23 April 2026
EMADOC-1700519818-3013065
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Venclyxto

International non-proprietary name: Venetoclax

Procedure No. EMA/VR/0000322240

## 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, Abbvie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 4 January 2026 an application for a variation.

The following variation was requested:

| **Variation(s) requested** | | **Type** |
|---|---|---|
| C.I.6.a | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II |

Extension of indication to include, in combination with acalabrutinib with or without obinutuzumab, the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for VENCLYXTO based on the results from the pivotal study ACE-CL-311/D8221C00001 (AMPLIFY); this is a randomized, multicenter, open-label, Phase 3 study to compare the efficacy and safety of acalabrutinib (ACP-196) 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. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 11.1 has also been submitted.

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/PE/0000235929 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000235929 was not yet completed as some measures were deferred.

## *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.

## *Information on paediatric requirements*

Not applicable

## *Information relating to orphan market exclusivity*

Not applicable

### *Scientific advice*

The MAH did not seek Scientific Advice at the CHMP.

## *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: Not applicable

| Timetable | Actual dates |
|---|---|
| Submission date | 4 January 2026 |
| Start of procedure: | 23 January 2026 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 20 March 2026 |
| PRAC Rapporteur's preliminary assessment report circulated on: | 26 March 2026 |
| PRAC RMP advice and assessment overview adopted by PRAC on: | 10 April 2026 |
| Joint Rapporteur's updated assessment report circulated on: | 16 April 2026 |
| CHMP opinion: | 23 April 2026 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

This is an application to extend the use of venetoclax in combination with acalabrutinib with or without obinutuzumab in patients with chronic lymphocytic leukaemia (CLL).

### *Claimed therapeutic indication*

The claimed indication is:

Venclyxto is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL):

- in combination with acalabrutinib with or without obinutuzumab

### *Epidemiology*

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.

## *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 $10^9$ 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 BTKi and BCL2 inhibitor, 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 is the therapy of choice in most front-line CLL settings regardless of mutational status. However, the combination of fludarabine, cyclophosphamide and rituximab (FCR) is also indicated in young and fit patients with mutated IGHV.

Randomised clinical studies had previously established the combination of FCR 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 plus rituximab (BR) versus FCR, the results showed a median 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 SoC option for front-line therapy in fit patients with CLL, but BR is associated with less safety concerns. The CLL10 study informed the selection of FCR and BR as the comparator regimens (Arm C) at the time of the pivotal AMPLIFY study initiation.

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.

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.

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 patients. 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

Venetoclax is a selective, potent, orally bioavailable, small molecule, B-cell lymphoma-2 (BCL-2) inhibitor that restores programmed cell death (apoptosis) in cancer cells.

Venclyxto is currently approved in the EU for:

- Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).
- Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.
- Venclyxto monotherapy is indicated for the treatment of CLL:
    - in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or
    - in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.
- Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

In addition, acalabrutinib in combination with venetoclax with or without obinutuzumab is approved in the EU for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL); see Calquence (acalabrutinib) product information.

In the present application, the MAH applies to add this indication to Venclyxto based on data previously assessed and approved for Calquence.

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application.

### 2.2.1. Ecotoxicity/environmental risk assessment

The applicant did not submit a new environmental risk assessment (ERA) but instead refers to the ERAs from previous submissions of Venetoclax, which includes an application in the same indication and dose as this submission.

In the Phase I assessment, the Predicted Environmental Concentration (PEC) for $PEC_{SURFACEWATER}$ was calculated with the $Fpen_{ACTUAL}$ value of 0.00048 (0.048%) as reported by Orphanet. The resulting PEC of 0.096 µg/L exceeded the action limit of 0.01 µg/L, triggering a Phase II assessment. Persistence, bioaccumulation, and toxicity (PBT) were assessed in Phase II Tiers A and B.

A Phase II Tier A base set of fate and effect studies were conducted with the exception of ready biodegradability (OECD 301). The $PEC_{SURFACEWATER}$ of 0.000096 mg/L (0.096 µg/L) was used to develop the PEC/Predicted No Effect Concentration (PNEC) ratios. All the Phase II Tier A PEC/PNEC ratios were < 1.

### 2.2.2. Discussion on non-clinical aspects

No new non-clinical studies or information has been submitted for this procedure which was considered acceptable by the CHMP.

The previous ERA study on which the present application is based are not fully in line with the current CHMP ERA guideline.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

- a chronic toxicity on earthworms in accordance with OECD 222 tobe provided
- the PEC and PNEC values for the soil compartment to be calculated in accordance with the EMEA/CHMP/SWP/4447/00 Rev.1 guideline.
- a BCF to be estimated from the fish bioaccumulation study and be used to determine whether to conduct a secondary poisoning assessment.

### 2.2.3. Conclusion on the non-clinical aspects

As the ERA submitted is not in line with the current CHMP ERA Guideline, its conclusions have to be reevaluated before concluding definitively on the potential risk of venetoclax to the environment.

Overall, the new indication in CLL in combination with acalabrutinib is approvable from a non-clinical point of view.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

**GCP**

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

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

- Tabular overview of clinical studies

| Study 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<br>CSR location: Module 5.3.5.1 | Randomized, open-label, multicenter study | Patients with previously untreated CLL; N = 867<br>Randomized:<br>AV = 291;<br>AVG = 286;<br>Chemo = 290<br>Sex:<br>Male = 559,<br>Female = 308;<br>Age: median (range)<br>61 yrs (26-86);<br>Race:<br>White = 765 (88.2%),<br>Asian = 31 (3.6%),<br>Black or African American = 21 (2.4%) | Acalabrutinib 100 mg, administered twice daily, provided as hard gelatin capsules for oral administration.<br>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.<br>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 plasma sampling. Venetoclax, acalabrutinib and the active metabolite ACP-5862 were quantified.

The commercial Venetoclax tablet formulation was used (10 mg, 50 mg, or 100 mg tablets, administered orally from 20 to 400 mg QD).

Bioanalytical methods

A validated venetoclax bioanalytical method (Final Method Validation Report, Labcorp Study Number 8421-675; Labcorp Study Number 8421681 Report Addendum No. 1) was used to support detection of venetoclax in the AMPLIFY study (Bioanalytical report, Labcorp Study Number 8421679). Plasma concentrations of venetoclax were determined with an LC/MS/MS method using Venetoclax-d8 as internal standard. Calibration standard data, QC sample data, incurred sample reproducibility data, and chromatograms indicate that the method performed acceptably during the sample analysis. No relevant interference with acalabrutinib was noted. There were 1053 of 4059 (26%) samples that were not analysed within the established stability period (1064 days). Samples were analysed within 1477 days.

### *Target population*

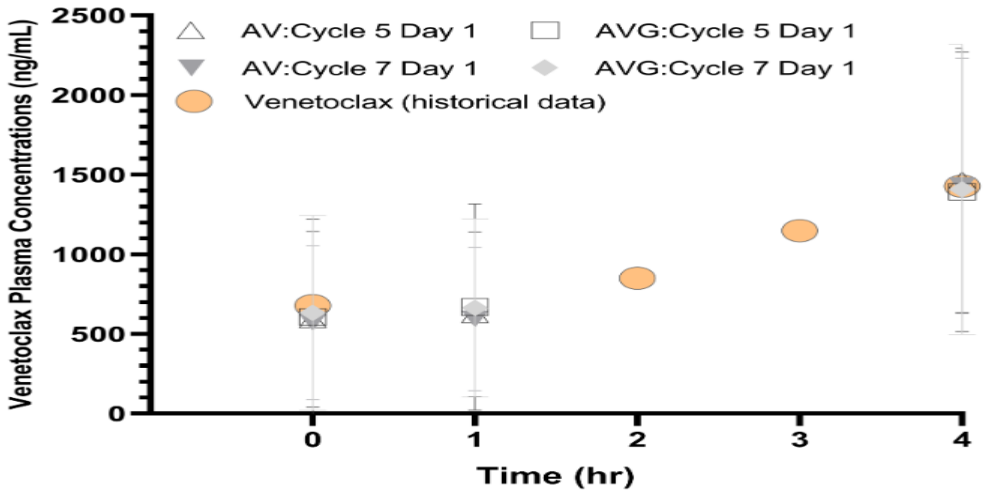
In the AV and AVG arms of Study ACE-CL-311 (AMPLIFY), acalabrutinib 100 mg capsules were orally administered from Cycle 1 at a fixed twice daily (BID) dose for 14 cycles; venetoclax oral dosing was to begin at Cycle 3 and continued following a 5-week ramp-up at a fixed daily dose of 400 mg (higher doses were not given) until the end of Cycle 14, or until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurred first.

In the AVG arm, dosing of acalabrutinib and venetoclax was the same as in the AV arm, and obinutuzumab was administered as IV infusion at an absolute (flat) dose of 1000 mg and was to begin at Cycle 2 and continued through Cycle 7.

In addition, the PK of acalabrutinib and its metabolite in the target population as observed in the AMPLIFY study was compared to previously conducted studies with acalabrutinib in other populations (data not shown).

Plasma concentrations of venetoclax were measured in the AMPLIFY study (patients treated with AV (n=255) or AVG (n=239) combination) and compared to previously reported venetoclax concentrations following monotherapy in patients (n = 75) with CLL/ Non-Hodgkin Lymphoma (NHL) (**Figure 1**, Salem et al 2017).

**Figure 1.** Comparison of Plasma concentrations of Venetoclax in AMPLIFY versus monotherapy (historical data, AV: acalabrutinib+venetoclax; AVG: acalabrutinib+venetoclax+obinutuzumab)




The data shows mean/mean ± SD concentrations for venetoclax. Venetoclax concentrations for AMPLIFY represent concentrations from Arm A (AV) and Arm B (AVG). Venetoclax concentrations (historical data) following monotherapy are based on data reported by Salem et al 2017.
In AMPLIFY, PK samples for venetoclax and acalabrutinib assessment were collected on Day 1 of Cycles 5 and 7 at pre-dose, 1 hour and 4 hours after dosing.

## 2.3.3. Discussion on clinical pharmacology

A main role of the clinical pharmacology data package in the current variation is to describe venetoclax PK in first-line CLL patients (the target population) co-treated with acalabrutinib and to characterise potential PK differences compared to monotherapy. In addition, acalabrutinib PK with venetoclax and potential PK differences of acalabrutinib without co-treatment with venetoclax was described. The main clinical study (AMPLIFY) supporting this application included collection of PK data. No exposure-response analysis for venetoclax has been performed.

*Bioanalysis*

Overall, the bioanalytical methods for venetoclax and acalabrutinib were adequately validated and the performance is deemed acceptable. For venetoclax, 26% of samples were not analysed within the stability period. The results of the 1067 days stability were within the acceptance criteria (-3% bias). It is unlikely that the additional storage time would result in a significant impact on measured concentrations and overall interpretation of the data, therefore this is considered acceptable. Additional frozen matrix stability to cover the sample storage duration will be established and reported within the validation study.

*Descriptive pharmacokinetics*

Venetoclax is a substrate for CYP3A4 and BCRP. Acalabrutinib may be a CYP3A4 inhibitor at the intestinal level (*in vitro)* and acalabrutinib and its active metabolite, ACP-5862, are BCRP inhibitors, thus, a potential PK DDI cannot be excluded. However, the comparison of the sparse PK sampling conducted in the AMPLIFY study indicated similar concentrations between the target population (CLL patients) co-treated with acalabrutinib and CLL/NHL patients given venetoclax as monotherapy (historical data). The applicants' proposal to not update SmPC Section 4.5 and 5.2 is considered acceptable.

### 2.3.4. Conclusions on clinical pharmacology

Submitted PK data from the AMPLIFY study indicate similar PK for venetoclax in first-line CLL patients co-treated with acalabrutinib compared to venetoclax monotherapy and support the dosing regimen of the study in the claimed indication.

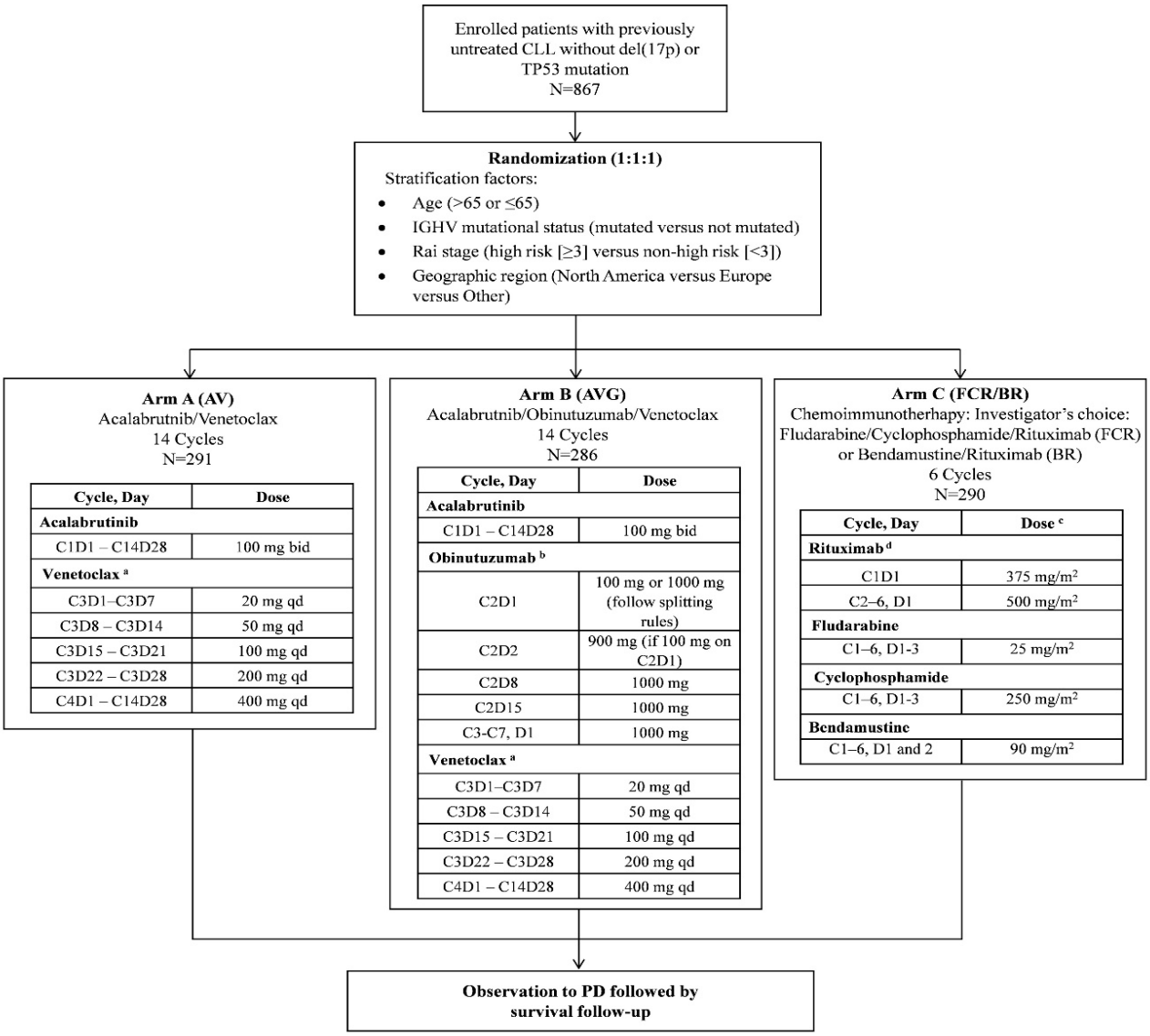
## *2.4. Clinical efficacy*

### 2.4.1. 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 2** shows the design of the study, the sequence of treatment periods, and the treatment regimens.

**Figure 2.** Flowchart of study ACE-CL-311 design




[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 (see Appendix 2 of the CSP version 7.0, Appendix 16.1.1).

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 leukemia.

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 randomization 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 randomization. Those who were hepatitis C PCR positive will be excluded.

9. History of bleeding diathesis (e.g., hemophilia, 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)**

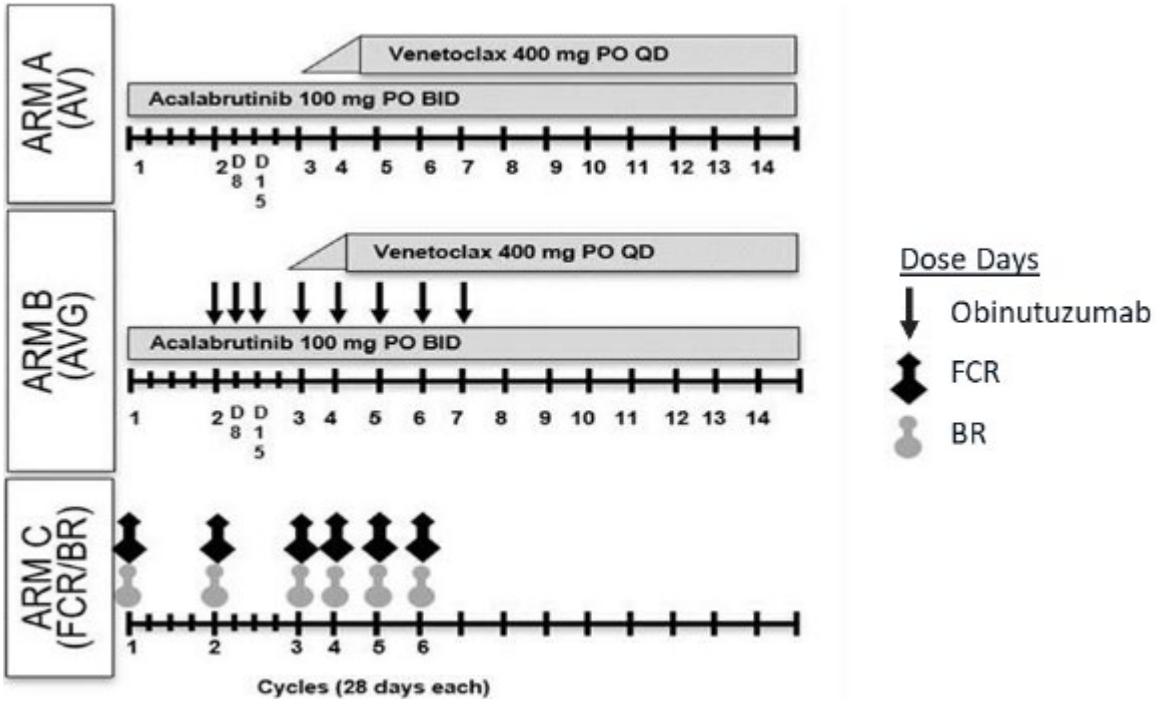
Acalabrutinib (100 mg capsules) were orally administered from Cycle 1 at a fixed BID dose for 14 cycles; obinutuzumab administered as IV infusion at an absolute (flat) dose of 1000 mg and was to begin at Cycle 2 and continued through Cycle 7; venetoclax dosing was to begin at Cycle 3 and continue following 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 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 $\leq$ 65 years of age with a creatinine clearance of $\geq$ 70 mL/min were restricted to FCR.

Treatment regimens in ACE-CL-311 are depicted in **Figure 3**.

**Figure 3.** 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**

- Progression Free Survival (PFS) assessed by Independet Review Committee (IRC) (Arm A vs Arm C)

**Key secondary endpoints**

- PFS assessed by IRC (Arm B vs Arm C)
- Minimal residual disease (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 (INV) 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**

- Patient reported outcomes (PROs) by EORTC-QLQ-C30, IL27, FACIT-Fatigue, PGIC, PGIS and EQ-5 D-5 L

## Sample size

According to Statistical analysis plan (SAP) version 4.0 dated 28 Feb 2024, the study was expected to randomize 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

This study, was expected to randomise 780 subjects in total, with approximately 260 subjects per Arm with a 1:1:1 randomisation 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 randomized 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 randomized (in both the global cohort and the China extension cohort).

The randomisation scheme would ensure approximately equal sample sizes in the 3 treatment arms. Subjects were planned to be randomised based on the following stratification factors:

- Age (>65 or <=65)

- immunoglobulin heavy-chain variable gene (IGHV) mutational status (mutated versus not mutated [inclusive of unproductive IGHV rearrangement])
- Rai stage (high risk >= 3 versus non-high risk <3)
- Geographic region (North America versus Europe versus Other)

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 declare the choice of FCR or BR for a subject before randomization. When the number of subjects randomized 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.

If a subject withdrew from the study, then his/her randomisation code could not be reused. Withdrawn subjects would not be replaced. Crossover treatment was not allowed in this study.

## Blinding (masking)

This was an open-label study.

## Statistical methods

***Analysis methods for primary efficacy 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 Full Analysis Set (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 ties = Efron 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. 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.

The distribution of IRC-assessed PFS was planned to be summarised 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.

***Analysis methods for key secondary efficacy endpoint***

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 randomized (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 Data Monitoring Committee (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 is 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 utilised 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 at a sensitivity threshold of $10^{-4}$ 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 at a sensitivity threshold of $10^{-4}$ 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. Rejection boundaries in P-value scale for each analysis are shown in Table 6 in the SAP.

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***

According to SAP v.4, 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 randomization.

***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 randomisation 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 randomised 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***

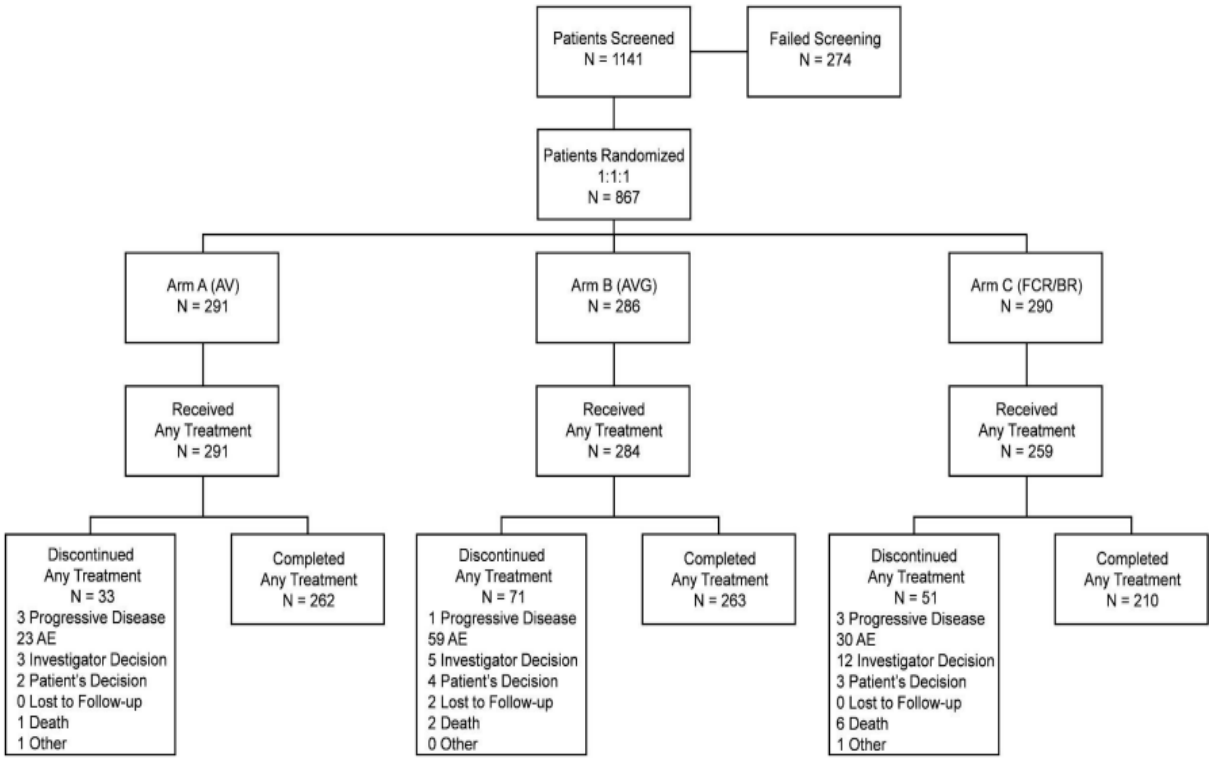
Subgroup analyses were planned to be performed using potential prognostic variables at screening or baseline listed below to investigate the consistency and robustness of PFS as assessed by IRC between Arms A versus C and Arms B versus C:

- Randomization 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. Details regarding the analysis method for each subgroup level can be found in subgroup section of the SAP.

## *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 1.** 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 2.** 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 |
| **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 3**. 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 (%)** | | | | |
| < 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) |

| | Arm A (AV) (N = 291) | Arm B (AVG) (N =286) | Arm C (FCR/BR) (N = 290) | Total (N = 867) |
|---|---|---|---|---|
| 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) |
| 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) |

| | Arm A (AV) (N = 291) | Arm B (AVG) (N =286) | Arm C (FCR/BR) (N = 290) | Total (N = 867) |
|---|---|---|---|---|
| **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 | | | | |
| 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) |

| | Arm A (AV) (N = 291) | Arm B (AVG) (N =286) | Arm C (FCR/BR) (N = 290) | Total (N = 867) |
|---|---|---|---|---|
| **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 |
| 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 4**. 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:<br>• Either did not take or discontinued early from at least one randomised treatment.<br>• Less than 75% RDI for any randomised treatment.<br>• Violated protocol inclusion or exclusion criteria that may affect interpretation of efficacy<br>• 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)***

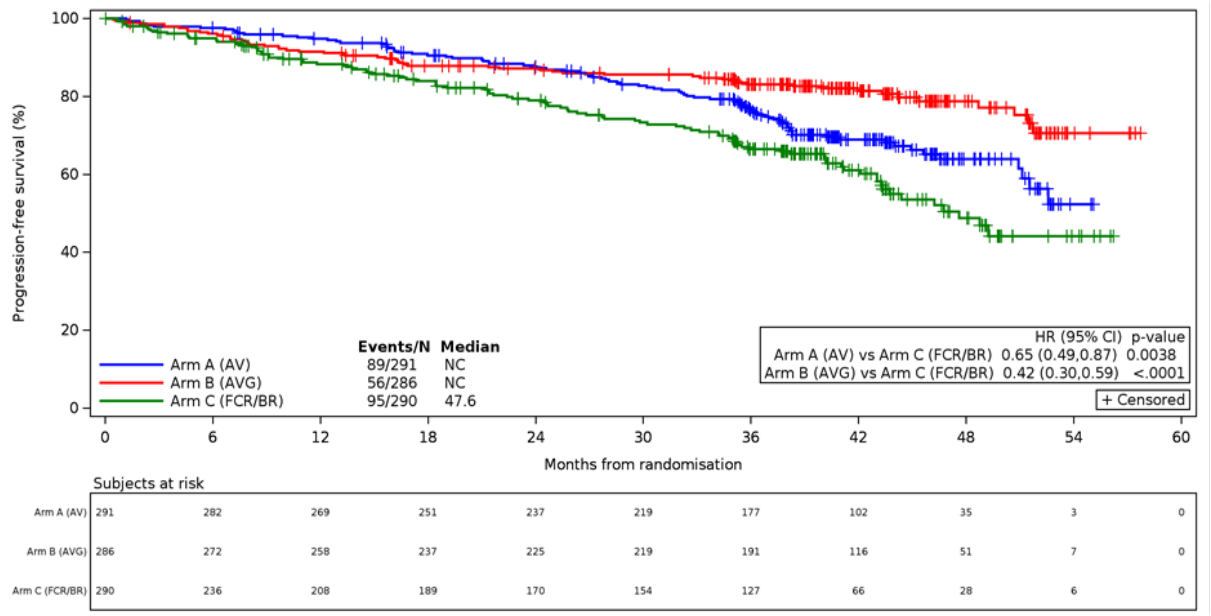
**Table 5**. Progression-free Survival by Blinded Independent Central Review (FAS), study ACE-CL-311

| | **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) |

| | Arm A (AV) (N = 291) | Arm C (FCR/BR) (N = 290) |
|---|---|---|
| **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 4**. Kaplan-Meier Plot for Progression-free Survival by Blinded Independent Central Review (FAS), study ACE-CL-311




***Sensitivity analyses***

**Table 6.** 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 | | | |
| 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 |

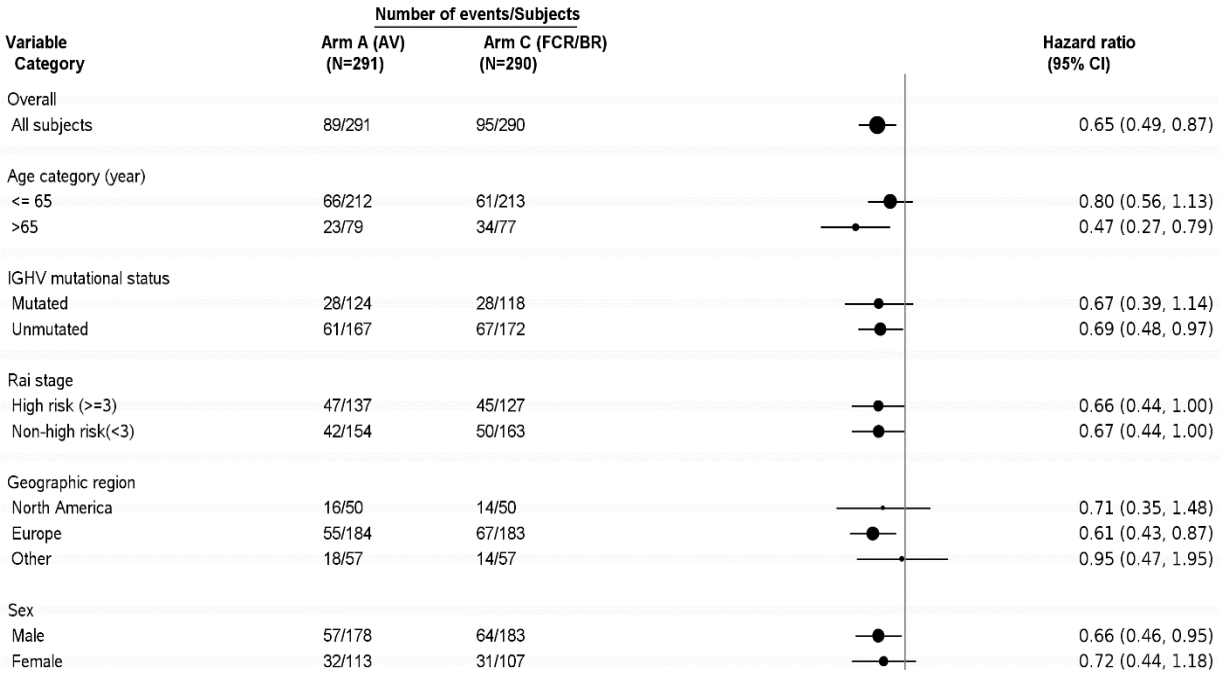
| | Group | Patients with event n (%) | Median time to event (months) | 95% CI | Comparison of treatment groups | | |
|---|---|---|---|---|---|---|---|
| | | | | | HR | 95% CI | p-value |
| | Arm C (FCR/BR) N = 199 | 71 (35.7) | 48.8 | 43.7, NC | | | |
| Censoring COVID-19 Deaths | Arm A (AV) N = 291 | 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 | | | |

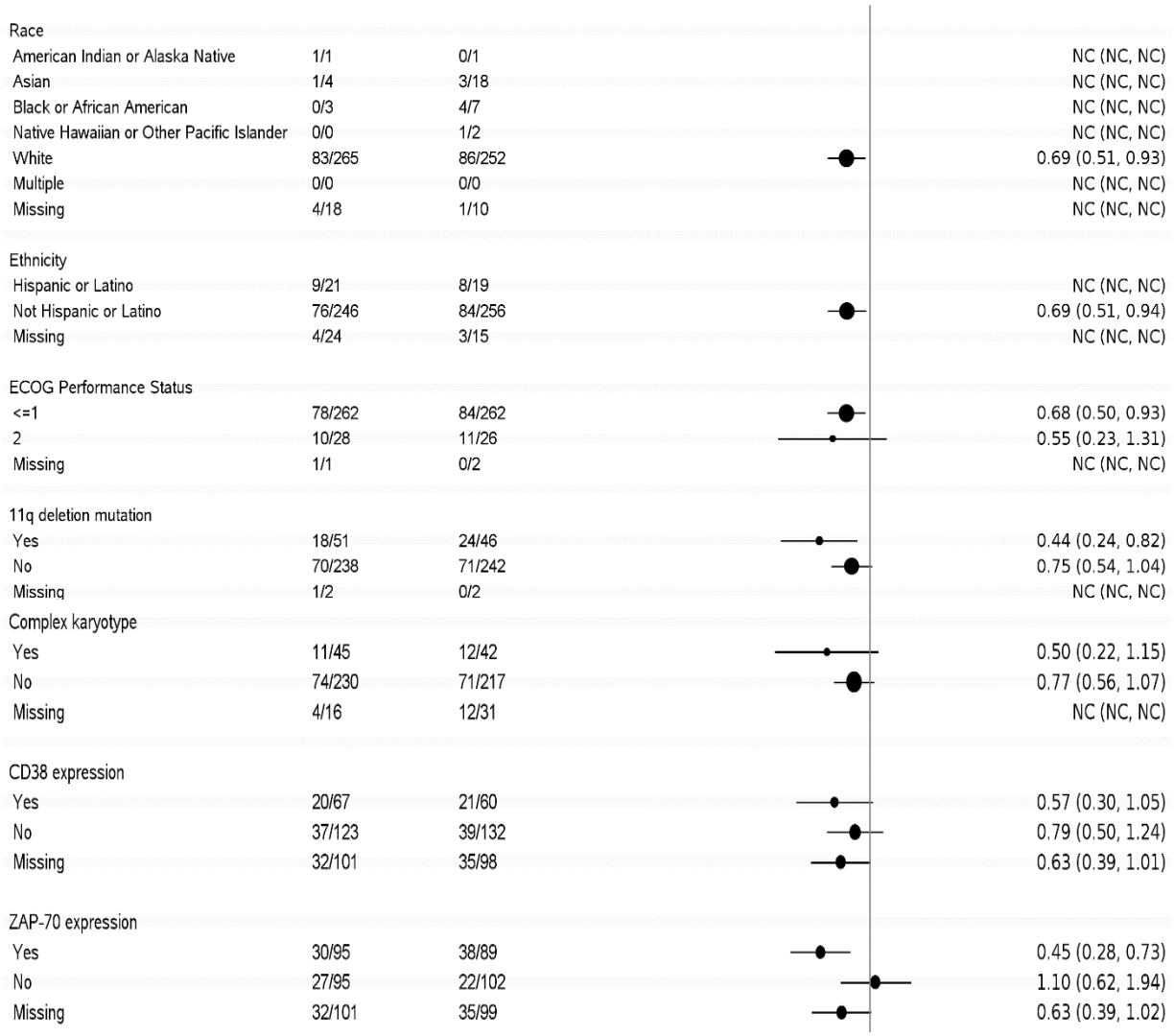
*A HR below 1 favours Arm A or Arm B over Arm C, respectively.*

*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 5.** 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






***Comparison with FCR only and BR only***

**Table 7**. 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.*
*[c] Progression-free at time of analysis.*
*[d] The calculation is based on the Kaplan-Meier technique.*
*[e] The CI for median PFS is derived based on Brookmeyer-Crowley method.*
*[f] The analysis is performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach. Patients with no observed events are censored at the date of randomization (if no baseline or post-baseline assessment) or last response assessment. A hazard ratio below 1 favors Arm A or Arm B over Arm C (FCR only), respectively.*
*[g] The analysis is performed using a stratified 2-sided log-rank test and a method that corresponds to the Breslow approach for handling ties*

**Table 8.** 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.*

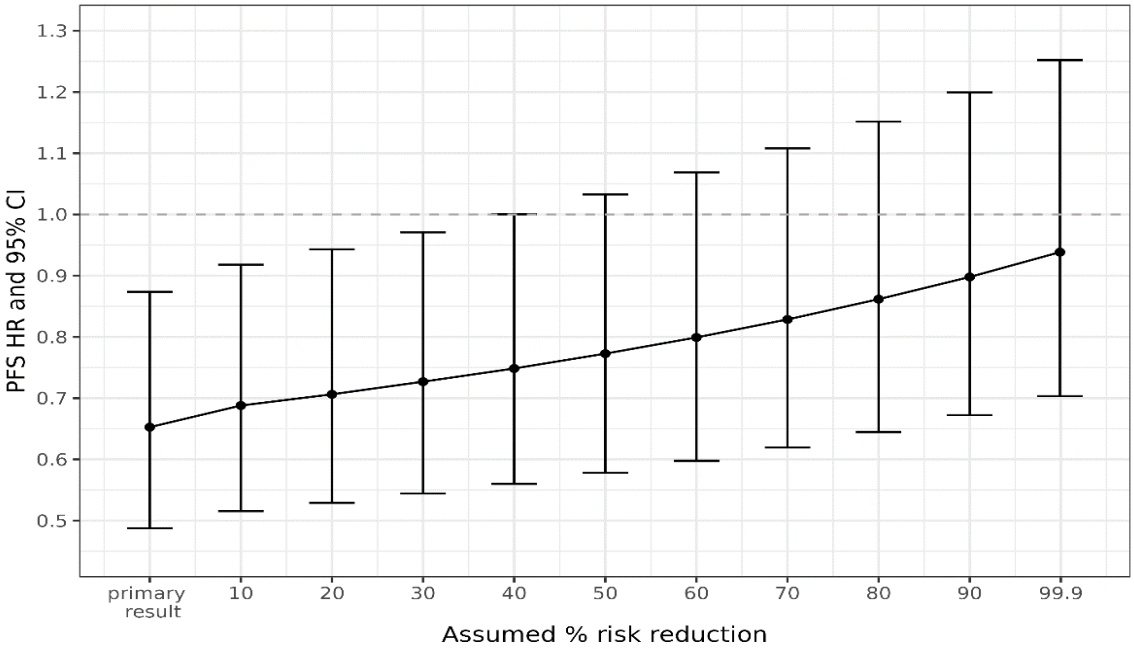
**Tipping point analysis**

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




**PFS (Arm B vs Arm C)**

**Table 9.** 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) |

| | Arm B (AVG) (N = 286) | Arm C (FCR/BR) (N = 290) |
|---|---|---|
| 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** | | |
| 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 10.** 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, 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 11.** Overall Survival (FAS, cut-off date 30 Oct 2024)), study ACE-CL-311

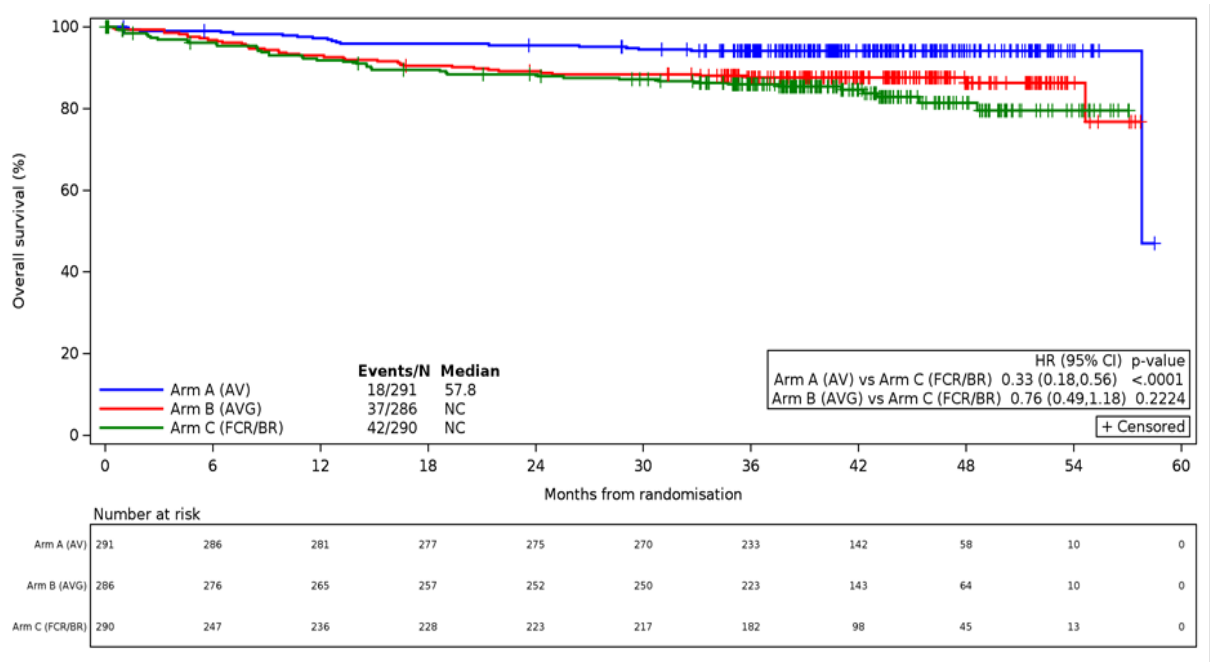
| | Arm A (AV) N = 291 | Arm B (AVG) N = 286 | Arm C (FCR/BR) N = 290 |
|---|---|---|---|
| Event, n (%) | | | |
| Death | 23 (7.9) | 37 (12.9) | 44 (15.2) |
| Censored observations, n (%) | | | |
| Any | 268 (92.1) | 249 (87.1) | 246 (84.8) |
| Still in survival follow up [a] | 264 (90.7) | 246 (86.0) | 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) [b, c] | | | |
| Median (95% CI) | NC (NC, NC) | NC (NC, NC) | NC (NC, NC) |
| P25, P75 | NC, NC | NC, NC | NC, NC |
| Comparison of treatment groups [d] | | | |

| | | | |
|---|---|---|---|
| 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) |

*a Includes patients not known to have died on or before 30 October 2024 DCO date.*
*b The calculation is based on the Kaplan-Meier technique.*
*c The CI for median overall survival is derived based on Brookmeyer-Crowley method.*
*d The analysis is performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach. Patients with no observed events are censored at the last known alive date. A hazard ratio below 1 favours Arm A or Arm B over Arm C, respectively. The p-value is based on the stratified log-rank test.*
*Abbreviations: CI, confidence interval; DCO, data cutoff; NC, not Calculable; P25, 25th percentile; P75, 75th percentile. Source: 14.2.6.1.*

*a Includes patients not known to have died on or before 30 October 2024 DCO date.*
*b The calculation is based on the Kaplan-Meier technique.*
*c The CI for median overall survival is derived based on Brookmeyer-Crowley method.*
*d The analysis is performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach. Patients with no observed events are censored at the last known alive date. A hazard ratio below 1 favours Arm A or Arm B over Arm C, respectively. The p-value is based on the stratified log-rank test.*
*Abbreviations: CI, confidence interval; DCO, data cutoff; NC, not Calculable; P25, 25th percentile; P75, 75th percentile.*

**Figure 7.** Kaplan-Meier Plot for Overall Survival (Full Analysis Set), study ACE-CL-311




***Sensitivity analysis***

**Table 12.** 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 |
| | 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.*
*The p-value is based on the stratified log-rank test.*

***Investigator assessed PFS***

**Table 13**. 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 14.** 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) | - |
| **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 15.** 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) |
| 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).*

***Time to next treatment***

**Table 16.**Time to Next Treatment (Full Analysis Set), study ACE-CL-311

| | **Arm A (AV) (N = 291)** | **Arm B (AVG) (N = 286)** | **Arm C (FCR/BR) (N = 290)** |
|---|---|---|---|
| **Event, n (%)** | | | |
| Any | 52 (17.9) | 50 (17.5) | 84 (29.0) |
| Initiation of subsequent anti-CLL therapy | 35 (12.0) | 14 (4.9) | 47 (16.2) |
| Death without progression or subsequent anti-CLL therapy | 17 (5.8) | 36 (12.6) | 37 (12.8) |
| **Censored observations, n (%)** | | | |
| Any[a] | 239 (82.1) | 236 (82.5) | 206 (71.0) |
| Alive without subsequent anti-CLL therapy | 236 (81.1) | 232 (81.1) | 168 (57.9) |
| Early study discontinuation | 3 (1.0) | 4 (1.4) | 18 (6.2) |

| | Arm A (AV) (N = 291) | Arm B (AVG) (N = 286) | Arm C (FCR/BR) (N = 290) |
|---|---|---|---|
| Lost to follow-up | 0 | 0 | 0 |
| Withdrew consent | 3 (1.0) | 1 (0.3) | 12 (4.1) |
| Study exit due to investigator decision or other | 0 | 3 (1.0) | 6 (2.1) |
| **Time to next anti-CLL therapy[b,c], median (95% CI) (months)** | NC (NC, NC) | 58.3[d] (54.6, NC) | 54.8[d] (48.6, NC) |
| **Comparison of treatment groups[e]** | | | |
| Hazard ratio[d] (95% CI) | 0.45 (0.32, 0.64) | 0.46 (0.32, 0.65) | - |
| p-value[f] | < 0.0001 | < 0.0001 | - |
| **Patients without next anti-CLL therapy (%)[b] (95% CI)** | | | |
| 12 months | 96.2 (93.2, 97.9) | 91.9 (88.1, 94.6) | 89.6 (85.2, 92.7) |
| 24 months | 93.4 (89.9, 95.8) | 88.0 (83.7, 91.3) | 82.8 (77.6, 86.9) |
| 36 months | 88.5 (84.1, 91.7) | 85.4 (80.8, 89.1) | 75.2 (69.3, 80.1) |
| 48 months | 79.8 (73.1, 85.0) | 81.4 (75.4, 86.0) | 60.2 (51.8, 67.6) |

e *Not initiated subsequent therapy or died at time of analysis.*

f *The calculation is based on the KM technique.*

g *The CI for time to next anti-CLL therapy is derived based on Brookmeyer-Crowley method.*

h *The median TTNT for Arm B and Arm C are unstable due to low number of patients at risk.*

i *The analysis is performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach. Patients with no observed events are censored at the date of last visit. A HR below 1 favours Arm A or Arm B over Arm C, respectively.*

j *The analysis is performed using a stratified 2-sided log-rank test and a method that corresponds to the Breslow approach for handling ties (Breslow 1974)*

**Supportive studies**

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 17**.

**Table 17.** Clinical trials with acalabrutinib and TP53 aberrations

| | CLL-14 | | |
|---|---|---|---|
| | Venetoclax + obinutuzumab | Obinutuzumab + chlorambucil | |
| **Number of patients**<br>Total<br>del17p<br>TP53 mut<br>TP53 unmutated | <br>216<br>17<br>19<br>152 | <br>216<br>14<br>13<br>144 | |
| **INV-PFS** HR (95% CI)<br>All patients<br>Del17p<br>TP53 mut<br>Tp53 unmutated | <br>0.32 (0.21, 0.49)<br>0.35 (0.13, 0.94)<br>0.31 (0.11, 0.88)<br>0.22 (0.12, 0.40) | <br>-<br>-<br>-<br>- | |
| **INV-ORR** % (95% CI)<br>All patients<br>Del17p<br>TP53 mut<br>Tp53 unmutated | <br>84.7% (79.2, 89.2)<br>82.4%<br>84.2%<br>86.8% | <br>71.3% (64.8, 77.2)<br>35.7%<br>53.8%<br>71.5% | |
| | **NCT03580928 (SAT)** | | |
| | Acalabrutinib + venetoclax + obinutuzumab | | |
| Number of patients<br>TP53 aberration | 37<br>10 | | |
| **ORR at cycle 25** (%)<br>All patients<br>TP53 aberration | <br>97%<br>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 18.** Summary of Efficacy for study ACE-CL-311 (AMPLIFY)

| **Title: AMPLIFY** | | |
|---|---|---|
| Study identifier | Study Code: ACE-CL-311 (D8221C00001)<br>EudraCT/EU CT Number: 2018-002443-28<br>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:<br>Duration of Run-in phase:<br>Duration of Extension phase: | <time><br><time> <not applicable><br><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+ | | 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. |
| | obinutuzumab; AVG) | | 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 ≤ 65 years of age with a creatinine clearance of ≥ 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 subjects | 291 | 286 | 290 |
| | **PFS**<br>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**<br>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**<br>Death events, n (%) | 18 (6.2) | 37 (12.9) | 42 (14.5) |
| | Median OS (months) (95% CI) | 57.8 (57.8, NC) | NC (NC, NC) | NC (NC, NC) |
| | HR (95% CI), p-value | 0.33 (0.18, 0.56), <0.0001 | 0.76 (0.49, 1.18), 0.2224 | - |
| 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. | | | |

## 2.4.2. Discussion on clinical efficacy

To support a first-line indication of venetoclax plus acalabrutinib with or without obinutuzumab in CLL results from one pivotal study (ACE-CL-311, AMPLIFY) were reported.

**Design and conduct of clinical studies**

AMPLIFY is a randomised, open-label, Phase III study designed to evaluate whether fixed duration of venetoclax in combination with acalabrutinib 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.

First subject enrolment was on 25 Feb 2019. The initial SAP version was dated 23 Dec 2021 and the latest SAP version 4.0 finalised 28 Feb 2024.

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) and received fixed duration therapy. 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). The primary and key secondary endpoints were done in accordance with pre-specified analysis methods.

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 randomization) in the analyses were pre-specified and done in accordance with pre-specification, which is appreciated.

Seven protocol amendments were done during the study and amendments 1, 5 and 6 are considered substantial. According to Amendment 6.0 version 7.0, 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 timing of the analysis submitted in this application (data cut-off 30 April 2024) occurred at 184 PFS events, which is (depending on the protocol version) 98% of the information fraction of the 188 PFS events required for the final analysis.

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.

PFS

Statistically significant IRC-assessed PFS was shown for Arm A as compared with Arm C (primary endpoint), 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. 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 due to informative censorings. PFS sensitivity analyses were pre-specified in the SAP and done according to pre-specification. However, since all SAP versions were finalised after start of study enrolment, sensitivity analyses could be potentially data driven.

For the primary endpoint, relevant subgroup results are mainly consistent. When not evidently so, there is a lack of plausibility for effect modification (e.g. age and sex).

Statistically significant IRC-assessed PFS was also 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 the PFS analyses, potentially informative censoring is seen for 7.9% in Arm A, 10.1% in Arm B and 25.5% of patients in Arm C. Of note, 31 patients who were randomised to, but did not receive, FCR/BR treatment were censored at Day 1 as they did not have a post-baseline assessment.

Post-hoc tipping point analyses of PFS was performed to evaluate the impact of imbalanced early censoring between arms on the PFS results. In these analyses, the PFS time was imputed for the 75 patients in Arm C (FCR/BR) who were censored informatively, and it was assumed that these patients had a reduced risk of death or progression compared to all other patients in the arm (i.e. those still in follow-up or who had an event) in Arm C.

A grid search algorithm was used to find the minimal percent reduction of hazard rate needed such that the 95% CI of the HR would include 1. 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. A 40% risk reduction would translate to a HR of approximately 0.60, comparing the 75 informatively censored patient's and the 215 patients still in follow-up or with an event in Arm C. The positive PFS result from comparison of Arm B and Arm C does not tip at all under the range of modelled conditions.

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

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 HR's 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 HR's 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.

In updated INV-PFS analyses with DCO date 30 October 2024, in Arm A, Arm B and Arm C, 102 (35.1%), 51 (17.8%) and 103 (35.5%) INV-PFS events were reported, respectively. This resulted in a

HR 0.68 (95% CI; 0.52, 0.90) for Arm A vs Arm C and a HR of 0.36 (95% CI: 0.25, 0.50) for Arm B vs Arm C. Both AV and AVG continues to show improvement in PFS over FCR/BR.

MRD negativity

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 increased the likelihood of MRD negativity.

Of note, MRD measurement was missing for >30% of patients in both Arm B and Arm C lots and this large proportion of missing data may influence the results. Upon request, the MAH provided a discussion on reasons for the discrepancies in missing MRD measurements between arms as well as baseline characteristics that enabled comparisons of patients with and without MRD measurement within each trial arm. Patients randomized 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. Both high Rai stage and complex karyotype are prognostic markers associated with worse outcome. High Rai stage was more common among patients without MRD measurement (seen in arm B and arm C) whereas patients with MRD measurement more often have a complex karyotype (seen in Arm A and Arm B). A pattern of worse prognostic markers being more common in either patients with or without MRD measurement cannot be recognised from the baseline data. The differences seen are therefore not considered to affect whether samples for MRD measurement were taken or not.

Given the different direction of the risk ratios from the comparisons between Arm A and C (0.5) and Arm B and C (1.3), baseline characteristics for patients with MRD measurements were compared between Arm A and Arm B and appears well balanced between. It is therefore agreed that the higher uMRD rates in Arm B (AVG) are likely due to the addition of the anti-CD20 antibody.

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.

OS

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%) had died in Arm C (FCR/BR, Table 12). Median OS was 57.8 months in Arm A but not met in either Arm B or Arm C.

Updated OS analyses (DCO of 30 October 2024) included 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.

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 the CHMP recommended that the final OS results should be submitted when available.

ORR

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%, Table 15). An assessment of ORR by investigator assessment was consistent with the IRC assessment for both Arm A and Arm B vs Arm C.

*Use in del(17p) and TP53 mutated disease*

Venetoclax in combination with obinutuzumab (VG) as well as acalabrutinib with or without obinutuzumab (A or AG) are approved in the EU and recommended first-line therapy regimens of symptomatic CLL in the ESMO guideline. With this submission, the MAH seeks approval of an all-comer CLL indication in combination with acalabrutinib with or without obinutuzumab. However, 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. Support of the proposed indication (i.e. all-comer, previously untreated CLL), comes from 2 additional studies to extrapolate efficacy to patients with del(17p) and/or TP53.

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

Preliminary data from the ongoing SAT NCT03580928 evaluating the combination of three drugs - acalabrutinib, venetoclax, and obinutuzumab have shown that at cycle 25 all patients with TP53 aberrations had achieved CR or PR.

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

### 2.4.3. 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*

Venetoclax is a selective, orally bioavailable small-molecule inhibitor of the anti-apoptotic protein B-cell lymphoma (BCL)-2, the safety profile of Venclyxto monotherapy in CLL is dominated by haematological toxicity, infections and low-grade gastrointestinal toxicity.

## *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 19-Table 21**).

**Table 19**. 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 20.** 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 21.** 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 |

## *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 22.** 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) |
| 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) |
| 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) |
| 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 23.** Overview of Treatment-Emergent Adverse Events (Safety Population), study ACE-CL-311

| | **Pivotal AMPLIFY data** | | |
|---|---|---|---|
| | **Arm A AV (N = 291) n (%)** | **Arm B AVG (N=294) n (%)** | **Arm C FCR/BR (N = 259) n (%)** |
| **Serious TEAEs** | | | |
| Any grade | 72 (24.7) | 109 (38.4) | 71 (27.4) |
| Grade ≥ 3 | 65 (22.3) | 94 (33.1) | 64 (24.7) |

| | | | |
|---|---|---|---|
| **Fatal/Grade 5 TEAEs** | 10 (3.4) | 17 (6.0) | 9 (3.5) |
| **Treatment-related TEAEs** | | | |
| Any study drug | 230 (79.0) | 238 (83.8) | 215 (83.0) |
| **Treatment-related Grade ≥ 3 TEAEs** | | | |
| Any study drug | 117 (40.2) | 157 (55.3) | 143 (55.2) |
| **TEAEs leading to study drug discontinuation** | | | |
| Any study drug | 23 (7.9) | 57 (20.1) | 28 (10.8) |
| **TEAEs leading to study drug dose reduction** | | | |
| Any study drug | 41 (14.1) | 59 (20.8) | 29 (11.2) |
| **TEAEs leading to study drug withholding** | | | |
| Any study drug | 145 (49.8) | 184 (64.8) | 81 (31.3) |
| **TEAEs leading to infusion interruption (for infusion drug only)** | | | |
| Any study drug | 0 | 49 (17.3) | 83 (32.0) |

*[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 24**).

**Table 24.** TEAEs experienced by ≥ 10% of patients in any treatment arm. Safety Population, study ACE-CL-311

| | **Pivotal AMPLIFY data** | | |
|---|---|---|---|
| **Preferred Term** | **Arm A AV (N = 291) n (%)** | **Arm B AVG (N = 284) n (%)** | **Arm C FCR/BR (N = 259) n (%)** |
| Patients with ≥1 TEAE | 270 (92.8) | 269 (94.7) | 236 (91.1) |
| Headache | 102 (35.1) | 80 (28.2) | 20 (7.7) |
| Diarrhoea | 95 (32.6) | 103 (36.3) | 28 (10.8) |
| Neutropenia | 90 (30.9) | 114 (40.1) | 99 (38.2) |

| Preferred Term | Pivotal AMPLIFY data | | |
|---|---|---|---|
| | Arm A AV (N = 291) n (%) | Arm B AVG (N = 284) n (%) | Arm C FCR/BR (N = 259) n (%) |
| COVID-19 | 55 (18.9) | 58 (20.4) | 6 (2.3) |
| Nausea | 43 (14.8) | 62 (21.8) | 93 (35.9) |
| Fatigue | 43 (14.8) | 41 (14.4) | 35 (13.5) |
| Contusion | 40 (13.7) | 44 (15.5) | 4 (1.5) |
| Arthralgia | 37 (12.7) | 31 (10.9) | 9 (3.5) |
| Pruritis | 32 (11.0) | 13 (4.6) | 14 (5.4) |
| Back pain | 31 (10.7) | 19 (6.7) | 14 (5.4) |
| Rash | 24 (8.2) | 34 (12.0) | 18 (6.9) |
| Upper respiratory tract infection | 24 (8.2) | 18 (6.3) | 5 (1.9) |
| COVID-19 pneumonia | 21 (7.2) | 35 (12.3) | 7 (2.7) |
| Anaemia | 20 (6.9) | 13 (4.6) | 25 (9.7) |
| Myalgia | 20 (6.9) | 23 (8.1) | 9 (3.5) |
| Constipation | 19 (6.5) | 23 (8.1) | 31 (12.0) |
| Neutrophil count decreased | 18 (6.2) | 29 (10.2) | 27 (10.4) |
| Pyrexia | 17 (5.8) | 44 (15.5) | 47 (18.1) |
| Vomiting | 16 (5.5) | 19 (6.7) | 31 (12.0) |
| Dizziness | 16 (5.5) | 19 (6.7) | 8 (3.1) |
| Cough | 14 (4.8) | 23 (8.1) | 13 (5.0) |
| Thrombocytopenia | 13 (4.5) | 24 (8.5) | 33 (12.7) |
| Hypertension | 12 (4.1) | 9 (3.2) | 6 (2.3) |
| Pneumonia | 11 (3.8) | 15 (5.3) | 8 (3.1) |
| Dyspnoea | 10 (3.4) | 16 (5.6) | 10 (3.9) |
| Oedema peripheral | 10 (3.4) | 16 (5.6) | 8 (3.1) |
| Insomnia | 9 (3.1) | 20 (7.0) | 10 (3.9) |
| Sinusitis | 8 (2.7) | 7 (2.5) | 2 (0.8) |
| Infusion related reaction | 0 | 56 (19.7) | 85 (32.8) |

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 25**).

**Table 25.** Treatment-Emergent CTCAE Grade≥3 Adverse Events Reported in ≥5% of Patients in Any Treatment Arm (Safety Population), study ACE-CL-311

| Preferred Terms | Pivotal AMPLIFY data | | |
|---|---|---|---|
| | Arm A AV (N = 291) n (%) | Arm B AVG (N = 284) n (%) | Arm C FCR/BR (N = 259) n (%) |
| Patients with ≥1 Grade ≥3 TEAE | 156 (53.6) | 197 (69.4) | 157 (60.6) |
| Neutropenia | 78 (26.8) | 100 (35.2) | 84 (32.4) |
| COVID-19 pneumonia | 16 (5.5) | 33 (11.6) | 7 (2.7) |
| Neutrophil count decreased | 16 (5.5) | 29 (10.2) | 22 (8.5) |
| Anaemia | 11 (3.8) | 6 (2.1) | 17 (6.6) |
| COVID-19 | 8 (2.7) | 19 (6.7) | 4 (1.5) |
| Febrile neutropenia | 5 (1.7) | 7 (2.5) | 24 (9.3) |
| Thrombocytopenia | 4 (1.4) | 17 (6.0) | 22 (8.5) |
| Pneumonia | 4 (1.4) | 11 (3.9) | 6 (2.3) |

## *Serious adverse event/deaths/other significant events*

### *Serious adverse event*

**Table 26.** Serious Treatment-Emergent Adverse Events Reported in ≥ 1% of Patients in Any Treatment Arm (Safety Population), study ACE-CL-311

| System organ Class | Pivotal AMPLIFY data | | | | | |
|---|---|---|---|---|---|---|
| | Arm A AV (N = 291) n (%) | | Arm B AVG (N = 284) n (%) | | Arm C FCR/BR (N = 259) n (%) | |
| Preferred term | All Grade | Grade ≥3 | All Grade | Grade ≥3 | ll 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) |
| COVID-19 pneumonia | 17 (5.8) | 16 (5.5) | 32 (11.3) | 31 (10.9 | 6 (2.3) | 6 (2.3) |

| System organ Class | Pivotal AMPLIFY data | | | | | |
|---|---|---|---|---|---|---|
| | Arm A AV (N = 291) n (%) | | Arm B AVG (N = 284) n (%) | | Arm C FCR/BR (N = 259) n (%) | |
| Preferred term | All Grade | Grade ≥3 | All Grade | Grade ≥3 | ll Grade | Grade ≥3 |
| COVID-19 | 9 (3.1) | 7 (2.4) | 17 (6.0) | 15 (5.3) | 4 (1.5) | 4 (1.5) |
| Febrile neutropenia | 5 (1.7) | 5 (1.7) | 5 (1.8) | 5 (1.8) | 21 (8.1) | 21 (8.1) |
| Pneumonia | 4 (1.4) | 3 (1.0) | 10 (3.5) | 10 (3.5) | 8 (3.1) | 6 (2.3) |
| Anaemia | 3 (1.0) | 3 (1.0) | 2 (0.7) | 1 (0.4) | 3 (1.2) | 3 (1.2) |
| Abdominal pain | 2 (0.7) | 2 (0.7) | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Pyrexia | 2 (0.7) | 1 (0.3) | 6 (2.1) | 3 (1.1) | 8 (3.1) | 4 (1.5) |
| Acute kidney injury | 1 (0.3) | 1 (0.3) | 3 (1.1) | 3 (1.1) | 2 (0.8) | 2 (0.8) |
| Dyspnoea | 1 (0.3) | 0 | 0 | 0 | 0 | 0 |
| Neutropenia | 1 (0.3) | 1 (0.3) | 3 (1.1) | 3 (1.1) | 2 (0.8) | 2 (0.8) |
| Pulmonary embolism | 1 (0.3) | 1 (0.3) | 3 (1.1) | 2 (0.7) | 1 (0.4) | 1 (0.4) |
| Sepsis | 1 (0.3) | 1 (0.3) | 2 (0.7) | 2 (0.7) | 2 (0.8) | 2 (0.8) |
| Thrombocyto penia | 1 (0.3) | 1 (0.3) | 1 (0.4) | 1 (0.4) | 3 (1.2) | 3 (1.2) |
| Infusion related reaction | 0 | 0 | 3 (1.1) | 1 (0.4) | 5 (1.9) | 5 (1.9) |
| Lower respiratory tract infection | 0 | 0 | 2 (0.7) | 2 (0.7) | 0 | 0 |
| Atrial fibrillation | 0 | 0 | 1 (0.4) | 1 (0.4) | 2 (0.8) | 2 (0.8) |
| Neutrophil count decreased | 0 | 0 | 1 (0.4) | 1 (0.4) | 3 (1.2) | 3 (1.2) |
| TLS | 0 | 0 | 1 (0.4) | 1 (0.4) | 6 (2.3) | 6 (2.3) |
| Urinary tract infection | 0 | 0 | 1 (0.4) | 0 | 0 | 0 |
| Cellulitis | 0 | 0 | 0 | 0 | 0 | 0 |
| Respiratory tract infection | 0 | 0 | 0 | 0 | 0 | 0 |

| System organ Class / 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 Grade | Grade ≥3 | All Grade | Grade ≥3 | All Grade | Grade ≥3 |
| Upper respiratory tract infection | 0 | 0 | 0 | 0 | 0 | 0 |

***Deaths***

**Table 27.** Summary of Deaths (Safety Population), study ACE-CL-311

| | Pivotal AMPLIFY data | | |
|---|---|---|---|
| | Arm A AV (N = 291) n (%) | Arm B AVG (N = 284) n (%) | Arm C FCR/BR (N = 259) n (%) |
| **Deaths** | 18 (6.2) | 36 (12.7) | 42 (16.2) |
| Primary cause of death | | | |
| Adverse event | 16 (5.5) | 29 (10.2) | 28 (10.8) |
| Other | 2 (0.7) | 5 (1.8) | 6 (2.3) |
| Disease progression | 0 | 0 | 4 (1.5) |
| Unknown | 0 | 2 (0.7) | 4 (1.5) |
| Richter's Transformation | 0 | 0 | 0 |
| **Within 30 days of last dose of study drug** | | | |
| Deaths | 10 (3.4) | 11 (3.9) | 7 (2.7) |
| Primary cause of death | | | |
| Disease progression | 0 | 0 | 0 |
| Adverse event | 10 (3.4) | 11 (3.9) | 7 (2.7) |
| Richter's Transformation | 0 | 0 | 0 |
| Other | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| **More than 30 days after last dose of study drug** | | | |
| Deaths | 8 (2.7) | 25 (8.8) | 35 (13.5) |
| Primary cause of death | | | |
| Disease progression | 0 | 0 | 4 (1.5) |
| Adverse event | 6 (2.1) | 18 (6.3) | 21 (8.1) |
| Richter's Transformation | 0 | 0 | 0 |
| Other | 2 (0.7) | 5 (1.8) | 6 (2.3) |
| Unknown | 0 | 2 (0.7) | 4 (1.5) |

**Table 28.** 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** | | |
|---|---|---|---|
| | **Arm A AV (N = 291) n (%)** | **Arm B AVG (N = 284) n (%)** | **Arm C FCR/BR (N = 259) n (%)** |
| Patients with a Grade 5 TEAE | 10 (3.4) | 17 (6.0) | 9 (3.5) |
| COVID-19 pneumonia | 6 (2.1) | 10 (3.5) | 4 (1.5) |
| COVID-19 | 2 (0.7) | 5 (1.8) | 3 (1.2) |
| Cardiac arrest | 1 (0.3) | 0 | 1 (0.4) |
| Infection | 1 (0.3) | 0 | 0 |
| Pneumonia | 0 | 1 (0.4) | 0 |
| Sudden death | 0 | 1 (0.4) | 0 |
| Septic shock | 0 | 0 | 0 |
| Sepsis | 0 | 0 | 0 |
| Cerebrovascular accident | 0 | 0 | 0 |
| Respiratory failure | 0 | 0 | 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 were: cardiac events, cytopenias, haemorrhages, hepatotoxicity, hypertension, infections, Interstitial lung disease (ILD)/pneumonitis, Second Primary Malignancies (SPMs), and Tumour Lysis Syndrome (TLS).

**Cardiac events**

**Table 29.** Treatment-Emergent Events of Clinical Interest and Adverse Events of Special Interest: Cardiac Events (Safety Population), study ACE-CL-311

| ECI/AESI category<br>ECI/AESI subcategory<br>Preferred term | Pivotal AMPLIFY data | | | | | |
|---|---|---|---|---|---|---|
| | Arm A<br>AV<br>(N = 291)<br>n (%) | | Arm B<br>AVG<br>(N = 284)<br>n (%) | | Arm C<br>FCR/BR<br>(N = 259)<br>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 |
| 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 30.** 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<br>ECI subcategory<br>Preferred term | Pivotal AMPLIFY data | | | | | |
|---|---|---|---|---|---|---|
| | Arm A<br>AV<br>(N = 291)<br>n (%) | | Arm B<br>AVG<br>(N = 284)<br>n (%) | | Arm C<br>FCR/BR<br>(N = 259)<br>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) |
| 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 31.** 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<br>Preferred term | Pivotal AMPLIFY data | | | | | |
|---|---|---|---|---|---|---|
| | Arm A<br>AV<br>(N = 291)<br>n (%) | | Arm B<br>AVG<br>(N = 284)<br>n (%) | | Arm C<br>FCR/BR<br>(N = 259)<br>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 |

| ECI subcategory | Pivotal AMPLIFY data | | | | | |
|---|---|---|---|---|---|---|
| | Arm A AV (N = 291) n (%) | | Arm B AVG (N = 284) n (%) | | Arm C FCR/BR (N = 259) n (%) | |
| Preferred term | All Grades | Grade ≥ 3 | All Grades | Grade ≥ 3 | All Grades | Grade ≥ 3 |
| 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 32.** 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 | Pivotal AMPLIFY data | | | | | |
|---|---|---|---|---|---|---|
| | Arm A AV (N = 291) n (%) | | Arm B AVG (N = 284) n (%) | | Arm C FCR/BR (N = 259) n (%) | |
| Preferred term | 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 33.** Treatment-Emergent Adverse Events of Clinical Interest: Infections Reported for ≥ 5% Patients in Any Group (Safety Population), study ACE-CL-311

| ECI category<br>Preferred term | Pivotal AMPLIFY data | | | | | |
|---|---|---|---|---|---|---|
| | Arm A<br>AV<br>(N = 291)<br>n (%) | | Arm B<br>AVG<br>(N = 284)<br>n (%) | | Arm C<br>FCR/BR<br>(N = 259)<br>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) |
| 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 34**.

**Table 34.** 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) |
| 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) |

[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)**

Events of SPM were reported in 5.2%, 4.2%, and 0.8% of patients in the AV, AVG, and FCR/BR arms, respectively. Excluding non-melanoma skin malignancies, SPMs were reported in 2.7%, 2.5%, and 0.4% of patients, respectively. Grade ≥ 3 SPMs were reported in 1.7% and 1.8% of patients in the AVG and AV arms, respectively. No patients in the FCR/BR arm had Grade ≥ 3 SPMs. The overall low incidence of SPM in all arms could be partly due to the short treatment-emergent AE observation period.

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).

**Tumour Lysis Syndrome (TLS)**

The incidence of TLS events in the AV and AVG arms was low with 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.

## *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.

### 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 (data not shown).

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 35.** 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)**<br><br>**N = 291 n (%)** | **Arm B (AVG)**<br><br>**N = 284 n (%)** |
|---|---|---|
| Patients with ≥ 1 AE leading to discontinuation of<br>**Any study treatment** | 23 (7.9) | 57 (20.1) |
| Patients with ≥ 1 AE leading to discontinuation of<br>**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<br>**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<br>**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

Venetoclax is a selective inhibitor of the anti-apoptotic protein B-cell lymphoma-2 (BCL-2). The safety profile of Venclyxto monotherapy in CLL is dominated by haematological toxicity, infections and low-grade gastrointestinal toxicity. Other toxicities that have been associated with venetoclax include tumour lysis syndrome (TLS).

The safety profiles of acalabrutinib and obinutuzumab are also well described, including e.g., GI-side effects 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.

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 times shorter than for venetoclax 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 venetoclax, SAEs, and AEs leading to discontinuation of any 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 in 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 and frequency of severe and potentially fatal infections is highlighted in Section 4.8 of the SmPC for both the AV and AVG treatments.

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 current warnings in the SmPC section 4.2 with dose modifications in relation to Grade 3 neutropenia with infection or fever; or Grade 4 haematologic toxicities (except lymphopenia) and other non-haematological grade 3 or greater toxicities. In the SmPC section 4.4 there is relevant information present in a separate paragraph with subheading "Neutropenia and infections".

The haematological ADR frequencies for the AV and AVG combinations are now reflected in section 4.8 of the SmPC.

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.

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 with one patient in each of the AV 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 in principle following the venetoclax SmPC. 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). In the venetoclax SmPC section 4.2 there are dose modification advice for restarting dose following blood chemistry changes or symptoms suggestive of TLS, and also clear warning in 4.4 including description of which patients may be considered at risk, assessment and monitoring advice.

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 6.2% in AV and 13.0% in AVG who discontinued venetoclax due to TEAEs. The most common TEAE leading to discontinuation was Covid-19 pneumonia in AV and Covid-19 and Covid-19 pneumonia in AVG.

### 2.5.2. Conclusions on clinical safety

The combination of venetoclax with acalabrutinib 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 appropriate 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 RMP version with this application.

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

The PRAC considered that the risk management plan version 12.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 12.0 with the following content:

## *Safety concerns*

| **Summary of Safety Concerns** | |
|---|---|
| Important identified risks | Tumor lysis syndrome |
| Important potential risks | Embryofetal toxicity<br>Medication error<br>Richter's transformation (for CLL only)<br>Second primary malignancy<br>Toxicity in patients with severe hepatic impairment |
| Missing information | Safety in long-term exposure (> 12 months) (for CLL only) |

## *Pharmacovigilance plan*

| **Study Name Status** | **Summary of Objectives** | **Safety Concerns Addressed** | **Milestones** | **Due Dates** |
|---|---|---|---|---|
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| Study P16-562<br>Prospective Observational Cohort Study to Assess the Long Term Safety of Venetoclax in the Swedish Cohort of Chronic Lymphocytic Leukaemia Patients<br><br>Ongoing | To characterize long term safety of venetoclax including determining the incidence of select adverse events in CLL patients exposed to venetoclax. | Safety in long-term exposure (> 12 months) of venetoclax<br><br><u>Select list of adverse events:</u><br><br>• Second primary malignancies<br>• Richter's transformation (DLBCL, HL)<br>• Opportunistic serious infections<br>• Autoimmune hematological event<br>  ○ Other autoimmune hemolytic anemia<br>  ○ Idiopathic thrombocytopenic purpura<br>• Tumor Lysis syndrome | Interim CSR<br><br>Final report | Every second year over a study period of 8 years<br><br>Planned Q2 2026 |

## *Risk minimisation measures*

### Summary Table of Risk Minimisation Activities by Safety Concern

| **Safety Concern** | **Risk Minimization Measures** |
|---|---|
| Tumor lysis syndrome (TLS) | <u>Routine risk minimization measures:</u><br>Posology and method of administration, including prophylactic measures for TLS, are described in section 4.2 of the SmPC (CLL and AML). |

| Safety Concern | Risk Minimization Measures |
|---|---|
| | Warnings and precautions for TLS are listed in section 4.4 of the SmPC (CLL and AML).<br>Interaction with other medicinal products is described in section 4.5 of the SmPC (CLL and AML).<br>TLS is described in section 4.8 of the SmPC (CLL and AML).<br><u>Other routine risk minimization measures:</u><br>• Prescription only medicine<br>• Use of treatment should be initiated and supervised by specialists<br>• Packaging design and language to facilitate adherence to the dose-titration schedule<br>• Pack size and package leaflet<br><br><u>Additional risk minimization measures:</u><br>• Distribution of DHPC in European countries (CLL only) (activity completed in 2021 and effectiveness evaluation completed in 2025)<br>• Distribution of a patient card in European countries (CLL only) |
| Embryofetal toxicity | <u>Routine risk minimization measures:</u><br>Language concerning embryofetal toxicity is included in section 4.6 and section 5.3 of the SmPC (CLL and AML).<br><br><u>Other routine risk minimization measures:</u><br>• Prescription only medicine<br>• Use of treatment should be initiated and supervised by specialists<br>• Package leaflet<br><br><u>Additional risk minimization measures:</u> None |
| Medication error | <u>Routine risk minimization measures:</u><br>Posology and method of administration are described in section 4.2 of the SmPC (CLL and AML).<br>Description of contents of venetoclax container, including dose strength, shape and color of tablets, in section 3 and section 6.5 of SmPC (CLL).<br>Language concerning overdose is included in section 4.9 of the SmPC (CLL and AML).<br><br><u>Other routine risk minimization measures:</u><br>• Prescription only medicine |
| | • Use of treatment should be initiated and supervised by specialists<br>• In CLL, each carton will be dispensed weekly to the patient during the first 4 weeks of the dose titration<br>• In AML, only 100 mg tablets will be dispensed to minimize medication errors<br>• Labeling and packaging layout (immediate and outer packaging) has been designed to minimize medication errors<br>• Pack size and package leaflet<br><br><u>Additional risk minimization measures:</u> None |

| Safety Concern | Risk Minimization Measures |
|---|---|
| Richter's transformation (for CLL only) | Routine risk minimization measures: None<br><br>Other routine risk minimization measures:<br>• Prescription only medicine<br>• Use of treatment should be initiated and supervised by specialist<br><br>Additional risk minimization measures: None |
| Second primary malignancy | Routine risk minimization measures: None<br><br>Other routine risk minimization measures:<br>• Prescription only medicine<br>• Use of treatment should be initiated and supervised by specialist<br><br>Additional risk minimization measures: None |
| Toxicity in Patients with severe hepatic impairment | Routine risk minimization measures:<br>Posology and method of administration of dose adjustments in patients with severe hepatic impairment are described in section 4.2 of the SmPC (CLL and AML).<br>PK study results pertaining to hepatic impairment are described in section 5.2 of the SmPC (CLL and AML).<br>Other routine risk minimization measures:<br>• Prescription only medication<br>• Use of treatment should be initiated and supervised by specialist<br>• Package leaflet<br><br>Additional risk minimization measures: None |
| Safety in long-term exposure (> 12 months) (for CLL only) | Routine risk minimization measures:<br>Median duration of treatment is included in section 5.1 of the SmPC (CLL)<br><br>Other routine risk minimization measures:<br>• Prescription only medicine<br>• Use of treatment should be initiated and supervised by specialists<br><br>Additional risk minimization measures: None |

## *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 has been updated accordingly.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes to the package leaflet are minimal and do not change the format or layout of the approved package leaflet and thus do not require user consultation with target patient groups.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Chronic lymphocytic leukaemia (CLL) is the most prevalent form of adult leukaemia. It is characterized 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:

"Venclyxto in combination with acalabrutinib 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 characterized 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, FCR is also indicated in young and fit patients with mutated IGHV while BR is used for older and unfit patients.

### 3.1.3. Main clinical studies

Study ACE-CL-311 or AMPLIFY is 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 (fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab (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:

(i) acalabrutinib for 14 cycles and venetoclax cycle 3-14 (Arm A),

(ii) acalabrutinib for 14 cycles; obinutuzumab cycle 2-7 and venetoclax Cycle 3-14 (Arm B)

(iii) 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. A BTKi is presently the ESMO guideline recommended therapy for these patients and data that support extrapolation of efficacy to patients with these aberrations has been provided.

## *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 MAH is requested to the submit the final OS results when available.

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 times shorter than for venetoclax 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 venetoclax discontinuation was 6.0 % in AV and 13.0% in AVG. The most frequently reported TEAEs that led to discontinuation of venetoclax in the AV and AVG arms were COVID-19 pneumonia (1.4% and 3.2%, respectively) and COVID-19 (0.3% and 3.2%, respectively).

## *3.5. Uncertainties and limitations about unfavourable effects*

Exposure time is approximately 2 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 control arm.

## *3.6. Effects Table*

**Table 36.** Effects Table for Venclyxto in combination with acalabrutinib with or without obinutuzumab for the treatment of adult patients with previously untreated CLL (30 October 2024).

| Effect | Short description | Unit | Arm A<br>AV | Arm B<br>AVG | Arm C<br>FCR/BR | Uncertainties / Strength of evidence | Refe-rences |
|---|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | | |
| PFS | Time from randomisation until disease progression (according to | N (%)<br>HR<br>(95% | 89 (30.6)<br>0.65<br>(0.49,0.87) | 56 (19.6)<br>0.42<br>(0.30, 0.59) | 95 (32.8)<br>- | SoE:<br>Statistically significant IRC assessed PFS for | AMPLIFY study |

| Effect | Short description | Unit | Arm A<br>AV | Arm B<br>AVG | Arm C<br>FCR/BR | Uncertainties /<br>Strength of evidence | Refe-rences |
|---|---|---|---|---|---|---|---|
| | the IWCLL 2018 criteria - IRC-assessed) | CI) | | | | Arm A vs Arm C and for Arm B vs Arm C<br><br>Consistent results with Investigator assessed PFS | |
| | | 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. p-value not significant after adjusting for multiplicity | |
| | | HR (95% CI) | 0.42 (0.25, 0.70) | 0.75 (0.48, 1.16) | - | | |
| **Unfavourable Effects** | | | | | | | |
| Grade 3/4 TEAE | Incidence:<br>Any<br>Infections<br>Neutropenia<br>Hepatotoxicity<br>Cardiac events | % | <br>53.6<br>12.4<br>32.3<br>3.4<br>1.7 | <br>69.4<br>23.6<br>46.1<br>2.8<br>2.5 | <br>60.6<br>10.0<br>43.2<br>1.5<br>1.2 | SoE: Data from adequately sized RCT<br><br>Unc: Exposure time approx. 2.3 times longer in AV and AVG vs. FCR/BR. | AMPLIFY study |
| Discontin uation | TEAE leading to discon-tinuation 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 survival; IWCLL: International Workshop on Chronic Lymphocytic Leukaemia; IRC: independent review committee; HR: hazard ratio; CI: confidence interval; OS: overall survival; SoE: strength of evidence; Unc: uncertainty; 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.

The addition of obinutuzumab to acalabrutinib and venetoclax results in an increased side effect burden. However, it also provides more antitumoral activity. OS data maturity and statistical robustness is not sufficient to infer any differences in survival outcomes between AV and AVG. It is reasonable that the prescriber determines whether to add obinutuzumab based on the individual patient characteristics.

While patients with del(17p) or TP53 mutations were excluded from the study because of the unsuitable comparator, the efficacy of acalabrutinib and venetoclax against such disease has been characterised in previously conducted studies, and their use is recommended per guideline. Therefore, beneficial effects may be extrapolated to these.

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.

### 3.7.2. Balance of benefits and risks

The benefit of increased PFS observed with the combination of venetoclax with acalabrutinib with or without obinutuzumab is deemed to outweigh the increased toxicity of the combination treatments.

## *3.8. Conclusions*

The overall B/R of Venclyxto in combination with acalabrutinib 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 changes:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II | Annex I, IIIA |

Extension of indication to include, in combination with acalabrutinib with or without obinutuzumab, the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for VENCLYXTO based on the results from the pivotal study ACE-CL-311/D8221C00001 (AMPLIFY); this is a

randomized, multicentre, open-label, Phase 3 study to compare the efficacy and safety of acalabrutinib (ACP-196) in combination with venetoclax with and without obinutuzumab compared to investigator's choice of chemoimmunotherapy in subjects with previously untreated chronic lymphocytic leukaemia without del(17p) or TP53 mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 12.0 has also been submitted.

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annexes I, and IIIA, and to the Risk Management Plan are recommended.

This recommendation is subject to the following conditions:

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the use of Venclyxto in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at:

- Informing haematologists on the risk of TLS, strict adherence to dose-titration schedule and TLS risk minimisation measures for Venclyxto in the updated SmPC.
- Informing haematologists to provide each patient with the patient card, which includes a list of symptoms of TLS to prompt patient actions including to seek immediate medical attention in case of their occurrence, and patient behaviours to prevent TLS.

The MAH shall ensure that in each Member State where Venclyxto is marketed, all healthcare professionals (HCPs) and patients/carers who are expected to prescribe, dispense, or use Venclyxto have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

**Physician educational material**:

- The Summary of Product Characteristics
- Patient card

- **Patient card**:
  - Contact details of the venetoclax prescriber and patient
  - Instruction to patients on how to minimise TLS risk
  - List of TLS symptoms to prompt patient actions including to seek immediate medical attention in case of their occurrence
  - Instructions that the patient should carry the patient card at all times and to share it with HCPs involved in their care (i.e., urgent care HCPs, etc.)
  - Information for the HCPs treating the patient that venetoclax treatment is associated with the risk of TLS.

**The patient information pack**:

- Package leaflet

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this <group of variations><variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

## *Scope*

Please refer to the Recommendations section above.

## *Summary*

Please refer to Scientific Discussion EMA/VR/0000322240.