics were summarised among the FAS.
Safety Population	All randomised patients who received any amount of study drug. Safety data were summarised using the Safety Population, according to the actual treatment that a patient received.
PK Evaluable Population	All patients who received acalabrutinib or venetoclax with an evaluable post-dose PK value were included in the PK evaluable population.
Per-protocol Population	All patients in the FAS with exclusion of patients meeting at least one specific criterion or IPD that may have affected the efficacy of the trial therapy, as defined below: • Either did not take or discontinued early from at least one randomised treatment. • Less than 75% RDI for any randomised treatment. • Violated protocol inclusion or exclusion criteria that may affect interpretation of efficacy • At least one important protocol deviation in category 6 (excluded medications taken).

Outcomes and estimation

All results presented in this section are based on the data cut-off date of 30 April 2024 unless otherwise specified.

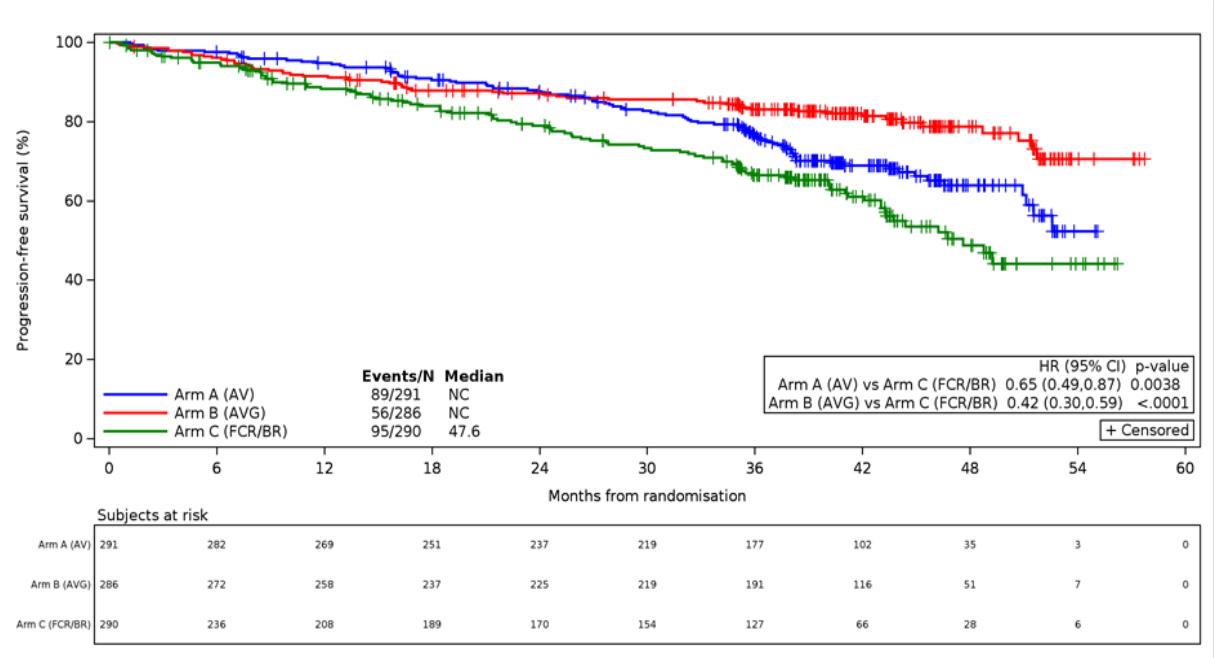
Primary endpoint: PFS (Arm A vs Arm C)

Table 10. Progression-free Survival by Blinded Independent Central Review (FAS), study ACE-CL-311

	Arm A (AV) (N = 291)	**Arm C (FCR/BR) (N = 290)**
Event[a]		
Any	89 (30.6)	95 (32.8)
Progression	77 (26.5)	66 (22.8)
Death without progression	12 (4.1)	29 (10.0)
Censored observations		
Any	202 (69.4)	195 (67.2)
Censored at Day 1	1 (0.3)	33 (11.4)
No baseline disease assessment	0	1 (0.3)
No post-baseline response assessment	1 (0.3)	32 (11.0)
Censored due to 2 or more consecutively missed response assessments[b]	20 (6.9)	31 (10.7)
Censored due to subsequent anti-CLL therapy	2 (0.7)	5 (1.7)
Progression-free	179 (61.5)	126 (43.4)
Progression-free at time of the analysis	178 (61.2)	120 (41.4)
Early study discontinuation	1 (0.3)	6 (2.1)
Lost to follow-up	0	0
Withdrew consent	1 (0.3)	4 (1.4)
Study exit due to investigator decision or other	0	2 (0.7)
PFS, months		
Median (95% CI)	NC (51.1, NC)	47.6 (43.3, NC)
P25, P75	36.8, NC	27.7, NC
Comparison of treatment groups		
Hazard ratio (95% CI)	0.65 (0.49, 0.87)	
p-value	0.0038	
Progression free survival rate[d] (%)		
12 months (95% CI)	94.8 (91.5, 96.8)	88.3 (83.6, 91.7)
24 months (95% CI)	87.6 (83.1, 90.9)	79.0 (73.2, 83.6)
36 months (95% CI)	76.5 (71.0, 81.1)	66.5 (59.8, 72.3)
48 months (95% CI)	63.9 (56.6, 70.3)	48.8 (39.5, 57.4)

a. Includes events that occur within 28 weeks of last evaluable assessment (in the first 3 years after randomisation) or within 56 weeks of last evaluable assessment (3 years and later from randomisation).
b. The threshold for 2 or more consecutively missed response assessments is 28 weeks in the first 3 years after randomisation and 56 weeks thereafter.

Figure 7. Kaplan-Meier Plot for Progression-free Survival by Blinded Independent Central Review (FAS), study ACE-CL-311



Sensitivity analyses

Table 11. Progression-free Survival by Blinded Independent Central Review - Sensitivity Analysis (FAS), study ACE-CL-311

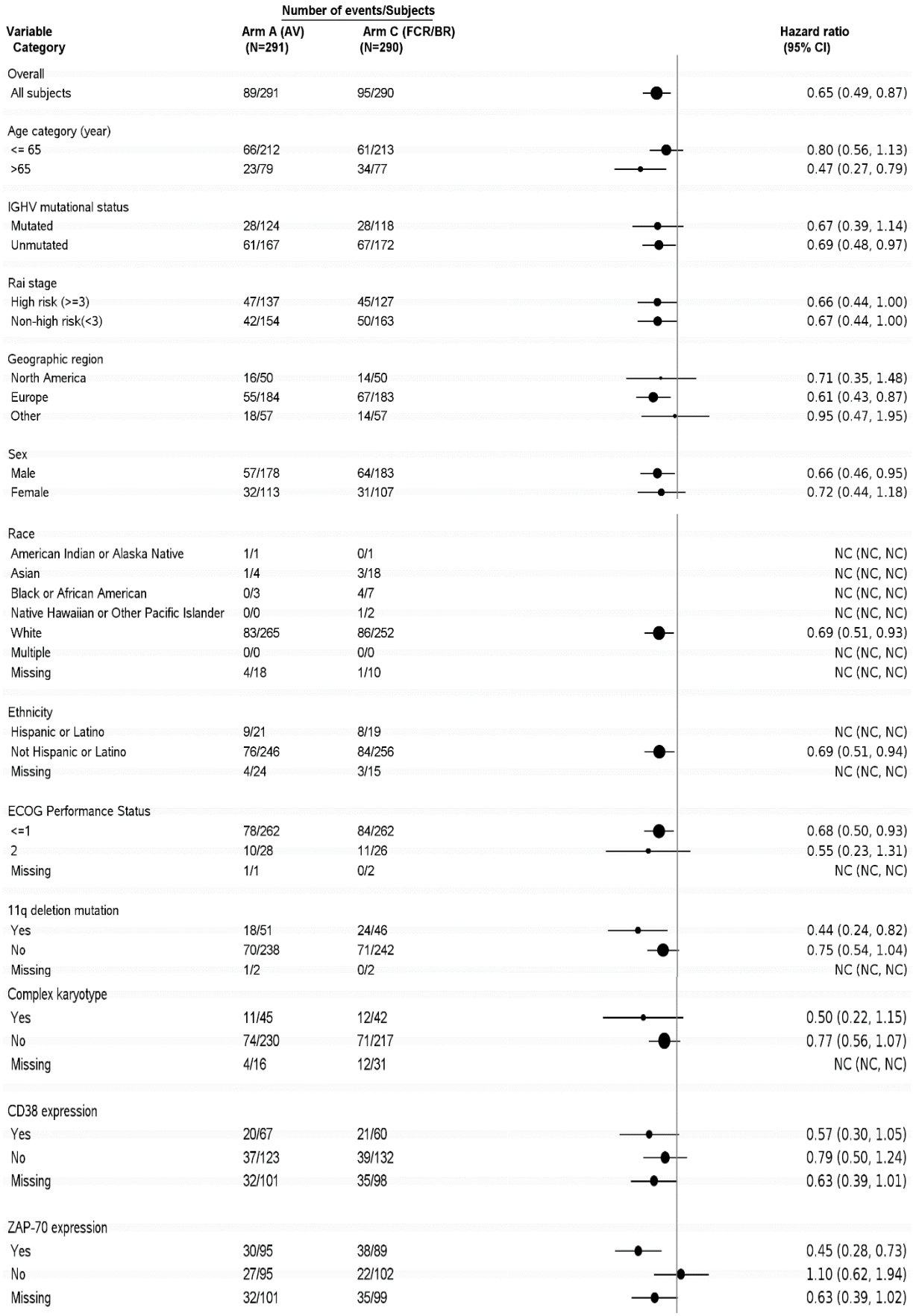
	Group	Patients with event n (%)	Median time to event (months)	95% CI	Comparison of treatment groups		
					HR	95% CI	p-value
Unstratified analysis	Arm A (AV) N = 291	89 (30.6)	NC	51.1, NC	0.68	0.51, 0.91	0.0080
	Arm B (AVG) N = 286	56 (19.6)	NC	NC, NC	0.43	0.30, 0.59	< 0.0001
	Arm C (FCR/BR) N = 290	95 (32.8)	47.6	43.3, NC			
Not censoring due to subsequent anticancer therapy	Arm A (AV) N = 291	91 (31.3)	NC	51.1, NC	0.66	0.50, 0.89	0.0054
	Arm B (AVG) N = 286	56 (19.6)	NC	NC, NC	0.42	0.30, 0.59	< 0.0001
	Arm C (FCR/BR) N = 290	95 (32.8)	47.6	43.3, NC			

	Group	Patients with event n (%)	Median time to event (months)	95% CI	Comparison of treatment groups		
					HR	95% CI	p-value
Not censoring due to 2 or more consecutively response assessments	Arm A (AV) N = 291	93 (32.0)	NC	51.5, NC	0.67	0.50, 0.89	0.0054
	Arm B (AVG) N = 286	60 (21.0)	NC	54.6, NC	0.45	0.32, 0.62	< 0.0001
	Arm C (FCR/BR) N = 290	99 (34.1)	48.8	43.3, NC			
Stratification according to IxRS	Arm A (AV) N = 291	89 (30.6)	NC	51.1, NC	0.66	0.49, 0.88	0.0051
	Arm B (AVG) N = 286	56 (19.6)	NC	NC, NC	0.41	0.29, 0.57	< 0.0001
	Arm C (FCR/BR) N = 290	95 (32.8)	47.6	43.3, NC			
Per-protocol Population	Arm A (AV) N = 239	66 (27.6)	NC	51.5, NC	0.63	0.45, 0.88	0.0071
	Arm B (AVG) N = 186	24 (12.9)	NC	NC, NC	0.27	0.17, 0.43	< 0.0001
	Arm C (FCR/BR) N = 199	71 (35.7)	48.8	43.7, NC			
Censoring COVID-19 Deaths	Arm A (AV) N = 291	81 (27.8)	NC	51.5, NC	0.71	0.52, 0.98	0.0356
	Arm B (AVG) N = 286	31 (10.8)	NC	NC, NC	0.26	0.17, 0.39	< 0.0001
	Arm C (FCR/BR) N = 290	77 (26.6)	49.2	44.4, NC			

A HR below 1 favours Arm A or Arm B over Arm C, respectively.
The p-value is based on the stratified log-rank test and the HR is based on the stratified Cox proportional hazards model, except for in the "unstratified" analysis.

Subgroup analysis

Figure 8. Forest Plot for Subgroup Analysis of Progression-Free Survival by Blinded Independent Central Review: Arm A (AV) and Arm C (FCR/BR) (FAS), study ACE-CL-311


Number of events/Subjects
Variable Category
Arm A (AV) (N=291)
Arm C (FCR/BR) (N=290)
Hazard ratio (95% CI)
Overall
All subjects 89/291 95/290 0.65 (0.49, 0.87)
Age category (year)
<= 65 66/212 61/213 0.80 (0.56, 1.13)
>65 23/79 34/77 0.47 (0.27, 0.79)
IGHV mutational status
Mutated 28/124 28/118 0.67 (0.39, 1.14)
Unmutated 61/167 67/172 0.69 (0.48, 0.97)
Rai stage
High risk (>=3) 47/137 45/127 0.66 (0.44, 1.00)
Non-high risk(<3) 42/154 50/163 0.67 (0.44, 1.00)
Geographic region
North America 16/50 14/50 0.71 (0.35, 1.48)
Europe 55/184 67/183 0.61 (0.43, 0.87)
Other 18/57 14/57 0.95 (0.47, 1.95)
Sex
Male 57/178 64/183 0.66 (0.46, 0.95)
Female 32/113 31/107 0.72 (0.44, 1.18)
Race
American Indian or Alaska Native 1/1 0/1 NC (NC, NC)
Asian 1/4 3/18 NC (NC, NC)
Black or African American 0/3 4/7 NC (NC, NC)
Native Hawaiian or Other Pacific Islander 0/0 1/2 NC (NC, NC)
White 83/265 86/252 0.69 (0.51, 0.93)
Multiple 0/0 0/0 NC (NC, NC)
Missing 4/18 1/10 NC (NC, NC)
Ethnicity
Hispanic or Latino 9/21 8/19 NC (NC, NC)
Not Hispanic or Latino 76/246 84/256 0.69 (0.51, 0.94)
Missing 4/24 3/15 NC (NC, NC)
ECOG Performance Status
<=1 78/262 84/262 0.68 (0.50, 0.93)
2 10/28 11/26 0.55 (0.23, 1.31)
Missing 1/1 0/2 NC (NC, NC)
11q deletion mutation
Yes 18/51 24/46 0.44 (0.24, 0.82)
No 70/238 71/242 0.75 (0.54, 1.04)
Missing 1/2 0/2 NC (NC, NC)
Complex karyotype
Yes 11/45 12/42 0.50 (0.22, 1.15)
No 74/230 71/217 0.77 (0.56, 1.07)
Missing 4/16 12/31 NC (NC, NC)
CD38 expression
Yes 20/67 21/60 0.57 (0.30, 1.05)
No 37/123 39/132 0.79 (0.50, 1.24)
Missing 32/101 35/98 0.63 (0.39, 1.01)
ZAP-70 expression
Yes 30/95 38/89 0.45 (0.28, 0.73)
No 27/95 22/102 1.10 (0.62, 1.94)
Missing 32/101 35/99 0.63 (0.39, 1.02)

Comparison with FCR only and BR only

Table 12. PFS by IRC: Arm A (AV) and Arm B (AVG) and Arm C (FCR only) (FAS), study ACE-CL-311

	Arm A (AV) (N = 291)	**Arm B (AVG) (N = 286)**	**Arm C (FCR Only) (N = 143)**
Event[a]			
Any	89 (30.6)	56 (19.6)	38 (26.6)
Progression	77 (26.5)	23 (8.0)	23 (16.1)
Death without progression	12 (4.1)	33 (11.5)	15 (10.5)
Censored observations			
Any	202 (69.4)	230 (80.4)	105 (73.4)
Censored at Day 1	1 (0.3)	2 (0.7)	21 (14.7)
No baseline disease assessment	0	1 (0.3)	0
No post-baseline response assessment	1 (0.3)	1 (0.3)	21 (14.7)
Censored due to 2 or more consecutively missed response assessments[b]	20 (6.9)	25 (8.7)	15 (10.5)
Censored due to subsequent anti-CLL therapy	2 (0.7)	2 (0.7)	4 (2.8)
Progression-free[c]	179 (61.5)	201 (70.3)	65 (45.5)
Progression-free at time of the analysis	178 (61.2)	200 (69.9)	62 (43.4)
Early study discontinuation	1 (0.3)	1 (0.3)	3 (2.1)
Lost to follow-up	0	0	0
Withdrew consent	1 (0.3)	1 (0.3)	2 (1.4)
Study exit due to investigator decision or other	0	0	1 (0.7)
PFS, months			
Median (95% CI)	NC (51.1, NC)	NC (NC, NC)	NC (43.0, NC)
P25, P75	36.8, NC	51.4, NC	27.8, NC
Comparison of treatment groups			
Hazard ratio (95% CI)	0.69 (0.47, 1.03)	0.47 (0.31, 0.73)	-
p-value[g]	0.0581	0.0004	-
Progression-free survival rate (%)			
12 months (95% CI)	94.8 (91.5, 96.8)	91.5 (87.6, 94.2)	87.1 (79.5, 92.0)
24 months (95% CI)	87.6 (83.1, 90.9)	87.1 (82.6, 90.5)	79.5 (70.7, 85.9)
36 months (95% CI)	76.5 (71.0, 81.1)	83.1 (78.1, 87.1)	68.9 (59.0, 76.9)
48 months (95% CI)	63.9 (56.6, 70.3)	78.8 (72.7, 83.7)	56.1 (42.3, 67.8)

[a] Includes events that occur within 28 weeks of last evaluable assessment (in the first 3 years after randomization) or within 56 weeks of last evaluable assessment (3 years and later from randomization).
[b] The threshold for 2 or more consecutively missed response assessments is 28 weeks in the first 3 years after randomization and 56 weeks thereafter.

Table 13. PFS by Blinded Independent Central Review: Arm A (AV) and Arm B (AVG) and Arm C (BR only) (FAS)

	Arm A (AV) (N = 291)	**Arm B (AVG) (N = 286)**	**Arm C (BR Only) (N = 147)**
Event[a]			
Any	89 (30.6)	56 (19.6)	57 (38.8)
Progression	77 (26.5)	23 (8.0)	43 (29.3)
Death without progression	12 (4.1)	33 (11.5)	14 (9.5)
Censored observations			
Any	202 (69.4)	230 (80.4)	90 (61.2)
Censored at Day 1	1 (0.3)	2 (0.7)	12 (8.2)
No baseline disease assessment	0	1 (0.3)	1 (0.7)
No post-baseline response assessment	1 (0.3)	1 (0.3)	11 (7.5)
Censored due to 2 or more consecutively missed response assessments[b]	20 (6.9)	25 (8.7)	16 (10.9)
Censored due to subsequent anti-CLL therapy	2 (0.7)	2 (0.7)	1 (0.7)
Progression-free	179 (61.5)	201 (70.3)	61 (41.5)
Progression-free at time of the analysis	178 (61.2)	200 (69.9)	58 (39.5)
Early study discontinuation	1 (0.3)	1 (0.3)	3 (2.0)
Lost to follow-up	0	0	0
Withdrew consent	1 (0.3)	1 (0.3)	2 (1.4)
Study exit due to investigator decision or other	0	0	1 (0.7)
PFS, months			
Median (95% CI)	NC (51.1, NC)	NC (NC, NC)	46.2 (41.0, NC)
P25, P75	36.8, NC	51.4, NC	27.7, NC
Comparison of treatment groups			
Hazard ratio (95% CI)	0.63 (0.45, 0.88)	0.39 (0.27, 0.57)	-
p-value	0.0062	< 0.0001	-
Progression-free rate[d] (%)			
12 months (95% CI)	94.8 (91.5, 96.8)	91.5 (87.6, 94.2)	89.3 (82.7, 93.6)

24 months (95% CI)	87.6 (83.1, 90.9)	87.1 (82.6, 90.5)	78.5 (70.2, 84.8)
36 months (95% CI)	76.5 (71.0, 81.1)	83.1 (78.1, 87.1)	64.5 (55.1, 72.3)
48 months (95% CI)	63.9 (56.6, 70.3)	78.8 (72.7, 83.7)	44.3 (32.4, 55.6)

[a]Includes events that occur within 28 weeks of last evaluable assessment (in the first 3 years after randomization) or within 56 weeks of last evaluable assessment (3 years and later from randomization).
[b]The threshold for 2 or more consecutively missed response assessments is 28 weeks in the first 3 years after randomization and 56 weeks thereafter.

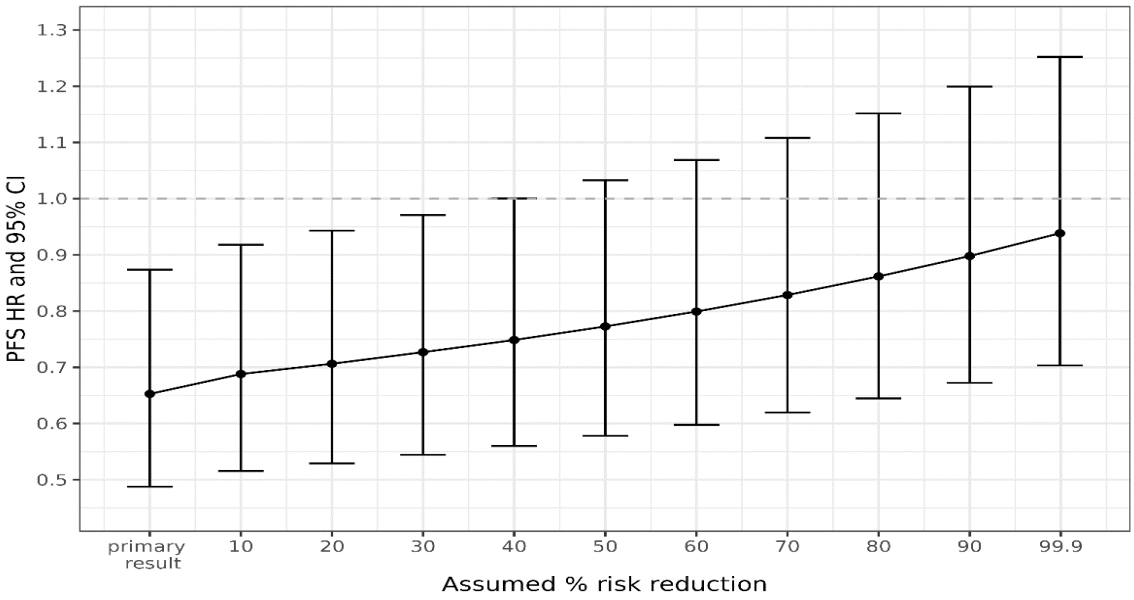
Evaluation of Imbalanced Early Censoring

A tipping point analysis was performed to evaluate the impact of imbalanced early censoring between arms on the PFS by IRC results. In this analysis, the PFS time was imputed for the 75 patients in Arm C (FCR/BR) who were censored informatively, i.e. censored for any reason other than not having an event before the data cutoff date. For the tipping point analysis, it was assumed that these patients had a reduced risk (i.e. reduced hazard rate) compared to all other patients in the arm (i.e. those still in follow-up or who had an event) in Arm C (FCR/BR). A grid search algorithm was used to find the minimal percent reduction of hazard rate needed (in increments of 10%) such that the 95% confidence interval of the hazard ratio would include 1. For each set of imputed PFS data, the Cox model adjusting for the stratification factors was used to generate the logarithm of the hazard ratio and the corresponding standard error. The pooled mean and standard error of the logarithm of the hazard ratio were calculated from 10,000 simulations (assuming an exponential distribution for event time) based on Rubin's rule (Rubin 1987). The estimate and confidence interval for the HR were derived by exponentiating the mean and the corresponding confidence interval of the log (hazard ratio). If the death date was reported, the imputed time was restricted to be shorter than the OS time. Patients who had imputed time after the data cutoff date were censored at the data cutoff date.

Additionally, baseline characteristics of the patients informatively censored vs non-informatively censored were summarised by arm. In Arm C (FCR/BR), a higher proportion of the informatively censored patients compared with the non-informatively censored patients had Rai stage ≥3 (50.7% vs 36.7%), unmutated IGHV (62.7% vs 48.3%), 11q deletion (16.0% vs 8.3%), and anaemia (41.3% vs 25.8%). Otherwise, baseline characteristics appeared to be well-balanced between the patients informatively censored vs non-informatively censored in Arm C (FCR/BR).

For the comparison of Arm A (AV) vs C (FCR/BR), **Figure 9** suggests that the 95% confidence interval of the estimated hazard ratio will include 1 if the 75 patients in Arm C (FCR/BR) were assumed to have at least 40% lower risk of progression or death compared to those still in follow-up or with an event in Arm C (FCR/BR).

Figure 9. Tipping Point Analysis of PFS by IRC in Arm A (AV) vs Arm C (FCR/BR)



PFS (Arm B vs Arm C)

Table 14. Progression-free Survival by Blinded Independent Central Review: Arm B (AVG) and Arm C (FCR/BR) (FAS), study ACE-CL-311

	Arm B (AVG) (N = 286)	**Arm C (FCR/BR) (N = 290)**
Event[a]		
Any	56 (19.6)	95 (32.8)
Progression	23 (8.0)	66 (22.8)
Death without progression	33 (11.5)	29 (10.0)
Censored observations		
Any	230 (80.4)	195 (67.2)
Censored at Day 1	2 (0.7)	33 (11.4)
No baseline disease assessment	1 (0.3)	1 (0.3)
No post-baseline response assessment	1 (0.3)	32 (11.0)
Censored due to 2 or more consecutively missed response assessments[b]	25 (8.7)	31 (10.7)
Censored due to subsequent anti-CLL therapy	2 (0.7)	5 (1.7)
Progression-free	201 (70.3)	126 (43.4)
Progression-free at time of the analysis	200 (69.9)	120 (41.4)
Early study discontinuation	1 (0.3)	6 (2.1)
Lost to follow-up	0	0
Withdrew consent	1 (0.3)	4 (1.4)
Study exit due to investigator decision or other	0	2 (0.7)
PFS, months		

	Arm B (AVG) (N = 286)	Arm C (FCR/BR) (N = 290)
Median (95% CI)	NC (NC, NC)	47.6 (43.3, NC)
P25, P75	51.4, NC	27.7, NC
Comparison of treatment groups		
Hazard ratio (95% CI)	0.42 (0.30, 0.59)	
p-value	< 0.0001	
Progression free survival rate (%)		
12 months (95% CI)	91.5 (87.6, 94.2)	88.3 (83.6, 91.7)
24 months (95% CI)	87.1 (82.6, 90.5)	79.0 (73.2, 83.6)
36 months (95% CI)	83.1 (78.1, 87.1)	66.5 (59.8, 72.3)
48 months (95% CI)	78.8 (72.7, 83.7)	48.8 (39.5, 57.4)

a. Includes events that occur within 28 weeks of last evaluable assessment (in the first 3 years after randomisation) or within 56 weeks of last evaluable assessment (3 years and later from randomisation).
b. The threshold for 2 or more consecutively missed response assessments is 28 weeks in the first 3 years after randomisation and 56 weeks thereafter.

MRD negativity rate

Table 15. Flow Cytometry Minimal Residual Disease in Peripheral Blood (Full Analysis Set), study ACE-CL-311

	Arm A (AV) N = 291	Arm B (AVG) N = 286	Arm C (FCR/BR) N = 290
Patients with MRD measurement[a], n (%)	244 (83.8)	202 (70.6)	190 (65.5)
uMRD[b], n (%)	78 (26.8)	190 (66.4)	148 (51.0)
95% CI	22.0, 32.1	60.8, 71.7	45.3, 56.8
Comparison of treatment groups	0.5 (0.4, 0.7)	1.3 (1.1, 1.5)	-
Risk ratio	0.5	1.3	-
95% CI	0.4, 0.7	1.1, 1.5	-
p-value	< 0.0001	0.0003	-
uMRD and BoR CR/CRi by IRC	*10 (3.4)*	*35 (12.2)*	*11 (3.8)*

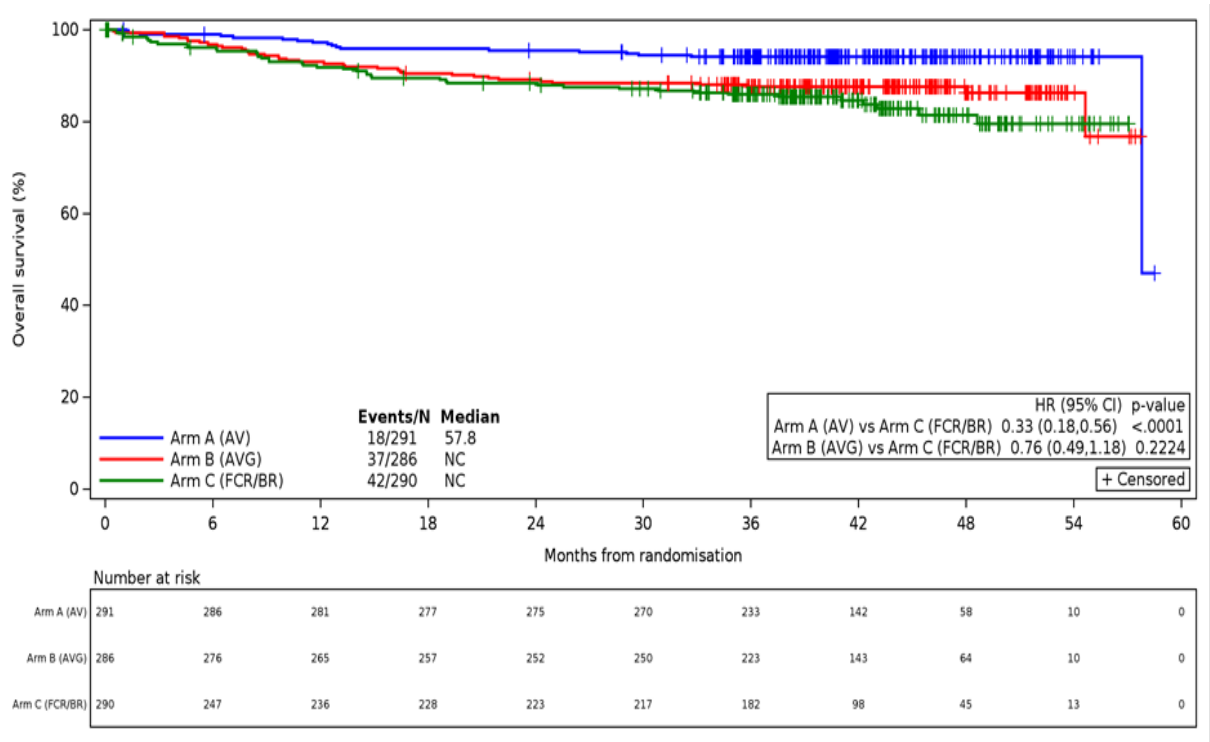
[a] Patients with an MRD measurement at Cycle 9 (Arm A), Cycle 10 (Arm B), or 12 weeks after the start of Cycle 6 (Arm C).
[b]uMRD is defined as < 1 CLL cell per 10,000 (10^{-4}) leukocytes unless otherwise indicated. uMRD is based on Arm A at the start of Cycle 9, Arm B at the start of Cycle 10, and Arm C at 12 weeks after the start of Cycle 6.

Overall Survival

Table 16. Overall Survival (FAS, cut-off date 30 Oct 2024)), study ACE-CL-311

	Arm A (AV) N = 291	**Arm B (AVG) N = 286**	**Arm C (FCR/BR) N = 290**
Event, n (%)			
Death	23 (7.9)	37 (12.9)	44 (15.2)
Censored observations, n (%)			
Any	268 (92.1)	249 (87.1)	246 (84.8)
Still in survival follow up	264 (90.7)	246 (86.0)	217 (74.8)
Early study discontinuation	4 (1.4)	3 (1.0)	29 (10.0)
Lost to follow-up	0	0	0
Withdrew consent	4 (1.4)	1 (0.3)	26 (9.0)
Study exit due to investigator decision or other	0	2 (0.7)	3 (1.0)
Overall survival (months)			
Median (95% CI)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
P25, P75	NC, NC	NC, NC	NC, NC
Comparison of treatment groups			
Hazard ratio (95% CI)	0.42 (0.25, 0.70)	0.75 (0.48, 1.16)	
nominal p-value	0.0006	0.1943	
Overall survival rate [b] (%)			
6 months (95% CI)	99.0 (96.8, 99.7)	96.9 (94.0, 98.4)	96.2 (93.1, 98.0)
12 months (95% CI)	97.2 (94.5, 98.6)	93.0 (89.4, 95.4)	91.7 (87.6, 94.4)
18 months (95% CI)	95.9 (92.8, 97.6)	90.6 (86.5, 93.4)	89.4 (85.0, 92.6)
24 months (95% CI)	95.5 (92.4, 97.4)	89.2 (84.9, 92.2)	88.3 (83.7, 91.6)
30 months (95% CI)	94.5 (91.1, 96.6)	88.5 (84.1, 91.6)	87.1 (82.4, 90.6)
36 months (95% CI)	94.1 (90.7, 96.3)	87.7 (83.4, 91.0)	85.9 (81.1, 89.6)
42 months (95% CI)	93.7 (90.3, 96.0)	87.7 (83.4, 91.0)	85.1 (80.2, 88.9)
48 months (95% CI)	91.9 (87.7, 94.7)	87.1 (82.4, 90.5)	83.4 (78.1, 87.5)
54 months (95% CI)	91.1 (86.4, 94.2)	87.1 (82.4, 90.5)	81.5 (75.5, 86.1)
60 months (95% CI)	87.4 (76.9, 93.4)	85.6 (80.0, 89.8)	81.5 (75.5, 86.1)

Figure 10. Kaplan-Meier Plot for Overall Survival (Full Analysis Set), study ACE-CL-311



Sensitivity analysis

Table 17. Overall Survival Sensitivity Analysis (FAS), study ACE-CL-311

	Group	Patients with event n (%)	Median time to event (months)	95% CI	Comparison of treatment groups		
					HR	95% CI	p-value
Censoring COVID-19 deaths	Arm A (AV) N = 291	8 (2.7)	57.8	57.8, NC	0.27	0.11, 0.60	0.0013
	Arm B (AVG) N = 286	12 (4.2)	NC	NC, NC	0.47	0.22, 0.95	0.0341
	Arm C (FCR/BR) N = 290	21 (7.2)	NC	NC, NC			
Censoring due to subsequent anti-CLL therapy	Arm A (AV) N = 291	17 (5.8)	NC	NC, NC	0.35	0.19, 0.62	0.0002

	Group	Patients with event n (%)	Median time to event (months)	95% CI	Comparison of treatment groups		
					HR	95% CI	p-value
	Arm B (AVG) N = 286	36 (12.6)	NC	NC, NC	0.81	0.51, 1.27	0.3550
	Arm C (FCR/BR) N = 290	38 (13.1)	NC	43.3, NC			

A HR below 1 favours Arm A or Arm B over Arm C, respectively.

Investigator assessed PFS

Table 18. Progression-free Survival by Investigator Assessment (FAS), DCO date 30 Oct 2024), study ACE-CL-311

	Arm A (AV) N = 291	Arm B (AVG) N = 286	Arm C (FCR/BR) N = 290
Event [a]			
Any	102 (35.1)	51 (17.8)	103 (35.5)
Progression	89 (30.6)	18 (6.3)	72 (24.8)
Death without progression	13 (4.5)	33 (11.5)	31 (10.7)
Censored observations			
Any	189 (64.9)	235 (82.2)	187 (64.5)
Censored at Day 1	1 (0.3)	2 (0.7)	33 (11.4)
No baseline disease assessment	0	1 (0.3)	1 (0.3)
No post-baseline response assessment	1 (0.3)	1 (0.3)	32 (11.0)
Censored due to 2 or more consecutively missed response assessments [b]	19 (6.5)	28 (9.8)	29 (10.0)
Censored due to subsequent anti-CLL therapy	4 (1.4)	3 (1.0)	2 (0.7)
Progression-free	165 (56.7)	202 (70.6)	123 (42.4)
Progression-free at time of the analysis	164 (56.4)	201 (70.3)	119 (41.0)
Early study discontinuation	1 (0.3)	1 (0.3)	4 (1.4)
Lost to follow-up	0	0	0
Withdrew consent	1 (0.3)	1 (0.3)	3 (1.0)
Study exit due to investigator decision or other	0	0	1 (0.3)

Progression-free survival (months)			
Median (95% CI)	58.2 (51.7, NC)	NC (62.9, NC)	55.6 (45.4, NC)
P25, P75	38.6, NC	62.9, NC	29.0, NC
Comparison of treatment groups			
Hazard ratio (95% CI)	0.68 (0.52, 0.90)	0.36 (0.25, 0.50)	
nominal p-value	0.0069	< 0.0001	
Progression-free survival rate (%)			
6 months (95% CI)	97.9 (95.4, 99.1)	96.8 (94.0, 98.3)	94.9 (91.4, 97.0)
12 months (95% CI)	96.2 (93.2, 97.9)	92.5 (88.8, 95.1)	87.9 (83.2, 91.4)
18 months (95% CI)	93.3 (89.7, 95.7)	89.6 (85.4, 92.7)	83.7 (78.4, 87.8)
24 months (95% CI)	91.1 (87.2, 93.9)	88.1 (83.7, 91.4)	79.2 (73.5, 83.8)
30 months (95% CI)	87.0 (82.5, 90.5)	87.3 (82.8, 90.7)	74.2 (68.0, 79.3)
36 months (95% CI)	78.7 (73.4, 83.2)	84.9 (80.1, 88.7)	66.3 (59.8, 72.1)
42 months (95% CI)	71.5 (65.7, 76.5)	84.5 (79.6, 88.3)	61.5 (54.8, 67.5)
48 months (95% CI)	64.3 (57.8, 70.1)	82.2 (76.8, 86.5)	54.8 (47.6, 61.5)
54 months (95% CI)	55.2 (47.1, 62.5)	77.2 (69.8, 83.0)	50.2 (42.2, 57.7)
60 months (95% CI)	43.0 (29.1, 56.1)	77.2 (69.8, 83.0)	47.4 (38.1, 56.1)

[a] *Includes events that occur within 28 weeks of last evaluable assessment (in the first 3 years after randomisation) or within 56 weeks of last evaluable assessment (3 years and later from randomisation).*
[b] *The threshold for 2 or more consecutively missed response assessments is 28 weeks in the first 3 years after randomisation and 56 weeks thereafter.*

Objective response rate

Table 19. Best Overall Response and Overall Response Rate by Blinded Independent Central Review and Investigator Assessment (FAS), study ACE-CL-311

	IRC assessment			**Investigator assessment**		
	Arm A (AV) (N = 291)	**Arm B (AVG) (N = 286)**	**Arm C (FCR/BR) (N = 290)**	**Arm A (AV) (N = 291)**	**Arm B (AVG) (N = 286)**	**Arm C (FCR/BR) (N = 290)**
Response, n (%)	270 (92.8)	265 (92.7)	218 (75.2)	282 (96.9)	275 (96.2)	238 (82.1)
Estimated risk difference (95% CI)	17.6 (11.5, 23.6)	17.5 (11.4, 23.5)	-	14.8 (10.0, 20.0)	14.1 (9.0, 19.4)	-

	IRC assessment			Investigator assessment		
	Arm A (AV) (N = 291)	**Arm B (AVG) (N = 286)**	**Arm C (FCR/BR) (N = 290)**	**Arm A (AV) (N = 291)**	**Arm B (AVG) (N = 286)**	**Arm C (FCR/BR) (N = 290)**
Comparison of treatment groups, p-value	< 0.0001	< 0.0001	-	< 0.0001	< 0.0001	-
Complete response	26 (8.9)	40 (14.0)	15 (5.2)	40 (13.7)	69 (24.1)	24 (8.3)
Complete response with incomplete bone marrow recovery	0	5 (1.7)	1 (0.3)	3 (1.0)	4 (1.4)	6 (2.1)
Nodular partial response	1 (0.3)	0	1 (0.3)	11 (3.8)	1 (0.3)	2 (0.7)
Partial response	243 (83.5)	220 (76.9)	201 (69.3)	228 (78.4)	201 (70.3)	206 (71.0)
Non-response, n (%)						
Any	21 (7.2)	21 (7.3)	72 (24.8)	9 (3.1)	11 (3.8)	52 (17.9)
Stable disease	14 (4.8)	11 (3.8)	26 (9.0)	7 (2.4)	8 (2.8)	14 (4.8)
Progression	3 (1.0)	2 (0.7)	2 (0.7)	0	0	0
Not evaluable	0	0	3 (1.0)	0	0	0
Not done	4 (1.4)	8 (2.8)	41 (14.1)	2 (0.7)	3 (1.0)	38 (13.1)

Duration of Response

Table 20. Duration of Response by Blinded Independent Central Review and Investigator Assessment (FAS), study ACE-CL-311

	IRC assessment			Investigator assessment		
	Arm A (AV) (N = 291)	**Arm B (AVG) (N = 286)**	**Arm C (FCR/BR) (N = 290)**	**Arm A (AV) (N = 291)**	**Arm B (AVG) (N = 286)**	**Arm C (FCR/BR) (N = 290)**
Patients with response	270 (92.8)	265 (92.7)	218 (75.2)	282 (96.9)	275 (96.2)	238 (82.1)
Responders who subsequently progressed or died, n (%)	76 (28.1)	40 (15.1)	74 (33.9)	73 (25.9)	39 (14.2)	83 (34.9)
Progression	68 (25.2)	19 (7.2)	57 (26.1)	65 (23.0)	14 (5.1)	62 (26.1)
Death without progression	8 (3.0)	21 (7.9)	17 (7.8)	8 (2.8)	25 (9.1)	21 (8.8)

	IRC assessment			Investigator assessment		
	Arm A (AV) (N = 291)	**Arm B (AVG) (N = 286)**	**Arm C (FCR/BR) (N = 290)**	**Arm A (AV) (N = 291)**	**Arm B (AVG) (N = 286)**	**Arm C (FCR/BR) (N = 290)**
Median DoR (95% CI) (months)	50.4 (48.5, NC)	NC (NC, NC)	47.6 (44.0, NC)	NC (49.7, NC)	NC (NC, NC)	48.6 (41.5, NC)
Percentage remaining in response						
12 months	97.0	94.7	91.9	96.4	93.4	90.8
24 months	88.0	91.0	81.7	89.6	89.8	80.9
36 months	73.6	87.9	68.7	76.0	87.2	67.2
48 months	62.2	81.4	47.1	64.0	80.7	51.1

DoR is the time from the first documentation of response until the date of progression or death or the last evaluable assessment for patients that do not progress or do not progress within 28 weeks of last evaluable assessment (in the first 3 years after randomisation), or within 56 weeks of last evaluable assessment (3 years and later from randomisation).

Ancillary analysis

A backdated data cutoff (DCO) date of 08 November 2023 (the date that the originally planned 153 events IRC-PFS events occurred across Arms A [AV] and C [FCR/BR] total) was applied to the interim analysis data. P-value scale boundaries for Arm A (AV) compared to those of Arm C (FCR/BR) and those of Arm B (AVG) compared to those of Arm C (FCR/BR), respectively, were re-calculated based on the observed events at this DCO date in relation to the 229 final analysis events initially planned.

Primary endpoint: PFS by IRC assessment Arm A (AV) compared to Arm C (FCR/BR)

Based on the originally planned 153 events, the results for PFS, as assessed by the IRC, demonstrated that AV showed statistically significantly superior efficacy compared with that of FCR/BR in previously untreated patients with CLL (HR: 0.61; 95% CI: 0.44, 0.84; p-value: 0.0025 [p-value scale boundary: 0.012]). Median PFS for Arm A was not calculable (NC); the median PFS for Arm C (FCR/BR) was 46.8 months (95% CI: 42.1, NC).

Key secondary endpoint: PFS by IRC assessment Arm B (AVG) compared to Arm C (FCR/BR)

At the time of 153 observed events across Arm A and Arm C in total, there were 129 events across Arm B and Arm C. The results of this key secondary endpoint analysis for PFS, demonstrated that AVG showed statistically significantly superior efficacy compared to that of FCR/BR in previously untreated patients with CLL (HR: 0.42; 95% CI: 0.29, 0.60; p-value: < 0.0001 [p-value scale boundary: 0.006]). Median PFS for Arm B was 51.7 months (95% CI: 51.7, NC); the median PFS for Arm C was 46.8 months (95% CI: 42.1, NC).

Supportive studies

In the three-arm, Phase 3 study ELEVATE-TN (originally submitted with the initial Marketing Authorisation Application for Calquence) previously untreated CLL patients were randomised to i) acalabrutinib plus obinutuzumab (AG), ii) acalabrutinib monotherapy (A), or iii) obinutuzumab plus chlorambucil (control arm, CIT). Patients with del17p/TP53 mutation comprised more than 10% of the trial population and the results for both A monotherapy and AG demonstrate improved clinical benefit for this subgroup of patients in terms of PFS.

In the open-label phase 3 trial CLL14 investigating venetoclax + obinutuzumab (VG) versus obinutuzumab + chlorambucil (control arm, CIT) in patients with previously untreated CLL, 14% of the patients had a del17p or/and TP53 mutation. Efficacy in terms of investigator assessed PFS was established in the primary analysis and subgroup analyses demonstrated less, but still beneficial, efficacy of VG therapy in patients with *TP53* mutation or del17).

The AVG regimen is being studied in the SAT NCT03580928 enriched for patients with TP53 aberrancy. In this ongoing SAT, 10 out of 27 randomised patients (27%) had del17p and concomitant TP53 mutation.

Results from these studies are summarised in **Table 22**.

Table 21. Clinical trials with acalabrutinib and TP53 aberrations

	ELEVATE-TN		
	Acalabrutinib + obinutuzumab	Acalabrutinib monotherapy	Obinutuzumab + chlorambucil
Number of patients			
Total	179	179	177
TP53 aberration	25	23	25
IRC PFS HR (95% CI)			
All patients	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
Del17p or/and TP53 mut:			
Yes	0.10 (0.03, 0.34)	0.23 (0.09, 0.61)	-
No	0.10 (0.05, 0.18)	0.19 (0.11, 0.31)	-
IRC-ORR % (95% CI)			
All patients	93.9% (89.3, 96.5)	85.5% (79.6, 89.9)	78.5% (71.9, 83.9)
Del17p or/and TP53 mut:			
Yes	84.0 (65.3, 93.6)	82.6 (62.9, 93.0)	56.0% (37.1, 73.3)
No	95.5 (90.9, 97.8)	85.9 (79.6, 90.5)	82.1% (75.2, 87.4)
	CLL-14		
	Venetoclax + obinutuzumab	Obinutuzumab + chlorambucil	
Number of patients			
Total	216	216	
del17p	17	14	
TP53 mut	19	13	
TP53 unmutated	152	144	
INV-PFS HR (95% CI)			
All patients	0.32 (0.21, 0.49)	-	
Del17p	0.35 (0.13, 0.94)	-	
TP53 mut	0.31 (0.11, 0.88)	-	
Tp53 unmutated	0.22 (0.12, 0.40)	-	
INV-ORR % (95% CI)			
All patients	84.7% (79.2, 89.2)	71.3% (64.8, 77.2)	
Del17p	82.4%	35.7%	
TP53 mut	84.2%	53.8%	
Tp53 unmutated	86.8%	71.5%	
	NCT03580928 (SAT)		
	Acalabrutinib + venetoclax + obinutuzumab		
Number of patients	37		
TP53 aberration	10		
ORR at cycle 25 (%)			
All patients	97%		
TP53 aberration	100%		

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 22. Summary of Efficacy for trial study ACE-CL-311 (AMPLIFY)

Title: AMPLIFY			
Study identifier	Study Code: ACE-CL-311 (D8221C00001) EudraCT/EU CT Number: 2018-002443-28 NCT Number: 2023-505867-35		
Design	AMPLIFY is a randomized, multicenter, open-label, Phase III study to compare the efficacy and safety of acalabrutinib in combination with venetoclax with and without obinutuzumab compared to investigator's choice of chemo-immunotherapy in patients with previously untreated CLL without del(17p) or TP53 mutation.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		<time> <time> <not applicable> <time> <not applicable>
Hypothesis	Superiority		
Treatments groups	Arm A (acalabrutinib+venetoclax; AV)		Acalabrutinib 100 mg capsules were orally administered from Cycle 1 at a fixed twice daily (BID) dose for 14 cycles; venetoclax oral dosing was to begin at Cycle 3 and continued following a 5-week ramp-up at a fixed daily dose of 400 mg until the end of Cycle 14, or until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurred first.
	Arm B (acalabrutinib+venetoclax+ obinutuzumab; AVG)		Acalabrutinib (100 mg capsules) were orally administered from Cycle 1 at a fixed BID dose for 14 cycles; obinutuzumab administered as IV infusion at an absolute (flat) dose of 1000 mg and was to begin at Cycle 2 and continued through Cycle 7; venetoclax dosing was to begin at Cycle 3 and continue following a 5-week ramp-up at a fixed daily dose of 400 mg until the end of Cycle 14, or until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurred first.
	Arm C (chemoimmunotherapy; Investigator's choice of fludarabine+cyclophosphamide+rituximab or bendamustine+rituximab; FCR/BR)		All patients who were randomized to standard chemoimmunotherapy were to receive up to 6 cycles of either FCR or BR as IV infusions, according to standard institutional practice. Patients $\leqslant$ 65 years of age with a creatinine clearance of $\geqslant$ 70 mL/min were restricted to FCR.
Endpoints and definitions	Primary endpoint	PFS	Determined by IRC assessment for the primary efficacy objective (Arm A vs Arm C); by investigator assessment for the secondary efficacy objective (Arm A vs Arm C)
	Secondary endpoint	PFS	By both IRC and investigator assessment for the secondary efficacy objective (Arm B vs arm C).

	Secondary endpoint	MRD negativity rate	Determined as the proportion of patients with MRD negativity, measured in the peripheral blood by flow cytometry (10-4) at the start of Cycle 9 (in Arm A), the start of Cycle 10 (in Arm B), and 12 weeks after the start of Cycle 6 (in Arm C)
	Secondary endpoint	OS	Time from randomization to death from any cause.
Database lock	30 April 2024		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS)			
Descriptive statistics and estimate variability	Treatment group	Arm A (AV)	Arm B (AVG)	Arm C (FCR/BR)
	Number of subject	291	286	290
	PFS Any event, n (%)	89 (30.6)	56 (19.6)	95 (32.8)
	Median PFS (months)	NC (51.1, NC)	NC (NC, NC)	47.6 (43.3, NC)
	HR (95% CI), p-value	0.65 (0.49, 0.87), 0.0038	0.42 (0.30, 0.59), < 0.0001	-
	MRD Negativity Rate uMRD, n (%)	78 (26.8)	190 (66.4)	148 (51.0)
	Patient with MRD measurement	244 (83.8)	202 (70.6)	190 (65.5)
	Risk ratio (95% CI), p-value	0.5 (0.4, 0.7), <0.0001	1.3 (1.1, 1.5), 0.0003	-
	OS Death events, n (%)	23 (7.9)	37 (12.9)	44 (15.2)
	Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
	HR (95% CI), p-value	0.42 (0.25, 0.70)	0.75 (0.48, 1.16)	-
Notes	OS maturity rate 10% (Arm A vs Arm C) and 14% (Arm B vs Arm C) at DCO for the interim analysis. The study is not powered to detect statistically significant OS. OS DCO is 30 October 2024.			

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

AMPLIFY is a randomised, open-label, Phase III study designed to evaluate whether fixed duration of acalabrutinib in combination with venetoclax with or without obinutuzumab as a first-line treatment setting could improve long-term treatment outcomes in patients with previously untreated CLL without del(17p) or TP53 mutation.

A total of 867 patients were randomised in the global cohort in 1:1:1 ratio into 3 Arms (Arm A, Arm B, and Arm C). In the experimental arms A and B, participants received acalabrutinib (A) 100 mg BID for 14 cycles with the addition of venetoclax (V) from cycle 3 through cycle 7. In addition, patients in Arm B received IV obinutuzumab (G, cycle 2-7).

The primary endpoint was PFS assessed by IRC (Arm A vs Arm C) and key secondary endpoint was PFS assessed by IRC (Arm B vs Arm C). Other secondary endpoints included MRD negativity rate, OS, and ORR (all tested in Arm A vs Arm C and Arm B vs Arm C, respectively).

Overall, the sample size calculation, randomisation procedure, application of analysis population sets in analyses, multiplicity control as well as the handling of stratification factors (used during randomisation) in the analyses were pre-specified and done in accordance with pre-specification.

Seven protocol amendments were done during the study and amendments 1, 5 and 6 were considered substantial. According to Amendment 6.0, the HR in the sample size calculation for the primary endpoint was changed from 0.65 to 0.62. This change in assumed HR was based on the results from the interim analysis of the GAIA-CLL13 trial. Additionally, the information fraction at interim analysis was updated from 67% to 75% to ensure sufficient data maturity. As a result of these changes, the required number of PFS events changed from 153 (67% information fraction) to 141 (75% information fraction) for the PFS interim analysis and from 229 to 188 for the final analysis. The analysis submitted in this application (data cut-off 30 April 2024) included 184 PFS events, (98% of the information fraction of the 188 PFS events required for the final analysis).

The rationale behind the changes in the assumed HR is understood, however it is not clear why the analysis was performed at 184 PFS events instead of the 188 that was concluded in the updated calculations. Nevertheless, this issue is not considered to impact the overall conclusions of the study, as the MAH provided results for the PFS analyses based on the originally planned interim at 153 PFS events which were consistent with the results submitted as the primary analysis of the study.

The MAH has also confirmed that the IRC stopped assessing disease progression following the positive interim analyses. The reason for discontinuing IRC assessments on disease progression was that the interim analysis met its primary objective (IRC-assessed PFS of AV versus PFS of FCR/BR) thereby serving as the final analysis of the study. Patients are still being followed for investigator-assessed (INV) PFS events.

At the data cut-off for the PFS interim analysis, 30 April 2024, none of the patients randomised into the global cohort were on study treatment. The majority of patients (83.6%) were in follow-up phase: 269 patients (92.4%) in Arm A, 245 patients (85.7%) in Arm B and 211 patients (72.8%) in Arm C.

Efficacy data and additional analyses

Among 867 patients randomised in the global cohort, the FAS included 291 patients in Arm A, 286 patients in the Arm B, and 290 patients in the Arm C. Median age was 61 years in all trial arms and two-thirds of participants were men. Median time from diagnosis to randomisation was similar between arms: 28.5 months in Arm A, 26.1 months in Arm B and 29.6 months in Arm C. Baseline characteristics are balanced between the three study arms.

Statistically significant IRC-assessed PFS was shown for Arm A as compared with Arm C, with HR 0.65 (95% CI [0.49, 0.87]). Median PFS was 47.6 months in Arm C and, at the DCO, not yet reached in Arm A. A PFS event was registered for 30.6% of patients in Arm A and 32.8% in Arm C.

It is noted that the proportion of deaths in the PFS analysis is higher in Arm C (10.0%) compared with Arm A (4.1%), whereas disease progression was a more frequently observed event among patients in Arm A (26.5% vs 22.8% among patients in Arm C).

In sensitivity analyses, inclusion of events after subsequent anticancer therapy and inclusion of events after >2 consecutively missed visits (according to EMA censoring rules) resulted in HR of 0.66 and 0.67 respectively 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.

For the primary endpoint, relevant subgroup results are mainly consistent.

Post-hoc tipping point analyses of PFS was performed to evaluate the impact of imbalanced early censoring between arms on the PFS results, imputing the time for PFS for the 75 patients in Arm C (FCR/BR) who were censored informatively and assuming that they were at a reduced risk of progression or death compared to all other patients in the arm. In addition, the MAH provided baseline characteristics enabling comparison of patients with informative censoring and the other patients in each treatment arm. Overall, the baseline data indicate a trend toward more advanced disease and worse prognosis among informatively censored patients of the control arm, compared to those in the same arm that were not informatively censored.

For the primary endpoint, PFS in Arm A vs Arm C, the tipping point analysis demonstrates that if the 75 patients in Arm C were assumed to have at least 40% lower risk of progression or death compared to those still in follow-up or with an event in Arm C, the 95% CI of the estimated HR would include 1.

Given the comparison of baseline characteristics depending on censoring status, the tipping point analyses, and the PFS results from comparison of Arm A and Arm C are deemed robust.

Statistically significant IRC-assessed PFS was shown for Arm B (AVG) as compared with Arm C (FCR/BR), with HR 0.42 (95% CI [0.30, 0.59]. Median PFS was 47.6 months in Arm C and, at the DCO, not yet reached in Arm B. A PFS event was registered for 19.6% of patients in Arm B and 32.8% in Arm C.

Progression was more prevalent in Arm C than in Arm B (22.8% and 8.0%, respectively). It is, however, noted that the proportion of deaths is higher in Arm B (11.5%) as compared with Arm C (10.0%).

In subgroup analyses based on the upfront choice of treatment in Arm C (FCR or BR), PFS analyses of Arm A and Arm B against the FCR subgroup resulted in HRs of 0.69 (95% CI [0.47, 1.03], p=0.0581) and 0.47 (95% CI [0.31, 0.73], p=0.0004), respectively. PFS analyses of Arm A and Arm B against the BR subgroup resulted in HRs of 0.63 (95% CI [0.45, 0.88], p=0.0062) and 0.39 (95% CI [0.27, 0.57], p<0.0001), respectively. The FCR regimen is used in younger, more fit patients with less comorbidities and, as expected, a higher number of PFS events were observed in the BR subgroup of Arm C.

The MAH has provided updated INV-PFS analyses with DCO date 30 October 2024. In the Arm A vs Arm C analysis, 102 (35.1%) INV-PFS events were reported in Arm A, and 103 (35.5%) INV-PFS events were reported in Arm C (HR: 0.68; 95% CI; 0.52, 0.90). The median PFS was 58.2 months and 55.6 months for patients in Arm A and Arm C, respectively. In the Arm B versus Arm C analysis, 51 (17.8%) INV-PFS events were reported in Arm B and 103 (35.5%) INV-PFS events were reported in Arm C (HR: 0.36; 95% CI: 0.25, 0.50). Both AV and AVG continues to show improvement in PFS over FCR/BR.

A total of 78 patients (26.8%) in Arm A (AV), 190 patients (66.4%) in Arm B and 148 patients (51.0%) in Arm C (FCR/BR) achieved MRD negativity at Cycle 9 and at 12 weeks post Cycle 6, respectively. In comparison between Arm A and Arm C, the risk ratio was 0.5 (95% CI: 0.4, 0.7; p-value < 0.0001). This translates to an inverse association, with decreased chance of MRD negativity among participants treated with AV (Arm A) as compared with participants in the control arm. Between Arm B and Arm C, the risk ratio was 1.3 (95% CI: 1.1, 1.5; nominal p-value = 0.0003), favouring treatment with AVG. Thus, the addition of obinutuzumab to the AV combination appeared to increase the likelihood of MRD negativity.

Of note, MRD measurement was missing for >30% of patients in both Arm B and Arm C lot and this large proportion of missing data may influence the results. Patients randomised to Arm C had a higher rate of withdrawal or were lost to follow-up (12.41%) compared to those in Arm A (0.69%) and Arm B (1.40%). Also, there were more patients with death before reaching the MRD timepoint in Arm B and Arm C compared to those in Arm A. The most common reason for missing data was however missing sample collection for various reasons.

It is, however, noted that MRD sampling is performed at different time points in Arm A (cycle 9), Arm B (cycle 10) and that the MRD sample at PTFU1 in the control arm (i.e. 12 weeks after cycle 6, corresponding to cycle 9) is used as reference in both analyses. As expected, a progressive increase in MRD negativity is seen over time (i.e. between each sampling). It is therefore possible that the later sampling in Arm B has an impact on the result of the MRD analysis.

At time of the interim analysis, 18 (6.2%) patients had died in Arm A, 37 (12.9%) had died in Arm B (AVG), and 42 (14.5%) ha died in Arm C (FCR/BR). Median OS was 57.8 months in Arm A but not met in either Arm B or Arm C. Upon request, the MAH provided updated OS analyses with DCO of 30 October 2024. With 7 additional deaths since the previous DCO of 30 April 2024 (5 in Arm A, 0 in Arm B and 2 in Arm C), data maturity was 12% in the Arm A versus Arm C analysis, and 14% in the Arm B vs Arm C analysis. In the analysis of Arm A versus Arm C, the OS HR was 0.42 (95% CI: 0.25, 0.70). The OS HR for Arm B versus Arm C was 0.75 (95% CI: 0.48, 1.16). It is agreed that the treatment benefit with both AV and AVG remains stable and consistent with the primary OS analysis.

In the updated OS data, the median OS in Arm A was updated from the 57.8 months (95% CI [57.8, NC]) stated in the original analysis with DCO of 30 Apr 2024, to NC (NC, NC).

Of note, in the control arm, 11.0% of patients were censored due to withdrawal of consent. In Arm A and B, 1.4% and 0.3% of patients were censored due to consent withdrawal. This may impact the OS analysis.

Nonetheless, OS data demonstrate a trend towards improvement in OS for patients treated with AV and AVG as compared with FCR/BR. It is, however, emphasized that OS data are very immature and thus the CHMP recommend that the final OS results should be submitted when available.

Numerically higher ORR per IRC assessment were observed for both Arm A (92.8%) and Arm B (92.7%) as compared with Arm C (75.2%). An assessment of ORR by investigator assessment was consistent with the IRC assessment for both Arm A and Arm B vs Arm C.

Scarce evidence was provided by the MAH to support the contribution of both acalabrutinib and venetoclax to the observed treatment effect, based on cross study comparisons between the AMPLIFY and ELEVATE-TN studies. It is noted that the ORR was higher with AV compared with acalabrutinib monotherapy (96.9% [282/291] vs 91.7% [143/156]), when excluding del(17p) and TP53 mutated patients.

However, acalabrutinib and venetoclax target B-cells by two different and complementary mechanisms, which renders additive effects likely. The concept of combining a BTKi and venetoclax has

previously been accepted by the CHMP in the approval of combination use with ibrutinib. Moreover, time-limited use of a BTKi and venetoclax is presently a recommended treatment alternative for all patients in need of a first line therapy regardless of del(17p)/TP53 mutation status (ESMO Guidelines, Eichhorst et al 2024). Thus, the rationale for the combination was accepted by the CHMP.

With this submission, the MAH seeks approval of the following indication: "*Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).*"

Due to the choice of chemoimmunotherapy (BR/FCR) as control arm, patients with a detected del17p or TP53 mutation were excluded from study enrolment as BTK inhibitors and venetoclax-based therapy are considered SoC over chemoimmunotherapy combination for these high-risk patients. Thus, to support the proposed indication (i.e. all-comer, previously untreated CLL), the MAH provided data from 3 additional studies to extrapolate efficacy to patients with del(17p) and/or TP53.

In the Phase 3 study ELEVATE-TN, among patients receiving the AG combination, ORR was higher in the del17p/TP53 mutation-negative subgroup (95%) than in the patients with TP53 aberration (84%), while similar for the subgroups with A monotherapy. Among patients without TP53 aberration, the ORR of the control regimen is roughly similar to A monotherapy but considerably lower than both experimental arms in del17p/TP53 positive disease (56%).

In the open-label phase 3 trial CLL14, for the VG regimen, investigator-assessed ORR was close to 85% irrespective of TP53 or del17p status.

Preliminary data from the ongoing SAT NCT03580928 have showed that at cycle 25 all patients with TP53 aberrations had achieved CR or PR.

Results from these studies are considered sufficient of bridging the obtained efficacy results in the pivotal AMPLIFY study to patients with TP53 aberrations.

2.4.4. Conclusions on the clinical efficacy

Efficacy has been established in the form of a clinically meaningful prolongation of PFS with both AV and AVG treatment. OS data are very immature but trending towards improvement in OS for patients treated with the experimental treatments.

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 30 April 2024) from the AMPLIFY study. A total of 867 patients were enrolled from 25 February 2019 up to the 31 March 2021, including 291 patients in AV arm, 286 patients in AVG arm, and 290 patients in the FCR/BR arm. Of these, 834 patients (291, 284, and 259 patients, respectively)

received at least one dose of any study treatment and are included in this safety summary referred as the Safety Population (**Table 24**-**Table 26**).

Table 23. Exposure, Arm A, acalabrutinib and venetoclax (AV), Safety population, study ACE-CL-311

	Arm A (AV) (N = 291)	
	Acalabrutinib	**Venetoclax**
Duration of exposure (month)		
Mean (SD)	12.7 (2.2)	10.9 (1.6)
Median	12.9	11.1
Min, Max	1, 18	2, 14
Actual cumulative dose (g)		
Mean (SD)	73.70 (13.32)	115.194 (25.174)
Median	78.00	125.330
Min, Max	5.8, 93.6	1.98, 138.99
Average daily dose (mg/day)		
Mean (SD)	191.249 (16.037)	344.071 (60.212)
Median	196.835	346.994
Min, Max	77.71, 200.00	20.00, 376.54
Relative dose intensity (%)		
Mean (SD)	94.008 (16.993)	91.577 (20.013)
Median	99.490	99.635
Min, Max	7.40, 119.39	1.57, 110.49

Table 24. Exposure Arm B, acalabrutinib, venetoclax and obinutuzumab (AVG), Safety population, study ACE-CL-311

	Arm B (AVG) (N = 284)		
	Acalabrutinib	**Venetoclax**	**Obinutuzumab**
Duration of exposure (month)			
Mean (SD)	12.2 (3.0)	10.5 (2.5)	5.4 (1.1)
Median	12.9	11.0	5.5
Min, Max	0, 18	0, 15	1, 8
Actual cumulative dose (g)			
Mean (SD)	68.78 (17.68)	106.117 (32.853)	7.538 (1.348)
Median	76.90	123.910	8.000
Min, Max	2.2, 85.4	0.12, 129.74	0.04, 8.90
Average daily dose (mg/day)			
Mean (SD)	186.123 (20.725)	327.487 (75.406)	-
Median	195.385	320.538	-
Min, Max	93.80, 200.00	19.70, 375.51	-
Relative dose intensity (%)			
Mean (SD)	87.734 (22.555)	84.360 (26.117)	94.221 (16.852)
Median	98.090	98.505	100.000
Min, Max	2.81, 108.93	0.10, 103.14	111.25

Table 25. Exposure, Arm C, FCR and BR, Safety population, study ACE-CL-311

	Arm C (FCR/BR)				
	FCR (N = 122)			BR (N = 137)	
	Fludarabine	Cyclophosphamide	Rituximab	Bendamustine	Rituximab
Duration of exposure (month)					
Mean (SD)	5.2 (1.4)	5.2 (1.4)	5.2 (1.4)	5.4 (1.4)	5.4 (1.3)
Median	5.6	5.6	5.5	5.6	5.6
Min, Max	1, 8	1, 8	1, 8	1, 11	1, 11
Actual cumulative dose (g)					
Mean (SD)	0.778 (0.250)	7.568 (2.269)	4.954 (1.531)	1.775 (0.503)	4.983 (1.342)
Median	0.830	8.277	5.357	1.869	5.246
Min, Max	0.13, 1.51	1.27, 11.30	7.22, 0.63	0.28, 2.64	7.48, 0.58
Relative dose intensity (%)					
Mean (SD)	87.930 (25.883)	85.611 (23.481)	87.639 (24.532)	86.198 (22.063)	91.109 (22.415)
Median	97.550	96.380	98.235	95.510	98.640
Min, Max	16.02, 150.69	16.37, 103.59	12.81, 121.11	16.19, 106.20	12.73, 126.80

Supportive safety data for the acalabrutinib safety and tolerability profile is provided from a more representative pooled data set including patients treated with acalabrutinib for various indications in hematologic malignancies (**Table 27**).

Table 26. Safety Pools for AMPLIFY Interim Analysis Submission

Study/Protocol number	Phase	Indication(s)	Treatments	Acalabrutinib monotherapy	Combination therapy	
				N	N	Treatment
ACE-CL-311 (AMPLIFY)	3	TN CLL	AV, AVG, FCR/BR	NA	291 284	AV AVG
ACE-CL-007[a] (ELEVATE TN)	3	TN CLL	GC, AG, A	258 [79[d]]	178	AG
ACE-CL-309[a] (ASCEND)	3	R/R CLL	A, IR, BR	234 [80[d]]	NA	NA
ACE-LY-004	2	R/R MCL	A	124	NA	NA
ACE-CL-001	1 and 2	CLL/SLL. RS. PLL	A	301	NA	NA
ACE-CL-003	1b	CLL/SLL. RS. PLL	AG, ARV, AR	NA	45	AG
ACE-WM-001	2	WM	A	106	NA	NA
15-H-0016	2	CLL/SLL	A	48	NA	NA
ACE-LY-002	1b	R/R DLBCL	A	21	NA	NA
ACE-LY-003[b]	1b/2	FL/ MZL	A, AR	14/ 43	NA	NA
ACE-MY-001[b]	1b	R/R MM	A, AD	13	NA	NA
ACE-CL-006 (ELEVATE RR)	3	R/R CLL	A	265	NA	NA

Study/Protocol number	Phase	Indication(s)	Treatments	Acalabrutinib monotherapy	Combination therapy	
				N	N	Treatment
ACE-LY-308[c] (ECHO)	3	TN MCL	ABR, PBR	51 [51[d]]	297	ABR
Total No. patients				**1478**	**1095**	

[e] *Study has data from acalabrutinib monotherapy arms and from who underwent crossover from control arms to acalabrutinib monotherapy arm.*

[f] *Study has both acalabrutinib monotherapy and combination therapy arms. Only monotherapy patients were included in the integrated analysis of pooled data.*

[g] *Study has combination therapy arms. Only crossover patients who received acalabrutinib monotherapy were included in the integrated analysis of pooled data.*

[h] *Subset of patients who crossed over to acalabrutinib monotherapy.*

Abbreviations: TN: treatment naïve; CLL: chronic lymphocytic leukaemia; R/R: relapsed/refractory; MCL: Mantle Cell Lymphoma, SLL: small lymphocytic lymphoma; RS: Richter's syndrome; PLL: prolymphocytic leukaemia; WM: Waldenström macroglobulinemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma; MM: multiple myeloma.

Adverse events

For the safety evaluation MedDRA v26.1 was used to code all Adverse Events (AEs) to a System Organ Class (SOC) and a Preferred term (PT). Adverse event severity was assessed by the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), using the CTCAE versions and severities reported in the individual studies. Study drug-related AEs were those assessed by the investigators as related in each individual study.

Treatment-emergent AEs in all studies were defined as those events that occurred or worsened on or after the first dose of study drug, through the treatment phase, and within 30 days following the last dose of study drug or until new anticancer therapy had started, whichever came first.

Study drug action due to treatment emergent adverse events (TEAEs) (i.e., discontinuation, reduction, or withholding) was based on investigator decision as recorded in the electronic case report form (eCRF).

In this section, patients with multiple occurrences are counted once per system organ class and preferred term regardless of the number of occurrences.

Similarly, a patient with multiple severity grades for the same preferred term is counted only once in the most severe grade.

Overview of Adverse Events

Table 27. Overall Summary of Adverse Events (Safety Population), study ACE-CL-311

	Arm A (AV) N = 291 n (%)	Arm B (AVG) N = 284 n (%)	ARM C (FCR/BR)		
			Total N = 259 n (%)	FCR only N = 122 n (%)	BR only N = 137 n (%)
Any AE	270 (92.8)	269 (94.7)	236 (91.1)	109 (89.3)	127 (92.7)
Treatment-related	230 (79.0)	238 (83.8)	215 (83.0)	99 (81.1)	116 (84.7)
Acalabrutinib-related	221 (75.9)	223 (78.5)	NA	NA	NA
Venetoclax-related	195 (67.0)	197 (69.4)	NA	NA	NA
Obinutuzumab-related	NA	176 (62.0)	NA	NA	NA
Bendamustine-related	NA	NA	108 (41.7)	0	108 (78.8)
Rituximab-related	NA	NA	197 (76.1)	87 (71.3)	110 (80.3)
Fludarabine-related	NA	NA	94 (36.3)	94 (77.0)	0
Cyclophosphamide-related	NA	NA	93 (35.9)	93 (76.2)	0
Any Grade ≥ 3 AE	156 (53.6)	197 (69.4)	157 (60.6)	74 (60.7)	83 (60.6)
Treatment-related	117 (40.2)	157 (55.3)	143 (55.2)	67 (54.9)	76 (55.5)
Acalabrutinib-related	99 (34.0)	135 (47.5)	NA	NA	NA
Any SAE	72 (24.7)	109 (38.4)	71 (27.4)	36 (29.5)	35 (25.5)
Treatment-related	27 (9.3)	48 (16.9)	52 (20.1)	28 (23.0)	24 (17.5)
Acalabrutinib-related	24 (8.2)	43 (15.1)	NA	NA	NA
Any AE with outcome death	10 (3.4)	17 (6.0)	9 (3.5)	5 (4.1)	4 (2.9)
Treatment-related	0	0	1 (0.4)	0	1 (0.7)
Acalabrutinib-related	0	0	NA	NA	NA
Any AE leading to discontinuation of					
Treatment	23 (7.9)	57 (20.1)	28 (10.8)	16 (13.1)	12 (8.8)
Acalabrutinib	22 (7.6)	39 (13.7)	NA	NA	NA
Venetoclax	18 (6.2)	37 (13.0)	NA	NA	NA
Obinutuzumab	NA	27 (9.5)	NA	NA	NA
Bendamustine	NA	NA	10 (3.9)	0	10 (7.3)
Rituximab	NA	NA	27 (10.4)	16 (13.1)	11 (8.0)
Fludarabine	NA	NA	15 (5.8)	15 (12.3)	0
Cyclophosphamide	NA	NA	16 (6.2)	16 (13.1)	0

Table 28. Overview of Treatment-Emergent Adverse Events (Safety Population), study ACE-CL-311

	Pivotal AMPLIFY data			Pooled populations	
	Arm A AV (N = 291) n (%)	**Arm B AVG (N=284) n (%)**	**Arm C FCR/BR (N = 259) n (%)**	**Acalabrutinib monotherapy (N = 1478) n (%)**	**Combination therapy (N = 1095) n (%)**
Any TEAEs					
Any grade	270 (92.8)	269 (94.7)	236 (91.1)	1446 (97.8)	1057 (96.5)
Grade ≥ 3	156 (53.6)	197 (69.4)	157 (60.6)	988 (66.8)	807 (73.7)
Serious TEAEs					
Any grade	72 (24.7)	109 (38.4)	71 (27.4)	753 (50.9)	509 (46.5)
Grade ≥ 3	65 (22.3)	94 (33.1)	64 (24.7)	671 (45.4)	463 (42.3)
Fatal/Grade 5 TEAEs	10 (3.4)	17 (6.0)	9 (3.5)	125 (8.5)	80 (7.3)
Treatment-related TEAEs					
Any study drug	230 (79.0)	238 (83.8)	215 (83.0)	1103 (74.6)	933 (85.2)
Acalabrutinib	221 (75.9)	223 (78.5)	0	1103 (74.6)	879 (80.3)
Treatment-related Grade ≥ 3 TEAEs					
Any study drug	117 (40.2)	157 (55.3)	143 (55.2)	451 (30.5)	606 (55.3)
Acalabrutinib	99 (34.0)	135 (47.5)	0	451 (30.5)	526 (48.0)
TEAEs leading to study drug discontinuation					
Any study drug	23 (7.9)	57 (20.1)	28 (10.8)	234 (15.8)	279 (25.5)
Acalabrutinib	22 (7.6)	39 (13.7)	0	234 (15.8)	235 (21.5)
TEAEs leading to study drug dose reduction					
Any study drug	41 (14.1)	59 (20.8)	29 (11.2)	87 (5.9)	228 (20.8)
Acalabrutinib	17 (5.8)	18 (6.3)	0	87 (5.9)	85 (7.8)
TEAEs leading to study drug withholding					
Any study drug	145 (49.8)	184 (64.8)	81 (31.3)	724 (49.0)	728 (66.5)
Acalabrutinib	140 (48.1)	172 (60.6)	0	724 (49.0)	663 (60.5)
TEAEs leading to infusion interruption (for infusion drug only)					
Any study drug	0	49 (17.3)	83 (32.0)	0	99 (9.0)

[a] Possibly related is defined as reasonable possibility that the AE was caused by treatment, as assessed by investigator. Missing responses are counted as possibly related.

Common Treatment-emergent Adverse Events

The most common TEAEs reported in the AV and AVG arms in the AMPLIFY study were consistent with the known individual safety profiles of acalabrutinib, venetoclax, and obinutuzumab (**Table 30**).

Table 29. TEAEs experienced by ≥ 10% of patients in any treatment arm. Safety Population, study ACE-CL-311

	Pivotal AMPLIFY data			**Pooled populations**	
Preferred Term	**Arm A AV (N = 291) n (%)**	**Arm B AVG (N = 284) n (%)**	**Arm C FCR/BR (N = 259) n (%)**	**Acalabrutinib monotherapy (N = 1478) n (%)**	**Combination therapy (N = 1095) n (%)**
Patients with ≥1 TEAE	270 (92.8)	269 (94.7)	236 (91.1)	1446 (97.8)	1057 (96.5)
Headache	102 (35.1)	80 (28.2)	20 (7.7)	539 (36.5)	12 (1.1)
Diarrhoea	95 (32.6)	103 (36.3)	28 (10.8)	543 (36.7)	419 (38.3)
Neutropenia	90 (30.9)	114 (40.1)	99 (38.2)	229 (15.5)	384 (35.1)
COVID-19	55 (18.9)	58 (20.4)	6 (2.3)	110 (7.4)	249 (22.7)
Nausea	43 (14.8)	62 (21.8)	93 (35.9)	322 (21.8)	301 (27.5)
Fatigue	43 (14.8)	41 (14.4)	35 (13.5)	349 (23.6)	246 (22.5)
Contusion	40 (13.7)	44 (15.5)	4 (1.5)	298 (20.2)	191 (17.4)
Arthralgia	37 (12.7)	31 (10.9)	9 (3.5)	355 (24.0)	213 (19.5)
Pruritis	32 (11.0)	13 (4.6)	14 (5.4)	99 (6.7)	114 (10.4)
Back pain	31 (10.7)	19 (6.7)	14 (5.4)	191 (12.9)	148 (13.5)
Rash	24 (8.2)	34 (12.0)	18 (6.9)	182 (12.3)	150 (13.7)
Upper respiratory tract infection	24 (8.2)	18 (6.3)	5 (1.9)	381 (25.8)	181 (16.5)
COVID-19 pneumonia	21 (7.2)	35 (12.3)	7 (2.7)	30 (2.0)	114 (10.4)
Anaemia	20 (6.9)	13 (4.6)	25 (9.7)	245 (16.6)	131 (12.0)
Myalgia	20 (6.9)	23 (8.1)	9 (3.5)	168 (11.4)	118 (10.8)
Constipation	19 (6.5)	23 (8.1)	31 (12.0)	224 (15.2)	169 (15.4)
Neutrophil count decreased	18 (6.2)	29 (10.2)	27 (10.4)	38 (2.6)	117 (10.7)
Pyrexia	17 (5.8)	44 (15.5)	47 (18.1)	262 (17.7)	184 (16.8)
Vomiting	16 (5.5)	19 (6.7)	31 (12.0)	207 (14.0)	164 (15.0)
Dizziness	16 (5.5)	19 (6.7)	8 (3.1)	206 (13.9)	139 (12.7)
Cough	14 (4.8)	23 (8.1)	13 (5.0)	373 (25.2)	197 (18.0)
Thrombocytopenia	13 (4.5)	24 (8.5)	33 (12.7)	129 (8.7)	101 (9.2)
Hypertension	12 (4.1)	9 (3.2)	6 (2.3)	166 (11.2)	96 (8.8)
Pneumonia	11 (3.8)	15 (5.3)	8 (3.1)	233 (15.8)	106 (9.7)
Dyspnoea	10 (3.4)	16 (5.6)	10 (3.9)	209 (14.1)	105 (9.6)
Oedema peripheral	10 (3.4)	16 (5.6)	8 (3.1)	176 (11.9)	125 (11.4)
Insomnia	9 (3.1)	20 (7.0)	10 (3.9)	153 (10.4)	93 (8.5)
Sinusitis	8 (2.7)	7 (2.5)	2 (0.8)	168 (11.4)	73 (6.7)
Infusion related reaction	0	56 (19.7)	85 (32.8)	13 (0.9)	144 (13.2)

In the AMPLIFY study, the treatment arm with the numerically lowest incidence of Grade ≥ 3 TEAEs was the AV arm (53.6%) followed by the FCR/BR (60.6%) and AVG arms (69.4%) (**Table 31**).

Table 30. Treatment-Emergent CTCAE Grade≥3 Adverse Events Reported in ≥5% of Patients in Any Treatment Arm (Safety Population), study ACE-CL-311

	Pivotal AMPLIFY data			Pooled populations	
Preferred Terms	**Arm A AV (N = 291) n (%)**	**Arm B AVG (N = 284) n (%)**	**Arm C FCR/BR (N = 259) n (%)**	**Acalabrutinib monotherapy (N = 1478) n (%)**	**Combination Therapy (N = 1095) n (%)**
Patients with ≥1 Grade ≥3 TEAE	156 (53.6)	197 (69.4)	157 (60.6)	988 (66.8)	807 (73.7)
Neutropenia	78 (26.8)	100 (35.2)	84 (32.4)	209 (14.1)	338 (30.9)
COVID-19 pneumonia	16 (5.5)	33 (11.6)	7 (2.7)	28 (1.9)	99 (9.0)
Neutrophil count decreased	16 (5.5)	29 (10.2)	22 (8.5)	31 (2.1)	106 (9.7)
Anaemia	11 (3.8)	6 (2.1)	17 (6.6)	140 (9.5)	60 (5.5)
COVID-19	8 (2.7)	19 (6.7)	4 (1.5)	29 (2.0)	69 (6.3)
Febrile neutropenia	5 (1.7)	7 (2.5)	24 (9.3)	25 (1.7)	31 (2.8)
Thrombocytopenia	4 (1.4)	17 (6.0)	22 (8.5)	73 (4.9)	54 (4.9)
Pneumonia	4 (1.4)	11 (3.9)	6 (2.3)	128 (8.7)	57 (5.2)

Serious adverse event/deaths/other significant events

Serious adverse event

Table 31. Serious Treatment-Emergent Adverse Events Reported in ≥ 1% of Patients in Any Treatment Arm (Safety Population), study ACE-CL-311

	Pivotal AMPLIFY data						Pooled populations			
System organ Class	**Arm A AV (N = 291) n (%)**		**Arm B AVG (N = 284) n (%)**		**Arm C FCR/BR (N = 259) n (%)**		**Acalabrutinib monotherapy (N = 1478) n (%)**		**Combination therapy (N = 1095) n (%)**	
Preferred term	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
Patients with ≥1 serious TEAE	72 (24.7)	65 (22.3)	109 (38.4)	94 (33.1)	71 (27.4)	64 (24.7)	753 (50.9)	671 (45.4)	509 (46.5)	463 (42.3)
COVID-19 pneumonia	17 (5.8)	16 (5.5)	32 (11.3)	31 (10.9)	6 (2.3)	6 (2.3)	28 (1.9)	27 (1.8)	101 (9.2)	96 (8.8)
COVID-19	9 (3.1)	7 (2.4)	17 (6.0)	15 (5.3)	4 (1.5)	4 (1.5)	33 (2.2)	28 (1.9)	66 (6.0)	57 (5.2)
Febrile neutropenia	5 (1.7)	5 (1.7)	5 (1.8)	5 (1.8)	21 (8.1)	21 (8.1)	22 (1.5)	21 (1.4)	24 (2.2)	24 (2.2)

System organ Class	Pivotal AMPLIFY data						Pooled populations			
	Arm A AV (N = 291) n (%)		Arm B AVG (N = 284) n (%)		Arm C FCR/BR (N = 259) n (%)		Acalabrutinib monotherapy (N = 1478) n (%)		Combination therapy (N = 1095) n (%)	
Preferred term	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Pneumonia	4 (1.4)	3 (1.0)	10 (3.5)	10 (3.5)	8 (3.1)	6 (2.3)	122 (8.3)	113 (7.6)	60 (5.5)	51 (4.7)
Anaemia	3 (1.0)	3 (1.0)	2 (0.7)	1 (0.4)	3 (1.2)	3 (1.2)	40 (2.7)	36 (2.4)	16 (1.5)	15 (1.4)
Abdominal pain	2 (0.7)	2 (0.7)	0	0	1 (0.4)	1 (0.4)	16 (1.1)	9 (0.6)	4 (0.4)	3 (0.3)
Pyrexia	2 (0.7)	1 (0.3)	6 (2.1)	3 (1.1)	8 (3.1)	4 (1.5)	37 (2.5)	17 (1.2)	30 (2.7)	13 (1.2)
Acute kidney injury	1 (0.3)	1 (0.3)	3 (1.1)	3 (1.1)	2 (0.8)	2 (0.8)	17 (1.2)	15 (1.0)	12 (1.1)	11 (1.0)
Dyspnoea	1 (0.3)	0	0	0	0	0	16 (1.1)	16 (1.1)	10 (0.9)	6 (0.5)
Neutropenia	1 (0.3)	1 (0.3)	3 (1.1)	3 (1.1)	2 (0.8)	2 (0.8)	6 (0.4)	6 (0.4)	9 (0.8)	8 (0.7)
Pulmonary embolism	1 (0.3)	1 (0.3)	3 (1.1)	2 (0.7)	1 (0.4)	1 (0.4)	5 (0.3)	3 (0.2)	8 (0.7)	7 (0.6)
Sepsis	1 (0.3)	1 (0.3)	2 (0.7)	2 (0.7)	2 (0.8)	2 (0.8)	24 (1.6)	22 (1.5)	15 (1.4)	15 (1.4)
Thrombocytopenia	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	3 (1.2)	3 (1.2)	10 (0.7)	10 (0.7)	5 (0.5)	5 (0.5)
Infusion related reaction	0	0	3 (1.1)	1 (0.4)	5 (1.9)	5 (1.9)	1 (0.1)	0	9 (0.8)	4 (0.4)
Lower respiratory tract infection	0	0	2 (0.7)	2 (0.7)	0	0	17 (1.2)	13 (0.9)	8 (0.7)	8 (0.7)
Atrial fibrillation	0	0	1 (0.4)	1 (0.4)	2 (0.8)	2 (0.8)	23 (1.6)	19 (1.3)	12 (1.1)	9 (0.8)
Neutrophil count decreased	0	0	1 (0.4)	1 (0.4)	3 (1.2)	3 (1.2)	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.2)
TLS	0	0	1 (0.4)	1 (0.4)	6 (2.3)	6 (2.3)	5 (0.3)	5 (0.3)	4 (0.4)	4 (0.4)
Urinary tract infection	0	0	1 (0.4)	0	0	0	24 (1.6)	21 (1.4)	8 (0.7)	6 (0.5)
Cellulitis	0	0	0	0	0	0	15 (1.0)	13 (0.9)	12 (1.1)	12 (1.1)
Respiratory tract infection	0	0	0	0	0	0	15 (1.0)	14 (0.9)	4 (0.4)	4 (0.4)
Upper respiratory tract infection	0	0	0	0	0	0	15 (1.0)	11 (0.7)	3 (0.3)	2 (0.2)

Deaths

Table 32. Summary of Deaths (Safety Population), study ACE-CL-311

	Pivotal AMPLIFY data			Pooled populations	
	Arm A AV (N = 291) n (%)	**Arm B AVG (N = 284) n (%)**	**Arm C FCR/BR (N = 259) n (%)**	**Acalabrutinib monotherapy (N = 1478) n (%)**	**Combination therapy (N = 1095) n (%)**
Deaths	18 (6.2)	36 (12.7)	42 (16.2)	355 (24.0)	187 (17.1)
Primary cause of death					
Adverse event	16 (5.5)	29 (10.2)	28 (10.8)	142 (9.6)	110 (10.0)
Other	2 (0.7)	5 (1.8)	6 (2.3)	37 (2.5)	25 (2.3)
Disease progression	0	0	4 (1.5)	127 (8.6)	35 (3.2)
Unknown	0	2 (0.7)	4 (1.5)	34 (2.3)	15 (1.4)
Richter's Transformation	0	0	0	10 (0.7)	2 (0.2)
Within 30 days of last dose of study drug					
Deaths	10 (3.4)	11 (3.9)	7 (2.7)	182 (12.3)	73 (6.7)
Primary cause of death					
Disease progression	0	0	0	54 (3.7)	9 (0.8)
Adverse event	10 (3.4)	11 (3.9)	7 (2.7)	108 (7.3)	61 (5.6)
Richter's Transformation	0	0	0	6 (0.4)	0
Other	0	0	0	9 (0.6)	1 (0.1)
Unknown	0	0	0	5 (0.3)	2 (0.2)
More than 30 days after last dose of study drug					
Deaths	8 (2.7)	25 (8.8)	35 (13.5)	173 (11.7)	114 (10.4)
Primary cause of death					
Disease progression	0	0	4 (1.5)	73 (4.9)	26 (2.4)
Adverse event	6 (2.1)	18 (6.3)	21 (8.1)	34 (2.3)	49 (4.5)
Richter's Transformation	0	0	0	4 (0.3)	2 (0.2)
Other	2 (0.7)	5 (1.8)	6 (2.3)	28 (1.9)	24 (2.2)
Unknown	0	2 (0.7)	4 (1.5)	29 (2.0)	13 (1.2)

Table 33. Treatment-Emergent Adverse Events with a Fatal Outcome Reported for ≥ 0.3% of Patients (CTCAE Grade 5) in Any Group (Safety Population), study ACE-CL-311

	Pivotal AMPLIFY data			Pooled populations	
	Arm A AV (N = 291) n (%)	Arm B AVG (N = 284) n (%)	Arm C FCR/BR (N = 259) n (%)	Acalabrutinib monotherapy n (%) (N = 1478)	Combination therapy n (%) (N = 1095)
Patients with a Grade 5 TEAE	10 (3.4)	17 (6.0)	9 (3.5)	125 (8.5)	80 (7.3)
COVID-19 pneumonia	6 (2.1)	10 (3.5)	4 (1.5)	5 (0.3)	34 (3.1)
COVID-19	2 (0.7)	5 (1.8)	3 (1.2)	12 (0.8)	18 (1.6)
Cardiac arrest	1 (0.3)	0	1 (0.4)	3 (0.2)	1 (0.1)
Infection	1 (0.3)	0	0	0	1 (0.1)
Pneumonia	0	1 (0.4)	0	16 (1.1)	6 (0.5)
Sudden death	0	1 (0.4)	0	1 (0.1)	1 (0.1)
Septic shock	0	0	0	8 (0.5)	0
Sepsis	0	0	0	5 (0.3)	4 (0.4)
Cerebrovascular accident	0	0	0	4 (0.3)	1 (0.1)
Respiratory failure	0	0	0	4 (0.3)	0
Acute kidney injury	0	0	1 (0.4)		

Events of clinical interest (ECI)

Events of clinical interest (ECI) were identified based on nonclinical findings, emerging data from clinical studies relating to 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).

Adverse events of special interest associated with acalabrutinib are ventricular arrythmias (Acalabrutinib Investigator Brochure, 13th Edition, 14 March 2024). Suspected transmission of an infectious agent via product is an AESI for study treatments containing biologic products (e.g., obinutuzumab).

Cardiac events

Table 34. Treatment-Emergent Events of Clinical Interest and Adverse Events of Special Interest: Cardiac Events (Safety Population), study ACE-CL-311

ECI/AESI category ECI/AESI subcategory Preferred term	Pivotal AMPLIFY data					
	Arm A AV (N = 291) n (%)		Arm B AVG (N = 284) n (%)		Arm C FCR/BR (N = 259) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Cardiac events	27 (9.3)	5 (1.7) [a]	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Atrial flutter	0	0	0	0	0	0
Ventricular tachyarrhythmias	2 (0.7)	0	3 (1.1)	0	0	0
Ventricular extrasystoles	1 (0.3)	0	2 (0.7)	0	0	0
Ventricular arrhythmias	0	0	0	0	0	0
Ventricular fibrillation	0	0	0	0	0	0

ECI/AESI category ECI/AESI subcategory Preferred term	Pivotal AMPLIFY data					
	Arm A AV (N = 291) n (%)		Arm B AVG (N = 284) n (%)		Arm C FCR/BR (N = 259) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Ventricular tachycardia	1 (0.3)	0	1 (0.4)	0	0	0
Other cardiac events						
Other cardiac events with ≥ 2% incidence in any group	24 (8.2)	4 (1.4)	27 (9.5)	5 (1.8)	7 (2.7)	1 (0.4)
Palpitations	8 (2.7)	0	11 (3.9)	0	0	0
Angina pectoris	3 (1.0)	0	5 (1.8)	1 (0.4)	1 (0.4)	0
Tachycardia	5 (1.7)	0	2 (0.7)	0	1 (0.4)	0
Cardiac failure	1 (0.3)	1 (0.3)	0	0	1 (0.4)	0

[a] One patient in the AV arm had a Grade 5 cardiac arrest on Study Day 391

The median time from first dose of study drug to onset of the ECI ventricular tachyarrhythmia in the AV and AVG arms was 44 days (range: 15 to 73) and 311 days (range: 100 to 332 days), respectively, and for atrial fibrillation in the AV, AVG, and FCR/BR arms it was 351 days (range: 314 to 388 days), 85 days (range: 28 to 377), and 59 days (range: 57 to 61 days), respectively.

Cytopenias

Table 35. Treatment-Emergent Adverse Events of Events of Clinical Interest: Cytopenia in ≥10% of Patients in Any Group (Safety Population), study ACE-CL-311

ECI category ECI subcategory Preferred term	Pivotal AMPLIFY data					
	Arm A AV (N = 291) n (%)		Arm B AVG (N = 284) n (%)		Arm C FCR/BR (N = 259) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Anaemia	20 (6.9)	11 (3.8)	13 (4.6)	6 (2.1)	25 (9.7)	17 (6.6)
Anaemia	20 (6.9)	11 (3.8)	13 (4.6)	6 (2.1)	25 (9.7)	17 (6.6)
Leukopenia	109 (37.5)	95 (32.6)	147 (51.8)	135 (47.5)	140 (54.1)	120 (46.3)
Neutropenia	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Neutropenia	90 (30.9)	78 (26.8)	114 (40.1)	100 (35.2)	99 (38.2)	84 (32.4)
Neutrophil count decreased	18 (6.2)	16 (5.5)	29 (10.2)	29 (10.2)	27 (10.4)	22 (8.5)
Other leukopenia	11 (3.8)	6 (2.1)	12 (4.2)	6 (2.1)	23 (8.9)	16 (6.2)

ECI category ECI subcategory Preferred term	Pivotal AMPLIFY data					
	Arm A AV (N = 291) n (%)		Arm B AVG (N = 284) n (%)		Arm C FCR/BR (N = 259) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
WBC count decreased	7 (2.4)	4 (1.4)	2 (0.7)	0	9 (3.5)	4 (1.5)
Thrombocytopenia	17 (5.8)	6 (2.1)	35 (12.3)	26 (9.2)	39 (15.1)	28 (10.8)
Thrombocytopenia	13 (4.5)	4 (1.4)	24 (8.5)	17 (6.0)	33 (12.7)	22 (8.5)
Platelet count deceased	4 (1.4)	2 (0.7)	12 (4.2)	9 (3.2)	8 (3.1)	7 (2.7)

Haemorrhages

Table 36. Treatment-Emergent Adverse Events of Clinical Interest: Haemorrhage and Major Haemorrhage Reported in ≥ 2% of Patients in Any Group (Safety Population), study ACE-CL-311

ECI subcategory Preferred term	Pivotal AMPLIFY data					
	Arm A AV (N = 291) n (%)		Arm B AVG (N = 284) n (%)		Arm C FCR/BR (N = 259) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Haemorrhage	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Contusion	40 (13.7)	0	44 (15.5)	0	4 (1.5)	0
Haematuria	3 (1.0)	0	8 (2.8)	1 (0.4)	2 (0.8)	0
Haematoma	17 (5.8)	1 (0.3)	9 (3.2)	0	1 (0.4)	0
Conjunctival haemorrhage	2 (0.7)	0	2 (0.7)	0	0	0
Ecchymosis	8 (2.7)	0	11 (3.9)	0	0	0
Epistaxis	5 (1.7)	0	12 (4.2)	0	2 (0.8)	0
Purpura	5 (1.7)	0	6 (2.1)	0	0	0
Petechiae	14 (4.8)	0	15 (5.3)	0	0	0
Increased tendency to bruise	4 (1.4)	0	1 (0.4)	0	0	0
Rectal haemorrhage	0	0	2 (0.7)	1 (0.4)	0	0
Major haemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)

Major hemorrhage was defined as any hemorrhagic event that was serious or Grade ≥ 3 in severity, or that was a CNS hemorrhage (any severity grade).

Hepatotoxicity

Table 37. Treatment-Emergent Adverse Events of Clinical Interest: Hepatotoxicity Reported in ≥ 0.5% of Patients in Any Group (Safety Population), study ACE-CL-311

ECI category Preferred term	Pivotal AMPLIFY data					
	Arm A AV (N = 291) n (%)		Arm B AVG (N = 284) n (%)		Arm C FCR/BR (N = 259) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Hepatotoxicity	17 (5.8)	10 (3.4)	19 (6.7)	8 (2.8)	9 (3.5)	4 (1.5)
ALT increased	6 (2.1)	3 (1.0)	10 (3.5)	5 (1.8)	4 (1.5)	2 (0.8)
AST increased	5 (1.7)	2 (0.7)	6 (2.1)	1 (0.4)	2 (0.8)	0
Transaminases increased	2 (0.7)	1 (0.3)	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.4)
Blood bilirubin increased	0	0	1 (0.4)	0	1 (0.4)	0
GGT increased	1 (0.3)	1 (0.3)	1 (0.4)	0	2 (0.8)	1 (0.4)

Hypertension

Hypertension events occurred in 4.1%, 3.9%, and 2.7% of patients in the AV, AVG, and FCR/BR arms, respectively. Grade ≥ 3 hypertension events occurred in 2.7%, 2.1%, and 0.8% of patients, respectively.

Median time from first dose of study drug to onset of hypertension of any grade was 197 days (range: 16 to 442 days) in the AV arm, 197 days (range: 15 to 424 days) in the AVG arm, and 44 days (range: 1 to 142 days) in the FCR/BR arm.

Infections

Table 38. Treatment-Emergent Adverse Events of Clinical Interest: Infections Reported for ≥ 5% Patients in Any Group (Safety Population), study ACE-CL-311

ECI category Preferred term	Pivotal AMPLIFY data					
	Arm A AV (N = 291) n (%)		Arm B AVG (N = 284) n (%)		Arm C FCR/BR (N = 259) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Infections	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)

ECI category Preferred term	Pivotal AMPLIFY data					
	Arm A AV (N = 291) n (%)		Arm B AVG (N = 284) n (%)		Arm C FCR/BR (N = 259) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
COVID-19	55 (18.9)	8 (2.7)	58 (20.4)	19 (6.7)	6 (2.3)	4 (1.5)
Upper respiratory tract infection	24 (8.2)	1 (0.3)	18 (6.3)	0	5 (1.9)	0
Pneumonia	11 (3.8)	4 (1.4)	15 (5.3)	11 (3.9)	8 (3.1)	6 (2.3)
COVID-19 pneumonia	21 (7.2)	16 (5.5)	35 (12.3)	33 (11.6)	7 (2.7)	7 (2.7)
Urinary tract infection	9 (3.1)	0	17 (6.0)	1 (0.4)	10 (3.9)	0
Herpes zoster	5 (1.7)	0	4 (1.4)	1 (0.4)	4 (1.5)	1 (0.4)
Bronchitis	6 (2.1)	0	7 (2.5)	0	2 (0.8)	1 (0.4)
Sinusitis	8 (2.7)	0	7 (2.5)	0	2 (0.8)	0
Nasopharyngitis	4 (1.4)	0	3 (1.1)	0	5 (1.9)	0
Respiratory tract infection	3 (1.0)	0	1 (0.4)	0	1 (0.4)	0
Lower respiratory tract infection	0	0	5 (1.8)	2 (0.7)	0	0

An evaluation of concomitant infection and neutropenia (based on laboratory values) was also provided. Infections and Grade ≥ 3 infections with onset 2 weeks prior to or after onset of neutropenia (any grade and Grade ≥3 based on laboratory values) are summarized in **Table 40**.

Table 39. Infections and Neutropenia (Safety Population), study ACE-CL-311

	Patients with any neutropenia n (%)	Patients with neutropenia Grade ≥ 3 n (%)	Patients without any neutropenia n (%)
Patients with any infection[a]			
AV (N = 148)	42 (28.4)	13 (8.8)	106 (71.6)
AVG (N = 153)	51 (33.3)	25 (16.3)	102 (66.7)
FCR/BR (N = 82)	30 (36.6)	16 (19.5)	52 (63.4)
Acalabrutinib Monotherapy Pool (N = 1098)	111 (10.1)	59 (5.4)	987 (89.9)
Combination Therapy Pool (N = 724)	194 (26.8)	93 (12.8)	530 (73.2)
Patients with any Grade ≥ 3 infection[a]			
AV (N = 36)	6 (16.7)	1 (2.8)	30 (83.3)
AVG (N = 67)	15 (22.4)	8 (11.9)	52 (77.6)
FCR/BR (N = 26)	11 (42.3)	7 (26.9)	15 (57.7)
Acalabrutinib Monotherapy Pool (N = 390)	30 (7.7)	18 (4.6)	360 (92.3)
Combination Therapy Pool (N = 302)	52 (17.2)	26 (8.6)	250 (82.8)

[a] Treatment emergent neutropenia by laboratory within 2 weeks or on the same day of infection onset date.

Infections Grade ≥ 3 with concomitant Grade ≥ 3 neutropenia occurred at higher incidence in the AVG arm (11.9%) compared to the AV arm (2.8%).

Grade 5 infections reported in 2 or more patients included COVID-19 pneumonia (2.1%, 3.5%, and 1.5%) and COVID-19 (0.7%, 1.8%, and 1.2%). TEAEs with fatal outcome due to infection were 9 (3%) in the AV, 16 (5.6%) in AVG and 7 (2.7%) in FCR/BR arms.

ILD/pneumonitis

Interstitial lung disease/pneumonitis of any grade occurred in 1.8% of patients in the AVG arm and 1 patient (0.4%) experienced a Grade 3 event in the FCR/BR arm. No patient had an event of ILD/pneumonitis in the AV arm.

Detailed review of the reported events of pneumonitis in AVG patients revealed that all of them reported prior events of lung infection, including pneumonia or lower respiratory tract infection.

Second Primary malignancies (SPMs)

Table 40. Treatment-Emergent Events of Clinical Interest: Second Primary Malignancies Occurring in ≥ 2 Patients in Any Arm (Safety Population), study ACE-CL-311

ECI Subcategory *ECI Subcategory* Preferred Term	Arm A (AV) N = 291 n (%)	Arm B (AVG) N = 282 n (%)	Arm C (FCR/BR)		
			Total N = 259 n (%)	FCR only N = 122 n (%)	BR only N = 137 n (%)
Second primary malignancies					
Any Grade	15 (5.2)	12 (4.2)	2 (0.8)	2 (1.6)	0
Grade ≥ 3	5 (1.7)	5 (1.8)	0	0	0
Basal Cell Carcinoma					
Any Grade	6 (2.1)	4 (1.4)	1 (0.4)	1 (0.8)	0
Grade ≥ 3	0	1 (0.4)	0	0	0
Squamous Cell Carcinoma of Skin					
Any Grade	4 (1.4)	1 (0.4)	0	0	0
Grade ≥ 3	0	0	0	0	0
Malignant Melanoma					
Any Grade	2 (0.7)	0	1 (0.4)	1 (0.8)	0
Grade ≥ 3	2 (0.7)	0	0	0	0
Second primary malignancy – excluding non-melanoma skin					
Any Grade	8 (2.7)	7 (2.5)	1 (0.4)	1 (0.8)	0
Grade ≥ 3	5 (1.7)	4 (1.4)	0	0	0
Malignant Melanoma					
Any Grade	2 (0.7)	0	1 (0.4)	1 (0.8)	0
Grade ≥ 3	2 (0.7)	0	0	0	0

The median time from first dose of study drug to onset of first SPM in the AV, AVG, and FCR/BR arms was 169 days (range: 57 to 425), 193 days (range: 11 to 360 days), and 107.5 days (range: 84 to 131 days), respectively. The median time from first dose of study drug to onset of first SPM, excluding

non-melanoma skin was 218.5 days (range: 57 to 351 days), 259 days (range: 37 to 360 days), and 84 days (range: 84 to 84) (see ISS Table 25.1, Module 5.3.5.3).

Tumour Lysis Syndrome (TLS)

The incidence of TLS events in the AV and AVG arms was low. One (0.3%) patient in the AV arm and one (0.4%) patient in the AVG arm. There were 8 (3.1%) patients in the FCR/BR arm (all of whom received BR) who had TLS events. All TLS events reported were Grade ≥ 3 in severity. No Grade 5 TLS events were reported.

TLS mitigation strategies were employed per the AMPLIFY protocol because Grade 3 TLS is a known risk of venetoclax. These mitigations strategies included the following: Initiation of acalabrutinib for 2 cycles before initiation of venetoclax. A 5-week dose ramp-up schedule for venetoclax. Gradual debulking with acalabrutinib (and obinutuzumab in Arm B) prior to initiation of venetoclax. Restaging with computed tomography at Cycle 3 prior to initiation of venetoclax to determine appropriate TLS risk and initiate most appropriate prophylaxis. Optional hospitalization for observation during 1st week at investigator's discretion following re-staging at Cycle 3.

Adverse Drug Reactions

No new ADRs were identified specific for acalabrutinib in the AV and AVG combination regimen based on the AMPLIFY study data **(**

Table 42).

Table 41. Frequency and CTCAE Grades of Acalabrutinib-Related Adverse Drug Reactions by Treatment Arms in AMPLIFY Study and in Acalabrutinib Monotherapy and Combination Therapy Pools (Safety Population), study ACE-CL-311

ADR system organ class/ ADR term	Pivotal AMPLIFY (N = 834)						Acalabrutinib monotherapy pool (N = 1478)		Acalabrutinib combination therapy Pool (N = 1095)	
	AV (N = 291)		AVG (N = 284)		FCR/BR (N = 259)					
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Blood and lymphatic system disorders										
Leukopenia	109 (37.5%)	95 (32.6%)	147 (51.8%)	135 (47.5%)	140 (54.1%)	120 (46.3 %)	308 (20.8%)	269 (18.2%)	509 (46.5%)	459 (41.9%)
Neutropenia	108 (37.1%)	94 (32.3%)	143 (50.4%)	131 (46.1%)	132 (51.0%)	112 (43.2 %)	286 (19.4%)	259 (17.5%)	490 (44.7%)	444 (40.5%)
Anaemia	20 (6.9%)	11 (3.8%)	13 (4.6%)	6 (2.1%)	25 (9.7%)	17 (6.6%)	253 (17.1%)	140 (9.5%)	138 (12.6%)	61 (5.6%)
Thrombocytopenia	17 (5.8%)	6 (2.1%)	35 (12.3%)	26 (9.2%)	39 (15.1%)	28 (10.8 %)	170 (11.5%)	92 (6.2%)	155 (14.2%)	81 (7.4%)
Cardiac disorders										
Atrial fibrillation/flutter	2 (0.7%)	1 (0.3%)	6 (2.1%)	2 (0.7%)	2 (0.8%)	2 (0.8 %)	109 (7.4%)	34 (2.3%)	45 (4.1 %)	19 (1.7%)

ADR system organ class/ ADR term	Pivotal AMPLIFY (N = 834)						Acalabrutinib monotherapy pool (N = 1478)		Acalabrutinib combination therapy Pool (N = 1095)	
	AV (N = 291)		AVG (N = 284)		FCR/BR (N = 259)					
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Nervous system disorders										
Headache	102 (35.1%)	4 (1.4%)	80 (28.2%)	1 (0.4%)	20 (7.7%)	1 (0.4%)	539 (36.5%)	17 (1.2%)	369 (33.7%)	12 (1.1%)
Dizziness	16 (5.5%)	0	19 (6.7%)	0	8 (3.1%)	0	206 (13.9%)	2 (0.1%)	139 (12.7%)	4 (0.4%)
Respiratory, thoracic and mediastinal disorders										
Epistaxis	5 (1.7%)	0	12 (4.2%)	0	2 (0.8%)	0	118 (8.0%)	4 (0.3%)	50 (4.6%)	0
Gastrointestinal disorders										
Diarrhoea	95 (32.6%)	5 (1.7%)	103 (36.3%)	4 (1.4%)	28 (10.8%)	1 (0.4%)	543 (36.7%)	39 (2.6%)	419 (38.3%)	33 (3.0%)
Nausea	43 (14.8%)	0	62 (21.8%)	2 (0.7%)	93 (35.9%)	0	322 (21.8%)	12 (0.8%)	301 (27.5%)	6 (0.5%)
Constipation	19 (6.5%)	1 (0.3%)	23 (8.1%)	0	31 (12.0%)	1 (0.4%)	224 (15.2%)	1 (0.1%)	169 (15.4%)	4 (0.4%)
Abdominal pain	23 (7.9%)	3 (1.0%)	23 (8.1%)	2 (0.7%)	11 (4.2%)	2 (0.8%)	215 (14.5%)	18 (1.2%)	129 (11.8%)	16 (1.5%)
Vomiting	16 (5.5%)	0	19 (6.7%)	0	31 (12.0%)	0	207 (14.0%)	11 (0.7%)	164 (15.0%)	5 (0.5%)
General disorders and administration site conditions										
Fatigue	43 (14.8%)	1 (0.3%)	41 (14.4%)	0	35 (13.5%)	2 (0.8%)	349 (23.6%)	30 (2.0%)	246 (22.5%)	14 (1.3%)
Asthenia	12 (4.1%)	0	9 (3.2%)	0	10 (3.9%)	2 (0.8%)	103 (7.0%)	13 (0.9%)	73 (6.7%)	4 (0.4%)
Metabolism and nutrition disorders										
Tumour Lysis Syndrome	1 (0.3%)	1 (0.3%)	1 (0.4%)	1 (0.4%)	8 (3.1%)	8 (3.1%)	7 (0.5%)	6 (0.4%)	10 (0.9%)	10 (0.9%)
Musculoskeletal and connective tissue disorders										
Arthralgia	37 (12.7%)	3 (1.0%)	31 (10.9%)	1 (0.4%)	9 (3.5%)	0	355 (24.0%)	14 (0.9%)	213 (19.5%)	11 (1.0%)
Musculoskeletal Pain	70 (24.1%)	2 (0.7%)	62 (21.8%)	3 (1.1%)	34 (13.1%)	2 (0.8%)	471 (31.9%)	27 (1.8%)	351 (32.1%)	22 (2.0%)
Infections and Infestations										
Infection	148 (50.9%)	36 (12.4%)	153 (53.9%)	67 (23.6%)	82 (31.7%)	26 (10.0%)	1098 (74.3%)	388 (26.3%)	724 (66.1%)	302 (27.6%)

ADR system organ class/ ADR term	Pivotal AMPLIFY (N = 834)						Acalabrutinib monotherapy pool (N = 1478)		Acalabrutinib combination therapy Pool (N = 1095)	
	AV (N = 291)		AVG (N = 284)		FCR/BR (N = 259)					
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Neoplasms benign, malignant and unspecified										
SPM	15 (5.2%)	5 (1.7%)	12 (4.2%)	5 (1.8%)	2 (0.8%)	0	260 (17.6%)	99 (6.7%)	133 (12.1%)	52 (4.7%)
SPM excluding non-melanoma ski	8 (2.7%)	5 (1.7%)	7 (2.5%)	4 (1.4%)	1 (0.4%)	0	143 (9.7%)	81 (5.5%)	74 (6.8%)	40 (3.7%)
Non-Melanoma Skin Malignancy	9 (3.1%)	0	5 (1.8%)	1 (0.4%)	1 (0.4%)	0	146 (9.9%)	21 (1.4%)	79 (7.2%)	13 (1.2%)
Skin and subcutaneous tissue disorders										
Bruising	60 (20.6%)	0	62 (21.8%)	0	4 (1.5%)	0	457 (30.9%)	0	262 (23.9%)	1 (0.1%)
Rash	35 (12.0%)	1 (0.3%)	46 (16.2%)	3 (1.1%)	33 (12.7%)	2 (0.8%)	300 (20.3%)	14 (0.9%)	270 (24.7%)	37 (3.4%)
Vascular disorders										
Haemorrhage/ Haematoma	26 (8.9%)	2 (0.7%)	24 (8.5%)	3 (1.1%)	4 (1.5%)	0	241 (16.3%)	47 (3.2%)	149 (13.6%)	18 (1.6%)
Investigations										
Alanine aminotransferase increased	6 (2.1%)	3 (1.0%)	10 (3.5%)	5 (1.8%)	4 (1.5%)	2 (0.8%)	42 (2.8%)	16 (1.1%)	50 (4.6%)	26 (2.4%)
Aspartate aminotransferase increased	5 (1.7%)	2 (0.7%)	6 (2.1%)	1 (0.4%)	2 (0.8%)	0	31 (2.1%)	9 (0.6%)	39 (3.6%)	15 (1.4%)

Laboratory findings

Similar incidences of haematology parameters worsening by 3 grades (from Grade 0 at baseline to Grade 3 postbaseline [maximum grade] or Grade 1 at baseline to Grade 4 post baseline [maximum grade]) were reported in the AV, AVG, and FCR/BR arms, respectively, for ALC (0%, 0.7%, and 2.3%), ANC (21.4%, 27.8%, and 24.4%), haemoglobin (0.3%, 0%, and 0%), platelets (1.0%, 5.3%, and 3.9%), and leukocytes (25.2%, 25.4%, and 21.3%).

Worsening by 4 grades from Grade 0 at baseline to Grade 4 postbaseline (maximum grade) was reported in the AV, AVG, and FCR/BR arms, respectively, for ALC (0.3%, 0%, and 1.6%), ANC (11.7%, 21.1%, and 23.3%), platelets (0%, 0.4%, and 0.8%), and leukocytes (0.7%, 1.4%, and 8.5%).

Median durations for neutropenia were 9, 12, and 15 days, for thrombocytopenia was 22, 13, and 16 days; and for anaemia was 8, 7, and 9 days in the AV and AVG and FCR/BR arms respectively.

In the AMPLIFY study, the proportion of patients with lymphocytosis (defined as ALC of > 5,000 cells/μL and an increase above baseline) was higher in the AV (42.6%) and AVG (43.0%) arms compared to the FCR/BR (4.2%) arm. The median time to first onset of lymphocytosis was 4.1 weeks, 4.1, and 0.3 weeks in the AV, AVG and FCR/BR arms, respectively, and median duration was 5.3 days, 1.1 day, and 1.3 day, respectively.

The incidence of patients with Grade 4 treatment-emergent abnormal ANC values trended higher in the AVG and FCR/BR arms compared to the AV arm.

Clinical chemistry

Overall shifts in mean clinical chemistry grades over time were similar in the AV, AVG, and FCR/BR 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. No new safety signal was observed. No notable differences between the AV, AVG, and FCR/BR arms were noted for changes in creatine, albumin, calcium, glucose, potassium, LDH, phosphate, and sodium.

The incidence of shifts from baseline across serum chemistry parameters was generally consistent between the AV and AVG arms in AMPLIFY and the Acalabrutinib Monotherapy Pool.

Potential Hy's law

The review of liver enzymes levels for AST and ALT alongside bilirubin levels following the biochemical criteria for potential Hy's Law resulted in the identification of 1 patient in the AVG arm who fulfilled the biochemical criteria for potential Hy's law. After a comprehensive review of this patient, alternative infectious aetiology was identified, and it was concluded that this was not a Hy's Law case.

Serum immunoglobulin

No clinically significant changes in serum immunoglobulin values from baseline to last post-baseline values were noted for patients in all treatment arms.

Safety in special populations

There were no discernible differences in the safety profiles of AV and AVG with respect to sex, race, hepatic impairment, or renal impairment.

A trend towards more deaths at older age was observed, however, the groups are too small to draw conclusions.

Discontinuation due to adverse events

Table 42. Adverse Events Leading to Discontinuation of Study Treatment in ≥ 2 Patients in Any Treatment Arm (Safety Population), study ACE-CL-311

Preferred Term	Arm A (AV) N = 291 n (%)	Arm B (AVG) N = 284 n (%)
Patients with ≥ 1 AE leading to discontinuation of any study treatment	23 (7.9)	57 (20.1)
Patients with ≥ 1 AE leading to discontinuation of acalabrutinib	22 (7.6)	39 (13.7)
COVID-19 pneumonia	6 (2.1)	8 (2.8)
COVID-19	1 (0.3)	11 (3.9)
Thrombocytopenia	2 (0.7)	3 (1.1)
Neutrophil count decreased	0	2 (0.7)
Pneumonia	0	2 (0.7)
Pneumonitis	0	2 (0.7)
Patients with ≥ 1 AE leading to discontinuation of venetoclax	18 (6.2)	37 (13.0)
COVID-19 pneumonia	4 (1.4)	9 (3.2)
COVID-19	1 (0.3)	9 (3.2)
Thrombocytopenia	2 (0.7)	2 (0.7)
Neutropenia	1 (0.3)	2 (0.7)
Acute kidney injury	0	2 (0.7)
Diarrhoea	0	2 (0.7)
Pneumonia	0	2 (0.7)
Patients with ≥ 1 AE leading to discontinuation of obinutuzumab	NA	27 (9.5)
COVID-19	NA	6 (2.1)
Thrombocytopenia	NA	5 (1.8)
COVID-19 pneumonia	NA	4 (1.4)
Neutropenia	NA	3 (1.1)
Infusion related reaction	NA	2 (0.7)

2.5.1. Discussion on clinical safety

Acalabrutinib, is a selective BTKi. The qualitative safety profile of BTKi is well characterised. Class related concerns include gastrointestinal (GI) disturbances (diarrhoea, nausea, and vomiting), cytopenias, bleeding events, and infections. Other toxicities that have been associated with BTKi include atrial fibrillation and hypertension.

The safety profiles of venetoclax and obinutuzumab are also well described, including e.g., GI-side effects, TLS and infections for the former, and infections for the latter. Additive or synergistic effects are anticipated with regards to cytopenias and infection.

AMPLIFY study

A total of 834 patients (291 in AV arm, 284 in AVG arm, and 259 in FCR/BR arm) received at least one dose of any study treatment.

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 1095 patients in a Combination Therapy Pool, with data from 4 studies, including ABR (acalabrutinib + BR) and AG (acalabrutinib + obinutuzumab) combination regimens.

Exposure

The median durations of exposure to acalabrutinib (12.9 months in Arm A and Arm B) and venetoclax (Arm A: 11.1 months and Arm B: 11.0 months). The median duration of exposure to obinutuzumab was 5.5 months in Arm B. For Arm C, the median durations of exposure were approx. 2.3 times shorter than for acalabrutinib in Arm A and Arm B, i.e. for fludarabine, cyclophosphamide, and bendamustine it was 5.6 months each and 5.5 months for rituximab.

A total of 95.9% and 93.3% of patients in the AV and AVG arms, respectively, received > 6 months exposure to acalabrutinib, and 91.1% and 84.2% of patients received > 12 months exposure. The median exposure to acalabrutinib was 13 months with a maximum of 18 months.

The number of patients per treatment arm and overall exposure is sufficient to characterize the safety profile of the combination of acalabrutinib with venetoclax and Obinutuzumab.

Adverse Events and Deaths

Grade ≥ 3 TEAEs occurred in 53.6%, 69.4%, and 60.6% of patients in Arm A (AV), Arm B (AVG), and Arm C (FCR/BR), respectively. The incidence of serious TEAE of Grade ≥ 3 was similar in Arm A and Arm C (22.3% and 24.7%, respectively) but more frequent in Arm B (AVG) (33.1%).

The overall incidences of patients with CTCAE Grade ≥ 3 AEs, AEs leading to dose withholding of acalabrutinib, SAEs, and AEs leading to discontinuation of study drug were numerically higher in the AVG arm than in the AV arm.

The TEAEs by PT with the highest incidences were for the AV Arm: headache (35.1%), diarrhoea (32.6%), and neutropenia (30.9%); for the AVG Arm: neutropenia (40.1%), diarrhoea (36.3%), headache (28.2%), nausea (21.8%), and COVID-19 (20.4%); and for the FCR/BR: neutropenia (38.2%), nausea (35.9%), and infusion related reaction (32.8%).

The most common TEAEs reported in the AV and AVG arms in the AMPLIFY study were consistent with the known individual safety profiles of acalabrutinib, venetoclax, and obinutuzumab.

Patients experiencing ≥1 Grade ≥3 TEAE were; AV 156 patients (53.6%), in AVG 197 (69.4%) patients and in FCR/BR 157 (60.6%) patients. The most common Grade ≥ 3 TEAEs were neutropenia in all treatment arms with fairly similar frequencies: AV 26.8%, AVG 35.2% and FCR 29.5%, BR 35%). Grade ≥ 3 febrile neutropenia events were reported in 5 (1.7%) patients in the AV arm, 7 (2.5%) patients in the AVG arm, and 24 (9.3%) patients in the FCR/BR arm.

Overall, TE SAEs in the AMPLIFY study were reported in 24.7%, 38.4%, and 27.4% of patients in the AV, AVG, and FCR/BR arms, respectively. The SAEs with the highest incidence were in Arm A (AV) COVID-19 pneumonia (5.8%); in Arm B (AVG), COVID-19 pneumonia (11.3%) and COVID-19 (6.0%); and in Arm C (FCR/BR), febrile neutropenia (8.1%).

Deaths: In the safety population, at the DCO, 18 patients (6.2%) have died in Arm A (AV), 36 patients (12.7%) in Arm B (AVG) and 42 patients (14.5%) in Arm C (FCR/BR). The primary cause of death was due to adverse reaction; 16 patients (5.5%) in Arm A (AV), 29 patients (10.2%) in Arm B (AVG) and, 28 patients (10.8%) in Arm C (FCR/BR). In Arm A (AV) death *due to adverse event* within 30 days of last dose of study drug was reported for 10/16 patients (62%) and 6/16 patients (38%) died more than 30 days after last dose. In Arm B (AVG) 11/29 patients (38%) had died within 30 days of last dose and 18/29 patients (62%) died more than 30 days after last dose. In Arm C (FCR/BR) 7/28 patients (25%) had died within 30 days of last dose and 21/28 patients (75%) died more than 30 days after last dose.

The majority of deaths were reported with infection as the primary cause, mainly Covid-19 and Covid-19 pneumonia. Of the 291 patients treated with AV, fatal infections occurred in 3.1% of patients (most frequently reported COVID-19 or COVID-19 pneumonia). Of the 284 patients treated with AVG, fatal

infections occurred in 5.6% of patients (most frequently reported COVID-19 or COVID-19 pneumonia). In addition, for AVG there seemed to be a longer time from initiation of therapy to death when comparing to the FCR/BR arm, and 16 infectious deaths out of 24 were reported post-therapy. Thus, for the AVG combination the risk of death due to infection also longtime after therapy is of concern.

The risk of severe and potentially fatal infections is highlighted in Section 4.8 of the SmPC for both AV and AVG treated patients.

Cytopenias were also common in all three treatment arms. The rate of neutropenia in Arm A (AV) is 37.1% vs the similar rates in Arm B and Arm C, 50.4% and 51.0%, respectively.

Anaemia occurred at numerically lower incidences in the AV and AVG arms compared to the FCR/BR arm, for Grade >3 anaemia it was 3.8% and 2.1% versus 6.6%, respectively. Thrombocytopenia grade ≥3 was infrequent in the AV arm, 2.1% and occurred with similar rate in AVG and FCR/BR arms, 9.2% and 10.8%, respectively.

Cytopenias are covered by the present language in the SmPC section 4.2 with dose modifications in relation to grade 3 thrombocytopenia with bleeding, grade 4 thrombocytopenia or neutropenia, and other non-haematological grade 3 or greater toxicities. In the SmPC section 4.4 there is relevant information present in separate paragraphs with subheading "Infections" and "Cytopenias". The haematological ADR frequencies are reflected in table 4.8 of the SmPC. Overall, the current SmPC text is considered sufficient.

Infections and cytopenia's, mainly neutropenia, are frequent in the AV regimen and further increases in frequency with the addition of obinutuzumab in the AVG regimen.

All grade haemorrhages were more frequent in the acalabrutinib containing Arm A (AV) and Arm B (AVG), 32.3% and 30.3% respectively compared to the Arm C (FCR/BR) 4.2%. Which is consistent with the known BTKi toxicity profile including increased bleeding events. The majority was of low-grade: contusions, haematomas and petechias. The Grade ≥ 3 haemorrhages were infrequent for all treatment arms: Arm A (AV) 1.0%, Arm B (AVG) 2.1% and Arm C (FCR/BR) 0.4%. Also, the Major haemorrhages (any serious or Grade ≥ 3 or CNS haemorrhage of any severity grade) occurred at a low frequency in all arms 1.0%, 2.8% and 0.8% in the AV, AVG and FCR/BR arms respectively.

There was an exclusion of some patients at higher risk of intracranial haemorrhage in AMPLIFY study (patients with a history of stroke or intracranial haemorrhage within 6 months prior to randomisation). However, this is viewed as being standard exclusion criteria in haematological malignancies, and comparable exclusion of patients at increased risk of bleeding has been made in other BTKi registrational studies while not reflected in their respective SmPC. Thus, the current warning under the subheading "Haemorrhage" in the Calquence SmPC, section 4.4 is considered sufficient.

Grade ≥ 3 hepatotoxicity events were reported in 3.4%, 2.8%, and 1.5% of patients. There were no fatal hepatotoxicity events in either arm. The majority of hepatotoxicity events were low grade transaminase elevations.

Cardiac events of any grade were reported in 9.3%, 12.0%, and 3.5% of patients in the AV, AVG, and FCR/BR arms, respectively and Grade ≥ 3 cardiac events were reported in 1.7%, 2.5%, and 1.2%, respectively. One patient in the AV arm died of cardiac arrest. There were no cases with ventricular fibrillation or fatal atrial fibrillation reported in the AMPLIFY study.

The incidence and severity of hypertension events was similar in AV and AVG arms and slightly less in the FCR/BR arm. Any grade hypertension occurred in 4.1%, 3.9%, and 2.7% of patients in the AV, AVG, and FCR/BR arms respectively, and Grade ≥ 3 events occurred in 2.7%, 2.1%, and 0.8% of patients, respectively.

Interstitial lung disease (ILD)/pneumonitis of Grade 1 and 2 occurred in 1.8% of patients in the AVG arm and there was 1 patient (0.4%) in the FCR/BR arm who experienced a Grade 3 event. ILD/pneumonitis is not an ADR for venetoclax or obinutuzumab. No patient had an event of ILD/pneumonitis in the AV arm.

There was an overall low incidence of second primary malignancies (SPM) in all arms, likely due to the short TEAE observation period. SPM were reported in 5.2%, 4.2%, and 0.8% of patients in the AV, AVG, and FCR/BR arms, respectively.

TLS events in the AV and AVG arms was low. One patient each in the AV arm and AVG arm. There were 8 (3.1%) patients in the FCR/BR arm (all of whom received BR). All TLS events reported were Grade ≥ 3 in severity. No Grade 5 TLS events were reported. However, TLS mitigation strategies were employed in the AMPLIFY study. A lower frequency of any TLS prophylaxis was used in the FCR/BR arm (66%) compared to the AV and AVG -arms (79% and 74% respectively). TLS is listed as an ADR in the Calquence SmPC section 4.8, and now a warning has been 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.

The frequency of patients with ≥1 AE leading to discontinuation of any study treatment were 7.9%, 20.1% and 10.8% in the AV, AVG and FCR/BR arms respectively. There were 7.6% in AV and 13.7% in AVG who discontinued acalabrutinib due to TEAEs. The most common TEAE was Covid-19 pneumonia in AV and Covid-19 in AVG.

2.5.2. Conclusions on clinical safety

The combination of acalabrutinib and venetoclax with and without obinutuzumab results in clinically relevant toxicities, particularly with respect to the risks of cytopenias and infection. The addition of obinutuzumab results in a worse side effect profile with respect to these risks.

These risks are mostly anticipated and qualitatively well-known and can be managed with the current SmPC warnings.

Overall, the safety profile of the proposed combination treatment is sufficiently characterised.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated risk management plan (RMP) version 8.2 with this application.

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the RMP version 8.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the RMP version 8.2 with the following content:

Safety concerns

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

Pharmacovigilance plan

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

Risk minimisation measures

Safety concern	**Risk minimisation 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
Second primary malignancy	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8

Safety concern	Risk minimisation measures
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. 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 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

Chronic lymphocytic leukaemia is the most prevalent form of adult leukaemia. It is characterised by a progressive accumulation of functionally incompetent lymphocytes, which are usually monoclonal in origin. CLL has an age adjusted incidence of 3.3–6.4 per 100000 person-years and a median age at diagnosis of 70 years.

The presently sought indication is: "Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)."

3.1.2. Available therapies and unmet medical need

CLL is an incurable disease that is clinically and biologically heterogeneous, ranging from indolent with no treatment requirement, to a very aggressive disease characterised by chemo-refractoriness and poor survival.

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

The development of BTK inhibitors and the apoptosis regulator BCL2 antagonist venetoclax, has transformed the treatment paradigm for patients with CLL, particularly for those with high-risk disease who have inferior outcomes with chemotherapy-based regimens. Targeted treatment (BTKi or venetoclax) with or without anti-CD20 mAbs is the therapy of choice in most front-line CLL settings regardless of mutational status. However, immunochemotherapy (e.g. FCR or BR) is also indicated in young and fit patients with mutated IGHV.

3.1.3. Main clinical studies

Study ACE-CL-311 or AMPLIFY is a randomised, multicentre, open-label, Phase III study comparing the efficacy and safety of acalabrutinib in combination with venetoclax with and without obinutuzumab compared to investigator's choice of chemoimmunotherapy FCR or BR in patients with previously untreated CLL without del(17p) or TP53 mutation.

A total of 867 patients were randomised in the global cohort in 1:1:1 ratio into 3 arms to receive (study schema is presented in Figure 5): acalabrutinib for 14 cycles and venetoclax cycle 3-14 (Arm A), acalabrutinib for 14 cycles; obinutuzumab cycle 2-7 and venetoclax Cycle 3-14 (Arm B) or 6 cycles of either FCR or BR, according to investigator's choice (Arm C).

The primary endpoint was PFS assessed by IRC for Arm A vs Arm C. Secondary endpoints were alpha protected in a fixed hierarchical manner beginning with IRC assessed PFS for Arm B vs Arm C, followed by MRD negativity rate and OS (both tested in Arm A vs Arm C and Arm B vs Arm C, respectively).

The FAS included 291 patients in Arm A [AV], 286 patients in the Arm B [AVG]) and 290 patients in the Arm C [FCR/BR].

Due to the choice of chemoimmunotherapy (BR/FCR) as control arm, patients with a detected del17p or TP53 mutation were excluded from study enrolment.

3.2. Favourable effects

In the primary analysis, a PFS event was registered for 30.6% of patients in Arm A and 32.8% in Arm C. A statistically significant effect on IRC-assessed PFS was shown with a HR 0.65 (95% CI [0.49, 0.87]).

Statistically significant IRC-assessed PFS was also shown for Arm B as compared with Arm C, with HR 0.42 (95% CI [0.30, 0.59]). In this analysis, a PFS event was registered for 19.6% of patients in Arm B and 32.8% in Arm C.

Median PFS was 47.6 months in Arm C and, at the DCO, not yet reached in Arm A or Arm B.

In an updated OS analyses with DCO of 30 October 2024, data maturity was 12% in the Arm A versus Arm C analysis, and 14% in the Arm B vs Arm C analysis. In the analysis of Arm A versus Arm C, the OS HR was 0.42 (95% CI: 0.25, 0.70). The OS HR for Arm B versus Arm C was 0.75 (95% CI: 0.48, 1.16).

3.3. Uncertainties and limitations about favourable effects

The impact of treatment on OS remains uncertain due to lack of statistical significance, as well as low maturity of data.

The study was not powered for a comparison of AV versus AVG.

3.4. Unfavourable effects

The main safety population included a total of 834 patients (291 in AV arm, 284 in AVG arm, and 259 in FCR/BR arm) that received at least one dose of any study treatment.

The median duration of exposure to acalabrutinib were 12.9 months in Arm A and Arm B and for venetoclax it was 11.1 and 11.0 months in Arm A and Arm B, respectively. The median duration of exposure to obinutuzumab was 5.5 months in Arm B. For Arm C, the median durations of exposure were approx. 2.3 times shorter than for acalabrutinib in Arm A and Arm B, i.e. for fludarabine, cyclophosphamide, and bendamustine it was 5.6 months each and 5.5 months for rituximab.

The most frequently reported TEAEs by PT were for the AV Arm: headache (35.1%), diarrhoea (32.6%), and neutropenia (30.9%); for the AVG Arm: neutropenia (40.1%), diarrhoea (36.3%), headache (28.2%), nausea (21.8%), and COVID-19 (20.4%); and for the FCR/BR: neutropenia (38.2%), nausea (35.9%), and infusion related reaction (32.8%).

Although neutropenia rates were high in all three arms (30.9%, 40.1% and 38.2%, in AV, AVG and FCR/BR, respectively) there were more frequent COVID-19 infections in the AV and AVG arms (18.9% and 20.4%) than in the FCR/BR arm 2.3%. This pattern was also seen for COVID-19 pneumonia (7.2% in AV, 12.3% in AVG and 2.7% in FCR/BR) and upper respiratory tract infection (8.2% in AV, 6.3% in AVG and 1.9% in FCR/BR), while the frequency of pneumonia was more similar across all arms (3.8% in AV, 5.3% in AVG and 3.1% in FCR/BR).

The most common Grade ≥ 3 TEAEs were neutropenia in all treatment arms: AV 26.8%, AVG 35.2% and FCR 29.5%, BR 35%). Grade ≥ 3 febrile neutropenia events were less frequent in AV (1.7%) and AVG (2.5%) compared to the FCR/BR arm (9.3%). Grade ≥3 COVID-19 and COVID-19 pneumonia were most frequently reported in the AVG arm (11.6% and 6.7%), while less frequent in the AV arm (5.5% and 2.7%) and in the FCR/BR arm only 2.7% and 1.5% experienced COVID19 pneumonia and COVID-19, respectively.

Grade 5 TEAEs, were reported for 10 (3.4%), 17 (6.0%), and 9 (3.5%) patients in the AV, AVG, and FCR/BR arms, respectively. The most frequently reported Grade 5 TEAEs were COVID-19, COVID-19 pneumonia, and suspected COVID-19, accounting for 8 of 10 deaths deemed treatment emergent in the AV arm, 15 of 17 such deaths in the AVG arm, and 7 of 9 such deaths in the FCR/BR arm, or 2.7%, 5.3%, and 2.7% of patients overall, respectively. Deaths > 30 days after of the last dose of study treatment occurred in 8 (2.7%), 25 (8.8%), and 35 (13.5%) patients in the AV, AVG, and FCR/BR arms, respectively.

The incidence of TEAEs leading to discontinuation of any study treatment was 7.9% in AV, 20.1% in AVG, and 10.8% in FCR/BR. The incidence of TEAEs leading to acalabrutinib discontinuation was 7.6 % in AV and 13.7% in AVG. The most frequently reported TEAEs that led to discontinuation of acalabrutinib in the AV and AVG arms were COVID-19 pneumonia (2.1% and 2.8%, respectively) and COVID-19 (0.3% and 3.9%, respectively).

3.5. Uncertainties and limitations about unfavourable effects

Exposure time is approximately 2.3 times longer in AV and AVG arms compared to the FCR/BR arm which complicates the direct comparison of TEAE rates between the experimental regimens and the reference arm.

3.6. Effects Table

Table 43. Effects Table for Calquence in combination with venetoclax with or without obinutuzumab for the treatment of adult patients with previously untreated CLL (30 October 2024).

Effect	Short description	Unit	Arm A AV	Arm B AVG	Arm C FCR/BR	Uncertainties / Strength of evidence	References
Favourable Effects							
PFS	Time from randomisation until disease progression (according to the IWCLL 2018 criteria - IRC-assessed)	N (%)	89 (30.6)	56 (19.6)	95 (32.8)	SoE: Statistically significant IRC assessed PFS for Arm A vs Arm C and for Arm B vs Arm C Consistent results with Investigator assessed PFS	AMPLIFY study
		HR (95% CI)	0.65 (0.49,0.87)	0.42 (0.30, 0.59)	-		
		p-value	0.0038	< 0.0001	-		
OS	Time from randomisation to death from any cause	n (%)	23 (7.9)	37 (12.9)	44 (15.2)	Unc: Study not powered for OS, immature data, median not calculable for any arm	
		HR (95% CI)	0.42 (0.25, 0.70)	0.75 (0.48, 1.16)	-		
Unfavourable Effects							
Grade 3/4 TEAE	Incidence: Any Infections Neutropenia Hepatotoxicity Cardiac events	%	53.6 12.4 32.3 3.4 1.7	69.4 23.6 46.1 2.8 2.5	60.6 10.0 43.2 1.5 1.2	SoE: Data from adequately sized RCT Unc: Exposure time approx. 2.3 times longer in AV and AVG vs. FCR/BR.	AMPLIFY study
Discontinuation	TEAE leading to discont-inuation of acalabrutinib	%	7.6	13.7	-		

Abbreviations: CLL: chronic lymphocytic leukaemia; AV: acalabrutinib and venetoclax; AVG: acalabrutinib, venetoclax and obinutuzumab FCR: fludarabine, cyclophosphamide and rituximab; BR: Bendamustine and

Rituximab; NC: Not calculable; PFS: progression free surbvival; IWCLL: International Workshop on Chronic Lymphocytic Leukemia; IRC: independent review committee;HR: hazard ratio; CI: confidence inetval; OS: overall survival; SoE: strength of evidence; Unc: uncertainity; TEAE: Treatment Emergent Adverse Event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy has been established in the form of a clinically meaningful prolongation of PFS with fixed-duration therapy with AV or AVG as compared with investigator's choice of chemoimmunotherapy (FCR or BR). Safety concerns primarily relate to cytopenias and infection risks.

While patients with del(17p) or TP53 mutations were excluded from the AMPILFY study because of the unsuitable comparator, the efficacy of acalabrutinib and venetoclax in the claimed indication has been characterised in other studies (ELEVATE-TN, CLL14 and SAT NCT03580928). Therefore, beneficial effects of the proposed new treatment regimens may be extrapolated to these patients as well.

The addition of obinutuzumab to acalabrutinib and venetoclax results in an increased side effect burden. However, it also provides more antitumoral activity as evidenced by the reduced HR in PFS compared to acalabrutinib and venetoclax alone.

While OS data are immature, the trends are reassuring, favouring the test arms, and the levels of uncertainty acceptable. There is no indication of a detrimental effect on OS. OS data maturity and statistical robustness is not sufficient to infer any differences in survival outcomes between AV and AVG.

3.7.2. Balance of benefits and risks

The benefit of the longer PFS of acalabrutinib in combination with venetoclax with or without obinutuzumab is deemed to outweigh the observed increased toxicity of these combinations and which can be managed with the risk minimisation measures as reflected in the product information.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Calquence in combination with venetoclax with or without obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) 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 venetoclax with or without obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), based on interim results from study AMPLIFY (D8221C00001); this is a randomised, multicentre, open-label, phase 3 study of acalabrutinib in combination with venetoclax with and without obinutuzumab compared to investigator's choice of chemoimmunotherapy in subjects with previously untreated CLL without del(17p) or TP53 Mutation. 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 8.2 of the RMP was also submitted.

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.

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/28'