23 April 2026
EMADOC-1700519818-3010802
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Venclyxto

International non-proprietary name: Venetoclax

Procedure No. EMA/VR/0000322237

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

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List of abbreviations

ADR	adverse drug reactions
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCL-2	B-cell lymphoma-2
BCR	B cell receptor
BM	bone marrow
BTK	Bruton's tyrosine kinase
CHMP	Committee for Medicinal Products for Human Use
CIRS	Cumulative Illness Rating Scale
Clb+Ob	chlorambucil plus obinutuzumab
CLL	chronic lymphocytic leukemia
COVID-19	Coronavirus Disease 2019
CR	complete response
CrCl	creatinine clearance
CRi	complete response with an incomplete marrow recovery
CSRs	clinical study reports
DE	disease evaluation
del17p	deletion of the short arm of chromosome
DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ER	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FCR	fludarabine, cyclophosphamide, and rituximab
FD	fixed duration
HR	hazard ratio

Ibr+Ob	ibrutinib plus obinutuzumab
Ibr+R	ibrutinib plus rituximab
Ibr+Ven	ibrutinib plus venetoclax
ICH	International Conference on Harmonisation
IGHV	immunoglobulin heavy-chain variable region
IRC	Independent Review Committee
iwCLL	International Workshop in CLL
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NGS	Next-Generation Sequencing
NF-κB	nuclear factor-kappa B
ORR	overall response rate
OS	overall survival
PB	peripheral blood
PBRER	Periodic Benefit Risk Evaluation Report
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PT	preferred term
RMP	Risk management plan
SAE(s)	serious adverse event(s)
SLL	small lymphocytic lymphoma
SmPC	Summary of product characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TP53	tumor-suppressor protein 53
Ven+Ob	venetoclax plus obinutuzumab

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 ibrutinib, the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for VENCLYXTO based on the results of the phase 3 study 54179060CLL3011 (GLOW) and phase 2 study PCYC-1142-CA (CAPTIVATE). GLOW is a randomized, open-label, phase 3 study of the combination of ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab for the first-line treatment of subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). CAPTIVATE study is a phase 2, multicenter, international, efficacy and safety study assessing treatment with venetoclax plus ibrutinib in subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). 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. Version 11.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor changes to the PI and to update the list of local representatives in the Package Leaflet.

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

Scientific advice

The MAH did not seek scientific advice from 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:	19 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

Chronic lymphocytic leukaemia (CLL) is characterised by a progressive accumulation of leukemic clonal B-lymphocytes in the peripheral blood (PB), bone marrow (BM), and lymphoid tissues.

Claimed therapeutic indication

The proposed changes to the currently approved indication for venetoclax in previously untreated CLL is to include its combined use with ibrutinib.

Thus, the proposed indication in CLL, is:

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

- *in combination with obinutuzumab (see section 5.1)*
- *in combination with ibrutinib*

Epidemiology

CLL is the most prevalent adult leukemia in Western countries with an incidence of 4.2/100,000/year and a median age of 72 years at diagnosis. In the literature, the median survival of patients with CLL is approximately 10 years, but individual prognosis can vary considerably.

Biologic features

CLL/SLL is a neoplastic disorder characterized by the clonal expansion of mature B-cells in PB, BM, and lymphoid tissues driven primarily by chronic B-cell receptor (BCR)–dependent signalling and impaired programmed cell death.

Tonic BCR signalling in CLL results in the activation of a host of downstream effectors that modulate several pathways affecting the survival, proliferation, and migration of CLL cells. Among the key kinases that are constitutively activated are BTK and phosphatidyl-inositol 3 kinase (PI3K), effectors that trigger secondary signalling pathways such as JNK, ERK, mTOR, and NF-κB. Activation of the later pathway promotes the overexpression of the BCL-2 family of anti-apoptotic proteins (e.g., BCL-2, Bcl-xL, Mcl-1) allowing CLL cells to survive and escape programmed apoptosis.

Clinical presentation, diagnosis

The disease is characterized by a spectrum of clinical manifestations, ranging from indolent disease requiring no treatment for decades, to markedly aggressive disease that requires urgent intervention.

Management

Therapy for patients with previously untreated CLL includes agents with distinct mechanisms of action such as BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), alkylating agents (chlorambucil, bendamustine, cyclophosphamide), nucleoside analogue (fludarabine), anti-CD20 monoclonal antibodies (rituximab, obinutuzumab), Pi3K inhibitor (idelalisib), and BCL-2 inhibitor (venetoclax).

Several different treatment strategies are available for first-line therapy including continuous treatment with BTKis until progression, or time-limited therapies such as venetoclax plus obinutuzumab or venetoclax plus ibrutinib.

According to ESMO guideline 2024, time-limited chemoimmunotherapy (CIT) such as fludarabine-cyclophosphamide-rituximab (FCR) should only be considered for patients with a good genetic risk profile (i.e., mutated immunoglobulin heavy chain variable (IGHV) status and no TP53 aberrations) and, a non-complex karyotype (defined by less than five aberrations, if complex karyotype was evaluated), and if targeted therapies are not reimbursed. In addition, exposure to chemoimmunotherapy may be associated with significant toxicities including myelosuppression, immune suppression, and treatment-related malignancies such as myelodysplasia, and acute myeloid leukemia.

For patients with a TP53 mutation and/or del (17p), ESMO guideline 2024 recommend first-line therapy with BTKis. As alternatives, venetoclax monotherapy, venetoclax plus ibrutinib, or venetoclax plus obinutuzumab, are mentioned.

The choice of upfront therapy in treatment-demanding disease is generally guided by several factors, such as age and comorbidities (particularly cardiac assessment when planning to use a BTKi), as well as disease-related aspects, notably high-risk features such as unmutated IGHV status and TP53 aberrations.

2.1.2. About the product

Venetoclax is an orally administered B-cell lymphoma (BCL)-2 inhibitor that restores programmed cell death in cancer cells.

In EU, venetoclax is currently approved for the following indications:

- 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.

Moreover, since 2022, ibrutinib in combination with venetoclax is approved in EU for the treatment of previously untreated CLL, following the submission of a variation from Janssen-Cilag International NV (Janssen), which is the MAH for ibrutinib, see EPAR EMEA/H/C/003791/II/0070 and Imbruvica SmPC.

In the present procedure, AbbVie the MAH now submits this variation for venetoclax to also add the same combination therapy of ibrutinib plus venetoclax based on data previously assessed and approved in the context of the MA for Imbruvica.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH did not submit a new 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 was 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 to be 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, the CHMP recommended that the MAH has to reevaluate the ERA before concluding definitively on the potential risk of venetoclax to the environment.

The new indication in CLL in combination with ibrutinib is approvable from the 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	Study Design	Study Population	Endpoints	Region	Number of Subjects
Study CLL3011	Phase 3, randomized, open-label, multicenter, international efficacy and safety study of Ven+Ibr versus chemoimmunotherapy (Clb+Ob)	Previously untreated CLL/SLL (without del17p or known *TP53* mutation); ≥ 65 years of age or 18 to 64 years of age with comorbidities	Primary: PFS as assessed by IRC Secondary: MRD negativity rate by NGS in BM, CR rate, ORR, OS, rate of sustained platelet improvement, rate of sustained hemoglobin improvement, and time to improvement in FACIT-Fatigue score, and safety	US, EU, ROW (Canada; Great Britain; Israel; Russia; Turkey)	Randomized: 211 (106 Ven+Ibr, 105 chemoimmunotherapy)
Study 1142	Phase 2, multicenter, international efficacy and safety study of Ven+Ibr	Previously untreated CLL/SLL (with or without del17p/*TP53* mutation); **FD Cohort**: ≤ 70 years of age with an ECOG PS of 0-2 **MRD Cohort**: < 70 years of age with an ECOG PS of 0-1	**FD cohort**: Primary: CR rate (per INV assessment) Secondary: DOR, MRD-negativity rate, ORR, TLS risk reduction, PFS, OS, and safety **MRD Cohort**: Primary: 1-yr DFS rate in confirmed uMRD subjects Secondary: MRD-negativity rate, ORR, CR rate, DOR, TLS risk reduction, PFS, and OS, and safety, PK of Ven+Ibr	US, EU (Spain, Italy), ROW (Australia, New Zealand)	**FD Cohort**: 159 subjects incl. 136 subjects without del17p **MRD Cohort**: 164

BM = bone marrow; Clb+Ob = chlorambucil plus obinutuzumab; CLL = chronic lymphocytic leukemia; CR = complete response; CSR = clinical study report; del17p = deletion of short arm of chromosome 17; DFS = disease-free survival; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; EU = European Union; FACIT = Functional Assessment of Chronic Illness Therapy; FD = fixed duration; INV = investigator; IRC = Independent Review Committee; MRD = minimal residual disease; NGS = Next-Generation Sequencing; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; ROW = rest of world; SLL = small lymphocytic lymphoma; TLS = tumor lysis syndrome; TP53 = tumor-suppressor protein 53; uMRD = undetectable minimal residual disease; US = United States; Ven+Ibr = venetoclax plus ibrutinib

2.3.2. Pharmacokinetics

Plasma concentration data on venetoclax, ibrutinib and ibrutinib metabolite PCI-45227 from the pivotal Studies CLL3011 and 1142 were submitted. Non-compartmental analysis (NCA) was applied for data from Study 1142, whereas only steady-state Ctrough were available from Study CLL3011.

Bioanalytical methods

An LC-MS/MS method for the concentration determination of venetoclax in K2EDTA anticoagulated plasma was developed at Abbvie, report A1195425 (ABT199). Samples from studies CLL3011 and 1142 were analysed within the established long-term stability for venetoclax. No ISR was performed for venetoclax. QCs and calibration standards performed within preset acceptance criteria.

Analytical methods for ibrutinib and its metabolite PCI-45227 were validated and have been assessed earlier and deemed acceptable. Ibrutinib and PCI-45227 samples were analysed within 665 days of storage, which is within the 973 days established with an earlier method. QCs and calibration standards performed within preset acceptance criteria in both studies CLL3011 and 1142, including ISR in the latter. Testing for interference of venetoclax with the analysis of ibrutinib and PCI-45227 within 15% of the low QC nominal values, showing no interference.

Study CLL3011

CLL3011 (GLOW) was a randomised, open-label, multicentre, Phase 3 study to determine the efficacy and safety of the combination of Ibr+Ven, compared with Clb+Ob, administered to adults with previously untreated CLL/SLL. One of the secondary objectives in CLL3011 was to determine the Ctrough of ibrutinib and venetoclax when administered in combination.

Blood samples were collected at steady-state from all subjects assigned to Ibr+Ven treatment for measurement of trough plasma concentrations of venetoclax, ibrutinib and ibrutinib metabolite PCI-45227. The blood samples were obtained on Day 1 of Cycles 2 and 3 (ibrutinib and PCI-45227 only) and on Day 1 of Cycles 5 and 6 (ibrutinib, PCI-45227, and venetoclax).

Ibrutinib, and venetoclax plasma concentrations following administration of ibrutinib as a single-agent in Cycles 2 and 3, and in combination with venetoclax in Cycles 5 and 6, are shown in **Table 3.**

Table 1. Descriptive Statistics of Ibrutinib, Metabolite PCI-45227, and Venetoclax Plasma Concentrations Following Once-daily Oral Administration of 420 mg Ibrutinib in Combination With 400 mg Venetoclax in Subjects With Previously Untreated CLL/SLL – (Study 54179060CLL3011)

	Ng/mL			
Parameter	**Predose Cycle 2 Day 1 (Ibrutinib Alone)**	**Predose Cycle 3 Day 1 (Ibrutinib Alone)**	**Predose Cycle 5 Day 1 (Ibrutinib+Venetoclax)**	**Predose Cycle 6 Day 1 (Ibrutinib+Venetoclax)**
Ibrutinib				
N	63	59	65	60
Mean	5.7	6.2	6.37	5.9
SD	5.58	7.78	6.71	6.74
PCI-45227				
N	68	66	69	63
Mean	19.4	18.3	22.8	19.1
SD	15.8	16.3	23.6	16.9
Venetoclax				
N	NA	NA	79	65
Mean	NA	NA	1,139	1,765
SD	NA	NA	959	1,573

CLL=chronic lymphocytic leukemia; N=maximum number of subjects with data; NA=not applicable; PK=pharmacokinetic; SD=standard deviation; SLL=small lymphocytic lymphoma.
Notes: In the PK dataset, there were ibrutinib and PCI-45227 data related to 104 subjects and venetoclax data related to 96 subjects.
Descriptive statistics of plasma concentrations in this table are attributed to the nominal PK occasions.

Study 1142

Study 1142 (CAPTIVATE) was a multicentre, 2-cohort Phase 2 study with the combination of Ibr+Ven in subjects with CLL/SLL. The pharmacokinetics of ibrutinib and venetoclax when administered in combination in subjects with CLL/SLL were determine in the MRD cohort (minimal residual disease-guided treatment discontinuation cohort) (secondary objective).

Blood samples for pharmacokinetic analysis were taken from all subjects treated in the MRD cohort (164 subjects were enrolled) of the study at Cycle 2 Day 1 and Cycle 6 Day 1. Pharmacokinetic parameters in plasma were determined for ibrutinib, metabolite PCI-45227 and venetoclax using standard noncompartmental methods.

Ibrutinib pharmacokinetic parameters on Cycle 2 Day 1 (i.e., without venetoclax) were comparable to those on Cycle 6 Day 1 (ie, with venetoclax) (**Table 4**).

Table 2. PK Parameters of ibrutinib, Metabolite PCI-45227, and venetoclax in Plasma Following Once-daily Oral Administration of 420 mg ibrutinib in combination With 400 mg venetoclax in Subjects With Previously Untreated CLL/SLL – Without Moderate/Strong CYP3A Inhibitors (Study PCYC-1142-CA)

Parameter	Mean (SD)	
	Cycle 2 Day 1	Cycle 6 Day 1
Ibrutinib		
N	147	130
t_{max}[a], h	2.00 (0.930-7.35)	2.00 (0.970-7.00)
C_{max}, ng/mL	124 (94.8)	117 (86.7)
AUC_{0-24}, ng.h/mL	641 (509)	637 (486)
AUC_{last}, ng.h/mL	631 (515)	629 (493)
$t_{1/2}$, h	5.86 (2.23)	5.57 (1.88)
CL_{ss}/F, L/h	1,147 (1,070)	1,084 (985)
PCI-45227		
N	147	130
t_{max}[a], h	2.07 (0.950-7.35)	2.26 (0.970-7.07)
C_{max}, ng/mL	113 (52.5)	95.8 (43.9)
AUC_{0-24}, ng.h/mL	1,181 (687)	1,035 (544)
AUC_{last}, ng.h/mL	1,178 (691)	1,030 (548)
$t_{1/2}$, h	6.78 (1.85)	6.78 (1.60)
AUC Ratio[b]	2.29 (2.11)	1.98 (1.42)
Venetoclax		
N	NA	131
t_{max}[a], h	NA	6.00 (0.00-8.08)
C_{max}, ng/mL	NA	3,532 (1,987)
AUC_{0-24}, ng.h/mL	NA	58,965 (39,040)
CL_{ss}/F, L/h	NA	9.90 (6.90)

AUC=area under the plasma concentration-time curve; AUC_{0-24}=area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{last}=area under the plasma concentration-time curve from time 0 to time of last measurable concentration; CLL=chronic lymphocytic leukemia; CL_{ss}/F=apparent total clearance at steady-state; C_{max}=observed maximum concentration; CYP=cytochrome P450; MW=molecular weight; N=maximum number of subjects with data; NA=not applicable; PK=pharmacokinetic; SD=standard deviation; SLL=small lymphocytic lymphoma; $t_{1/2}$=terminal elimination half-life; t_{max}=time of the maximum concentration.

[a] Median (range).

[b] AUC ratio=(AUC_{last} of PCI-45227/MW of PCI-45227)/(AUC_{last} of ibrutinib/MW of ibrutinib), where ibrutinib MW=440.50 g/mol and PCI-45227 MW=474.20 g/mol.

Effect of venetoclax on the pharmacokinetics of ibrutinib

Mean steady-state ibrutinib exposure, as based on the AUC_{0-24}, was similar when administered as a single agent at 420 mg once daily to MRD cohort subjects with CLL/SLL during the lead-in period of Study 1142 (641 ng.h/mL) or in combination with 400 mg venetoclax (637 ng.h/mL). The mean steady-state ibrutinib exposures for the combination study were also similar to those observed previously in CLL/SLL subjects at a 420 mg daily dose (AUC_{0-24} = 708 ng.h/mL in Study PCYC-1102-CA).

The pharmacokinetics of ibrutinib, with and without coadministration of venetoclax, were additionally analysed through population pharmacokinetic modelling (popPK), using data from Study 1142 and Study CLL3011. For details of the popPK analysis of ibrutinib, please refer to EMA procedure:

EMEA/H/C/003791/II/0070 (Imbruvica (ibrutinib)). No meaningful interaction of venetoclax on the pharmacokinetics of ibrutinib were found in the analysis (no significant effect on CL and F1 of ibrutinib when administered alone or with venetoclax).

Effect of ibrutinib on the pharmacokinetics of venetoclax

The effect of ibrutinib on the pharmacokinetics of venetoclax was investigated by comparing steady-state pharmacokinetic data from Study 1142, in which venetoclax was administered in combination with ibrutinib, with historical monotherapy data for venetoclax from Study M12-175 (**Table 3**). Study M12-175 evaluated the pharmacokinetics of venetoclax at a once-daily dose of 20 to 1,200 mg in subjects with relapsed or refractory CLL/SLL and non-Hodgkin lymphoma. Pharmacokinetic data from this study are provided for subjects with relapsed or refractory CLL/SLL who received venetoclax alone without concomitant use of moderate or strong CYP3A inhibitors under low-fat conditions. An increase of approximately 1.8-fold (based on AUC0-24) in venetoclax exposure was observed in subjects receiving venetoclax in combination with ibrutinib in Study 1142 compared with subjects receiving venetoclax alone in Study M12-175.

The venetoclax observed mean Ctrough at steady state in combination with ibrutinib in Study 3011 (Cycle 6 Day 1) was = 1,765 ng/mL. The venetoclax exposure was thus higher in this study in combination with ibrutinib compared with monotherapy based on historical data (mean range of 630 to 810 ng/mL) (NDA/BLA Multi-disciplinary Review and Evaluation Supplemental, 2016).

The biological reason for this increase in systemic exposure is unclear. In vitro studies suggest that ibrutinib may inhibit BCRP and P-gp transport at clinical doses. Venetoclax is a P-gp and BCRP substrate in vitro. Therefore, the observed increase in venetoclax exposure, when administered with ibrutinib, may be due to a transporter-mediated interaction, which may increase the bioavailability and/or reduce the clearance of the compound.

Table 3. Steady-state PK Parameters of Venetoclax Following Once-daily Oral Administration of 400 mg Venetoclax Alone or 400 mg Venetoclax in Combination With 420 mg Ibrutinib in Subjects With CLL/SLL (Without Moderate/Strong CYP3A Inhibitors; Studies M12-175 and PCYC-1142-CA)

Parameter	Study M12-175 Venetoclax 400 mg Alone	Study M12-175 Venetoclax 400 mg Alone[a]	Study PCYC-1142-CA Venetoclax 400 mg qd +Ibrutinib 420 mg qd
N	8	60	131
t_{max}, median (range), h	7.0 (4.0–11.2)	6.0 (2.0–24.7)	6.00 (0.0–8.08)
C_{max}, mean (SD), ng/mL	2,180 (1,080)	2,070 (1,070)	3,532 (1,987)
AUC_{0-24}, mean (SD), ng.h/mL	35,500 (20,300)	31,800 (15,500)	58,965 (39,040)

AUC=area under the plasma concentration-time curve; AUC_{0-24}=area under the plasma concentration-time curve from time 0 to 24 hours; CLL=chronic lymphocytic leukemia; C_{max}=observed maximum concentration; CYP=cytochrome P450; N=maximum number of subjects with data; PK=pharmacokinetic; qd=once daily; SD=standard deviation; SLL=small lymphocytic lymphoma; t_{max}=time of the maximum concentration.

[a] Steady-state data at Week 7 Day 1 in the expansion cohort.

2.3.3. Pharmacodynamics

Mechanism of action

Ibrutinib and venetoclax have complementary mechanisms of action targeting distinct B-cell pathways involved in the propagation of CLL cells. Ibrutinib arrests CLL cell proliferation. Venetoclax is pro-apoptotic and induces early cell death. Together the 2 drugs are expected to provide complementary and effective clearance of disease.

2.4. PK/PD modelling

Exposure-efficacy analysis

PFS was explored by Kaplan-Meier plots for each study separately. No relationship between PFS and exposure could be observed in any of the plots. The rates of response for CRR, ORR, MRD negativity by flow cytometry and MRD negativity by NGS were plotted by quartiles of the exposure measures. CRR and ORR appear to be essentially independent of ibrutinib or venetoclax concentrations. However, for MRD negativity by flow cytometry and MRD negativity by NGS, there is a trend towards an increase with increasing systemic exposure for both ibrutinib and venetoclax, which was further assessed using regression analysis. All ibrutinib and venetoclax systemic exposure metrics had significant effects on MRD negativity by flow cytometry and MRD negativity by NGS (the latter available only for Study CLL3011), with ibrutinib Ctrough providing the most significant effect. The relationships between venetoclax observed Ctrough and MRD negativity by flow cytometry and MRD negativity by NGS were also significant ($p=0.00561$ and $p=0.00603$, respectively). When including the most significant ibrutinib descriptor of systemic exposure (Ctrough) together with the venetoclax effect (Ctrough_obs_venetoclax) in the model, and their interaction, both were highly significant ($p<0.01$) for MRD negativity by flow cytometry and NGS, but with a significant negative interaction. Covariates were added in a stepwise fashion to the MRD negativity by flow cytometry model, in which ibrutinib Ctrough and venetoclax observed Ctrough are the independent variables, resulted in a significant effect of the IGHV (immunoglobulin heavy-chain variable region) prognostic factor. The probability of MRD negativity by flow cytometry is lower in subjects with mutated IGHV than in subjects with unmutated IGHV. There was no significant interaction between IGHV status and the ibrutinib or venetoclax effects.

Exposure-safety analysis

The incidence of the different types of TEAEs was plotted by quartiles of the summary exposure measures. On visual inspection, liver function abnormalities, all Grade ≥3 TEAEs, all serious TEAEs, and all TEAEs leading to ibrutinib and venetoclax dose reduction, dose interruption, or drug discontinuation appear to increase with increasing exposure for both ibrutinib and venetoclax. In addition, any events of hemorrhage, diarrhea, and infection appear to increase with increasing ibrutinib exposure, and neutropenia appears to increase with increasing venetoclax exposure. These TEAEs were therefore explored further using regression analysis.

There were significant associations of both ibrutinib and venetoclax exposure on the incidence of Grade ≥3 TEAEs, with the most significant effect being venetoclax observed Ctrough. Upon fitting effects of ibrutinib observed Ctrough and venetoclax observed Ctrough simultaneously, and also the interaction of these parameters, only the venetoclax association remains significant. Ibrutinib exposure was significantly associated with the incidence of TEAEs leading to ibrutinib dose reduction, dose interruption, or drug discontinuation. Age was a significant covariate for association with TEAEs leading to ibrutinib dose reduction, dose interruption, or drug discontinuation, with the risk increasing with

age. Sex was a significant covariate for association with TEAEs leading to venetoclax dose reduction, dose interruption, or drug discontinuation, with the risk found to be higher in females.

2.4.1. Discussion on clinical pharmacology

The main role of the clinical pharmacology data package in the current variation is to describe venetoclax PK in patients with CLL co-treated with ibrutinib and to characterise potential PK differences compared to monotherapy. In addition, ibrutinib PK with venetoclax and potential PK differences of ibrutinib without co-treatment with venetoclax was described. No dedicated DDI studies were included in the current submission. The potential for a DDI effects were evaluated based on comparison between the treatment arms in the pivotal studies CLL3011 (GLOW) and 1142 (CAPTIVATE) (for ibrutinib exposure) and on comparison with historical data on monotherapy (for venetoclax exposure).

Bioanalysis

An LC-MS/MS method for the concentration determination of venetoclax in K2EDTA anticoagulated plasma was developed. The bioanalysis is deemed acceptable. Analytical methods for ibrutinib and its metabolite JNJ-54243761 (PCI-45227) were validated and have been assessed earlier and deemed acceptable.

Descriptive pharmacokinetics

Plasma concentration data for venetoclax were sampled in both pivotal combination studies: CLL3011 and 1142. The pharmacokinetics of venetoclax were assessed using non-compartmental analysis. This is acceptable. Exposure metrics including AUC, Cmax and Ctrough were calculated from data in Study 1142. Steady state Ctrough in (cycle 6 Day 1) was derived from Study CLL3011.

The investigation of interaction effect of ibrutinib on venetoclax is based on a between-study comparison to historical data for venetoclax. This is not optimal, as inter-study variability cannot be accounted for, but is consider sufficient, given the totality of evidence for the combination treatment.

Venetoclax observed plasma concentration at steady state in the pivotal combination studies were higher compared to historical data. Approximately 1.8-fold higher AUC, 1.7-fold higher Cmax and 2.8-fold higher Ctrough, was observed in subjects receiving venetoclax in combination with ibrutinib in Study 1142 compared with subjects receiving venetoclax alone in Study M12-175. The observed mean Ctrough at steady state in combination with ibrutinib in Study 3011 (1,765 ng/mL) was higher compared with monotherapy based on historical data (mean range of 630 to 810 ng/mL) (NDA/BLA Multi-disciplinary Review and Evaluation Supplemental, 2016). The observed higher exposure of venetoclax when administered together with ibrutinib is now reflected in the SmPC section 4.5.

In vitro studies suggest that ibrutinib may inhibit BCRP and P-gp transport at clinical doses. Venetoclax is a P-gp and BCRP substrate, as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor in vitro. Therefore, the observed increase in venetoclax exposure, when administered with ibrutinib, may be due to a transporter-mediated interaction, which may increase the bioavailability and/or reduce the clearance of the compound.

For ibrutinib, data on exposure with and without venetoclax was available from the same studies. Non-compartmental analysis indicated that ibrutinib pharmacokinetics in both combination studies were similar when given with and without venetoclax and generally consistent with previously reported (historical) data. No effect of venetoclax on ibrutinib pharmacokinetics was thus observed. PopPK analysis of Ibrutinib with pooled data from the two combination studies confirmed that venetoclax had no significant effect on CL or F1 of ibrutinib. The popPK analysis have been assessed previously (EMA

procedure: EMEA/H/C/003791/II/0070 (Imbruvica (ibrutinib)) and are thus not further discussed in this application. Overall, the interaction potential of venetoclax on the exposure of ibrutinib have been adequately characterised.

Exposure-Response analysis

The clinical study design was not optimal for PK/PD modelling (a single-dose level, dose adjustments, relatively high correlation between exposure metrics, no information on monotherapy treatment). In addition, the current assessment evaluated numerous endpoints without any correction for multiplicity. It is possible that some of the significant ER relationships were highlighted by chance alone. The analysis should be considered purely exploratory, and the results should be interpreted with caution.

As the exposure of venetoclax is higher when given in combination with ibrutinib, adherence to the ibrutinib and venetoclax dose-modification guidelines is important in ensuring the safety of the combination. The dose-modification guidelines will ensure an optimal efficacious dose for most of the patients whilst providing the option for a more tolerable reduced dose for the patients who are more vulnerable for specific TEAEs.

2.4.2. Conclusions on clinical pharmacology

The pharmacokinetics of ibrutinib in combination with venetoclax have been adequately characterised and found to be consistent with previously reported (historical) assessments. Combination of venetoclax and ibrutinib results in an increased exposure of venetoclax and this had been reflected in section 4.5 of the SmPC.

2.5. Clinical efficacy

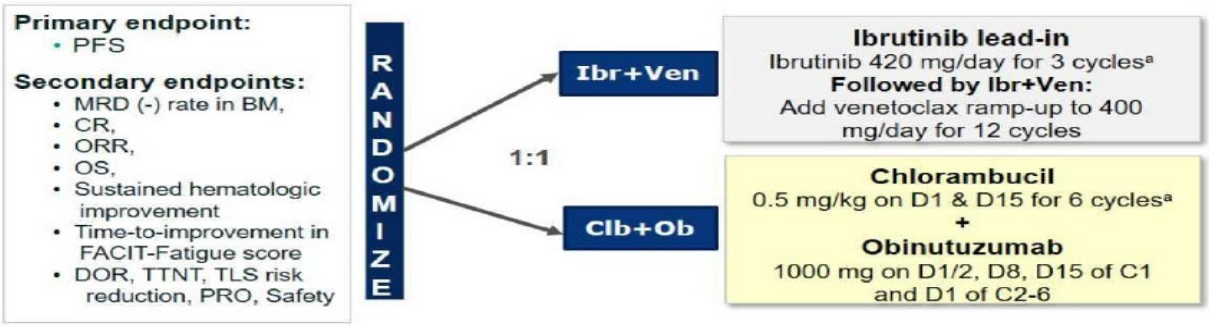
2.5.1. Main studies

54179060CLL3011 (GLOW)*:* A Randomized, Open-label, Phase 3 Study of the Combination of Ibrutinib plus Venetoclax versus Chlorambucil plus Obinutuzumab for the First-line Treatment of Subjects with-Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL).

Methods

The study design and diseases evaluation and treatment schedule are depicted in **Figure 1**.

Figure 1. Study CLL3011 design



Target Enrolment: N = 200

Stratification:

- *IGHV* status (mutated vs unmutated vs not available)
- del11q (yes vs no)

[a] 1 cycle=28 days

BM=bone marrow; C=cycle; CR=complete response; D=day; del11q=deletion of the long arm of chromosome 11; DOR=duration of response; Clb+Ob=obinutuzumab plus chlorambucil; FACIT=Functional Assessment of Chronic Illness Therapy; *IGHV*=immunoglobulin heavy-chain variable region; Ibr+Ven=ibrutinib plus venetoclax; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcomes; TLS=tumor lysis syndrome; TTNT=time to next treatment

Study participants

Key eligibility criteria

- ≥65 years of age, or 18 to 64 years of age and have at least 1 of the following:
    - cumulative illness rating scale (CIRS) score >6
    - creatinine clearance (CrCl) <70 mL/min using Cockcroft-Gault equation
- Diagnosis of CLL or SLL that met International Workshop in CLL (iwCLL) criteria
- Active CLL/SLL requiring treatment per the iwCLL criteria (Hallek 2008)
- Measurable nodal disease (by CT), defined as at least 1 lymph node >1.5 cm in longest-diameter
- ECOG PS score of 0, 1, or 2

Key exclusion criteria

- Prior anti-leukemic therapy for CLL or SLL
- Presence of del17p or known TP53 mutation detected at a threshold of >10% variable allele-frequency
- Central nervous system involvement or suspected Richter's syndrome

Treatments

Subjects assigned to Treatment Arm A (Ibrutinib+ Venetoclax (Ibr+Ven)) received ibrutinib (420 mg/day orally) given as lead-in treatment for 3 cycles. Starting at Cycle 4 and contingent on completion of TLS risk assessment, venetoclax dose ramp-up (from 20 to 400 mg over 5 weeks) was initiated. Combined treatment with ibrutinib and venetoclax was administered for 12 cycles, through Cycle 15, in the absence of PD or treatment-limiting toxicity. One cycle corresponds to 28 days.

Subjects assigned to Treatment Arm B were to receive 6 cycles (28 days/cycle) of Chlorambucil+ obinutuzumab (Clb+Ob) treatment in the absence of PD or treatment-limiting toxicity. Chlorambucil was to be administered orally at a dose of 0.5 mg/kg body weight on Days 1-and 15 of Cycles 1 to 6. Obinutuzumab was to be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2 to 6. Each dose of obinutuzumab given IV was equivalent to 1000 mg except for the initial-infusion in Cycle 1 where the same total dose was to be administered over Day 1 (100 mg) and-Day 2 (900 mg).

Objectives

The primary objective of the study was to compare PFS from treatment with Ibr+Ven with that from treatment with Clb+Ob. Secondary objectives were to evaluate MRD negativity rate, CR rate, ORR, DOR, OS, time-to-next treatment, hematologic improvement, patient-reported health status, trough levels of ibrutinib and venetoclax when given in combination, and safety associated with Ibr+Ven.

Outcomes/endpoints

Primary endpoint

PFS as assessed by the Indepenent Review Committee (IRC) and defined as the time between the date of randomisation and the date of progressive diseases (PD), or date of death due to any cause, whichever occurs first, regardless of the use of subsequent anti-leukemic therapy prior to documented PD or death.

Secondary endpoints: Minimal Residual Disease (MRD) negativity rate in bone marrow; Complete Response (CR); Overall Response Rate (ORR); Overall Survival (OS); Rate of sustained platelet improvement; Rate of sustained hsemoglobin improvement; Time to improvement in Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score.

MRD negativity rate

MRD negativity rate was defined as the proportion of subjects who reached MRD negative disease status (<1 CLL cell per 10,000 leukocytes) on or prior to initiation of subsequent anti-leukemic therapy (including subsequent single-agent ibrutinib).

Sustained haematologic improvement

Defined as haematological improvement that was sustained continuously for ≥56 days without blood transfusion or growth factors on or prior to initiation of subsequent anti-leukemic therapy (including subsequent single-agent ibrutinib):

- Haemoglobin levels increased ≥2 g/dL from baseline and lasted for at least 56 days without blood transfusion or growth factors
- Platelet counts increased ≥50% over baseline and lasted for at least 56 days without blood transfusion or growth factors

Sample size

A median PFS of 27 months was reported for the Clb+Ob when it is used to treat patients with treatment naïve CLL (GAZYVAR US Product Information 2017). It is assumed that the PFS follows an exponential distribution with a constant hazard rate. Utilising a 1:1 randomisation, this study will enroll approximately 200 subjects (100 subjects into Ibr+Ven and 100 subjects into the Clb+Ob treatment groups) to observe 71 PFS events. The study was designed to detect a hazard ratio (HR) of 0.5 for the

Ibr+Ven-treatment group relative to the Clb+Ob group (corresponding to an improvement of 100% in-median PFS, e.g. from 27 months to 54 months) with 80% power at a 2-sided significance level of-0.05.

A uniform accrual rate of 20 subjects per month would result in a study duration of approximately 32 months after the first subject is randomised, with 10 months of enrollment and 22 months of-follow-up to observe 71 PFS events.

Randomisation

Central randomisation was implemented; Subjects were randomly assigned to 1 of 2 treatment groups based on a computer-generated randomisation schedule, the randomization was balanced by using permuted blocks and stratified by IGHV mutational status (mutated vs. unmutated vs. not-available) and presence of del11q (yes vs. no).

Blinding (masking)

In this open-label study, neither the subjects nor the investigators were blinded to treatment group-assignment. However, access to efficacy data was controlled so that the Sponsor's staff overseeing conduct of the study or analysing/summarizing data do not have an aggregated efficacy-summary by treatment until the database is locked for primary analysis. The IRC who performed tumour assessment were required to be blinded to study treatment group assignment.

Statistical methods

No formal interim analysis for efficacy was planned, due to the small sample size and short accrual-period of the study.

All statistical tests will be performed at a 2-sided significance level of 5%, unless otherwise-specified. All interval estimation will be reported using 2-sided 95% CIs.

Decision making will be based on the stratified log-rank test for statistical significance. Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. The non-stratified Cox regression model may be used to analyse treatment effect on PFS after adjusting for covariates (selected demographics and baseline characteristics) as appropriate.

Primary analysis

Estimand Scientific Question of Interest:

What is the effect on PFS of assigning subjects to Ibr+Ven vs. Clb+Ob? This primary estimand is the main clinical quantity of interest to be estimated in this study, which is defined by the following attributes:

- Population: subjects with CLL/SLL who are treatment naïve
- Treatment: fixed duration Ibr+Ven vs. Clb+Ob
- Variable: PFS (PD is based on IRC assessment)

Population-level summary: Kaplan-Meier estimates of PFS, hazard ratio of Ibr+Ven vs. Clb+Ob

- Intercurrent events: treatment discontinuation, use of subsequent anticancer therapy, death due to COVID-19.

Analysis methods

Assumptions

- Non-informative censoring assumed for all types of censoring.
- Distinct baseline hazard for each stratum, common proportional hazard ratio across strata.

Primary Estimator

- A stratified Cox regression model with study intervention as the sole explanatory variable will be performed, with stratification factors of IGHV gene mutational status and presence of del11q.
- Hazard ratio and its 95% CIs will be estimated.
- The treatment policy strategy is adopted for handling the intercurrent events of treatment-discontinuation, use of subsequent anti-cancer therapy and the composite variable strategy is adopted for handling the intercurrent events of pre-PD death (PFS event) due to COVID-19.

Supplementary Estimands

Supplementary estimands were provided:

- Subsequent anti-cancer therapy analysed according to a hypothetical strategy (Estimand 2)
- PD determined by investigator instead of IRC (Estimand 3)
- Death due to Covid -19 analysed according to a hypothetical strategy (Estimand 4)

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Treatment discontinuation (due to AE or other reasons other than AE or worsening of disease)	**Treatment policy strategy:** use time to PD or death, regardless of whether or not treatment discontinuation had occurred.
Use of subsequent anticancer therapy	**Treatment policy strategy:** use time to PD or death, regardless of whether or not used subsequent anti-cancer therapy. **Hypothetical strategy:** subjects are censored at the last disease assessment showing no evidence of PD before the use of subsequent anti-cancer therapy.
Death due to COVID-19	**Composite variable strategy:** consider (pre-PD) death as a PFS event. **Hypothetical strategy:** subjects are censored at the last disease assessment before (pre-PD) death due to COVID-19.

Multiplicity incurred from testing primary and secondary endpoints was to be controlled using the serial gatekeeping procedure. The hypothesis for a secondary endpoint were to be tested if and only if the null hypotheses for the primary endpoint and for the preceding secondary endpoints are rejected. The hierarchical order of secondary endpoint for testing is specified as follows:

- MRD negativity rate in bone marrow
- CR
- ORR
- OS
- Rate of sustained platelet improvement
- Rate of sustained haemoglobin improvement
- Time to improvement in FACIT fatigue score

Subgroup analyses were planned for age, sex, race, diagnosis, Rai stage at screening, Binet stage at screening, baseline ECOG PS, cumulative illness rating scale (CIRS) total score, bulky disease, IGHV mutation status, chromosome 11q deletion, high risk population, elevated LDH at baseline, cytopenias at baseline, Serum β2-microglobulin, Creatinine clearance, NCI-ODWG liver function classification, concomitant use of strong/moderate CYP3A inhibitor and concomitant use of strong/ CYP3A inhibitor.

The primary analysis was conducted with a clinical data cutoff of 26 February 2021. Six-month extended follow-up data based on a data cutoff date of 19 August 2021 were included with the primary analysis in the Clinical Study Report (CSR) dated 12 November 2021.

A CSR dated 1 August 2024, with 36-month extended follow-up from primary analysis and a median time on study for all subjects of 64.0 months (range: 1.7 to 69.7) at DCO 24 February 2024, is submitted in this procedure.

Results

Participant flow

Table 4. Treatment Disposition for Fixed Duration Treatment Phase; Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Subjects ongoing	0	0	0
Completed study treatment	82 (77.4%)	100 (95.2%)	182 (86.3%)
Discontinued study treatment	24 (22.6%)	5 (4.8%)	29 (13.7%)
Reason for discontinuation			
Adverse event	11 (10.4%)	2 (1.9%)	13 (6.2%)
Subject refused further study treatment	4 (3.8%)	1 (1.0%)	5 (2.4%)
Death	4 (3.8%)	0	4 (1.9%)
Progressive disease	3 (2.8%)	1 (1.0%)	4 (1.9%)
Physician decision	2 (1.9%)	1 (1.0%)	3 (1.4%)

Table 5. Study Disposition for Fixed Duration Treatment Phase; Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Subjects randomized	106 (100.0%)	105 (100.0%)	211 (100.0%)
Subjects treated	106 (100.0%)	105 (100.0%)	211 (100.0%)
Completed study participation	11 (10.4%)	11 (10.5%)	22 (10.4%)
Death	11 (10.4%)	11 (10.5%)	22 (10.4%)
Death - COVID-19 related	1 (0.9%)	4 (3.8%)	5 (2.4%)
Terminated study participation prematurely	2 (1.9%)	3 (2.9%)	5 (2.4%)
Reason for termination			
Withdrawal by subject	2 (1.9%)	3 (2.9%)	5 (2.4%)
Lost to follow-up	0	0	0

Completed study participation represents death cases before clinical cut-off.

One additional death in the Clb+Ob arm that occurred after the clinical cut and before the database lock is not counted in this table.

Recruitment

Date study initiated: 19 April 2018 (date first subject signed informed consent).

Date study completed: The study is ongoing.

Conduct of the study

Table 6. Summary of protocol amendments 1 to 4, Study CLL3011

Amendment 1 (6 June 2018; substantial)	The amendment was issued to address Health Authority feedback on the initial version of the protocol and to include language informing of early pharmacokinetic results from an ongoing Phase 2 study of Ibr+Ven.
Amendment 2 (22 January 2019; substantial)	The amendment was issued primarily to implement a change in the duration of Ibr+Ven treatment based on data from an ongoing Phase 2 study of the combination.
Amendment 3 (12 August 2019; substantial)	The primary reason for the amendment was to include a Subsequent Therapy Phase within the study to allow eligible subjects who progress after completing Ibr+Ven or Clb+Ob to receive continuous treatment with single-agent ibrutinib as part of the study.
Amendment 4 (19 December 2019; substantial)	The amendment was issued to include updated safety information that is aligned with the ibrutinib Investigator's Brochure and to clarify the requirement for pulse/heart rate and blood pressure assessments.

Important changes with Amendment 1

Rationale: Clarify the threshold by which the presence of a TP53 mutation is considered exclusionary.

4.2 Exclusion Criteria; 9.1.2 Screening Phase; References	Text was added to specify that subjects with known presence of *TP53* mutations detected at a threshold of >10% variable allele frequency will be excluded from the study. New publication (Malcikova 2018) added to References and citation to this publication added.

Important changes with Amendment 2

Rationale: The protocol has been adapted to reflect recent scientific insights from relevant Phase 2 studies indicating that the removal of the last 3 cycles (cycles 16, 17, and 18) of ibrutinib monotherapy is appropriate.

Synopsis: Dosage and Administration	Update of data from relevant Phase 2 studies in which I+VEN has been investigated for the treatment of CLL.
Table 1 Time and Events Schedule for Treatment Arm A; Table 2 Time and Events Schedule for Treatment Arm B; and Table 3	For Arm A, removal of 3 additional cycles of ibrutinib monotherapy following completion of combination therapy (I+VEN) in relevant Time and Events Schedules, study overview figure, and text.

Important changes with Amendment 3

Rationale: A Subsequent Therapy Phase was added in which eligible subjects will be treated continuously with single-agent ibrutinib.

3.1 Overview of Study Design	Added statements that eligible subjects for the Subsequent Therapy Phase must have completed the treatment with I+VEN or G-Clb and subsequently develop progressive disease (as confirmed by the Independent Review Committee [IRC]) that requires treatment per International Workshop on Chronic Lymphocytic Leukemia [iwCLL] criteria)
9.2.3 Response Categories	Clarified that responses will be based on assessment by the investigator during the Subsequent Therapy Phase. Noted that confirmation of responses by the IRC may be pursued by the sponsor for regulatory purposes.

Important changes with Amendment 4

Rationale: To clarify that subjects in Treatment Arm B remain eligible for subsequent therapy with single-agent ibrutinib even if they do not complete open-label therapy because this would not be expected to affect response and tolerability to ibrutinib.

Rationale: To remove specificity that a stratified analysis will be done for overall survival because the number of events may be too small in some of the strata.

11.4 Efficacy Analyses;	Deleted term "stratified" when describing the overall survival analysis. The details will be specified in the final Statistical Analysis Plan.

Additional amendments to the protocol are summarised below:

- **Amendment 5** (1 July 2022) - overall rationale for the amendment was to update information on dose modification for ibrutinib and the timepoints of MRD sample collection for flow cytometry and to clarify eligibility criteria for subsequent therapy with single agent ibrutinib, and
- **Amendment 6** (17 May 2023) included an update to (1) reduce the overall required data collection after completion of the primary analysis, (2) extend the study duration to assess long-term outcomes and (3) clarify that at the sponsor' s discretion all ongoing subjects may enter a Long-term Survival Follow-up Phase, during which data collection will be limited to survival follow-up via eCRF data collection and enrollment in the Subsequent Therapy Phase will be discontinued.

Changes to protocol-specified analyses

The following analyses are different from those described in the protocol:

- Additional supplementary/sensitivity analyses to mitigate the impact of the COVID-19 are-added.
- Time to next treatment is changed to be an exploratory endpoint, instead of a key secondary-endpoint.
- NGS is used as the primary method for MRD analyses, MRD by flow cytometry is used-for supplementary analyses.
- The definition for TLS risk category is updated to the following per Venetoclax USPI for CLL:
  - Low: all lymph node < 5cm AND ALC < 25x109/L
  - Medium: any lymph node 5cm to < 10cm OR ALC ≥ 25x109/L
  - High: any lymph node ≥ 10cm OR ALC ≥ 25x109/L AND any lymph node ≥ 5cm

Protocol deviations

Table 7. Summary of major protocol deviations, DCO 26 February 2021, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Subjects With Major Protocol Deviations	6 (5.7%)	6 (5.7%)	12 (5.7%)
Received Wrong Treatment Or Incorrect Dose	5 (4.7%)	3 (2.9%)	8 (3.8%)
Other	1 (0.9%)	3 (2.9%)	4 (1.9%)
Covid-19 related	1 (0.9%)	3 (2.9%)	4 (1.9%)
Entered But Did Not Satisfy Criteria	1 (0.9%)	0	1 (0.5%)

Note: Subjects may appear in more than one category.

Baseline data

Table 8. Demographics and Baseline Characteristics, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Age, years			
N	106	105	211
Mean (SD)	71.0 (8.02)	72.0 (6.16)	71.5 (7.15)
Median	71.0	71.0	71.0
Range	(47; 93)	(57; 88)	(47; 93)
<65	16 (15.1%)	11 (10.5%)	27 (12.8%)
>=65-69	23 (21.7%)	27 (25.7%)	50 (23.7%)
>=70-74	32 (30.2%)	30 (28.6%)	62 (29.4%)
>=75	35 (33.0%)	37 (35.2%)	72 (34.1%)
Sex			
N	106	105	211
Female	47 (44.3%)	42 (40.0%)	89 (42.2%)
Male	59 (55.7%)	63 (60.0%)	122 (57.8%)
Race			
N	106	105	211
Asian	0	1 (1.0%)	1 (0.5%)
White	101 (95.3%)	101 (96.2%)	202 (95.7%)
Multiple	1 (0.9%)	0	1 (0.5%)
Not reported	4 (3.8%)	3 (2.9%)	7 (3.3%)
Ethnicity			
N	106	105	211
Hispanic or Latino	1 (0.9%)	3 (2.9%)	4 (1.9%)
Not Hispanic or Latino	101 (95.3%)	99 (94.3%)	200 (94.8%)
Not reported	4 (3.8%)	3 (2.9%)	7 (3.3%)

Table 9. Baseline Disease Characteristics, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Time from initial diagnosis to randomization (months)			
N	106	105	211
Mean (SD)	43.53 (41.453)	47.36 (43.409)	45.43 (42.380)
Median	35.83	35.42	35.52
Range	(0.5; 227.8)	(0.7; 178.8)	(0.5; 227.8)
Diagnosis			
N	106	105	211
CLL	96 (90.6%)	101 (96.2%)	197 (93.4%)
SLL	10 (9.4%)	4 (3.8%)	14 (6.6%)
Rai Stage (CLL only)			
N	96	101	197
0-II	41 (42.7%)	48 (47.5%)	89 (45.2%)
III-IV	55 (57.3%)	53 (52.5%)	108 (54.8%)
Binet Stage (CLL only)			
N	96	101	197
A	7 (7.3%)	8 (7.9%)	15 (7.6%)
B	46 (47.9%)	53 (52.5%)	99 (50.3%)
C	43 (44.8%)	40 (39.6%)	83 (42.1%)
Ann Arbor Stage (SLL only)			
N	10	4	14
IV	10 (100.0%)	4 (100.0%)	14 (100.0%)
ECOG Performance Status			
N	106	105	211
0	35 (33.0%)	39 (37.1%)	74 (35.1%)
1-2	71 (67.0%)	66 (62.9%)	137 (64.9%)
1	58 (54.7%)	54 (51.4%)	112 (53.1%)
2	13 (12.3%)	12 (11.4%)	25 (11.8%)
CIRS Total Score			
N	106	105	211
≤6	32 (30.2%)	44 (41.9%)	76 (36.0%)
>6	74 (69.8%)	61 (58.1%)	135 (64.0%)
7 - 12	53 (50.0%)	46 (43.8%)	99 (46.9%)
13 - 18	19 (17.9%)	14 (13.3%)	33 (15.6%)
>18	2 (1.9%)	1 (1.0%)	3 (1.4%)
Bulky Disease			
N	105	105	210
≥5cm	41 (39.0%)	38 (36.2%)	79 (37.6%)
≥10cm	0	4 (3.8%)	4 (1.9%)
Cytopenia[a]			
N	106	105	211
Yes	58 (54.7%)	65 (61.9%)	123 (58.3%)
No	48 (45.3%)	40 (38.1%)	88 (41.7%)
Anemia[a]			
N	106	105	211
Yes	45 (42.5%)	52 (49.5%)	97 (46.0%)
No	61 (57.5%)	53 (50.5%)	114 (54.0%)

Thrombocytopenia[a]			
N	106	105	211
Yes	28 (26.4%)	30 (28.6%)	58 (27.5%)
No	78 (73.6%)	75 (71.4%)	153 (72.5%)
Neutropenia[a]			
N	106	105	211
Yes	6 (5.7%)	8 (7.6%)	14 (6.6%)
No	100 (94.3%)	97 (92.4%)	197 (93.4%)
TP53 mutation			
N	106	105	211
Yes	7 (6.6%)	2 (1.9%)	9 (4.3%)
No	99 (93.4%)	103 (98.1%)	202 (95.7%)
Chromosome 11q deletion			
N	106	105	211
Yes	20 (18.9%)	18 (17.1%)	38 (18.0%)
No	86 (81.1%)	87 (82.9%)	173 (82.0%)
IGHV			
N	106	105	211
Mutated	27 (25.5%)	27 (25.7%)	54 (25.6%)
Unmutated	55 (51.9%)	54 (51.4%)	109 (51.7%)
Unavailable	24 (22.6%)	24 (22.9%)	48 (22.7%)
High risk population[b]			
N	106	105	211
Yes	63 (59.4%)	60 (57.1%)	123 (58.3%)
No	43 (40.6%)	45 (42.9%)	88 (41.7%)
Elevated LDH			
N	106	105	211
Yes (> ULN)	35 (33.0%)	51 (48.6%)	86 (40.8%)
No (≤ ULN)	71 (67.0%)	54 (51.4%)	125 (59.2%)
Serum β2 - microglobulin			
N	106	105	211
≤ 3.5 mg/L	32 (30.2%)	27 (25.7%)	59 (28.0%)
> 3.5 mg/L	74 (69.8%)	77 (73.3%)	151 (71.6%)
Missing	0	1 (1.0%)	1 (0.5%)

[a] Anemia is defined as hemoglobin ≤ 110 g/L. Thrombocytopenia is defined as platelet counts ≤ 100 * 10^9/L. Neutropenia is defined as absolute neutrophil count ≤ 1.5*10^9/L. Cytopenia is defined as yes if hemoglobin ≤ 110 g/L, platelet counts ≤ 100 * 10^9/L, or absolute neutrophil count ≤ 1.5*10^9/L is observed.
[b] High risk population: subjects with TP53 mutation, del11q, or unmutated IGHV status at baseline.

Although subjects with del17p or known TP53 mutation at baseline were excluded from the study, subjects with unknown TP53 mutation status were allowed to participate. After randomization, central laboratory testing identified 9 (4.3%) subjects with a TP53 mutation, 7 (6.6%) in the Ibr+Ven arm and 2 (1.9%) in the Clb+Ob arm.

Numbers analysed

The primary analysis included 211 subjects who were randomized and treated (106 subjects in the Ibr+Ven arm and 105 subjects in the Clb+Ob arm).

Outcomes and estimation

***Primary endpoint*: PFS by IRC**

The primary analysis was performed using DCO 26 February 2021 with a median time on study for all subjects of 27.7 (95% CI: 27.60 to 27.89) months.

Table 10. Summary of Progression Free Survival PFS by IRC, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	22 (20.8%)	67 (63.8%)	
Progressive Disease	13 (12.3%)	65 (61.9%)	
Death	9 (8.5%)	2 (1.9%)	
Censored	84 (79.2%)	38 (36.2%)	
Time to event (months)			
25th percentile (95% CI)	31.24 (24.02, NE)	13.83 (13.70, 13.93)	
Median (95% CI)	NE (31.24, NE)	20.96 (16.59, 24.67)	
75th percentile (95% CI)	NE (31.41, NE)	31.08 (27.53, NE)	
Range	(0.0+, 32.7+)	(2.6, 31.5+)	
6-month event-free rate (95% CI)	0.943 (0.877, 0.974)	0.962 (0.902, 0.986)	
12-month event-free rate (95% CI)	0.885 (0.806, 0.933)	0.913 (0.840, 0.954)	
18-month event-free rate (95% CI)	0.866 (0.784, 0.918)	0.550 (0.448, 0.640)	
24-month event-free rate (95% CI)	0.844 (0.758, 0.901)	0.441 (0.342, 0.536)	
30-month event-free rate (95% CI)	0.756 (0.624, 0.848)	0.298 (0.198, 0.403)	
Hazard ratio (95% CI) [a]			0.216 (0.131, 0.357)
p-value [b]			<0.0001

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation, NE = not estimable

Figure 2. Kaplan-Meier plot for PFS by IRC, Intent-to-treat Analysis Set (Study CLL3011)

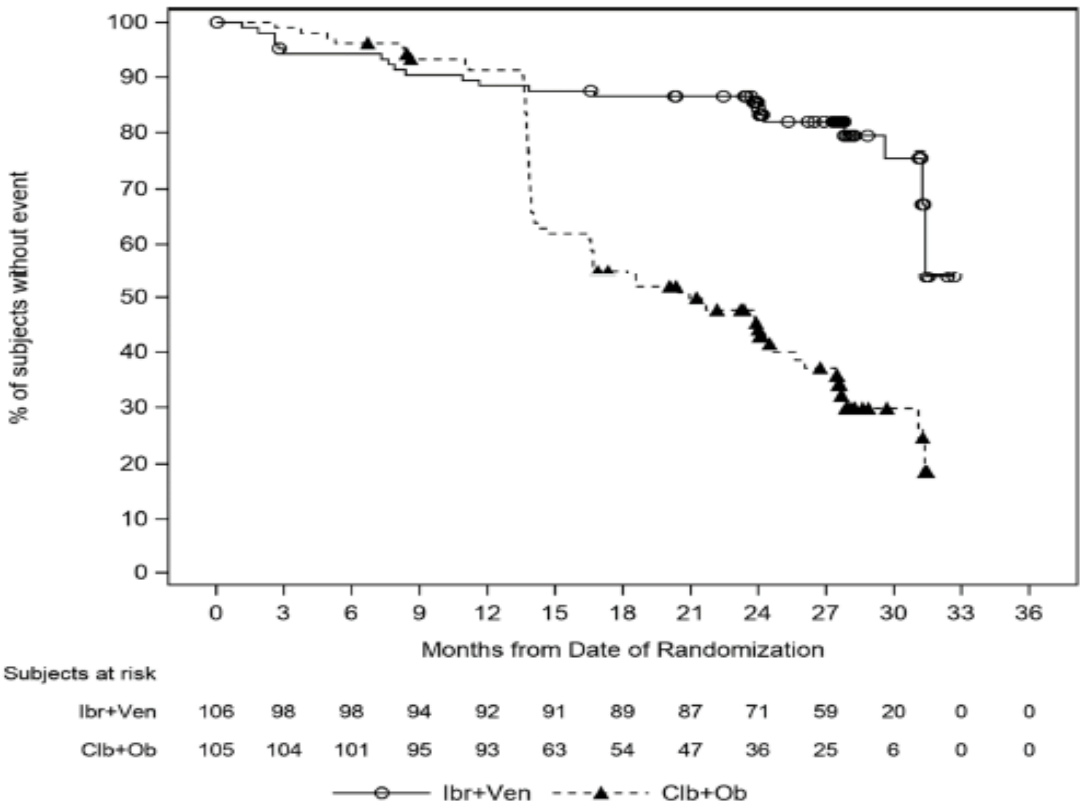


Table 11. PFS events by IRC, Reason for Censoring, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob
Analysis set: Intent-to-treat	106	105
Censored	84 (100.0%)	38 (100.0%)
Reason for Censoring		
Study cut off	82 (97.6%)	37 (97.4%)
Withdrew consent	2 (2.4%)	1 (2.6%)

Table 12. PFS events by IRC, Reason for Censoring by period of 3 months, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven				Clb+Ob			
	PD Event	Death Event	Cumulative Sum of PFS Events	Censored	PD Event	Death Event	Cumulative Sum of PFS Events	Censored
0-3	2	4	6	2	1	0	1	0
3-6	0	0	6	0	2	1	4	0
6-9	1	3	10	0	3	0	7	3
9-12	1	1	12	0	2	0	9	0
12-15	1	0	13	0	29	1	39	0
15-18	1	0	14	1	7	0	46	2
18-21	0	0	14	2	5	0	51	2
21-24	2	0	16	14	5	0	56	6
24-27	2	0	18	10	5	0	61	6
27-30	1	1	20	37	4	0	65	15
>=30	2	0	22	18	2	0	67	4

Key: PD = progressive disease, PFS = progression-free survival.
PD events are based on Independent Review Committee (IRC) assessments.

Alternative (sensitivity) analyses of PFS

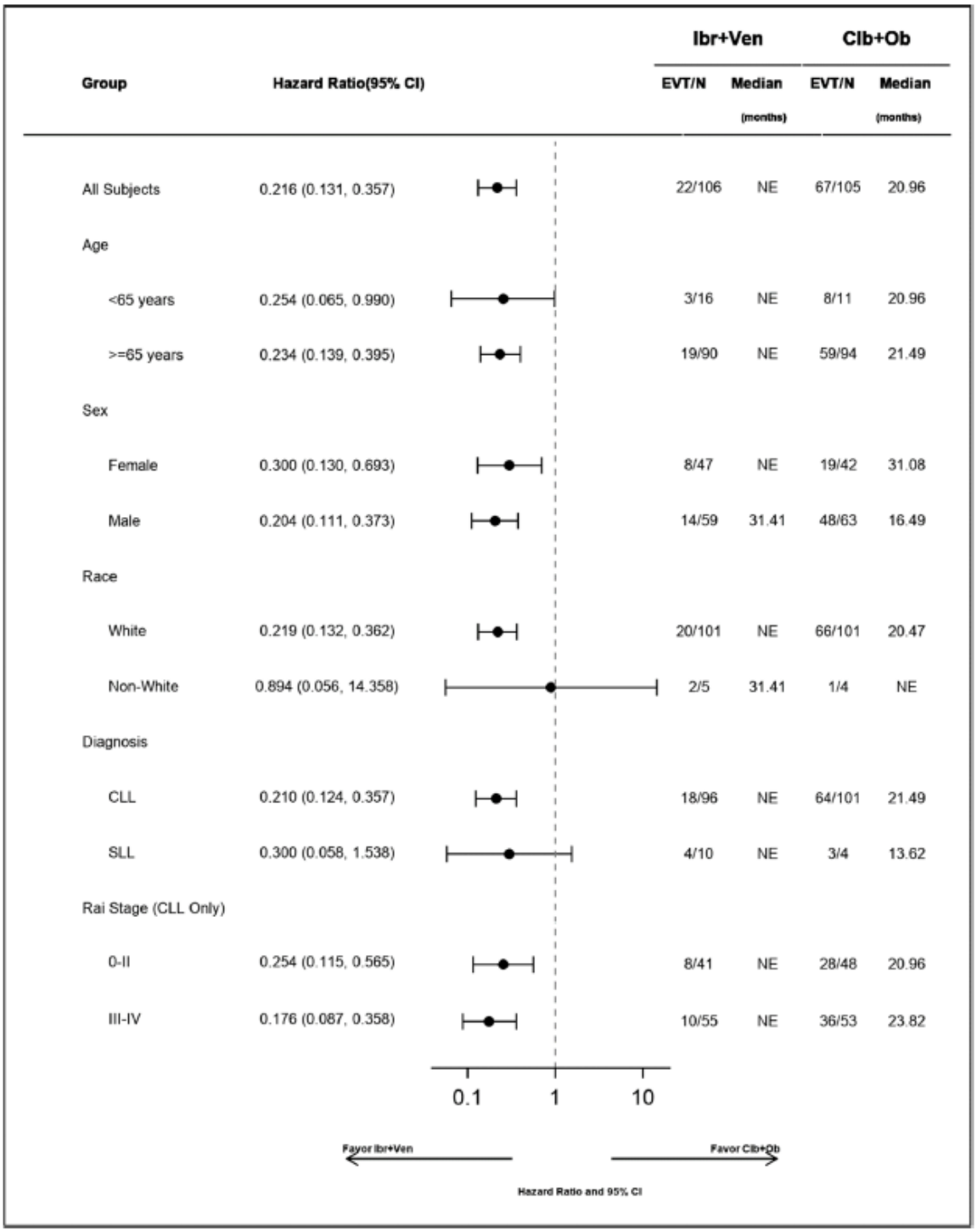
PFS by investigator: HR 0.207 (95% CI: 0.120, 0.357; nominal p<0.0001), based on event rates of 58% and 16% in the control and experimental arm, respectively. The overall concordance between IRC and investigator assessments of PD and non-PD events was 93.4% for the experimental arm and 81.0% for the control arm.

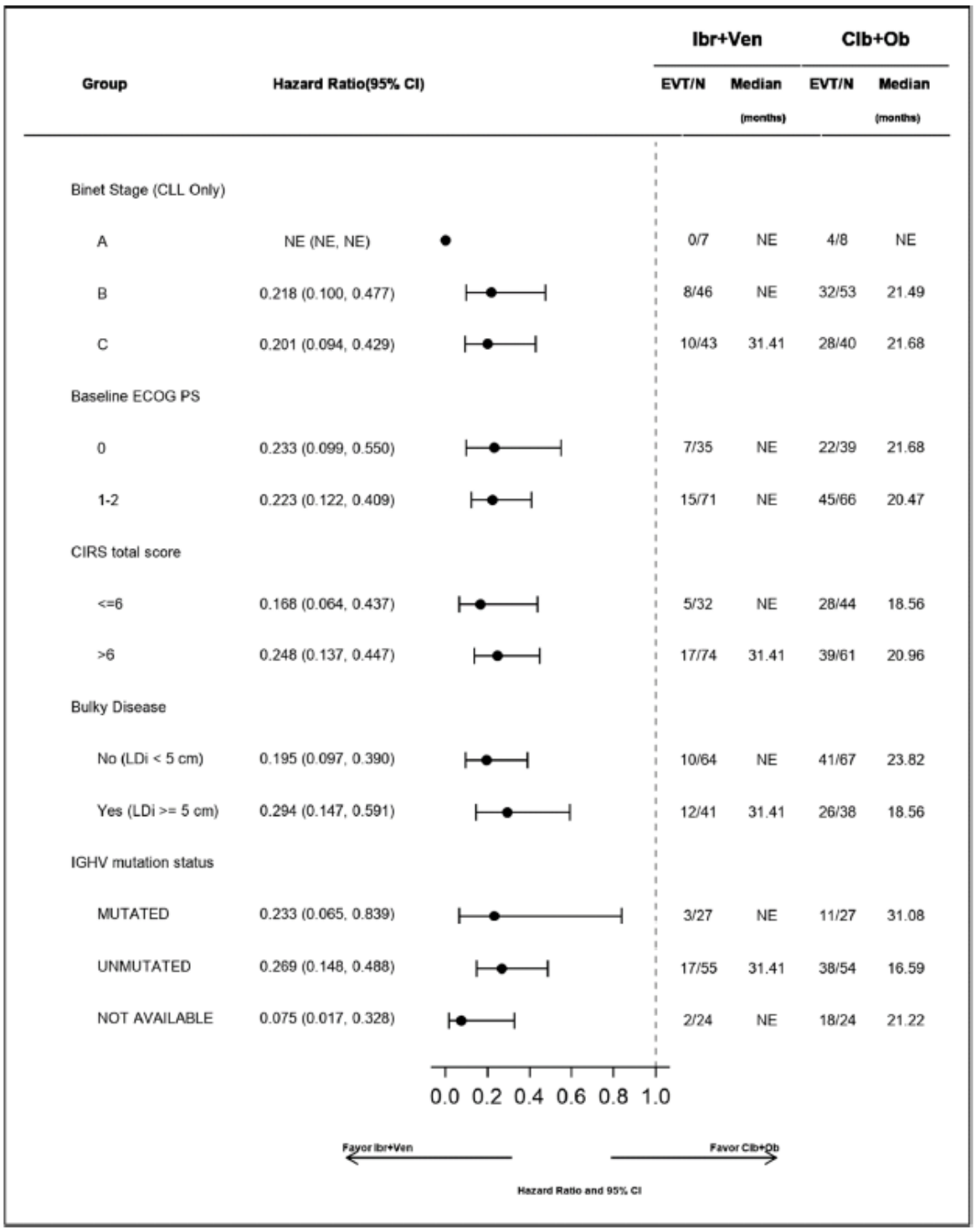
PFS analysis censoring subjects who started a subsequent anticancer therapy prior to PD: HR=0.216 (95% CI: 0.131, 0.356); p<0.0001.

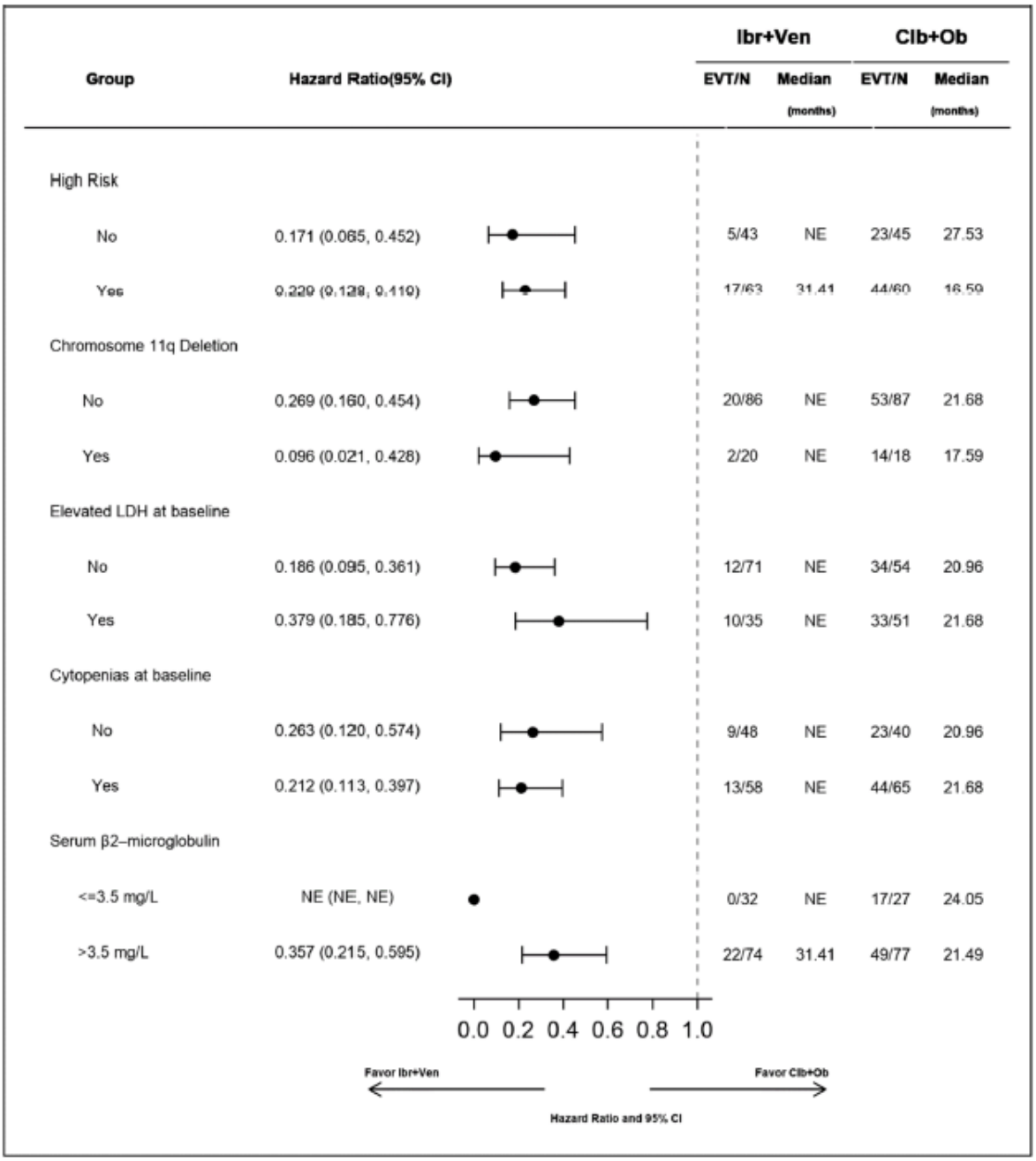
A *post-hoc* restricted mean survival time analysis was also performed: Subjects in the experimental arm, on average, were progression-free for 3 (95% CI: 1.4 to 4.6) and 5.7 (95% CI: 3.5 to 7.9) months more than subjects in the control arm at 24 and 30 months after randomization, respectively.

Subgroup analyses of PFS

Figure 3. Forest Plot of Progression Free Survival (IRC) for Subgroups Defined by Demographic and Baseline Clinical Disease Characteristics; Intent-to-treat Analysis Set (Study CLL3011)




Group
Hazard Ratio(95% CI)
Ibr+Ven
Clb+Ob
EVT/N
Median (months)
EVT/N
Median (months)
Binet Stage (CLL Only)
A NE (NE, NE) 0/7 NE 4/8 NE
B 0.218 (0.100, 0.477) 8/46 NE 32/53 21.49
C 0.201 (0.094, 0.429) 10/43 31.41 28/40 21.68
Baseline ECOG PS
0 0.233 (0.099, 0.550) 7/35 NE 22/39 21.68
1-2 0.223 (0.122, 0.409) 15/71 NE 45/66 20.47
CIRS total score
<=6 0.168 (0.064, 0.437) 5/32 NE 28/44 18.56
>6 0.248 (0.137, 0.447) 17/74 31.41 39/61 20.96
Bulky Disease
No (LDi < 5 cm) 0.195 (0.097, 0.390) 10/64 NE 41/67 23.82
Yes (LDi >= 5 cm) 0.294 (0.147, 0.591) 12/41 31.41 26/38 18.56
IGHV mutation status
MUTATED 0.233 (0.065, 0.839) 3/27 NE 11/27 31.08
UNMUTATED 0.269 (0.148, 0.488) 17/55 31.41 38/54 16.59
NOT AVAILABLE 0.075 (0.017, 0.328) 2/24 NE 18/24 21.22
0.0 0.2 0.4 0.6 0.8 1.0
Favor Ibr+Ven
Favor Clb+Ob
Hazard Ratio and 95% CI



A multivariate analysis was conducted for PFS to evaluate the treatment effect when controlling for potential prognostic factors. After adjustment for selected prespecified baseline factors, the treatment effect was consistent with the primary analysis, HR=0.177 (95% CI: 0.100, 0.313); nominal p<0.0001.

36-month extended follow-up from the primary analysis for PFS by INV (data cut-off 24 February 2024)

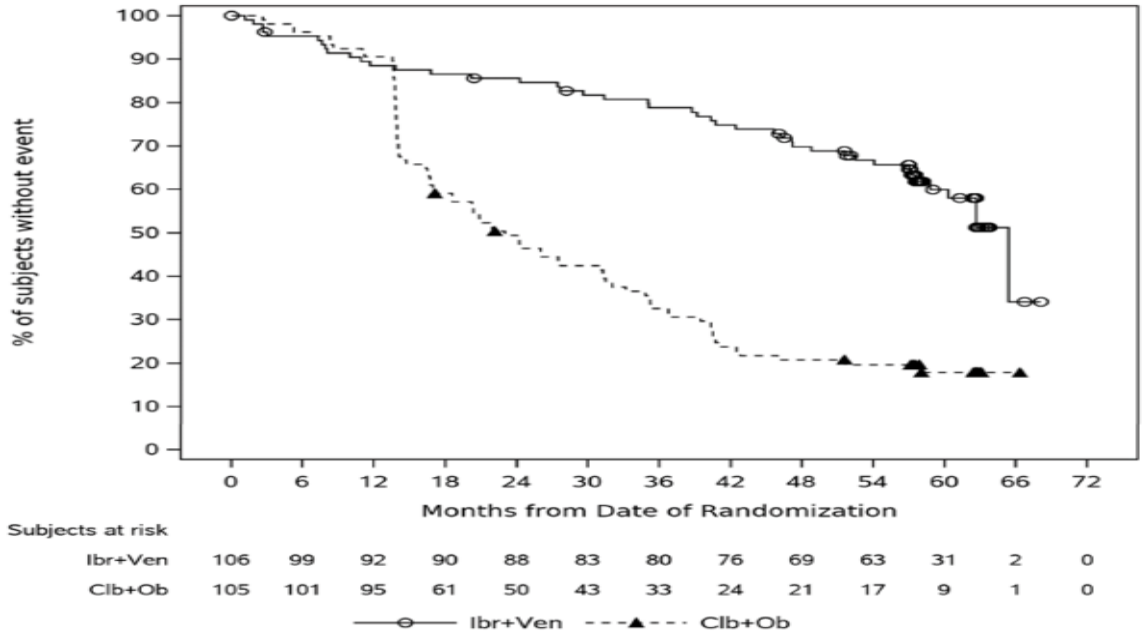
With a median time on study for all subjects of 64.0 months (range: 1.7 to 69.7), the PFS by INV HR was 0.267 (95% confidence interval [CI]: 0.182, 0.393; nominal p<0.0001).

Table 13 . Summary of Progression Free Survival by Investigator, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	43 (40.6%)	84 (80.0%)	
Progressive Disease	28 (26.4%)	76 (72.4%)	
Death	15 (14.2%)	8 (7.6%)	
Censored	63 (59.4%)	21 (20.0%)	
Time to event (months)			
25th percentile (95% CI)	40.74 (27.63, 52.47)	13.93 (13.73, 14.23)	
Median (95% CI)	65.38 (58.74, NE)	23.00 (16.92, 31.24)	
75th percentile (95% CI)	NE (65.38, NE)	40.71 (35.22, NE)	
Range	(0.0+, 68.1+)	(2.6, 66.3+)	
6-month event-free rate (95% CI)	0.952 (0.889, 0.980)	0.962 (0.902, 0.986)	
12-month event-free rate (95% CI)	0.885 (0.806, 0.933)	0.905 (0.830, 0.948)	
18-month event-free rate (95% CI)	0.866 (0.784, 0.918)	0.590 (0.490, 0.677)	
24-month event-free rate (95% CI)	0.856 (0.773, 0.911)	0.493 (0.395, 0.585)	
30-month event-free rate (95% CI)	0.817 (0.728, 0.879)	0.424 (0.328, 0.517)	
36-month event-free rate (95% CI)	0.788 (0.695, 0.855)	0.326 (0.238, 0.417)	
42-month event-free rate (95% CI)	0.748 (0.653, 0.821)	0.237 (0.160, 0.323)	
48-month event-free rate (95% CI)	0.698 (0.599, 0.777)	0.207 (0.135, 0.290)	
54-month event-free rate (95% CI)	0.667 (0.567, 0.750)	0.196 (0.125, 0.278)	
60-month event-free rate (95% CI)	0.599 (0.491, 0.692)	0.178 (0.108, 0.262)	
66-month event-free rate (95% CI)	0.341 (0.096, 0.611)	0.178 (0.108, 0.262)	
Hazard ratio (95% CI) [a]			0.267 (0.182, 0.393)
p-value [b]			<0.0001

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation, NE = not estimable.
Note: median PFS for Ibr+Ven arm was not reliable as only 2 subjects were at risk at 66 months.

Figure 4. Kaplan-Meier plot Progression Free Survival by Investigator, Intent-to-treat Analysis Set (Study CLL3011)



Secondary endpoints

MRD negativity rate

MRD negativity rates were assessed by NGS and flow cytometry (not further discussed in this AR). The overall MRD negativity rate (best MRD response) in BM assessed by NGS was the primary analysis used in the hierarchical testing.

Primary analysis: MRD negativity rates assessed by NGS (best MRD response)

Table 14. MRD negativity rates assessed by NGS, ITT, DCO 26 Feb 2021, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Rate Ratio [a]
Analysis set: Intent-to-treat	106	105	
MRD-negative disease status			
Bone marrow			
Samples obtained[c]	92 (86.8%)	84 (80.0%)	
MRD negativity, n(%)	59 (55.7%)	22 (21.0%)	2.65 (1.75, 3.99)
95% CI[d]	(46.2%, 65.1%)	(13.2%, 28.7%)	< 0.0001[b]
Peripheral blood			
Samples obtained[c]	93 (87.7%)	89 (84.8%)	
MRD negativity, n(%)	63 (59.4%)	42 (40.0%)	1.48 (1.10, 1.98)
95% CI[d]	(50.1%, 68.8%)	(30.6%, 49.4%)	0.0055[b]
Bone marrow or peripheral blood			
Samples obtained[c]	93 (87.7%)	89 (84.8%)	
MRD negativity, n(%)	66 (62.3%)	43 (41.0%)	1.52 (1.14, 2.01)
95% CI[d]	(53.0%, 71.5%)	(31.5%, 50.4%)	0.0023[b]
Bone marrow and peripheral blood			
Samples obtained[c]	92 (86.8%)	84 (80.0%)	
MRD negativity, n(%)	56 (52.8%)	21 (20.0%)	2.63 (1.71, 4.03)
95% CI[d]	(43.3%, 62.3%)	(12.3%, 27.7%)	< 0.0001[b]

Key: CI=confidence interval; BM=bone marrow; PB=peripheral blood.
[a] Rate ratio >1 in favors of Ibr+Ven.
[b] P-value is from a CMH chi-square test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no).
[c] Includes MRD samples supposed to be collected per protocol only.
[d] The 95% confidence interval for MRD negativity rate is based on normal approximation to the binomial distribution.

MRD negativity rates assessed by NGS at 3 and 12 months post-treatment

Table 15. MRD Negativity Rate at Selected Post-Treatment Time Points, ITT, DCO 26 Feb 2021, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Rate Ratio [a]
Analysis set: Intent-to-treat	106	105	
MRD-negative disease status 3-month post end of treatment			
Bone marrow			
Samples obtained[c,d]	85 (80.2%)	81 (77.1%)	
MRD negativity, n(%)	55 (51.9%)	18 (17.1%)	3.00 (1.90, 4.76)
95% CI[e]	(42.4%, 61.4%)	(9.9%, 24.4%)	< 0.0001[b]
Peripheral blood			
Samples obtained[c,d]	88 (83.0%)	88 (83.8%)	
MRD negativity, n(%)	58 (54.7%)	41 (39.0%)	1.39 (1.03, 1.89)
95% CI[e]	(45.2%, 64.2%)	(29.7%, 48.4%)	0.0259[b]
Bone marrow or peripheral blood			
Samples obtained[c,d]	88 (83.0%)	88 (83.8%)	
MRD negativity, n(%)	60 (56.6%)	42 (40.0%)	1.41 (1.05, 1.89)
95% CI[e]	(47.2%, 66.0%)	(30.6%, 49.4%)	0.0183[b]
Bone marrow and peripheral blood			
Samples obtained[c,d]	84 (79.2%)	79 (75.2%)	
MRD negativity, n(%)	52 (49.1%)	17 (16.2%)	3.00 (1.86, 4.84)
95% CI[e]	(39.5%, 58.6%)	(9.1%, 23.2%)	< 0.0001[b]
MRD-negative disease status 12-month post end of treatment			
Peripheral blood			
Samples obtained[c,d]	82 (77.4%)	52 (49.5%)	
MRD negativity, n(%)	52 (49.1%)	13 (12.4%)	3.97 (2.28, 6.90)
95% CI[e]	(39.5%, 58.6%)	(6.1%, 18.7%)	< 0.0001[b]

Key: CI=confidence interval; CR=complete response; CRi=complete response with an incomplete marrow recovery; BM=bone marrow; PB=peripheral blood.
[a] Rate ratio >1 in favors of Ibr+Ven.
[b] P-value is from a CMH chi-square test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no).
[c] Includes MRD samples supposed to be collected per protocol only.
[d] Includes MRD samples not collected at prespecified but at subsequent disease evaluation.
[e] The 95% confidence interval for MRD negativity rate is based on normal approximation to the binomial distribution.

At 3 months post-treatment of the 56 subjects in the experimental arm who were MRD-negative in peripheral blood and who had a matched bone marrow specimen collected, 52 (92.9%) were MRD-negative in both peripheral blood and bone marrow. At the same timepoint, of the 39 subjects from the control arm who were MRD-negative in peripheral blood and who had a matched bone marrow specimen collected, 17 (43.6%) were MRD-negative in both peripheral blood and bone marrow.

MRD negativity rates by NGS at Equivalent Timepoints

- At DE3 (9 months after randomisation): MRD negativity rates for subjects in the experimental arm and the control arm were 39.6% and 17.1% in the bone marrow, respectively; 46.2% and 39.0% in the peripheral blood.
- At DE6 (18 months after randomisation): MRD negativity rates for subjects in the experimental arm and the control arm were 51.9% and 9.5% in the bone marrow, respectively; 54.7% and 12.4% in the peripheral blood.
- At DE8 (26 months after randomisation): MRD negativity rates for subjects in the experimental arm and the control arm were 49.1% and 3.8% in the peripheral blood, respectively.

The rate ratios of MRD negativity rates comparing experimental arm versus control arm in the peripheral blood increased over time (DE3: 1.18; DE6: 4.41; DE8: 12.84).

MRD negativity rates by NGS by best overall response of CR/CRi per IRC

By use of a stratified CMH chi-square test, no statistical nominal differences were noted between study arms.

- **Summary of MRD negativity rates (% (n/N) in the experimental arm**

	Study CLL3011 Ibr+Ven N=106	
	NGS	FLOW Cytometry
Overall MRD negativity rate - % (n/N)		
BM	55.7 (59/106)	67.9% (72/106)
PB	59.4 (63/106)	80.2% (85/106)
MRD negativity rate at 3 months post-treatment -		
BM	51.9 (55/106)[b]	56.6 (60/106)[b]
PB	54.7 (58/106)[b]	61.3 (65/106)[b]
MRD negativity rate at 12 months post-treatment		
PB	49.1 (52/106)[c]	54.7 (58/106)[c]

[b] The time point corresponds to 72 weeks after randomization
[c] The timepoint corresponds to 104 weeks after randomization

Complete response (CR/CRi) rate

Primary analysis, per IRC

Table 16. Summary of CR by IRC, ITT, DCO 26 Feb 2021, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob
Analysis set: Intent-to-treat	106	105
Complete Response Rate (CR, CRi), n(%)	41 (38.7%)	12 (11.4%)
95% CI [a]	(29.4%, 48.0%)	(5.3%, 17.5%)
Rate ratio (95% CI) [b]	3.43 (1.91, 6.15)	
p-value [c]	< 0.0001	

CR = complete response. CRi = complete response with incomplete marrow recovery.
[a] The 95% confidence interval for response rates is based on normal approximation to the binomial distribution.
[b] Rate ratio >1 favors Ibr+Ven.
[c] P-value is from Cochran-Mantel-Haenszel chi-square test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no).

Table 17. Time to Complete Response by IRC, ITT, DCO 26 Feb 2021, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob
Analysis set: Intent-to-treat	106	105
Time to complete response (months) [a]		
N	41	12
Median (95% CI)	13.83(11.87,14.35)	8.66(8.17,13.24)
Range	(8.1; 20.0)	(8.2; 20.2)

[a] Time to complete response is calculated for subjects with CR or CRi and is defined as the interval between the date of randomization and the date of initial documentation of a CR/CRi.
Note: The above summaries are based on descriptive statistics. Analysis are based on IRC assessments.

At the primary analysis cut-off, only 3/41 subjects in the experimental arm and 1/12 subjects in the control arm had lost response (including death). The 12-month landmark estimate for duration of IRC-assessed CR (CR/CRi) was 100% in the experimental arm and 91.7% in the control arm.

CR rate as assessed by INV

Experimental arm: 45.3%

Control arm: 13.3%

The 12-month landmark estimate for duration of investigator-assessed CR (CR/CRi) was 93.9% in the experimental arm and 87.5% in the control arm.

CR rate per IRC: Extended follow-up

With 6 month extended follow-up from the primary analysis, an overall response of CR/CRi was reported for 3 additional subjects (2 subjects in the experimental arm and 1 subject in the control arm) compared with the primary analysis; CR/CRi rate 40.6% vs 12.4%.

The 18-month landmark estimate for duration of IRC-assessed CR (CR/CRi) was 97.5% in the experimental arm and 84.6% in the control arm.

Overall response rate (ORR) per IRC

Table 18. ORR by IRC, ITT, DCO 26 Feb 2021, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Overall Response Rate (PR+nPR+CRi+CR)			
Responder	92 (86.8%)	89 (84.8%)	
95% CI	(80.3%, 93.2%)	(77.9%, 91.6%)	
Rate ratio (95% CI)[a]			1.02 (0.92, 1.14)
p-value[b]			0.6991
Best Overall Response			
Complete Response (CR)	38 (35.8%)	12 (11.4%)	
Complete Response with Incomplete Marrow Recovery (CRi)	3 (2.8%)	0	
Nodular Partial Response (nPR)	4 (3.8%)	3 (2.9%)	
Partial Response (PR)	47 (44.3%)	74 (70.5%)	
Stable Disease (SD)	8 (7.5%)	13 (12.4%)	
Progressive Disease (PD)	2 (1.9%)	2 (1.9%)	
Not Evaluable (NE)	4 (3.8%)	1 (1.0%)	

[a] Rate ratio >1 favors Ibr+Ven.
[b] P-value is from Cochran-Mantel-Haenszel chi-square test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no).

Overall survival

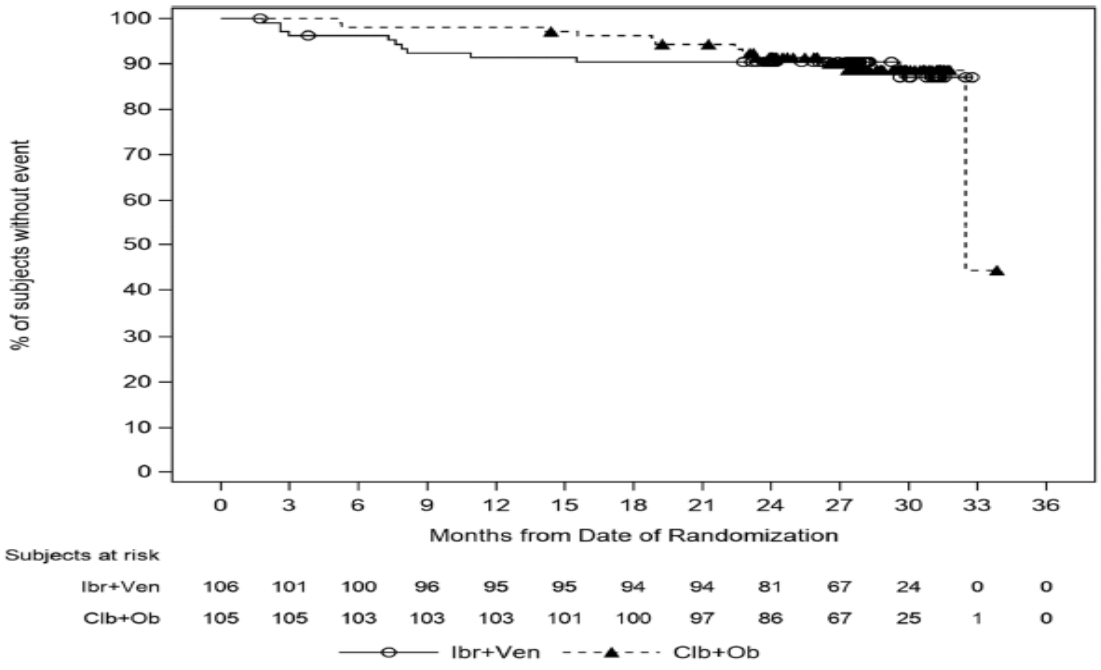
Primary analysis

Table 19. OS, ITT, DCO 26 Feb 2021, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	11 (10.4%)	12 (11.4%)	
Death	11 (10.4%)	12 (11.4%)	
Censored	95 (89.6%)	93 (88.6%)	
Overall Survival (months)			
25th percentile (95% CI)	NE (NE, NE)	32.49 (32.49, NE)	
Median (95% CI)	NE (NE, NE)	32.49 (32.49, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (32.49, NE)	
Range	(1.7+, 32.8+)	(5.1, 33.8+)	
6-month survival rate (95% CI)	0.962 (0.902, 0.986)	0.981 (0.926, 0.995)	
12-month survival rate (95% CI)	0.914 (0.841, 0.954)	0.981 (0.926, 0.995)	
18-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.962 (0.901, 0.985)	
24-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.913 (0.839, 0.954)	
30-month survival rate (95% CI)	0.871 (0.757, 0.934)	0.886 (0.802, 0.936)	
Hazard ratio (95% CI) [a]			1.048 (0.454, 2.419)
p-value [b]			0.9121

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation, NE = not estimable.
Includes deaths up to database lock date.

Figure 5. KM-plot OS, ITT, DCO 26 Feb 2021, Intent-to-treat Analysis Set (Study CLL3011)



includes deaths up to database lock date.

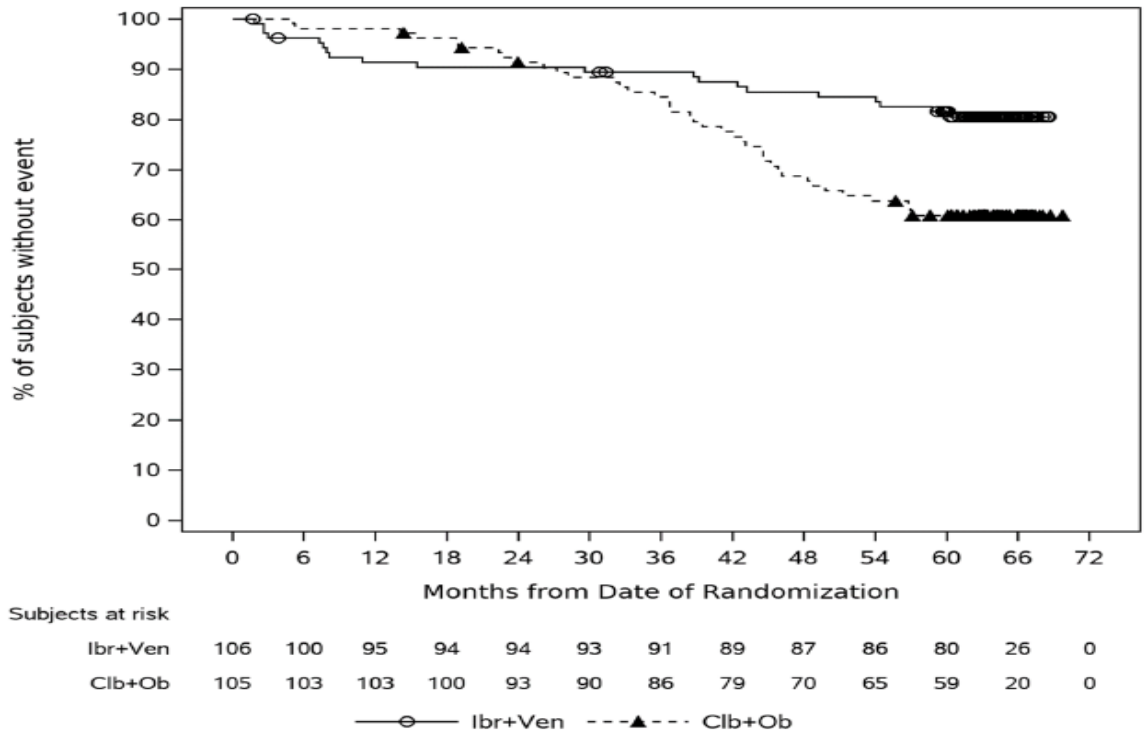
36-month extended follow-up from the primary analysis for OS (DCO 24 February 2024)

Table 20. OS, ITT, DCO 24 February 2024, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	20 (18.9%)	40 (38.1%)	
Death	20 (18.9%)	40 (38.1%)	
Censored	86 (81.1%)	65 (61.9%)	
Overall Survival (months)			
25th percentile (95% CI)	NE (54.08, NE)	43.10 (36.50, 49.81)	
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Range	(1.7+, 68.6+)	(5.1, 69.7+)	
6-month survival rate (95% CI)	0.962 (0.902, 0.986)	0.981 (0.926, 0.995)	
12-month survival rate (95% CI)	0.914 (0.841, 0.954)	0.981 (0.926, 0.995)	
18-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.962 (0.901, 0.985)	
24-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.913 (0.840, 0.954)	
30-month survival rate (95% CI)	0.895 (0.818, 0.940)	0.884 (0.805, 0.932)	
36-month survival rate (95% CI)	0.895 (0.818, 0.940)	0.845 (0.759, 0.902)	
42-month survival rate (95% CI)	0.875 (0.794, 0.925)	0.776 (0.682, 0.845)	
48-month survival rate (95% CI)	0.855 (0.771, 0.910)	0.688 (0.588, 0.768)	
54-month survival rate (95% CI)	0.845 (0.760, 0.902)	0.638 (0.537, 0.723)	
60-month survival rate (95% CI)	0.816 (0.727, 0.878)	0.608 (0.507, 0.696)	
66-month survival rate (95% CI)	0.805 (0.715, 0.870)	0.608 (0.507, 0.696)	
Hazard ratio (95% CI) [a]			0.462 (0.269, 0.791)
p-value [b]			0.0039

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation, NE = not estimable.

Figure 6. KM-plot OS, ITT, DCO 24 Feb 2024, Intent-to-treat Analysis Set (Study CLL3011)



Sustained hematologic improvement

At the primary analysis, the proportion of subjects with sustained improvement in haemoglobin was similar for the experimental arm compared with the control arm (44.3% vs. 50.5%). Also the proportion of subjects with sustained improvement in platelets was similar for experimental arm compared with the control arm (24.5% vs. 29.5%). These outcomes remained essentially similar at the additional 6-month extended follow-up analysis.

Time to improvement in FACIT-Fatigue score

As of the data cut-off for the primary analysis, the median time to clinically meaningful (≥3 points increase on 52-point scale) improvement in FACIT-Fatigue score was 5.59 months for subjects in the experimental arm versus 3.75 months for subjects in the control arm (HR=1.369; 95% CI: 0.959, 1.954).

Ancillary analyses

Duration of response (DOR)

As of the data cut-off 26 Feb 2021 for the primary analysis, with a median time on study for all subjects of 27.7 months, the median DOR for subjects who achieved an IRC-assessed PR or better was 28.9 months (95% CI: 28.68, NE) in the experimental arm and 21.1 months (95% CI: 15.93, 25.10) in the control arm.

The 24-month landmark estimate for IRC-assessed DOR was 89.9% in the experimental arm and 41.2% in the control arm.

6-month extended follow-up from the primary analysis, DCO 19 August 2021

With an overall median follow-up of 34.1 months, the median DOR for subjects who achieved an IRC-assessed PR or better was not reached in the experimental arm and was 21.4 months (95% CI: 18.83, 28.58) in the control arm.

The 30-month landmark estimate for IRC-assessed DOR was 86.7% in the experimental arm and 35.5% in the control arm.

Time to next treatment

Table 21. Time to subsequent anticancer therapy, DCO 26 Feb 2021, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	4 (3.8%)	27 (25.7%)	
Censored	102 (96.2%)	78 (74.3%)	
Time to event (months)			
25th percentile (95% CI)	NE (NE, NE)	27.40 (22.28, NE)	
Median (95% CI)	NE (NE, NE)	NE (31.54, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Range	(1.1, 32.8+)	(2.4, 32.5+)	
6-month event rate (95% CI)	0.991 (0.935, 0.999)	0.971 (0.914, 0.991)	
12-month event rate (95% CI)	0.970 (0.909, 0.990)	0.933 (0.864, 0.967)	
18-month event rate (95% CI)	0.970 (0.909, 0.990)	0.864 (0.781, 0.917)	
24-month event rate (95% CI)	0.970 (0.909, 0.990)	0.813 (0.722, 0.876)	
30-month event rate (95% CI)	0.955 (0.883, 0.983)	0.719 (0.607, 0.805)	
Hazard ratio (95% CI) [a]			0.143 (0.050, 0.410)
p-value [b]			<0.0001

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation, NE = not estimable.
Time to subsequent anti-cancer therapy is defined as the time interval between randomization and initiation of any subsequent anti-cancer treatment (including subsequent single-agent ibrutinib). Subjects who had not started any subsequent anti-cancer therapy are censored at the dates when the subjects were last known to be alive.

Table 22. Number of Subjects with Subsequent Anti-cancer Therapy, DCO 26 Feb 2021, Intent-to-treat Analysis Set (Study CLL3011)

	Ibr+Ven	Clb+Ob
Analysis set: Intent-to-treat	106	105
Number of subjects with subsequent therapy	4 (3.8%)	27 (25.7%)
High-dose therapy/Stem cell transplant	0	0
Radiotherapy	1 (0.9%)	2 (1.9%)
Surgery	1 (0.9%)	1 (1.0%)
Subsequent single-agent ibrutinib per protocol	1 (0.9%)	15 (14.3%)
Systemic therapy	3 (2.8%)	11 (10.5%)
ATC Level 2/ATC Level 4/Preferred Term		
Antineoplastic Agents	3 (2.8%)	11 (10.5%)
Nitrogen Mustard Analogues	3 (2.8%)	2 (1.9%)
Cyclophosphamide	2 (1.9%)	1 (1.0%)
Chlorambucil	1 (0.9%)	0
Bendamustine	0	2 (1.9%)
Anthracyclines And Related Substances	2 (1.9%)	0
Doxorubicin	2 (1.9%)	0
Monoclonal Antibodies	2 (1.9%)	5 (4.8%)
Brentuximab Vedotin	1 (0.9%)	0
Rituximab	1 (0.9%)	5 (4.8%)
Vinca Alkaloids And Analogues	2 (1.9%)	1 (1.0%)
Vinblastine	1 (0.9%)	0
Vincristine	1 (0.9%)	0
Vincristine Sulfate	0	1 (1.0%)
Folic Acid Analogues	0	1 (1.0%)
Methotrexate	0	1 (1.0%)
Methylhydrazines	0	1 (1.0%)
Procarbazine	0	1 (1.0%)
Other Antineoplastic Agents	0	2 (1.9%)
Idelalisib	0	1 (1.0%)
Venetoclax	0	1 (1.0%)
Protein Kinase Inhibitors	0	7 (6.7%)
Acalabrutinib	0	1 (1.0%)
Ibrutinib	0	6 (5.7%)
Corticosteroids For Systemic Use	0	2 (1.9%)
Glucocorticoids	0	2 (1.9%)
Dexamethasone	0	1 (1.0%)
Prednisolone	0	1 (1.0%)

Note: Recurrent medications are counted only once per subject.
Anti-cancer Therapy are presented by decreasing frequency of ATC Level 2, ATC Level 4 and preferred term within Ibr+Ven column; those with the same frequency are presented alphabetically.

Of 4 subjects from the experimental arm and 27 subjects from the control arm who had initiated subsequent anticancer therapy, 1 and 22 subjects received subsequent anticancer therapy with a BTK inhibitor. One subject from the control arm received subsequent anticancer therapy with venetoclax.

6-month extended follow-up from the primary analysis, DCO 19 August 2021

With an overall median follow-up of 34.1 months , the median time to subsequent anticancer therapy was still not reached in either treatment arm with a HR of 0.147 (95% CI: 0.062, 0.350).

Of 6 and 35 subjects in the experimental and control arm, respectively, who had initiated subsequent anticancer therapy, 2 and 28 subjects received subsequent anticancer therapy with a BTK inhibitor. Four subjects from the control arm received subsequent anticancer therapy with venetoclax.

36-month extended follow-up from the primary analysis, DCO 24 February 2024

With a median time on study for all subjects of 64.0 months (range: 1.7 to 69.7), the median time to subsequent therapy had not been reached for Ibr+Ven arm and was 65 months for the Clb+Ob arm, with 16 (15.1%) and 46 (43.8%) subjects in the Ibr+Ven and Clb+Ob arm initiating subsequent anticancer therapy after 36-months of extended follow-up (HR=0.233; 95% CI: 0.130, 0.416).

Tumour Lysis Syndrome Risk Reduction Based on Tumour Burden

At baseline, 26 (24.5%) subjects in the Ibr+Ven arm had TLS high risk based on high tumour burden (defined as any lymph node ≥10 cm, or any lymph node ≥5 cm and ALC ≥25×109/L). TLS risk remained high in 2 (1.9%) of 106 subjects after 3 cycles of ibrutinib lead-in therapy. TLS risk was reduced to medium or low for 22 (84.6%) of the 26 subjects with high TLS risk at baseline, after ibrutinib lead-in. No subjects with baseline TLS medium or low risk shifted to TLS high risk.

At baseline, 69 subjects in the experimental arm had an indication for hospitalization (26 due to TLS risk from high tumour burden and 43 due to TLS risk from medium tumour burden with CrCl <80 mL/min). After 3 cycles of ibrutinib lead-in, hospitalization was no longer indicated for 24 (34.8%) of these subjects.

Of 49 subjects for whom hospitalization was indicated after 3 cycles of ibrutinib, 2 subjects had TLS risk based on high tumour burden and 47 had TLS risk based on medium tumour burden but with a CrCl <80 mL/min.

Impact of Coronavirus Disease 2019 on Efficacy Results

As of the data cut-off for the primary analysis, there was limited impact of the COVID-19 pandemic on integrity of the study and the primary efficacy endpoint (PFS):

Six (2.8%) subjects were pending completion of the fixed duration treatment phase when the COVID-19 outbreak was declared a pandemic by WHO in March 2020.

Twenty-one (19.8%) subjects in the Ibr+Ven arm and 13 (12.4%) subjects in the Clb+Ob arm had at least 1 disease evaluation (DE) visit missed due to COVID-19. No subjects were lost to follow-up and no subject missed 2 or more consecutive DE visits due to the COVID-19 pandemic. Four subjects had missed DE visits that were considered as major protocol deviations for potentially delaying the detection of PD due to COVID-19. Sixteen (15.1%) and 23 (21.9%) subjects in the Ibr+Ven and Clb+Ob arms, respectively, had at least 1 DE visit delayed due to COVID-19.

Five deaths were reported as COVID-19 related during the study (1 in the Ibr+Ven arm and 4 in the Clb+Ob arm). All 5 deaths reported as COVID-19 related occurred post-fixed duration treatment; only 1 of these deaths occurred prior to PD. The impact of this death on the primary endpoint analysis was considered negligible.

A pre-planned supplementary PFS analysis censoring subjects who died pre-PD related to COVID-19 was not conducted because the threshold specified in the Statistical Analysis Plan was not met. A supplementary OS analysis censoring subjects who died due to COVID-19 was conducted and showed results consistent with the primary OS analysis.

A supplementary OS analysis censoring deaths related to COVID-19 at extended follow-up is summarised in **Table 20**.

Table 23. Supplementary OS analysis censoring for COVID-19 related death, DCO 17 August 2021, Intent-to-treat Analysis Set (Study CLL3011)

S_TEFOS03: Summary of Overall Survival – Supplementary Analysis; Intent-to-treat Analysis Set (Study 54179060CLL3011)			
	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	10 (9.4%)	12 (11.4%)	
Death	10 (9.4%)	12 (11.4%)	
Censored	96 (90.6%)	93 (88.6%)	
Overall Survival (months)			
25th percentile (95% CI)	NE (NE, NE)	NE (35.45, NE)	
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Range	(1.7+, 38.4+)	(5.1, 39.6+)	
6-month survival rate (95% CI)	0.962 (0.902, 0.986)	0.981 (0.926, 0.995)	
12-month survival rate (95% CI)	0.914 (0.841, 0.954)	0.981 (0.926, 0.995)	
18-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.962 (0.901, 0.985)	
24-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.932 (0.864, 0.967)	
30-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.922 (0.850, 0.960)	
36-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.846 (0.727, 0.916)	
Hazard ratio (95% CI) [a]			0.893 (0.386, 2.070)
p-value [b]			0.7920

[a] Hazard ratio is from nonstratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a nonstratified log-rank test.
Note: + = censored observation, NE = not estimable.
Subjects who died due to COVID-19 were censored at the death date.

Without such censoring, the HR was 0.760 (95% CI: 0.352, 1.642) at the cut-off for extended follow-up.

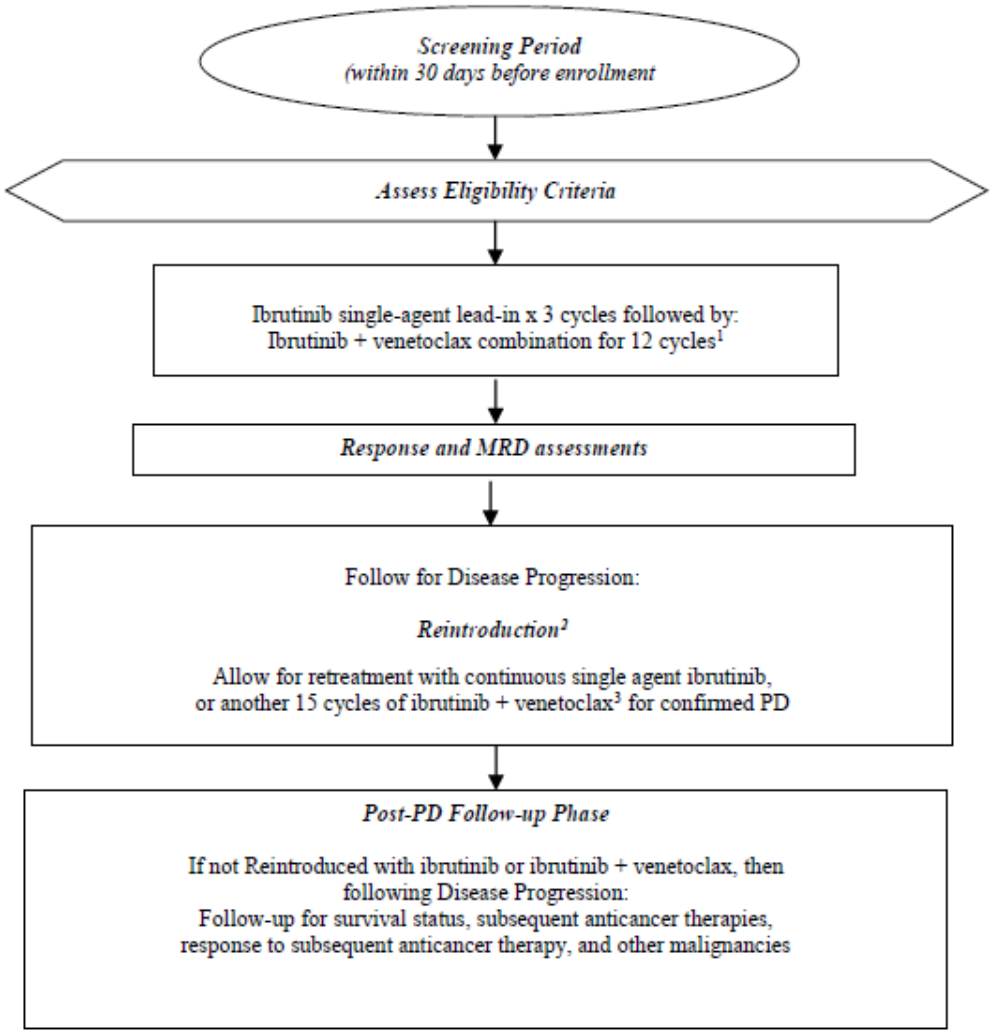
The impact of the COVID-19 pandemic on the integrity of the study and the primary efficacy endpoint (PFS) remained limited with 6-months extended follow-up. One additional subject from the Clb+Ob arm had at least 1 DE visit missed due to COVID-19. Four additional subjects from the Ibr+Ven arm had at least 1 DE visit delayed due to COVID-19. No new COVID-19 infection related deaths were reported.

PCYC-1142-CA (CAPTIVATE): A phase 2 study of the combination of ibrutinib plus venetoclax in subjects with treatment-naïve CLL/SLL.

Study 1142 was developed to evaluate if discontinuing ibrutinib in the setting of a confirmed MRD-negative response with the combination of ibrutinib + venetoclax, allows for a treatment holiday. Early response data from investigator-initiated trials in subjects with relapsed/refractory and previously untreated CLL informed the addition of a Fixed Duration (FD) cohort in which subjects received a fixed duration of Ibr+Ven.

Only the FD cohort is part of this application. The study design of the FD cohort is depicted in **Figure 7**.

Figure 7. PCYC-1142-CA study scheme



1 Administer 12 cycles of ibrutinib + venetoclax unless discontinue for PD or toxicity. Subjects who discontinue treatment for reasons other than confirmed PD should continue participating in ongoing response follow-up visits until confirmed PD

2 Refer to Sections 3.1.3 and 5.3.3 for details regarding FD cohort Reintroduction

3 Addition of venetoclax will follow the standard dose ramp up. Venetoclax for up to 2 yrs, until PD or unacceptable toxicity, or study arm closure, whichever is first

Methods

Study participants

Key inclusion criteria

- Diagnosis of CLL/SLL that meets iwCLL diagnostic criteria (Hallek 2008)
- Active disease meeting at least 1 of the iwCLL criteria (Hallek 2008) for requiring treatment
- Measurable nodal disease by CT
- Men and women ≥18 and ≤70 years of age
- ECOG performance status of 0-2

Key exclusion criteria

- Any prior therapy used for treatment of CLL or SLL.

- Known or suspected history of Richter's transformation.

Treatments

The Ibr+Ven treatment schedule for the Study 1142 FD cohort was identical to that used in Study CLL3011: ibrutinib (420 mg/day orally) given as lead-in treatment for 3 cycles. Starting at Cycle 4 and contingent on completion of TLS risk assessment, venetoclax dose ramp-up (from 20 to 400 mg over 5 weeks) was initiated. Combined treatment with ibrutinib and venetoclax was administered for 12 cycles, through Cycle 15, in the absence of PD or treatment-limiting toxicity. One cycle corresponds to 28 days.

If PD per iwCLL criteria was confirmed after completion of the FD regimen, single-agent ibrutinib could be reintroduced and given continuously until PD or unacceptable toxicity. In addition, for subjects with PD following durable efficacy after Ibr+Ven treatment (defined as time to progression after completion of fixed duration regimen of > 2 years), Ibr+Ven could be reintroduced and administered for the same 15-cycle FD period as given initially.

Objectives

The primary objective of the FD cohort was to evaluate the depth of response with the combination of Ibr+Ven administered for a fixed duration of therapy by assessment of the CR (CR/CRi) rate.

The secondary objectives of the FD cohort were to evaluate DOR, MRD-negative rate, ORR, TLS risk reduction, PFS, OS, and safety and tolerability.

Outcomes/endpoints

Primary Endpoint

Complete response (CR/CRi) rate by investigator.

Secondary Endpoints

• Duration of response

• MRD negativity rate

• Overall response rate

• TLS risk reduction

• Progression free survival

• Overall survival

Sample size

In the FD cohort, assuming the complete response rate for Ibr + Ven is 50%, 125 subjects without del 17p will provide 83% power to ensure the rate is > 37% at 1-side alpha 0.025. A CR rate of 50% would represent meaningful improvement compared to the CR rate seen with the fixed duration combination of bendamustine + rituximab (31%), and would be an improvement over the CR rate seen with the standard of care fixed duration regimen fludarabine, cyclophosphamide and rituximab (40%) which were obtained in the CLL10 study, which included only patients without del 17p.

Randomisation and blinding

Not applicable.

Statistical methods

The primary hypothesis was that the CR rate is > 37% after 12-cycle Ibr + Ven treatment. The hypothesis was to be tested at 1-sided α level of 0.025 using asymptotic test for the binomial proportion. Since the assumption for sample size and power of this cohort is based on the historical data of subjects without del 17p, the formal hypothesis testing was to be performed on the non-del 17p population. The Non-del 17p population includes enrolled subjects who received at least 1 dose of study drug, and who are without del 17p abnormality according to non-missing baseline FISH results. All analyses for the FD cohort were to be repeated on the All treated population as supportive analyses.

The primary analysis was to be based on investigator assessment and performed after the last enrolled FD subject has the opportunity to be followed for at least 30 cycles (15 cycles of treatment + 15 cycles of posttreatment follow-up). In addition to investigator assessment, an IRC blinded to the study treatment was to evaluate the responses for both cohorts independently.

Hypothesis testing was to be performed independently for the two cohorts (without multiplicity adjustment) for the primary endpoint only. Other endpoints were to be summarized descriptively with 95% CI whenever applicable.

Subgroup analyses were to be performed for Age, gender, race, ECOG score, Rai stage, bulky disease, Del 17p, Del 17p or TP53 mutated, FISH, IGHV per central lab, creatinine clearance and NCI ODWG Liver function classification.

No interim analysis was planned or performed.

Results

Participant flow

Table 24. Subject disposition at the primary analysis- FD cohort (All-treated population), study 1142

	FD Cohort All-treated N=159	
	Ibrutinib n (%)	Venetoclax n (%)
Treatment status		
Did not receive any study treatment	0	6 (3.8)
Ongoing	NA	NA
Completed	147 (92.5)	149 (93.7)
Discontinued	12 (7.5)	4 (2.5)
Primary reason for discontinuation of study treatment		
MRD-positive relapse	NA	NA
PD	1 (0.6)	1 (0.6)
Adverse event not related to PD	7 (4.4)	3 (1.9)
Death	1 (0.6)	0
Withdrawal of consent for treatment by subject	2 (1.3)	0
Investigator decision	1 (0.6)	0
Lost to follow-up	0	0
Subject became pregnant	0	0

FD: fixed duration; MRD: minimal residual disease; NA: not applicable; PD: progressive disease;
N=number of subjects in the specified population. n=number of subjects in each category. %=100*n/N.

All subjects in the FD cohort were already off treatment before the primary analysis.

At the time of the primary analysis (database lock date of 15 December 2020) the median time on study was 27.9 months (range: 0.8 to 33.2 months). The median time on study with the 9-months extended follow-up after the primary analysis was 38.7 months (range: 0.8 to 41.4 months).

At the time of the final analysis (database lock date was 21 May 2024) the median time on study was 69.0 months (range: 0.8 to 73.2 months).

Reintroduction/other subsequent anti-neoplastic therapies

At the primary analysis (database lock date of 15 December 2020), 4 subjects (2.5%) had reintroduced ibrutinib post-PD; 5 subjects had received other therapy (mainly systemic therapy).

With extended follow-up (database lock date of 04 October 2021), an additional 5 subjects had reintroduced ibrutinib post-PD relative to the primary analysis; 6 subjects had received other therapy (mainly systemic therapy).

Recruitment

First subject consented: 28 September 2016

Last Subject Last Visit: 27 March 2024

Study 1142 has three clinical study reports:

- Primary Analysis CSR (11 November 2021 [primary analysis database lock date of 15 December 2020 + 9-months long-term follow-up after the primary analysis database lock date of 04 October 2021]).
- Long-Term Follow-Up CSR (28 March 2023 [primary analysis + 21-month long-term follow-up after the primary analysis])
- Final analysis CSR (21 August 2024, after study closure, the database lock date was 21 May 2024) reporting the safety and efficacy analysis for the overall study period.

Conduct of the study

Table 25. Key changes in protocol amendments-Study 1142

Amendment Number and Date	Major Changes
1 25 Sep 2017	Defined MRD cohort and added a fixed duration cohort. Study to evaluate the depth of response immediately after 15 months fixed duration of therapy, in addition to the current MRD cohort assessing discontinuation based on MRD status. Included contraception up to 90 days for women of child-bearing age post-treatment in order to align with both venetoclax and ibrutinib products' current labelling. Excluded subjects with uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura. Included updates to align language with current version of the ibrutinib IB
2 29 Nov 2018	Included collection and storage of imaging for the MRD cohort in addition to the FD cohort Included collection of BM slides for the FD cohort in addition to the MRD cohort Combined endpoints for the MRD cohort pre-randomization and randomization phases Added DOR and TLS risk reduction as secondary endpoints Updated concomitant use with CYP3A inhibitor section Included updates to align language with current version of the ibrutinib IB
3 11 Sep 2019	Extended duration of study to enable extended follow-up in the FD cohort Increased frequency of efficacy assessment visits without CT scans in FD cohort Clarified duration of therapy and duration of study for the MRD cohort Clarified timing of primary analyses for FD and MRD cohorts Clarified choice and duration of reintroduction therapy for both MRD and FD cohorts Reduced frequency of both reintroduction visits and CT scans, CT assessments in response follow-up visits Clarified response to ibrutinib reintroduction as an exploratory endpoint in the MRD and FD cohorts Added an additional MRD assessment (added Cycle 28 in FD cohort) and additional biomarker assessments

In addition, major changes in amendment 5 (02 December 2022), included extending study duration to enable longer follow-up in the FD cohort, updated recommendations intended to improve tolerability for continued ibrutinib treatment in the study protocol, and update of risks to cardiac arrhythmia section.

Important protocol deviations (IPDs)

Table 26. Important Protocol Deviations – FD Cohort (All-treated Population), Study 1142

Classification	FD Cohort All-treated N=159 n (%)
Site level	
Efficacy	4 (2.5)
Procedures/tests	2 (1.3)
Subject level	
Inclusion/exclusion	2 (1.3)
Efficacy	1 (0.6)
Safety	1 (0.6)

Site-level IPDs: for one site, CT scans were not performed at Cycle 7 for 4 subjects.

At the subject level, IPDs related to unmet eligibility criteria, efficacy, and safety were reported:

- Two subjects had IPDs related to not meeting all eligibility criteria: 1 subject was enrolled despite the need to be treated with 20 mg prednisone during the screening period to control autoimmune haemolytic anaemia, while 1 subject did not have an activated partial thromboplastin time (aPTT) coagulation test performed at screening.

- One subject had an IPD impacting efficacy: 1 subject refused to have CT scans performed at multiple timepoints.
- One subject had an IPD related to safety: on 3 separate occasions, 1 subject experienced Grade 3-4 neutropenia related to venetoclax treatment, and venetoclax was not dose-reduced or withheld per protocol requirements.

No IPDs were reported for the FD cohort with 9-months extended follow-up.

Study conduct during the COVID-19 pandemic

The visit impact of logistical restrictions included subjects of the FD and MRD cohorts with virtual visits/phone calls (37.7% and 49.4%, respectively), missed visits (14.5% and 0.6%, respectively), and in-person, partial assessments (10.7% and 9.8%, respectively. Similar findings were observed after 9-months extended follow-up (virtual visits/phone calls: 41.5% and 51.2%, respectively; missed visits: 15.1% and 0.6%, respectively; partial assessments done in person: 10.7% and 11.6%, respectively.

With regard to post-treatment follow-up by investigator, most subjects in the FD cohort (> 98%) had their required assessments for overall response, radiology, haematology, and physical examination at the 3-month time point. Complete assessments for overall response, radiology, and haematology were reported for > 90% of subjects at the 12-month timepoint, but approximately 19% of subjects missed their physical examinations per lymphatic assessment due to COVID-19-related logistical restrictions.

For the evaluation of MRD negativity rate in peripheral blood (PB) at the 12-month time point in the FD cohort, a total of 39 subjects at the primary analysis and 9 subjects with extended follow-up did not have data available at the 12-month post-treatment timepoint and were thus classified as non-evaluable. For the majority of these subjects, the data were missing as a result of COVID-19 impact.

None of the deviations due to COVID-19 logistical restrictions were considered as IPDs by the MAH.

Baseline data

Table 27. Subject Demographics – FD Cohort (All-treated Population), primary analysis, Study 1142

	FD Cohort	
	Non-del 17p N=136	**All-treated N=159**
Age (years)		
Mean (standard deviation)	57.9 (8.68)	58.0 (8.51)
Median	59.5	60.0
Min, max	33, 71	33, 71
Age groups – n (%)		
<65 years	97 (71.3)	114 (71.7)
≥65 years	39 (28.7)	45 (28.3)
Gender – n (%)		
Male	88 (64.7)	106 (66.7)
Female	48 (35.3)	53 (33.3)
Race – n (%)		
Asian	3 (2.2)	3 (1.9)
Black or African American	1 (0.7)	1 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.7)	1 (0.6)
White	124 (91.2)	147 (92.5)
Not reported	7 (5.1)	7 (4.4)
Ethnicity – n (%)		
Hispanic or Latino	3 (2.2)	5 (3.1)
Not Hispanic or Latino	128 (94.1)	149 (93.7)
Not reported	5 (3.7)	5 (3.1)

del 17p: deletion of the short arm of chromosome 17; FD: fixed duration
N=number of subjects in the specified population. n=number of subjects in each category. %=100*n/N.

Table 28. Baseline Disease Characteristics – FD Cohort (All-treated Population), primary analysis, Study 1142

	FD Cohort	
	Non-del 17p N=136	**All-treated N=159**
Time from initial diagnosis (months)		
Mean (standard deviation)	46.7 (45.03)	44.4 (43.44)
Median	37.4	33.8
Min, Max	1, 284	1, 284
Baseline ECOG score		
0	97 (71.3%)	110 (69.2%)
1	39 (28.7%)	49 (30.8%)
2	0	0
Creatinine clearance rate (mL/min)		
Mean (standard deviation)	96.0 (28.29)	95.8 (27.26)
Median	89.5	90.0
Min, Max	53, 210	53, 210
< 60	6 (4.4%)	6 (3.8%)
≥ 60	130 (95.6%)	153 (96.2%)
Histology		
CLL	125 (91.9%)	146 (91.8%)
SLL	11 (8.1%)	13 (8.2%)
Rai stage		
Stage 0/I/II	100 (73.5%)	113 (71.1%)
Stage III/IV	34 (25.0%)	44 (27.7%)
Missing	2 (1.5%)	2 (1.3%)
Bulky disease[a]		
≥5 cm	44 (32.4%)	48 (30.2%)
≥10 cm	5 (3.7%)	5 (3.1%)
Cytopenia		
Hemoglobin ≤110 g/L	30 (22.1%)	37 (23.3%)
Platelets ≤100 x 10^9/L	18 (13.2%)	21 (13.2%)
Absolute neutrophil count ≤1.5 x 10^9/L	13 (9.6%)	13 (8.2%)
Any of the above	45 (33.1%)	54 (34.0%)

CLL: chronic lymphocytic leukemia; ECOG: Eastern Cooperative Oncology Group; FD: fixed duration; SLL: small lymphocytic lymphoma
N=number of subjects in the specified population and denominator of percentages.
Baseline is defined as the last measurement taken on or prior to first dose date of study treatment.
[a] Bulky disease is based on the largest longest diameter of target lymph node at screening per investigator assessment.

Table 29. Baseline Genomic Characteristics – FD Cohort (All-treated Population), primary analysis, Study 1142

	FD Cohort	
	Non-del 17p N=136 n (%)	All Subjects N=159 n (%)
Hierarchical Cytogenetics Classification[a]		
del 17p	0	20 (12.6)
del 11q	28 (20.6)	28 (17.6)
Trisomy 12	23 (16.9)	23 (14.5)
Normal	33 (24.3)	33 (20.8)
del 13q alone	52 (38.2)	54 (34.0)
Unknown	0	1 (0.6)
TP53		
Mutated	7 (5.1)	16 (10.1)
Not mutated	129 (94.9)	142 (89.3)
Unknown	0	1 (0.6)
Del 17p or TP53 mutated		
Yes	7 (5.1)	27 (17.0)
No	129 (94.9)	129 (81.1)
Unknown	0	3 (1.9)
IGHV		
Mutated	55 (40.4)	66 (41.5)
Not mutated	78 (57.4)	89 (56.0)
Unknown	3 (2.2)	4 (2.5)
Complex Karyotype[b]		
Yes	25 (18.4)	31 (19.5)
No	90 (66.2)	102 (64.2)
Unknown	21 (15.4)	26 (16.4)

CLL: chronic lymphocytic leukemia; del 11q: deletion of the long arm of chromosome 11; del 13q: deletion in chromosome 13; del 17p: deletion of the short arm of chromosome 17; FD: fixed duration; FISH: fluorescence in situ hybridization; IGHV: immunoglobulin heavy chain variable region; TP53: tumor suppressor protein 53 (p53)
N=number of subjects in the specified population. n = number of subjects in each category. %=100*n/N.

[a] Hierarchical order of cytogenetics abnormalities in CLL (Dohner et al,2000), del 17p > del 11q > trisomy 12 > normal >del 13q.

[b] Complex karyotype is defined as the presence of ≥ 3 chromosomal abnormalities (App22).

FISH results from central lab and local lab (when central lab results not available) were used. 'Normal' refers to none of del 17p, del 11q, trisomy 12 and del 13q presented. The classification is 'Unknown' when a FISH result is missing and none of the categories are abnormal.

Numbers analysed

Efficacy analyses were performed on the All-treated population.

For the FD cohort, a total of 159 subjects were analysed for efficacy; of these subjects, 136 subjects (85.5%) did not have del 17p; 20 subjects (12.6%) had del 17p.

Outcomes and estimation

Primary endpoint: CRR per investigator

Table 30. CR and ORR by INV and IRC, FD cohort, all-treated population, Study 1142, primary analysis and 9-months extended follow-up

	Investigator Assessment				IRC Assessment			
	Primary Analysis (12 November 2020)		Extended Follow-up (04 August 2021)		Primary Analysis (12 November 2020)		Extended Follow-up (04 August 2021)	
	Non-del 17p N=136 n (%)	All-treated N=159 n (%)	Non-del 17p N=136 n (%)	All-treated N=159 n (%)	Non-del 17p N=136 n (%)	All-treated N=159 n (%)	Non-del 17p N=136 n (%)	All-treated N=159 n (%)
Complete Response Rate (CR, CRi)	76 (55.9)	88 (55.3)	79 (58.1)	91 (57.2)	83 (61.0)	95 (59.7)	87 (64.0)	99 (62.3)
95% CI[a]	47.5, 64.2	47.6, 63.1	49.8, 66.4	49.5, 64.9	52.8, 69.2	52.1, 67.4	55.9, 72.0	54.7, 69.8
Durable Complete Response Rate[c]	66 (48.5)	78 (49.1)	73 (53.7)	85 (53.5)	70 (51.5)	81 (50.9)	79 (58.1)	90 (56.6)
95% CI[a]	40.1, 56.9	41.3, 56.8	45.3, 62.1	45.7, 61.2	43.1, 59.9	43.2, 58.7	49.8, 66.4	48.9, 64.3
Overall Response Rate (CR, CRi, nPR, or PR)	130 (95.6)	153 (96.2)	130 (95.6)	153 (96.2)	130 (95.6)	153 (96.2)	130 (95.6)	153 (96.2)
95% CI[a]	92.1, 99.0	93.3, 99.2	92.1, 99.0	93.3, 99.2	92.1, 99.0	93.3, 99.2	92.1, 99.0	93.3, 99.2
Best overall response								
Complete response (CR)	74 (54.4)	83 (52.2)	79 (58.1)	88 (55.3)	81 (59.6)	92 (57.9)	86 (63.2)	97 (61.0)
Complete response with incomplete bone marrow recovery (CRi)	2 (1.5)	5 (3.1)	0	3 (1.9)	2 (1.5)	3 (1.9)	1 (0.7)	2 (1.3)
Nodular partial response (nPR)	1 (0.7)	1 (0.6)	1 (0.7)	1 (0.6)	2 (1.5)	2 (1.3)	2 (1.5)	2 (1.3)
Partial response (PR)	53 (39.0)	64 (40.3)	50 (36.8)	61 (38.4)	45 (33.1)	56 (35.2)	41 (30.1)	52 (32.7)
Stable disease (SD)	1 (0.7)	1 (0.6)	1 (0.7)	1 (0.6)	2 (1.5)	2 (1.3)	2 (1.5)	2 (1.3)
Non-progressive disease	NA	NA	NA	NA	3 (2.2)	3 (1.9)	3 (2.2)	3 (1.9)
Progressive disease	0	0	0	0	0	0	0	0
Unknown/No assessment	5 (3.7)	5 (3.1)	5 (3.7)	5 (3.1)	1 (0.7)	1 (0.6)	1 (0.7)	1 (0.6)

CI: confidence interval; CRi: complete response with incomplete bone marrow recovery; CRR: complete response rate; del 17p: deletion in the short arm of chromosome 17; FD: fixed duration; IRC: independent review committee; NA: not applicable

N=number of subjects in the specified population. n=number of subjects in each category. %=100*n/N.

[a] The 95% confidence interval for response rates based on normal approximation to the binomial distribution.

[b] One-sided P value from asymptotic test for the binomial proportion (CRR≤ 37% vs CRR > 37%).

[c] Durable complete response rate defined as proportion of subjects with duration of complete response (CR/CRi) for 1 year (12 cycles). This table is based on all response assessments performed on or prior to initiation of subsequent antineoplastic therapy or, if applicable, reintroduction of study treatment, whichever occurs earlier.

Table 31. CR and ORR by INV by Del17p/TP53, FD cohort, all-treated population, primary analysis, Study 1142

	Del17p/TP53 Status	
	Yes (N=27) n (%)	No (N=129) n (%)
Complete Response Rate (CR, CRi)	15 (55.6)	71 (55.0)
95% CI [1]	(36.8, 74.3)	(46.5, 63.6)
Durable Complete Response Rate [2]	13 (48.1)	63 (48.8)
95% CI [1]	(29.3, 67.0)	(40.2, 57.5)
Overall Response Rate (CR, CRi, nPR, or PR)	26 (96.3)	124 (96.1)
95% CI [1]	(89.2, 100.0)	(92.8, 99.5)
Best Overall Response		
CR	14 (51.9)	69 (53.5)
CRi	1 (3.7)	2 (1.6)
nPR	0	1 (0.8)
PR	11 (40.7)	52 (40.3)
SD	0	1 (0.8)
PD	0	0
No assessment	1 (3.7)	4 (3.1)

N = number of subjects in the specified population. n=number of subjects in each category. % = 100*n/N.
CR = complete response. CRi = CR with incomplete blood count recovery. nPR = nodular partial response. PR = partial response.
SD = stable disease. PD = progressive disease.
[1] 95% confidence interval based on normal approximation to the binomial distribution.
[2] Durable complete response rate was defined as the proportion of subjects with duration of complete response (CR/CRi) for 1 year (defined as at least 12 cycles).
This table is based on response assessments performed on or prior to initiation of subsequent antineoplastic therapy or, if applicable, reintroduction of study treatment, whichever occurs earlier.

Figure 8. CR by INV, subgroup analysis for FD cohort, all-treated population, primary analysis, Study 1142

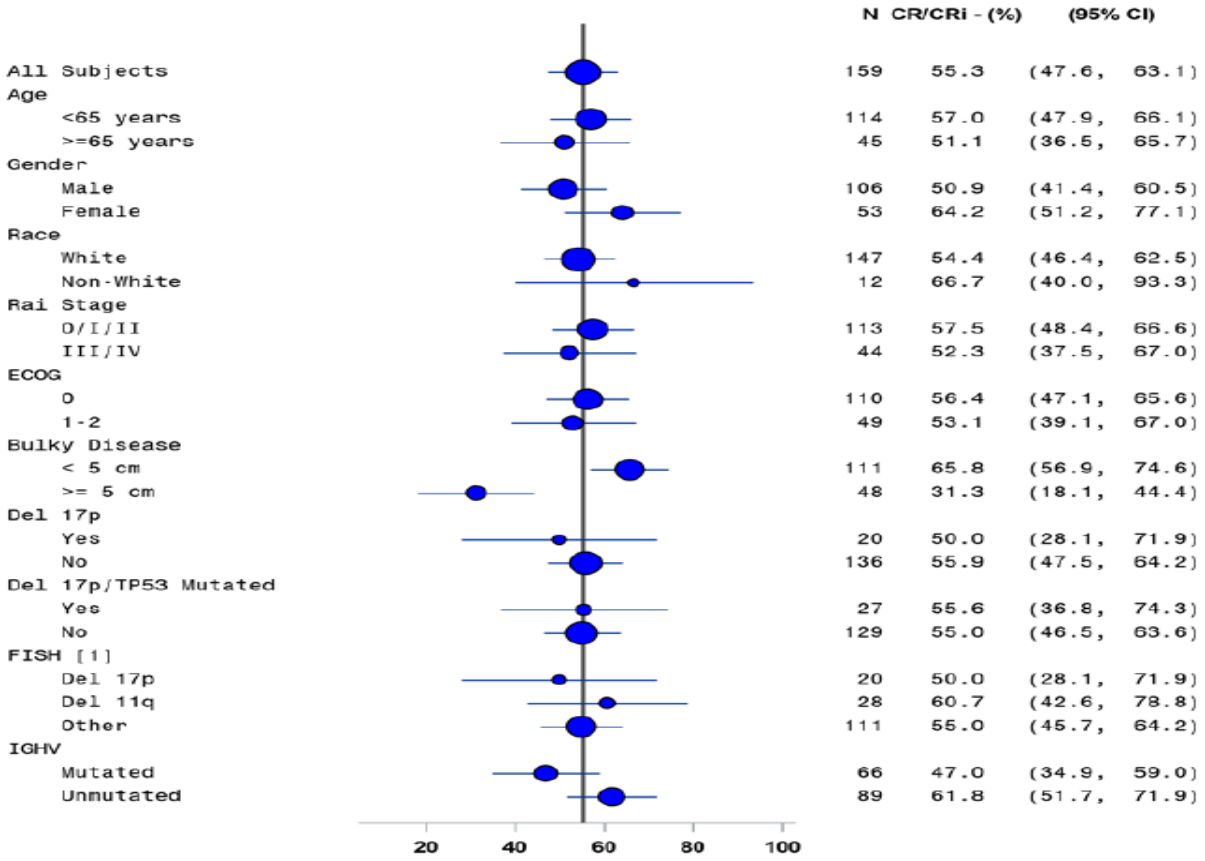
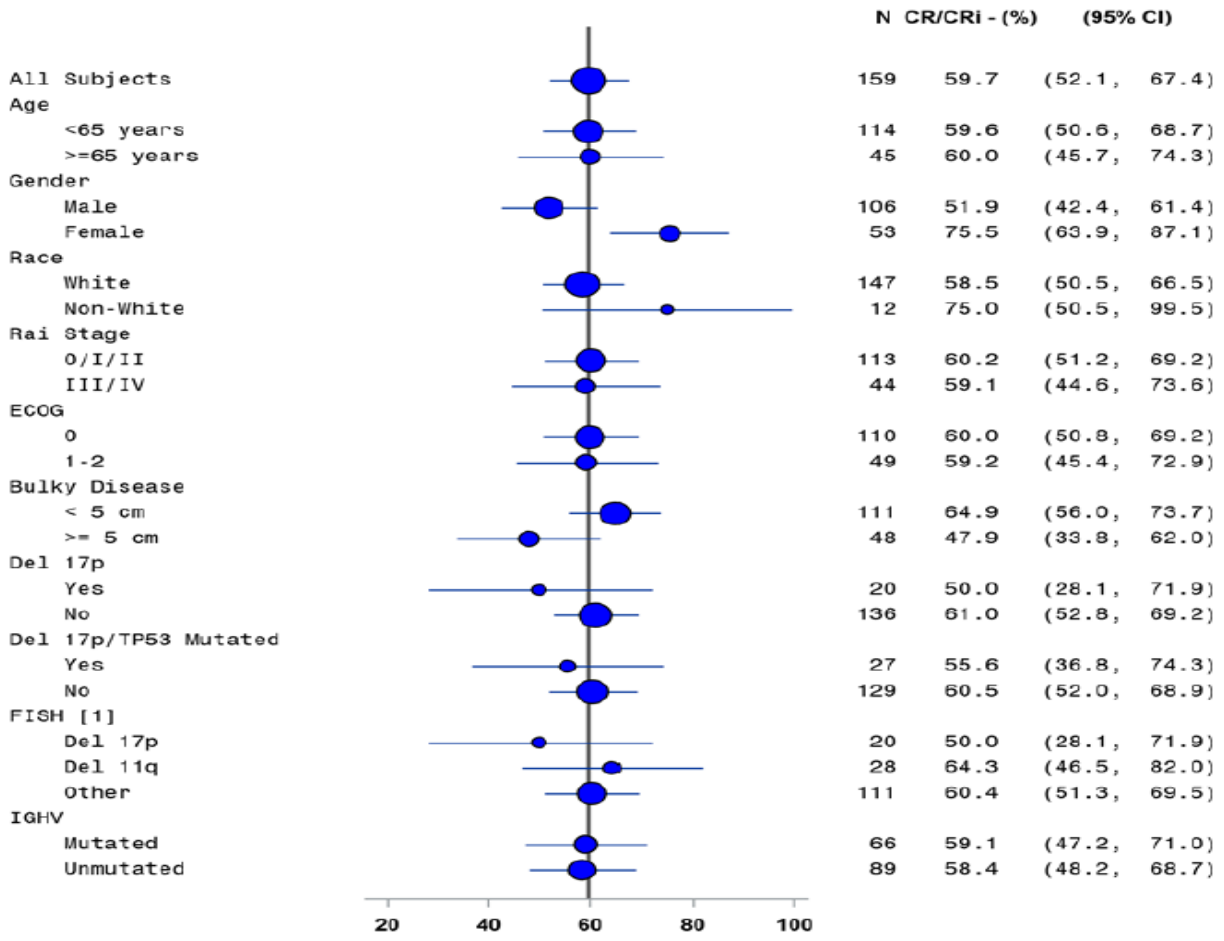


Figure 9. CR by IRC, subgroup analysis for FD cohort, all-treated population, primary analysis, Study 1142



In the final analysis, with a median follow-up of 69.0 months (database lock date was 21 May 2024), for all-treated subjects, the CR rate was 57.2% (95% CI: 49.5, 64.9), and for subjects without del 17p the CR rate was 58.1% (95% CI: 49.8, 66.4. Overall, durable CRRs (defined as the proportion of subjects with DOCR for 1 year [defined as at least 12 cycles]) were 56.6% for all-treated subjects and 57.4% for subjects without del 17p with this follow-up. In del 17p/TP53 mutated disease the CR rate 55.6% (95% CI: 36.8, 74.3) and the durable CRR was 51.9%.

Secondary endpoints

ORR

At the primary analysis, the ORR per investigator assessment as well as IRC was 96.2% for all subjects and 95.6% for subjects without del 17p. For subjects with del 17p/TP53 mutated, the ORR was 96.3% per investigator assessment as well as IRC. No change in ORR per investigator assessment was observed after 9-months extended follow-up.

DOR

At the primary analysis, the median durations of response per investigator assessment for the FD cohort were not reached for all subjects or for subjects without del 17p; the 24-month

landmark estimates were 94.7% for all subjects and 96.1% for subjects without del 17p based on an overall median follow-up of 27.9 months.
With 9-months extended follow-up, similar outcomes in DOR were observed for all subjects and subjects without del 17p (median not reached for both populations; 30-month landmark estimates of 88.6% and 89.8%, respectively) based on a median follow-up of 38.7 months.

In the final analysis, with a median follow-up duration of 69 months, the median DOR was not reached for all-treated subjects and subjects without del 17p. The K-M landmark estimate for DOR at 60 months was 60.5% for all-treated subjects and 63.6% for subjects without del 17p.

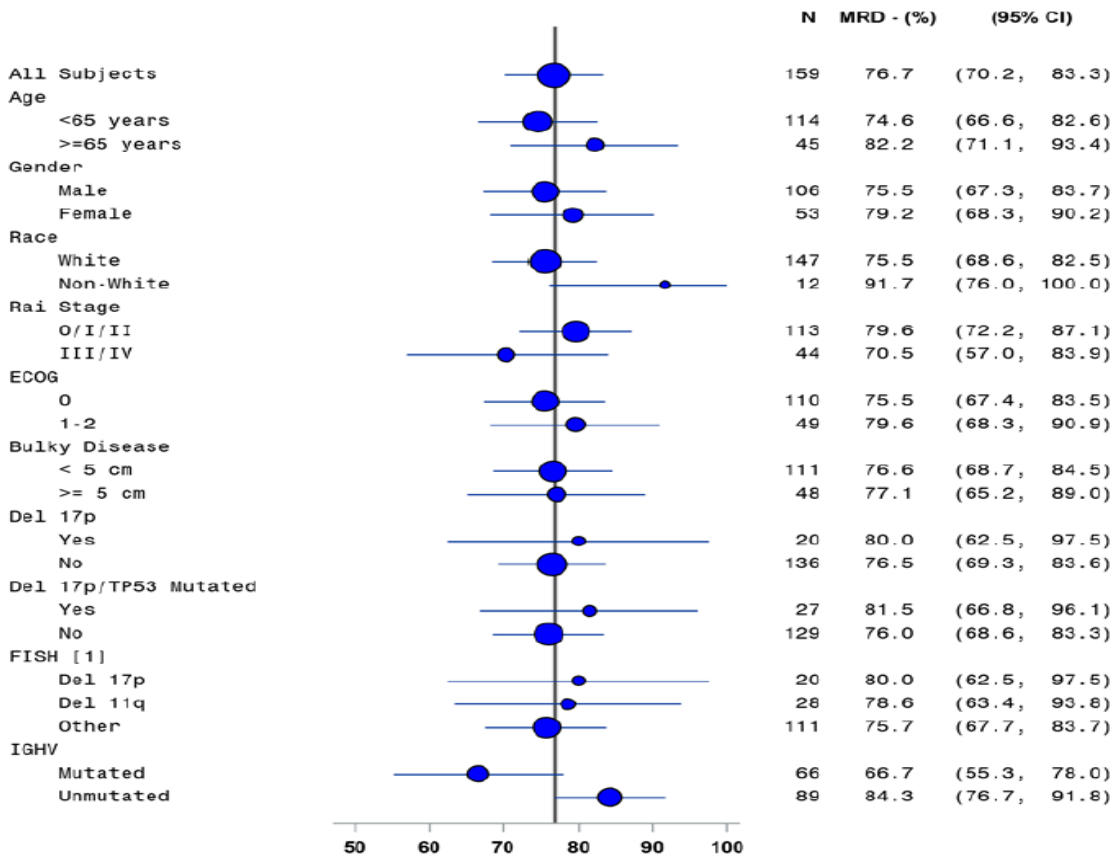
MRD-negativity rate

Table 32. MRD-negativity Rate, FD Cohort, all-treated population, primary analysis and 9-months extended follow-up, Study 1142

	Primary Analysis (12 November 2020)		Extended Follow-up (04 August 2021)	
	Non-del 17p	**All-treated**	**Non-del 17p**	**All-treated**
Overall MRD Negativity Rate	N=136	N=159	N=136	N=159
Bone marrow– n (%)	84 (61.8)	95 (59.7)	84 (61.8)	95 (59.7)
Peripheral blood – n (%)	104 (76.5)	122 (76.7)	104 (76.5)	122 (76.7)
MRD Negativity Rate 3 Months Post-Treatment[a]	N=136	N=159	N=136	N=159
Bone marrow– n (%)	74 (54.4)	83 (52.2)	74 (54.4)	83 (52.2)
Peripheral blood – n (%)	78 (57.4)	90 (56.6)	78 (57.4)	90 (56.6)
MRD Negativity Rate in Subjects with CR/CRi Based on Investigator Assessment	N=76	N=88	N=79	N=91
Bone marrow– n (%)	53 (69.7)	63 (71.6)	56 (70.9)	66 (72.5)
Peripheral blood – n (%)	67 (88.2)	79 (89.8)	70 (88.6)	82 (90.1)
MRD Negativity Rate in Subjects with CR/CRi Per Investigator 3 Months Post-Treatment[b]				
Subjects with CR/CRi - N	N=66	N=77	N=66	N=77
Bone marrow– n (%)	42 (63.6)	50 (64.9)	42 (63.6)	50 (64.9)
Peripheral blood – n (%)	43 (65.2)	51 (66.2)	43 (65.2)	51 (66.2)

BM: bone marrow; CR: complete response; CRi: complete response with incomplete bone marrow recovery; del 17p: deletion of the short arm of chromosome 17; FD: fixed duration; MRD: minimal residual disease; PB: peripheral blood
N=number of subjects in the specified population. n = number of subjects in each category. %=100*n/N.
[a] MRD assessment in BM and PB was scheduled at Cycle 19 Day 1 for the FD cohort. The first valid MRD result > 2 cycles(56 days) after the last dose date was used in this summary.
[b] The summary for 3 months post-treatment is based on overall response and MRD at first assessment > 2 cycles (56 days) after last dose and on or prior to initiation of subsequent antineoplastic therapy or, if applicable, reintroduction of study treatment, whichever occurs earlier.

Figure 10. Subgroup Analysis of MRD Negativity Rates in Peripheral Blood at Primary Analysis – FD Cohort, all-treated population, Study 1142



12 months post-treatment

At 12 months post-treatment, the MRD negativity rate in PB was 35.2% for all subjects and 34.6% for subjects without del 17p. The majority of the 39 non-evaluable subjects did not have valid MRD results due to COVID-19 impact (i.e., 18 subjects with non-evaluable samples plus 21 subjects with no sample taken within the required time window). At the 12-month time point, in an analysis based on evaluable subjects (i.e., those with valid MRD results > 11 cycles after the last dose date or had no sample taken within the time window due to PD, initiation of subsequent antineoplastic therapy, death, or study exit), the MRD negativity rate in the PB was 46.7% for all subjects and 46.1% for subjects without del 17p at the primary analysis.

With 9-months extended follow-up, the MRD negativity rate in PB at 12 months post-treatment was 42.8% in all subjects and 43.4% for subjects without del 17p. Only 9 non-evaluable subjects remained as more MRD samples had been collected. Similar MRD negativity rates were observed with extended follow-up and collection of addition of additional samples from subjects previously not evaluable due to COVID-19 compared to primary-analysis rates in the evaluable population (all subjects: 45.3%; subjects without del 17p: 45.7%).

48 months post-treatment

In the final analysis, with a median follow-up duration of 69 months, the MRD-negativity rates at 48 months post-treatment were 19.5% in the PB for all-treated subjects and 21.3% in the PB for subjects without del 17p subjects while the MRD-negativity rate for subjects with the del 17p/TP53 mutation was 7.4% in the PB.

PFS

Table 33. PFS by INV, FD Cohort, all-treated population, primary analysis and 9-months extended follow-up, Study 1142

	Primary Analysis (12 November 2020)		Extended Follow-up (04 August 2021)	
	Non-del 17p N=136	All-treated N=159	Non-del 17p N=136	All-treated N=159
Events - n (%)	16 (11.8)	20 (12.6)	23 (16.9)	28 (17.6)
PD- n	14	18	21	26
Death – n	2	2	2	2
Censored - n (%)	120 (88.2)	139 (87.4)	113 (83.1)	131 (82.4)
PFS (Months)				
Median (95% CI)[a]	NE (30.4, NE)	NE (30.4, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.8, 33.2+	0.8, 33.2+	0.8, 40.0+	0.8, 40.0+
Landmark Estimates - % (95% CI)[a]				
6 Months	99.3 (94.9, 99.9)	99.4 (95.6, 99.9)	99.3 (94.9, 99.9)	99.4 (95.6, 99.9)
12 Months	99.3 (94.9, 99.9)	99.4 (95.6, 99.9)	99.3 (94.9, 99.9)	99.4 (95.6, 99.9)
18 Months	97.0 (92.1, 98.8)	95.4 (90.7, 97.8)	97.0 (92.1, 98.8)	95.4 (90.7, 97.8)
24 Months	96.2 (91.1, 98.4)	94.8 (89.8, 97.3)	96.2 (91.1, 98.4)	94.8 (89.8, 97.3)
30 Months	80.9 (66.9, 89.4)	78.6 (64.6, 87.6)	89.9 (83.3, 94.0)	88.7 (82.5, 92.8)
36 Months	NA	NA	89.1 (82.3, 93.4)	88.1 (81.7, 92.3)

CI: confidence interval; del 17p: deletion of the short arm of chromosome 17; FD: fixed duration; NA: not applicable; NE: not estimable; PFS: progression-free survival

N=number of subjects in the specified population.

+ Indicates censored observation.

[a] Estimated by Kaplan-Meier method.

In the final analysis (CRS dated 21 August 2024, database lock date 21 May 2024) efficacy responses were evaluated by INV with a median follow-up duration of 69.0 months (range 0.8 to 73.2) in the FD cohort. The median PFS by INV for subjects with del17p/TP53 mutated was 49.7 (95% CI: 38.7, 61.7) months and was not reached for all subjects or for subjects without del17p. The Kaplan-Meier PFS rate estimates per INV at 66 months was 60.2% for all subjects and 63.2% for subjects without del 17p.

OS

At the primary analysis, the median OS for the FD cohort was not reached for all subjects or for subjects without del 17p based on an overall median follow-up of 27.9 months. A total of 3 deaths were reported (2 deaths due to cardiac events [including 1 death due treatment-emergent sudden death] and 1 death due to intracranial haemorrhage), with all the deaths occurring in subjects without del 17p. The Kaplan-Meier point estimates at 24 months were 98.1% for all subjects and 97.7% for non-del 17p subjects. For subjects with del 17p/TP53 mutated, the median OS was not reached, and the Kaplan-Meier point estimate at 24 months was 96.2%.

Analysis of OS with 9-months extended follow-up (overall median follow-up: 38.7 months) indicated no change in the findings observed at the primary analysis for all subjects and subjects without del 17p as well as for subjects with del 17p/TP53 mutated with no additional deaths reported.

In the final analysis, with a 69-month median follow-up, the K-M point estimate for OS at 66 months was > 95% for all-treated subjects and the subjects without del 17p. The median OS was also not reached for subjects with del 17p/TP53 and the K-M point estimate of OS rate at 66 months for these subjects was 88.1%.

TLS risk reduction

Table 34. TLS Risk at Baseline and after 3-Cycle Ibrutinib, primary analysis, Study 1142

TLS Risk	Baseline n (%)	After Ibrutinib Lead-in n (%)
High	34 (21.4)	1 (0.6)
LDi ≥ 10 cm	4 (2.5)	0
LDi ≥ 5 cm and ALC ≥ 25 x 10^9/L	30 (18.9)	1 (0.6)
Medium	97 (61.0)	106 (66.7)
Low	28 (17.6)	46 (28.9)
Missing	0	6 (3.8)

ALC: absolute lymphocyte count; LDi: the largest diameter of target lymph nodes. FD: fixed duration; TLS: tumor lysis syndrome

N=number of subjects in the specified population. n=number of subjects in each category. %=100*n/N.

TLS risk was assessed by investigator per criteria specified on App1, Protocol Amendment 3, Appendix H. Analysis include TLS risk at baseline and the last post-baseline value on or prior to the venetoclax first dose date (Cycle 4 Day 1) or, for subjects never received venetoclax, the post-baseline value closest to the scheduled Cycle 4 Day 1, ie, 84 days after the first dose date of ibrutinib.

At baseline, hospitalisation indicated per the VENCLEXTA USPI, 2020 and VENCLYXTO® SmPC, 2020 (based upon TLS risk and creatinine clearance) was observed for 39.6% of subjects and 17.6% of subjects after 3 cycles of single-agent ibrutinib lead-in therapy. For all subjects, 54.0% of subjects indicated for hospitalization due to TLS risk at baseline were no longer indicated for hospitalization after the 3-cycle ibrutinib lead-in.

Ancillary analyses

Rate of sustained haemoglobin improvement

At the primary analysis, the proportion of subjects achieving a sustained improvement in haemoglobin was 41.5% for all subjects in the FD Cohort. For those subjects with anaemia at baseline, the proportion of subjects achieving a sustained improvement in haemoglobin was 86.5%. Similar trends were observed after 9-months extended follow-up (i.e., sustained improvement in haemoglobin observed for 45.9% of all subjects and 91.9% of subjects with baseline anaemia.

Rate of sustained platelet improvement

At the primary analysis, the proportion of subjects achieving a sustained improvement in platelet count was 17.6% for all subjects in the FD Cohort. For those subjects with thrombocytopenia at baseline, the proportion of subjects achieving a sustained improvement in platelet count was 57.1%. Similar trends were observed after 9-months extended follow-up (ie, sustained improvement in platelet count observed for 19.5% of all subjects and 61.9% of subjects with baseline thrombocytopenia).

Summary of main studies

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 35. Summary of Efficacy for trials, CLL3011 and 1142 FD Cohort, primary analyses

	Study CLL3011				Study 1142 FD Cohort	
	Ibr+Ven N=106		Clb+Ob N=105		Ibr+Ven N=159	
Median time on study (months)	27.7		27.9		27.9	
Median PFS by IRC (months)	**NE**		**21.0**		**NE**	
Min, Max	0.03+, 32.7+		2.6, 31.5+		0.8, 33.2+	
24-mo landmark estimate (%)	84.4		44.1		88.9	
p-value	<0.0001				NA	
HR (95% CI)	0.216 (0.131, 0.357)				NA	
MRD						
Overall MRD negativity rate (%)	***BM***	***PB***	***BM***	***PB***	***BM***	***PB***
NGS	55.7	59.4	21.0	40.0	Not applicable	
Flow cytometry	67.9	80.2	22.9	46.7	59.7	76.7
MRD negativity, 3 mo post- treatment	***BM***	***PB***	***BM***	***PB***	***BM***	***PB***
NGS	51.9	54.7	17.1	39.0	NA	NA
Flow cytometry	56.6	61.3	16.2	41.0	52.2	56.6
MRD negativity, 12 mo post-treatment	***BM***	***PB***	***BM***	***PB***	***BM***	***PB***
NGS	-	49.1	-	12.4	Not applicable	
Flow cytometry	-	54.7	-	16.2	-	42.8 [a]
ORR (CR, CRi, nPR, PR)	86.8		84.8		96.2	
95% CI	80.3, 93.2		77.9, 91.6		93.3, 99.2	
Rate ratio (95% CI)	1.02 (0.92, 1.14)				NA	
p-value	0.6991				NA	
CR rate	38.7		11.4		59.7	
95% CI	29.4, 48.0		5.3, 17.5		52.1, 67.4	
Rate ratio (95% CI)	3.43 (1.91, 6.15)				NA	
p-value	<0.0001				NA	
OS						
Median OS (months)	NE		32.5		NE	
24-mo landmark estimate (%)	90.4		91.3		98.1	
p-value	0.9121				NA	
HR (95% CI)	1.048 (0.454, 2.419)				NA	
Extended follow-up: 30-mo landmark estimate (%)	89.4		88.4		98.1	
p-value	0.4837				NA	
HR (95% CI)	0.760 (0.352, 1.642)				NA	

Analysis performed across trials

Persistence of efficacy and/or tolerance effects

- **PFS rates were maintained after treatment completion**

In **Study CLL3011**, with a median follow-up of 27.7 months at the primary analysis, PFS was significantly improved with FD Ibr+Ven compared with Clb+Ob (HR: 0.216; 95% CI: 0.131, 0.357; p<0.0001). Kaplan-Meier PFS rate estimates per IRC at 24 months (ie 10 months after treatment completion of Ibr+Ven and Clb+Ob) were 84.4% for the Ibr+Ven arm and 44.1% for the Clb+Ob arm.

With 6-month extended follow up (median follow-up of 34.1 months), the improvement in PFS for Ibr+Ven was maintained with a HR of 0.212 (95% CI: 0.129, 0.349). The median PFS was not reached for the Ibr+Ven arm and was 23.7 months for the Clb+Ob arm. The Kaplan-Meier PFS rate estimate at 30 months was 80.5% for the Ibr+Ven arm and 35.8% for the Clb+Ob arm, demonstrating persistence of Ibr+Ven of PFS benefit at least 15 months after the end of treatment with Ibr+Ven.

Please refer to section Outcomes and estimation for study CLL3011 for PFS analyses with 36-month extended follow-up from the primary analysis, with median time on study for all subjects of 64 months.

Results from **Study 1142** corroborate these observations with a Kaplan-Meier PFS rate estimate per IRC at 24 months of 88.9% for all subjects and 90.8% for subjects without del17p at a median follow-up of 27.9 months at the primary analysis.

With 9-months extended follow-up (median follow-up of 38.7 months), Kaplan-Meier PFS rate estimates per IRC at 36 months (22 months post-treatment) were 85.5% for all subjects and 86.0%, for subjects without del17p.

Please refer to section Outcomes and estimation for study 1142 for PFS analyses with median follow-up duration of 69.0 months.

- **MRD Negativity Rates Sustained from 3 to 12 Months Post-treatment**

The MRD negativity rates at 3 months post-treatment as assessed by NGS in **Study CLL3011** were substantially higher with Ibr+Ven arm versus Clb+Ob in both the BM (51.9% vs 17.1%; respectively) and PB (54.7% vs 39.0%; respectively).

At 12 months post-treatment, the MRD negativity rates in PB in the Ibr+Ven arm and the Clb+Ob arms were 49.1% vs 12.4%, respectively. Similar sustained results for Ibr+Ven were observed by flow cytometry with MRD negativity rates of 61.3% for Ibr+Ven and 41.0% for Clb+Ob in PB at 3 months post-treatment and 54.7% for Ibr+Ven and 16.2% for Clb+Ob at 12 months post-treatment. These data indicate that the MRD negativity was sustained with Ibr+Ven throughout the first year after treatment completion while substantially decreased for subjects in the Clb+Ob arm.

In the FD cohort of **Study 1142**, at 3 months post-treatment, the MRD negativity rates were 52.2% in the BM and 56.6% in the PB. With 9-months extended follow-up and the collection of additional samples, the MRD negativity rate in the PB at 12-months post treatment was 42.8% (9 subjects still had missing samples primarily due to the COVID-19 pandemic).

Please refer to section Outcomes and estimation for study 1142 for MRD analyses with median follow-up duration of 69.0 months.

- **Duration of CR after treatment is completed**

In **Study CLL3011** at the primary analysis, FD Ibr+Ven resulted in significantly higher CR rates (CR or CRi) per IRC assessment compared with Clb+Ob (38.7% vs. 11.4%, respectively; p<0.0001). The 12-month landmark estimate for IRC-assessed duration of CR was 100% in the Ibr+Ven arm and 91.7% in the Clb+Ob arm. At 6 month extended follow-up, the 18-month landmark estimates for IRC-assessed duration of CR were 97.5% in the Ibr+Ven arm and 84.6% in the Clb+Ob arm.

Similar results were observed for the FD cohort in **Study 1142.** At the primary analysis, the CR rate per IRC assessment for all subjects was 59.7% (95% CI: 52.1, 67.4) and 61.0% (95% CI: 52.8, 69.2) for subjects without del17p. With a median follow-up of 27.9 months, the 18-month landmark estimates were 95.2% for all subjects and 95.7% without del17p. With 9 month extended follow-up (median: 38.7 months), the 30-month landmark estimates were 83.0% for all subjects and 81.6%, for subjects without del17.

2.6. Discussion on clinical efficacy

Venetoclax and ibrutinib have two distinct and complementary mechanisms of action on B-cells (pro-apoptosis through BCL-2 inhibition, and inhibition of proliferation through BTK inhibition). The appropriateness of this combination and the contribution of each agent have previously been found acceptable based on preclinical proof of concept and descriptive clinical data. The combination use of products with these mechanisms of actions for the treatment of first line CLL has previously been accepted for Imbruvica and Calquence (see the respective SmPC's).

Design and conduct of clinical studies

To support an unrestricted indication of fixed duration (FD) ibr+ven in previously untreated CLL, the outcomes of 2 main studies were reported:

- The randomised open study CLL3011 (GLOW) comparing FD ibr+ven (n=106) with clb+obi (n=105) in subjects ≥65 years of age or younger with comorbidities, excluding del17p/TP53 mutated disease. The primary outcome was IRC-assessed PFS.
- The FD cohort of study 1142 (CAPTIVATE), a SAT investigating FD ibr+ven in fit patients (n=159 whereof 27 with del17p/TP53 mutated disease). The primary endpoint was investigator-assessed CRR.

Regarding **CLL3011 study**, the study entry criteria define a population appropriate for treatment with the control regimen. Venetoclax, chlorambucil and obinutuzumab were administrated according to the EU label in untreated disease.

The statistical methods are generally considered acceptable. The assumption that all types of censoring are considered non-informative might be disputable. However, as further discussed below, censoring due to other reasons than study cut off were rare in the primary analysis.

The primary estimand had a treatment policy strategy for handling the intercurrent events of treatment discontinuation, use of subsequent anti-cancer therapy and a composite variable strategy is adopted for handling the intercurrent events of pre-PD death (PFS event) due to COVID-19. This is considered appropriate. Supplementary analyses with hypothetical strategies for subsequent anti-cancer therapy and death due to Covid-19 were provided.

Multiplicity was controlled using a serial gatekeeping procedure, which is acceptable. No interim analysis was performed. The primary estimator is stratified on the randomisation stratification variables, which is supported.

The amendments and changes to protocol-specified analyses are not considered to challenge the integrity of the study, and numbers of subjects with major protocol deviations were similar in the study arms and deemed unlikely to have a major impact on study outcomes. The potential impact of the COVID-19-related missed/delayed DE visits on study integrity and outcomes is difficult to dissect but with the large effect size noted with the primary analysis it is deemed unlikely that these have substantially altered the outcome estimations.

Regarding FD cohort of the **1142 study**, enrolment criteria are acceptable. Previously untreated subjects 18-70 years old with CLL/SLL in ECOG PS 0-2 with or without del 17p or TP53 mutation were recruited. The treatment was identical to the experimental regimen in study 3011.

The amendments to the study protocol are not considered to challenge the integrity of the study. At confirmed PD, ibrutinib monotherapy or, if >2 years since completion of study therapy, ibrutinib+venetoclax for 15 cycles FD could be (re)introduced.

Efficacy data and additional analyses

Study CLL3011 (GLOW)

In the control arm, 6 cycles of treatment were received, corresponding to ≈168 days or a little less than 6 months. In the experimental arm, ibrutinib was administrated for a total of 15 cycles (15x28=420 days, corresponding to approximately 14 months) and venetoclax was introduced after 3 cycles of ibrutinib monotherapy as an attempt to reduce frequency/severity of tumour lysis syndrome (TLS). This means that a SOC treatment of ≈6 months duration is compared to an experimental regimen of ≈14 months duration.

The primary analysis was event-driven, planned after 71 observed events, and based on a cut-off on 26 February 2021 with a median follow-up of ~28 months. An analysis with 6-months extended follow-up (cut-off 19 August 2021 with a median follow-up of ~34 months) was also included with the primary analysis in the CSR 54179060CLL3011 dated 12 November 2021.

The experimental regimen was statistically superior over control in terms of PFS, HR=0.216 (95% CI: 0.131, 0.357); p<0.0001, at the primary analysis by IRC, with an event rate of 64% for the control arm, and supported by presented alternative analyses, and a generally consistent treatment effect is noted in the predefined subgroups. By an additional follow-up of 6 months, the outcome remained stable.

At the time of the 36-months extended follow-up, with a median time on study was 64 months (range: 1.7 to 69.7), the PFS by INV showed a continued benefit with fixed duration ibrutinib plus venetoclax vs. chlorambucil plus obinutuzumab (HR: 0.267; 95% confidence interval [CI]: 0.182, 0.393), nominal p<0.0001, not type 1 error controlled. The median PFS was 65.38 months for Ven + Ibr and 23.00 months for chemoimmunotherapy; median PFS for Ven + Ibr could not be reliably determined as only 2 subjects were at risk at 66 months. PFS estimate rates at 60 months were 59.9% for the Ibr+Ven arm and 17.8% for the Clb+Ob arm, demonstrating further persistence of Ibr+Ven of PFS benefit.

Best MRD response in bone marrow (assessed by NGS) showed a response rate of 55.7% in the experimental arm and 21.0% in the control arm, rate ratio 2.65 (95% CI: 1.75, 3.99); p<0.0001.

The CR (CR and CRi) rate was significantly higher in the experimental arm, 38.7% vs 11.4% in the control arm; rate ratio 3.43 (95% CI: 1.91, 6.15); p<0.0001.

At the August 2021 cut-off (median follow-up 34.1 months), the HR for OS was 0.760 (0.352, 1.642).

Based on a data cut-off of 24 February 2024 for Study CLL3011, with a median time on study of 64.0 months and a maturity of 38 % in the control arm and 19 % in the experimental arm, the HR for OS was estimated at 0.462 (95% CI: 0.269, 0.791), nominal p=0.0039, not type 1 error controlled. Thus, with 30 months further follow-up after the August 2021 cut-off, the positive trend favouring the experimental treatment is maintained in this updated analysis and no longer-term detrimental effect on OS is noted.

FD cohort of study 1142 (CAPTIVATE)

The primary analysis was planned when the last enrolled subject had the opportunity to be followed for at least 30 cycles (15 cycles of treatment + 15 cycles of posttreatment follow-up) and based on a data extract on 12 November 2020, with a median follow-up of ~28 months. An analysis with 9-months extended follow-up was also provided, cut-off 4 August 2021 with a median follow-up of ~39 months, in the Primary analysis CSR.

At the primary analysis, the CRR per investigator for all subjects in the FD cohort was 55.3% (95%CI: 47.6, 63.1) and 55.9% (95% CI: 47.5, 64.2) for subjects without del 17p. The CR rate for subjects without del 17p was significantly higher than the study-assumed minimum rate of 37% (1-sided p-value < 0.0001) as well as the 40% rate achieved in this population with FCR. CRR in del 17p/TP53 mutated disease (n=27) was similar to the complement, 56%. With 9 month extended follow-up, CRR was 58% per investigator and 64% per IRC in the non-del17 population.

At the primary analysis, the median DOR per investigator assessment was not reached for all subjects or for subjects without del 17p. In the final analysis, with a median follow-up duration of 69 months, the median DOR was still not reached for all-treated subjects and subjects without del 17p.

At the primary analysis, with MRD assessed by flow cytometry in the all-treated population, the overall negativity rate was 60% in BM and 77% in PB. In the final analysis, the MRD-negativity rates at 48 months post-treatment were 19.5% in the PB for all-treated subjects and 21.3% in the PB for subjects without del 17p subjects while the MRD-negativity rate for subjects with the del 17p/TP53 mutation was 7.4% in the PB.

2.6.1. Conclusions on the clinical efficacy

The broad indication sought in previously untreated CLL is from an efficacy perspective considered supported by sufficiently robust data.

2.7. Clinical safety

Introduction

The safety data in support of this application is derived from 2 studies:

- Study CLL3011 a Phase 3, randomised, open-label, multicentre, efficacy and safety study of Ibr+Ven versus Clb+Ob in subjects with treatment-naïve CLL/SLL without del17p or known TP53 mutation.
- Study 1142 a Phase 2, multicentre, efficacy and safety study assessing Ibr+Ven in subjects with treatment-naïve CLL/SLL (with or without del17p/TP53 mutation) in a FD treatment cohort (FD cohort) and an MRD-guided treatment discontinuation cohort (MRD cohort) that included a pre-randomisation and randomisation phase. In the pre-randomization phase of the MRD cohort, subjects received ibrutinib and venetoclax as described above for the FD cohort plus an additional cycle of Ibr+Ven (Cycle 16) before proceeding with randomisation and further

treatment. Safety data from the FD cohort were pooled with safety data from the pre-randomization phase of the MRD cohort with 16 cycles of treatment, as these treatments and TEAE collection periods were similar.

Safety data are presented based on the primary analysis data cut-off date for each study (Study CLL3011: 26 February 2021; Study 1142: 12 November 2020).

Patient exposure

In Study CLL3011 and in the FD cohort of Study 1142, single-agent ibrutinib 420 mg/day was administered for 3 cycles followed by TLS risk assessment and subsequent Ibr+Ven combination treatment for 12 cycles (with a 5 week venetoclax dose titration to 400 mg/day once daily as described in the Venclyxto SmPC), using the approved doses of both medicinal products for subjects with previously untreated CLL/SLL (Imbruvica SmPC; Venclyxto SmPC). In the pre-randomization phase of the MRD cohort of Study 1142, this was followed by 1 cycle (Cycle 16) of Ibr+Ven, during which MRD status was assessed and confirmed prior to the randomization phase of the MRD cohort. In study CLL3011, subjects randomly assigned to Clb+Ob treatment received 6 cycles (28 days/cycle) of treatment in the absence of PD or treatment-limiting toxicity.

Patient exposure in the safety population on the two studies is summarised in **Table 33**

Table 36. Patient exposure in Studies CLL3011 and 1142

	Study CLL3011				**Study 1142**	
	Ven + Ibr N = 106 Safety Analysis Set		**Clb + Ob N = 105 Safety Analysis Set**		**FD + MRD (First 16 Cycles) Cohorts N = 323 All Treated Population**	
	Ibrutinib	**Venetoclax**	**Chlorambucil**	**Obinutuzumab**	**Ibrutinib**	**Venetoclax**
Treatment duration in months[a]						
n	106	98	105	105	323	312
Mean (SD)	11.89 (3.845)	10.21 (2.319)	5.05 (0.909)	4.68 (0.902)	13.8 (2.78)	11.4 (1.38)
Median	13.80	11.04	5.09	4.67	14.1	11.5
Range	(0.7, 14.7)	(0.9, 11.8)	(0.0, 7.9)	(0.0, 7.5)	(0.5, 24.9)	(0.8, 22.1)
< 3 Months	9 (8.5%)	3 (2.8%)	6 (5.7%)	5 (4.8%)	11 (3.4%)	3 (0.9%)
3 - < 6 Months	3 (2.8%)	5 (4.7%)	94 (89.5%)	97 (92.4%)	6 (1.9%)	1 (0.3%)
6 - < 12 Months	17 (16.0%)	90 (84.9%)	5 (4.8%)	3 (2.9%)	0	268 (83.0%)
12 - < 15 Months	77 (72.6%)	0	0	0	290 (89.8%)	39 (12.1%)

	Study CLL3011				Study 1142		
	Ven + Ibr N = 106 Safety Analysis Set Clb + Ob N = 105 Safety Analysis Set				FD + MRD (First 16 Cycles) Cohorts N = 323 All Treated Population		
	Ibrutinib	Venetoclax	Chlorambucil	Obinutuzumab	Ibrutinib		Venetoclax
≥ 15 Months	-	-		-	-	16 (5.0%)	1 (0.3%)
Cumulative dose received							
n	106	98		105	105	323	312
Mean (SD)	140235.1 (51658.13) mg	107582.1 (31098.60) mg		415.9 (124.20) mg	7725.0 (1211.17) mg	167.7 (36.62) g	123.0 (21.78) g
Median	170520.0 mg	123790.0 mg		408.0 mg	8000.0 mg	176.4 g	126.2 g
Range	(6300; 185220 mg)	(80; 128290 mg)		(42, 824 mg)	(2, 8001 mg)	(4.6, 257.9 g)	(1.8, 143.4 g)
Average daily dose (mg)[b]							
n	106	98		105	105	323	312
Mean (SD)	382.326 (58.8750)	336.730 (69.6665)		0.473 (0.0559)	978.774 (137.3082)	398.8 (40.36)	351.8 (53.00)
Median	410.190	365.470		0.500	1000.000	415.0	373.0
Range	(143.71, 420.00)	(3.08, 375.43)		(0.30, 0.54)	(2.00, 1000.08)	(162.6, 420.3)	(73.5, 377.3)
Relative dose intensity (%)[c]							
n	106	98	105	105	323		312
Mean (SD)	91.0 (14.02)	89.9 (18.61)	94.6 (11.19)	97.9 (13.73)	95.0 (9.61)		93.7 (14.11)
Median	97.7	97.6	100.0	100.0	98.8		99.4
Range	(34, 100)	(1, 100)	(59, 108)	(0, 100)	(38.7, 100.1)		(19.6, 100.3)

*N = number of subjects in the specified population; % = 100*n/N*

a. Treatment duration in months is calculated as (last dose date of study drug - first dose date of study drug + 1)/30.4375.

b. ***Study 3011****: for ibrutinib and venetoclax, average dose level per administration is calculated by total received dose/treatment duration (day). For chlorambucil and obinutuzumab, average dose level per administration is calculated by total received dose/total dosing days within treatment duration. Missed or withheld doses were considered as administered as Dose 0. For obinutuzumab, the doses at Days 1 + 2 of Cycle 1 were considered as one administration. The units are: mg for ibrutinib, venetoclax, obinutuzumab, and mg/kg for chlorambucil.* ***Study 1142****: Average daily dose calculated by total received dose / treatment duration (day). Missed or withheld doses were counted as Dose 0.*

c. *Calculated by average dose level per administration/planned dose intensity for Study CLL3011 and by average daily dose/average daily dose per protocol for Study 1142.*

Demographic and Other Characteristics of Study Population

For demographics and baseline characteristics, refer to **Table 5** (study CLL3011), **Table 24**, **Table 25** and **Table 26** (study 1142).

Adverse events

Study CLL3011 safety data presented in the following sections focus on the primary analysis of the safety population (Safety analysis set, N = 106 in the Ven + Ibr arm and N = 105 in the Clb + Ob arm) who received at least 1 dose of any study drug. At primary analysis, all subjects in the Ven + Ibr arm were off treatment and were post the treatment-emergent period; no changes in TEAEs were noted for the Ven + Ibr arm after the primary analysis.

Study 1142 safety data presented in the following sections focus on the primary analysis of the safety evaluable subjects (All-treated population, N = 323) in the pooled FD cohort + first 16 cycles of the MRD cohort. As all subjects in the FD cohort were already off treatment and all subjects in the MRD cohort completed the first 16 cycles of treatment at the time of the primary analysis for the FD cohort, limited updates were noted for the pooled FD cohort + first 16 cycles of the MRD cohort after the primary analysis. Treatment emergent adverse events in Studies CLL3011 and 1142 are summarised in **Table 34**

Table 37. Overall summary of TEAEs in Studies CLL3011 and 1142

	Study CLL3011		Study 1142
	Ven + Ibr N = 106 Safety Analysis Set n (%)	**Clb + Ob N = 105 Safety Analysis Set n (%)**	**FD + MRD (First 16 Cycles) Cohorts N = 323 All-treated Population n (%)**
Subjects with 1 or more AEs	105 (99.1)	99 (94.3)	322 (99.7)
Grade ≥ 3 AEs	80 (75.5)	73 (69.5)	209 (64.7)
Individual drug related AEs[a,b]	83 (78.3)/72 (67.9)	83 (79.0)/94 (89.5)	296 (91.6)/265 (82.0)
AEs leading to death[c]	7 (6.6)	2 (1.9)	1 (0.3)
Serious AEs	49 (46.2)	29 (27.6)	70 (21.7)
Related serious AEs[a]	26 (24.5)	20 (19.0)	39 (12.1)
Individual drug related serious AEs[b]	23 (21.7)/14 (13.2)	13 (12.4)/16 (15.2)	32 (9.9)/21 (6.5)
AEs leading to discontinuation of any study agent	22 (20.8)	8 (7.6)	21 (6.5)
Individual drug discontinuation[b]	21 (19.8)/12 (11.3)	6 (5.7)/4 (3.8)	19 (5.9)/9 (2.8)
AEs leading to dose reduction of any study agent	28 (26.4)	22 (21.0)	66 (20.4)
Individual drug dose reduction[b]	19 (17.9)/18 (17.0)	22 (21.0)/0	39 (12.1)/40 (12.4)

N = number of subjects in the specified population; n = number of subjects with the specified event; % = 100*n/N

a. An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to either study agent.

b. For Ven + Ibr arm, the numbers and percentages are displayed for Ibr and Ven respectively; for Clb + Ob arm, the numbers and percentages are displayed for Clb and Ob respectively.

c. AEs leading to death are based on AE outcome of Fatal.

Common TEAEs

Study CLL3011

In the Ven + Ibr arm, TEAEs occurred in 99.1% of subjects; the most frequently occurring TEAEs (≥ 20% of subjects) were diarrhoea (50.9%), neutropenia (34.0%), and nausea (26.4%). In the Clb + Ob arm, TEAEs occurred in 94.3% of subjects; the most frequently occurring TEAEs (≥ 20% of subjects) were neutropenia (53.3%), infusion related reaction (29.5%), thrombocytopenia (26.7%), and nausea (25.7%) (**Table 35**).

Table 38. Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study 3011

System Organ Class **Preferred Term**	**Ven + Ibr** **N = 106** **n (%)**	**Clb + Ob** **N = 105** **n (%)**
Subjects with 1 or more AEs	105 (99.1)	99 (94.3)
Gastrointestinal disorders	71 (67.0)	43 (41.0)
Diarrhoea	54 (50.9)	13 (12.4)
Nausea	28 (26.4)	27 (25.7)
Vomiting	15 (14.2)	14 (13.3)
Constipation	11 (10.4)	7 (6.7)
Infections and infestations	64 (60.4)	51 (48.6)
Urinary tract infection	17 (16.0)	5 (4.8)
Upper respiratory tract infection	13 (12.3)	14 (13.3)
Pneumonia	11 (10.4)	10 (9.5)
Blood and lymphatic system disorders	56 (52.8)	72 (68.6)
Neutropenia	36 (34.0)	56 (53.3)
Anaemia	19 (17.9)	19 (18.1)
Thrombocytopenia	12 (11.3)	28 (26.7)
Skin and subcutaneous tissue disorders	52 (49.1)	27 (25.7)
Rash	18 (17.0)	7 (6.7)
Metabolism and nutrition disorders	45 (42.5)	25 (23.8)
Decreased appetite	14 (13.2)	6 (5.7)
Hyperphosphataemia	11 (10.4)	0
General disorders and administration site conditions	42 (39.6)	44 (41.9)
Oedema peripheral	16 (15.1)	3 (2.9)
Fatigue	16 (15.1)	10 (9.5)
Pyrexia	7 (6.6)	20 (19.0)
Chills	2 (1.9)	12 (11.4)
Respiratory, thoracic and mediastinal disorders	38 (35.8)	30 (28.6)
Epistaxis	12 (11.3)	3 (2.9)
Cough	9 (8.5)	11 (10.5)
Investigations	36 (34.0)	27 (25.7)
Neutrophil count decreased	11 (10.4)	9 (8.6)
Musculoskeletal and connective tissue disorders	36 (34.0)	27 (25.7)
Arthralgia	12 (11.3)	7 (6.7)
Vascular disorders	27 (25.5)	24 (22.9)
Hypertension	14 (13.2)	5 (4.8)
Cardiac disorders	26 (24.5)	14 (13.3)
Atrial fibrillation	15 (14.2)	2 (1.9)
Injury, poisoning and procedural complications	25 (23.6)	36 (34.3)

System Organ Class Preferred Term	Ven + Ibr N = 106 n (%)	Clb + Ob N = 105 n (%)
Infusion related reaction	0	31 (29.5)

Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

Adverse events are presented by decreasing frequency of system organ class and preferred term within the Ven + Ibr column; those with the same frequency are presented alphabetically.

Adverse events are coded using MedDRA Version 23.0.

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, TEAEs occurred in 99.7% of subjects. The most frequently occurring TEAEs (≥ 20% of subjects) were diarrhoea (66.6%), nausea (44.0%), neutropenia (42.1%), arthralgia (33.7%), headache (26.6%), upper respiratory tract infection, fatigue (26.3% each), muscle spasms (24.5%), vomiting, and increased tendency to bruise (21.7% each) (**Table 36**).

Table 39. TEAEs by SOC and PT Reported for ≥ 10% of Subjects in FD Cohort* + First 16 Cycles of MRD Cohort of Study 1142 (All-treated Population)

System Organ Class Preferred Term	FD + MRD (First 16 Cycles) Cohorts N = 323 n (%)
Subjects with any TEAE	322 (99.7)
Blood and lymphatic disorders	202 (62.5)
Neutropenia	136 (42.1)
Increased tendency to bruise	70 (21.7)
Thrombocytopenia	51 (15.8)
Cardiac disorders	70 (21.7)
Palpitations	36 (11.1)
Gastrointestinal disorders	289 (89.5)
Diarrhoea	215 (66.6)
Nausea	142 (44.0)
Vomiting	70 (21.7)
Dyspepsia	57 (17.6)
Constipation	52 (16.1)
Stomatitis	45 (13.9)
Gastrooesophageal reflux disease	41 (12.7)
Abdominal pain	40 (12.4)
Mouth ulceration	38 (11.8)
General disorders and administration site conditions	166 (51.4)
Fatigue	85 (26.3)
Pyrexia	42 (13.0)
Infections and infestations	225 (69.7)

System Organ Class Preferred Term	FD + MRD (First 16 Cycles) Cohorts N = 323 n (%)
Upper respiratory tract infection	85 (26.3)
Injury, poisoning and procedural complications	116 (35.9)
Contusion	55 (17.0)
Musculoskeletal and connective tissue disorders	214 (66.3)
Arthralgia	109 (33.7)
Muscle spasms	79 (24.5)
Back pain	47 (14.6)
Myalgia	47 (14.6)
Pain in extremity	43 (13.3)
Nervous system disorders	143 (44.3)
Headache	86 (26.6)
Dizziness	52 (16.1)
Respiratory, thoracic and mediastinal disorders	157 (48.6)
Cough	55 (17.0)
Oropharyngeal pain	45 (13.9)
Epistaxis	42 (13.0)
Skin and subcutaneous tissue disorders	215 (66.6)
Rash maculo-papular	50 (15.5)
Petechiae	37 (11.5)
Dry skin	35 (10.8)
Pruritus	31 (9.6)
Onychoclasis	31 (9.6)
Vascular disorders	72 (22.3)
Hypertension	51 (15.8)

*N = Number of subjects in the specified population; n = number of subjects with the specified event; % = 100*n/N*

* *Data extraction date used was for primary analysis of FD cohort (12 November 2020).*

"First 16 cycles" refers to the pre-randomisation phase.

Subjects are counted once only at each level of summarisation using maximum severity.

Adverse events are coded by MedDRA Version 23.1.

Grade 3 or 4 TEAEs

Study CLL3011

In the Ven + Ibr arm, Grade 3 or higher TEAEs were reported in 75.5% of subjects; the most frequent Grade 3 or higher TEAEs (≥ 5% of subjects) were neutropenia (28.3%), diarrhea (10.4%), neutrophil count decreased (8.5%), hypertension (7.5%), atrial fibrillation (6.6%), pneumonia (6.6%), hyponatremia (5.7%), and thrombocytopenia (5.7%). In the Clb + Ob arm, Grade 3 or higher TEAEs were reported in 69.5% of subjects; the most frequent Grade 3 or higher TEAEs (≥ 5% of subjects)

were neutropenia (44.8%), thrombocytopenia (20.0%), neutrophil count decreased (6.7%), and tumour lysis syndrome (5.7%) (**Table 37**).

Table 40. Grade 3 or Higher TEAEs by PT and Toxicity Grade Reported for ≥ 2% of Subjects in Either Arm of Study CLL3011 (Safety Analysis Set)

	Ven + Ibr N = 106 n (%)		**Clb + Ob N = 105 n (%)**	
Preferred Term	**Grade 3 – 5**	**Grade 3 + 4**	**Grade 3 – 5**	**Grade 3 + 4**
Subjects with 1 or more AEs	80 (75.5)	73 (68.9)	73 (69.5)	71 (67.6)
Neutropenia	30 (28.3)	30 (28.3)	47 (44.8)	47 (44.8)
Diarrhoea	11 (10.4)	11 (10.4)	1 (1.0)	1 (1.0)
Neutrophil count decreased	9 (8.5)	9 (8.5)	7 (6.7)	7 (6.7)
Hypertension	8 (7.5)	8 (7.5)	2 (1.9)	2 (1.9)
Atrial fibrillation	7 (6.6)	7 (6.6)	0	0
Pneumonia	7 (6.6)	5 (4.7)	6 (5.7)	5 (4.8)
Hyponatraemia	6 (5.7)	6 (5.7)	0	0
Thrombocytopenia	6 (5.7)	6 (5.7)	21 (20.0)	21 (20.0)
Asthenia	4 (3.8)	4 (3.8)	0	0
Cardiac failure	4 (3.8)	3 (2.8)	0	0
Hyperuricaemia	4 (3.8)	4 (3.8)	2 (1.9)	2 (1.9)
Rash	4 (3.8)	4 (3.8)	0	0
Anaemia	3 (2.8)	3 (2.8)	2 (1.9)	2 (1.9)
Alanine aminotransferase increased	2 (1.9)	2 (1.9)	3 (2.9)	3 (2.9)
Febrile neutropenia	2 (1.9)	2 (1.9)	3 (2.9)	3 (2.9)
Aspartate aminotransferase increased	1 (0.9)	1 (0.9)	3 (2.9)	3 (2.9)
Leukopenia	0	0	3 (2.9)	3 (2.9)
Tumour lysis syndrome	0	0	6 (5.7)	6 (5.7)
Infusion related reaction	0	0	3 (2.9)	3 (2.9)

Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used.

Adverse events are presented by decreasing frequency of preferred term and preferred by Grade 3 - 5 column within Ven + Ibr group; those with the same frequency are presented alphabetically.

Adverse events are coded using MedDRA Version 23.0.

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, Grade 3 or higher TEAEs were reported in 64.7% of subjects; the most frequently occurring Grade 3 or higher TEAEs (≥ 5% of subjects) were neutropenia (34.1%) and hypertension (6.8%) (**Table 38**).

Table 41. Grade 3 or higher TEAEs by PT and Toxicity Grade Reported for ≥ 2% of Subjects in FD Cohort* + First 16 Cycles of MRD Cohort of Study 1142 (All-treated Population)

	FD + MRD (First 16 Cycles) Cohorts N = 323 n (%)	
Preferred Term	**Grade 3-5**	**Grade 3+4**
Subjects with any TEAE	209 (64.7)	208 (64.4)
Neutropenia	110 (34.1)	110 (34.1)
Hypertension	22 (6.8)	22 (6.8)
Diarrhoea	13 (4.0)	13 (4.0)
Neutrophil count decreased	11 (3.4)	11 (3.4)
Thrombocytopenia	10 (3.1)	10 (3.1)

*N = Number of subjects in the specified population; n = number of subjects with the specified event; % = 100*n/N*

* *Data extraction date used was for primary analysis of FD cohort (12 November 2020).*

"First 16 cycles" refers to the pre-randomisation phase.

Subjects are counted once only at each level of summarisation using maximum severity.

Serious adverse event/deaths/other significant events

Serious Adverse Events

Study CLL3011

Treatment-emergent SAEs were reported in 49 (46.2%) subjects in the Ven + Ibr arm, with 34 (32.1%) subjects experiencing Grade 3 or 4 SAEs. The most frequently reported (≥ 5% of subjects) SAEs in the Ven + Ibr arm were atrial fibrillation (6.6%) and pneumonia (5.7%). Treatment-emergent SAEs were reported in 29 (27.6%) subjects in the Clb + Ob arm, with 21 (20.0%) subjects experiencing Grade 3 or 4 SAEs. The most frequently reported (≥ 5% of subjects) SAE in the Clb + Ob arm was pneumonia (5.7%). SAEs reported for ≥ 2 subjects in either arm are presented in **Table 39**.

Table 42. Serious Treatment-Emergent Adverse Events by PT and Toxicity Grade Reported in ≥ 2 Subjects in Either Arm of Study CLL3011 (Safety Analysis Set)

	Ven + Ibr N = 106 n (%)			**Clb + Ob N = 105 n (%)**		
Preferred Term	**Any Grade**	**Grade 3+4**	**Grade 5**	**Any Grade**	**Grade 3+4**	**Grade 5**
Subjects with 1 or more serious AEs	49 (46.2)	34 (32.1)	7 (6.6)	29 (27.6)	21 (20.0)	2 (1.9)
Atrial fibrillation	7 (6.6)	5 (4.7)	0	0	0	0
Pneumonia	6 (5.7)	4 (3.8)	2 (1.9)	6 (5.7)	5 (4.8)	1 (1.0)
Anaemia	3 (2.8)	0	0	2 (1.9)	0	0
Cardiac failure	3 (2.8)	2 (1.9)	1 (0.9)	0	0	0
Diarrhoea	3 (2.8)	2 (1.9)	0	1 (1.0)	1 (1.0)	0
Acute myocardial infarction	2 (1.9)	2 (1.9)	0	1 (1.0)	1 (1.0)	0
Haematuria	2 (1.9)	2 (1.9)	0	0	0	0
Hyperphosphataemia	2 (1.9)	0	0	0	0	0
Ischaemic stroke	2 (1.9)	0	1 (0.9)	0	0	0
Neutropenia	2 (1.9)	2 (1.9)	0	1 (1.0)	1 (1.0)	0
Oedema peripheral	2 (1.9)	0	0	0	0	0
Sinus node dysfunction	2 (1.9)	1 (0.9)	1 (0.9)	0	0	0
Sudden death	2 (1.9)	0	2 (1.9)	0	0	0
Pyrexia	1 (0.9)	0	0	2 (1.9)	1 (1.0)	0
Febrile neutropenia	1 (0.9)	1 (0.9)	0	3 (2.9)	3 (2.9)	0
Alanine aminotransferase increased	0	0	0	2 (1.9)	2 (1.9)	0
Infusion related reaction	0	0	0	3 (2.9)	1 (1.0)	0
Tumour lysis syndrome	0	0	0	3 (2.9)	3 (2.9)	0

Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the total column for that adverse event.

Adverse events are presented by decreasing frequency of PT by Any Grade column within Ven + Ibr group; those with the same frequency are presented alphabetically.

Adverse events are coded using MedDRA Version 23.0.

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, treatment-emergent SAEs occurred in 70 (21.7%) subjects, with 58 (18.0%) subjects experiencing Grade 3 or 4 SAEs.

Table 43. Serious Treatment-Emergent Adverse Events by PT and Toxicity Grade Reported in ≥ 1% of Subjects in FD Cohort* + First 16 Cycles of MRD Cohort of Study 1142 (All-treated Population)

	FD + MRD (First 16 Cycles) Cohorts N = 323 n (%)		
Preferred Term	**Any Grade**	**Grade 3+4**	**Grade 5**
Subjects with any Serious TEAE	70 (21.7)	58 (18.0)	1 (0.3)
Pneumonia	6 (1.9)	6 (1.9)	0
Atrial fibrillation	6 (1.9)	5 (1.5)	0
Cellulitis	4 (1.2)	4 (1.2)	0
Febrile neutropenia	4 (1.2)	4 (1.2)	0

*N = Number of subjects in the specified population; n = number of subjects with the specified event; % = 100*n/N*

"First 16 cycles" refers to the pre-randomisation phase.

Subjects are counted once only at each level of summarisation using maximum severity.

Adverse events are coded by MedDRA Version 23.1.

Deaths

Study CLL3011

Overall, there were 11 (10.4%) deaths in the Ven + Ibr arm and 12 (11.4%) deaths in the Clb + Ob at the time of database lock for the primary analysis (28 April 2021); fatal TEAEs were reported in 7 (6.6%) subjects in the Ven + Ibr arm and 2 (1.9%) subjects in the Clb + Ob arm (**Table 41)**.

Among the 7 subjects with fatal TEAEs in the Ven + Ibr arm, 4 experienced the fatal events during lead-in treatment with ibrutinib. In 2 of these cases (PTs: neoplasm malignant and pneumonia), the conditions were likely present at baseline and unrelated to study treatment: the onset of the event malignant neoplasm was reported on Study Day 41 and resulted in death on Study Day 78. The short latency between start of ibrutinib and the diagnosis of the malignancy makes an association with ibrutinib unlikely. The subject who experienced the fatal event of pneumonia had pleural effusion and pulmonary oedema at study start which may have contributed to the event.

A third subject with a history of hypercholesterolemia, hypertension and likely symptomatic ischemic heart disease, as the subject was taking medication used for angina (trimetazidine), experienced cardiac arrest leading to withdrawal of ibrutinib on Study Day 85 and died on Study Day 89. The event was assessed as not related to ibrutinib by the investigator. A fourth subject who died during the ibrutinib lead-in period had a relevant cardiovascular history (including 3 prior episodes of myocardial infarction [MI]) and was reported to have died due to 3 fatal TEAEs (cardiac failure, pneumonia, and sinus node dysfunction); these events were reported as related to the study drug (ibrutinib) by the investigator. Among the 3 deaths from a fatal TEAE that occurred during combination treatment with Ven + Ibr, one subject (PT: ischemic stroke) had an autopsy that revealed obliterating atherosclerosis as the potential cause of death. The chronic nature of atherosclerosis development argues against the death being related to an acute study drug-related effect. The 2 remaining fatal TEAEs that occurred during combination treatment in the Ven + Ibr arm were both potentially cardiac in nature (PT: sudden death [n = 2]). Both subjects had a baseline CIRS score ≥ 10 or an ECOG performance status of 2 and both had underlying baseline cardiac risks.

The fatal TEAEs reported for the 2 treatment-emergent deaths in the Clb + Ob arm include pneumonia and cholestasis. The event of pneumonia was considered by the investigator as related to study treatment.

Table 44. Treatment-Emergent Adverse Events Leading to Death by PT in Study CLL3011 (Safety Analysis Set)

Preferred Term	**Ven + Ibr N = 106 n (%)**	**Clb + Ob N = 105 n (%)**
Subjects with 1 or more AEs	7 (6.6)	2 (1.9)
Pneumonia	2 (1.9)	1 (1.0)
Sudden death	2 (1.9)	0
Cardiac arrest	1 (0.9)	0
Cardiac failure	1 (0.9)	0
Ischaemic stroke	1 (0.9)	0
Neoplasm malignant	1 (0.9)	0
Sinus node dysfunction	1 (0.9)	0
Cholestasis	0	1 (1.0)

Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

Adverse events are presented by decreasing frequency of preferred term within Ven + Ibr column; those with the same frequency are presented alphabetically.

Adverse events are coded using MedDRA Version 23.0.

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, 1 (0.3%) subject with a history of tobacco use and an ongoing medical history including hypertension and congenital heart disease experienced sudden death within the first month of the study, which was during the 3-cycle ibrutinib lead-in period. The subject died in his sleep on Day 23; the autopsy report indicated that the cause of death was cardiomegaly and coronary artery disease. The event was assessed by the investigator as possibly related to ibrutinib.

Adverse events of clinical interest and other safety observations

TLS, serious infections, and neutropenia are all identified risks associated with venetoclax. Other potential risks include second primary malignancy.

Important events outlined in the Ibrutinib Pharmacovigilance Plan, in addition to other events of potential clinical relevance to ibrutinib treatment, were selected as other safety observations. These events include TLS, leukostasis, cytopenic adverse events, infections (including viral reactivation), atrial fibrillation, hepatic disorders, other cardiac arrhythmias, cardiac failure, other malignancies, hypertension, embryofetal toxicity, interstitial lung disease, and ischemic stroke.

Haemorrhage

Bleeding events were identified by haemorrhage (excluding laboratory terms) SMQ search. Major haemorrhage included any treatment-emergent serious or Grade ≥ 3 haemorrhagic event, or any central nervous system events; e.g., intracranial haemorrhage (including subdural hematoma) within the haemorrhage SMQ excluding laboratory terms.

Study CLL3011

The proportion of subjects who experienced a haemorrhagic event of any grade was higher in the Ven + Ibr arm compared with the Clb + Ob arm (34.9% vs. 7.6%). In the Ven + Ibr arm, the most frequently occurring (≥ 5% of subjects) haemorrhagic TEAEs of any grade were epistaxis (11.3%) and hematoma (7.5%); all events of epistaxis and hematoma were Grade 1 – 2. In the Clb + Ob arm, the only haemorrhagic TEAEs of any grade reported in more than 1% of subjects were epistaxis (2.9%) and hematoma and haematuria (1.9%, each); all events of epistaxis, hematoma, and haematuria were Grade 1 – 2.

At least 1 treatment-emergent major haemorrhagic event was reported for 4 (3.8%) subjects in the Ven + Ibr arm and 1 (1.0%) subject in the Clb + Ob arm. Haematuria was the only major haemorrhagic event reported in > 1 subject, reported in the Ven + Ibr arm. Of the 4 subjects in the Ven + Ibr arm who reported major haemorrhage events, 3 experienced these events during the ibrutinib lead-in; these 3 subjects reported events of haematuria, cerebral haemorrhage, and ecchymosis and haematuria, respectively. One subject who experienced haematuria during the lead-in experienced a second event of haematuria during combination treatment of Ven + Ibr. The fourth subject reported an event of haemoptysis during combination treatment with Ven + Ibr; this subject had a history of lung cancer.

None of the events led to study treatment discontinuation and none were fatal.

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, treatment-emergent bleeding events were reported in 60.7% of subjects; the most frequently occurring (≥ 10% of subjects) treatment-emergent bleeding events were increased tendency to bruise (21.7%), contusion (17.0%), epistaxis (13.0%), and petechiae (11.5%).

Treatment-emergent, major haemorrhage events occurred in 5 (1.5%) subjects; these TEAEs of cerebral haemorrhage, eye haemorrhage, haemorrhagic cerebral infarction, menorrhagia, and retinal haemorrhage were reported by 1 (0.3%) subject each. Of the 5 major haemorrhage TEAEs, 4 started during the ibrutinib lead-in (cerebral haemorrhage, eye haemorrhage, haemorrhagic cerebral infarction, and retinal haemorrhage. One subject had a Grade 4 event of cerebral haemorrhage during the ibrutinib lead-in that led to treatment discontinuation; the event subsequently resolved. One subject had a Grade 1 event of haemorrhagic cerebral infarction during the ibrutinib lead-in that led to treatment discontinuation; the event subsequently resolved. Menorrhagia was the only major haemorrhage TEAE with onset during combination treatment; the event with onset on Study Day 197 was assessed as not related to either study drug. None of the events of major haemorrhage resulted in a fatal outcome, all resolved.

Tumour Lysis Syndrome

TLS is an important identified risk for venetoclax. TLS events were identified by TLS SMQ narrow search. In addition, laboratory TLS per Howard criteria was also summarized for Ven + Ibr arm of Study CLL3011.

Study CLL3011

No TEAE of TLS was reported in the Ven + Ibr arm. Treatment-emergent TLS was reported for 6 (5.7%) subjects in the Clb + Ob arm including 3 (2.9%) subjects who reported serious TLS events.

Review of laboratory data obtained prior to the initiation of and up to 7 days after starting venetoclax identified 4 subjects in the Ven + Ibr arm who met Howard criteria for laboratory TLS but where no TEAE of TLS was reported. In all 4 subjects the abnormal lab values occurred one day after venetoclax initiation, and single adverse events of hyperuricemia, hypocalcaemia, hyperphosphatemia were reported in one subject each; three events (hyperphosphatemia, hyperuricemia, and increased creatinine) were reported in a fourth subject. Venetoclax was interrupted in 3 subjects and continued without dose modification in one subject. All reported adverse events resolved, and all subjects were able to continue the venetoclax ramp-up. No subject met Howard criteria for clinical TLS.

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, 1 subject experienced treatment-emergent TLS on Day 88 (second day of venetoclax dosing). The subject met the Howard criteria for laboratory TLS; the event was Grade 3 in severity, non-serious, and was assessed by the investigator as not related to ibrutinib and related to venetoclax. No action was taken with study treatment (ibrutinib and venetoclax) due to the event and the subject was able to continue treatment. No subject met Howard criteria for clinical TLS.

Cytopenic Events

Cytopenic AEs of potential clinical relevance for ibrutinib include neutropenia, febrile neutropenia, thrombocytopenia, anemia, and lymphopenia. In addition, neutropenia is an important identified risk for venetoclax.

Neutropenia

Study CLL3011

In the Ven + Ibr arm, 55.7% of subjects experienced treatment-emergent cytopenic TEAEs of any grade, with 39.6% of subjects reporting Grade 3 or 4 cytopenic TEAEs; in the Clb + Ob arm, 70.5% of subjects experienced treatment-emergent cytopenic TEAEs of any grade, with 58.1% of subjects reporting Grade 3 or 4 cytopenic TEAEs. The most frequently reported event in both arms was neutropenia (34.0% in the Ven + Ibr arm and 53.3% in the Clb + Ob arm).

In the Ven + Ibr arm, neutropenia events were reported in 44 (41.5%) subjects, with 37 (34.9%) subjects experiencing Grade 3 or 4 events and 3 (2.8%) subjects experiencing serious events. Neutropenia events led to dose reduction in 9 (8.5%) subjects and dose interruption in 20 (18.9%) subjects; none of the events led to discontinuation of study drug. In the Clb + Ob arm, neutropenia events were reported in 61 (58.1%) subjects, with 52 (49.5%) subjects experiencing Grade 3 or 4 events and 1 (1.0%) subject experiencing serious events.

Febrile neutropenia was reported in 2 (1.9%) subjects in the Ven + Ibr arm and 3 (2.9%) subjects in the Clb + Ob arm; all of whom experienced Grade 3 or 4 events. Serious febrile neutropenia was reported in 1 (0.9%) subject in the Ven + Ibr arm and 3 (2.9%) subjects in the Clb + Ob arm. No subject discontinued due to the event in either arm, and no event was fatal.

Study 1142

Neutropenia events (reported TEAEs of neutropenia or neutrophil count decreased) were reported in 153 (47.4%) subjects; with 119 (36.8%) subjects experiencing Grade 3 or 4 events and 2 (0.6%) subjects experiencing serious events. There were no fatal events of neutropenia. Using the neutropenia

"expanded search," neutropenia events of any grade, Grade 3 or 4 events, and serious events were reported in 47.7%, 37.5%, and 1.9% subjects, respectively.

For the FD cohort + the first 16 cycles of the MRD cohort, 4 (1.2%) subjects experienced febrile neutropenia; all 4 subjects experienced Grade 3 or 4 events.

Two (0.6%) subjects discontinued ibrutinib and one (0.3%) subject discontinued venetoclax due to an event with the PT neutropenia. No other events within the "expanded" search led to discontinuation of venetoclax.

Anemia

Study CLL3011

Anemia was reported in 19 (17.9%) subjects in the Ven + Ibr arm and 19 (18.1%) subjects in the Clb + Ob arm. Grade 3 or 4 anemia was reported in 3 (2.8%) subjects in the Ven + Ibr arm and 2 (1.9%) subjects in the Clb + Ob arm. Serious anemia was reported in 3 (2.8%) subjects in the Ven + Ibr arm and 2 (1.9%) subjects in the Clb + Ob arm. None of the events led to discontinuation of study drugs in the Ven + Ibr arm; one (1.0%) subject discontinued both study drugs due to anemia in the Clb + Ob arm.

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, there were 21 (6.5%) subjects with anemia. Six (1.9%) subjects experienced Grade 3 or 4 anemia, while serious anemia was reported in 1 (0.3%) subject. None of the events led to discontinuation of study drugs.

Thrombocytopenia

Study CLL3011

Thrombocytopenia, of any grade and Grade 3 or 4, was reported in 11.3% and 5.7% of subjects in the Ven + Ibr arm and 26.7% and 20.0% of subjects in the Clb + Ob arm. Platelet count decreased, of any Grade and Grade 3 or 4, was reported in 2.8% and 0.9% of subjects in the Ven + Ibr arm and 1.0% and 1.0% of subjects in the Clb + Ob arm. No subject had an SAE of thrombocytopenia or platelet count decreased. None of the events led to discontinuation of study drugs in either arm.

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, there were 51 (15.8%) subjects with thrombocytopenia and 15 (4.6%) subjects with platelet count decreased. For Grade 3 or higher events, there were 10 (3.1%) subjects with thrombocytopenia and 2 (0.6%) subjects with platelet count decreased. No subject had an SAE of thrombocytopenia or platelet count decreased. None of the events led to discontinuation of study drugs.

Infections including viral reactivation

All infection TEAEs

In Study CLL3011, a higher proportion of subjects in the Ibr+Ven arm (60.4%) than the Clb+Ob arm (48.6%) had TEAEs within the SOC of Infections and infestations. Treatment-emergent infection events reported in ≥10% of subjects in the Ibr+Ven arm were urinary tract infection (16.0%), upper respiratory tract infection (12.3%), and pneumonia (10.4%). Similarly, for the Clb+Ob arm, upper respiratory tract infection (13.3%) was reported in ≥10% of subjects. The proportion of subjects with Grade 3 or 4 TEAEs within the SOC of Infections and infestations were 15.1% in the Ibr+Ven arm and

10.5% in the Clb+Ob arm. The most frequently reported Grade 3 or 4 infection was pneumonia, with similar proportions between the Ibr+Ven arm and Clb+Ob arm (4.7% and 4.8%, respectively). Serious adverse events of any grade in the SOC of Infections and infestations were reported for 12.3% of subjects in the Ibr+Ven arm and 8.6% of subjects in the Clb+Ob arm. The most frequently reported serious adverse event of infection was pneumonia, reported in 5.7% of subjects in both arms. Two (1.9%) subjects in the Ibr+Ven arm and 1 (1.0%) subject in the Clb+Ob arm were reported with fatal pneumonia.

In Study 1142, 69.7% of subjects had TEAEs within the SOC of Infections and infestations. Treatment-emergent infection event reported in ≥10% of subjects was upper respiratory tract infection (26.3%). Grade 3 or 4 TEAEs within the SOC of Infections and infestations were reported for 8.4% of subjects. The most frequently reported Grade 3 or 4 infection was pneumonia (1.9%). Serious adverse events of any grade in the SOC of Infections and infestations were reported for 8.0% of subjects. The most frequently reported serious adverse events of infection was pneumonia, reported in 1.9% of subjects. Two subjects (0.6%) discontinued ibrutinib due to an infection TEAE. No subjects had an infection TEAE with a fatal outcome.

Viral reactivation TEAEs

In Study CLL3011 and in the FD cohort + the first 16 cycles of the MRD cohort for Study 1142, there were no treatment-emergent reports of hepatitis B reactivation.

Sepsis

Sepsis events were identified by PTs containing sepsis, bacteraemia, fungaemia, viraemia, or septic (excluding septic screen or aseptic).

In Study CLL3011, treatment-emergent septic shock was reported in 1 (0.9%) subject in the Ibr+Ven arm and pneumococcal sepsis was reported in 1 (1.0%) subject in the Clb+Ob arm. Both events were serious and Grade 3 or 4 in severity.

In the FD cohort + first 16 cycles of the MRD cohort of Study 1142, 3 subjects (0.9%) experienced treatment-emergent sepsis (ie, 1 subject with bacteraemia, 1 subject with Escherichia bacteraemia, 1 subject with Staphylococcal bacteraemia). Of these events, 2 events (Escherichia bacteraemia and Staphylococcal bacteraemia) were Grade 3 or 4 in severity. Two (0.6%) subjects had serious sepsis events and none of the events were fatal.

Cardiac arrhythmias

Atrial Fibrillation

In Study CLL3011, the proportion of subjects with atrial fibrillation (based on the PT of atrial fibrillation) was higher in the Ibr+Ven arm (14.2%) compared with the Clb+Ob arm (1.9%). Grade 3 or 4 TEAEs of atrial fibrillation were reported in 7 (6.6%) subjects in the Ibr+Ven arm and no subjects in the Clb+Ob arm. Similarly, atrial fibrillation as a serious adverse event was reported in 7 (6.6%) subjects in the Ibr+Ven arm and no subjects in the Clb+Ob arm. There were no fatal atrial fibrillation events. Atrial fibrillation led to ibrutinib discontinuation in 2 (1.9%) subjects, ibrutinib dose reduction in 1 subject (0.9%). None of the subjects with a TEAE of atrial fibrillation had an action taken against venetoclax nor a discontinuation of study treatment due to the event.

In Study 1142, treatment-emergent atrial fibrillation was reported for 5.9% of subjects. Five subjects (1.5%) had Grade 3 or 4 atrial fibrillation. Atrial fibrillation as a serious adverse event was reported in

6 (1.9%) subjects. There were no fatal atrial fibrillation events. Atrial fibrillation led to ibrutinib discontinuation for 1 subject (0.3%).

Ventricular Tachyarrhythmias

In Study CLL3011, no TEAEs of ventricular tachyarrhythmias (based on the ventricular tachyarrhythmia SMQ search) were reported.

In Study 1142, ventricular tachyarrhythmias TEAEs occurred in 3 subjects (0.9%), with ventricular extrasystoles, ventricular fibrillation, and ventricular tachyarrhythmia (serious) observed in individual subjects (0.3% each). Events of ventricular tachyarrhythmia did not result in ibrutinib dose reduction for any subjects. For 2 subject (0.6%), events of Grade 3 or 4 ventricular fibrillation or ventricular tachyarrhythmia resulted in ibrutinib discontinuation.

Other Cardiac Arrhythmias (excluding atrial fibrillation and ventricular tachyarrhythmias)

In Study CLL3011, cardiac arrhythmias (identified by the cardiac arrhythmia SMQ excluding the preferred term of atrial fibrillation and ventricular arrhythmias) were reported for 15 subjects (14.2%) in the Ibr+Ven arm and 11 subjects (10.5%) in the Clb+Ob arm. The PT of palpitations was reported in 6 (5.7%) subjects in the Ibr+Ven arm and 3 (2.9%) of subjects in the Clb+Ob arm. All other PTs were reported in 1 or 2 subjects in either treatment arm. The proportion of subjects with Grade 3 or 4 TEAEs of cardiac arrhythmias was similar between the Ibr+Ven arm and Clb+Ob arm (3 [2.8%] and 2 [1.9%] subjects, respectively). Fatal cardiac arrhythmias were reported in 4 (3.8%) subjects in the Ibr+Ven arm and no subjects in the Clb+Ob arm. The fatal events were sudden death (2 [1.9%] subjects), cardiac arrest (1 [0.9%] subject), and sinus node dysfunction (1 [0.9%] subject). No subjects had ibrutinib dose reductions as a result of cardiac arrhythmias, and 4 (3.8%) subjects had ibrutinib treatment discontinuation as a result of cardiac arrhythmias (2 [1.9%] subjects with the PT of sudden death and 1 [0.9%] subject each with PTs of fatal sinus node dysfunction and non-fatal cardiac arrest).

In Study 1142, cardiac arrhythmias excluding the preferred term of atrial fibrillation and ventricular arrhythmias, were reported for 56 subjects (17.3%) in the FD cohort + the first 16 cycles of the MRD cohort, with 2.2% having a Grade 3 or 4 event. The PT of palpitations was reported in 36 (11.1%) subjects, and sinus bradycardia, sinus tachycardia, and syncope in 4 (1.2%) subjects each. All other PTs were reported in 1 to 3 subjects. Fatal cardiac arrhythmias were reported in 1 (0.3%) subject (sudden death). One subject had an ibrutinib dose reduction as a result of palpitations. Ibrutinib treatment discontinuation resulted from cardiac arrest in 2 subjects (0.6%) and sinus arrest in 1 subject (0.3%).

Cardiac failure

In Study CLL3011, treatment-emergent cardiac failure events (identified by cardiac failure SMQ narrow search) were reported in 5 (4.7%) subjects in the Ibr+Ven arm and 1 (1.0%) subject in the Clb+Ob arm. All of these subjects had multiple comorbidities including cardiac disorders and/or hypertension at baseline. Grade 3 or 4 cardiac failure was reported in 3 (2.8%) subjects in the Ibr+Ven arm and 1 (1.0%) subject in the Clb+Ob arm. One subject in the Ibr+Ven arm was reported with a fatal cardiac failure event (0.9%), this subject had a history of myocardial infarction, myocardial ischemia, and atrial fibrillation at study entry. No subjects had ibrutinib dose reductions as a result of cardiac failure events, and all 5 (4.7%) subjects in the Ibr+Ven arm had ibrutinib treatment discontinuation as a result of cardiac failure events.

In Study 1142, 1 subject (0.3%) reported treatment-emergent cardiac failure event of Grade 3 or 4 severity. This cardiac failure event was serious and did not lead to a fatal outcome, dose ibrutinib reduction, or discontinuation of ibrutinib treatment.

Other malignancies

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib. In addition, second primary malignancy is an important potential risk for venetoclax. Other malignancies were identified by medical review of preferred terms under the SOC of Neoplasms benign, malignant and unspecified (incl cysts and polyps).

Study CLL3011

As of the time of the primary analysis, 8 (7.5%) subjects in the Ven + Ibr arm and 10 (9.5%) subjects in the Clb + Ob arm developed other malignancies during the entire study. Non-skin cancers were reported in 5 (4.7%) subjects in the Ven + Ibr arm and included hepatocellular carcinoma, lung neoplasm malignant, neoplasm malignant, plasma cell myeloma, and T-cell lymphoma (reported in 1 [0.9%] subject each). Non-skin cancers were reported in 6 (5.7%) subjects in the Clb + Ob arm and included adenocarcinoma gastric, lung adenocarcinoma, metastases to peritoneum, papillary thyroid cancer, prostate cancer, and prostate cancer metastatic (reported in 1 [1.0%] subject each).

Non-melanoma skin cancer was reported in 3 (2.8%) subjects in the Ven + Ibr arm and 2 (1.9%) of subjects in the Clb + Ob arm; basal cell carcinoma was reported in 2 (1.9%) subjects in the Ven + Ibr arm and 1 (1.0%) subject in the Clb + Ob arm; squamous cell carcinoma of the skin was reported in 1 (0.9%) subject in the Ven + Ibr arm and 1 (1.0%) subject in the Clb + Ob arm. In the Ven + Ibr arm, no subjects reported melanoma skin cancer. In the Clb + Ob arm, 2 (1.9%) subjects reported melanoma skin cancer; both malignant melanoma.

When limited to treatment-emergent events, other malignancies were reported in 7 (6.6%) subjects in the Ven + Ibr arm and 3 (2.9%) subjects in the Clb + Ob.

Study 1142

At the primary analysis for the pooled FD + MRD cohorts, other malignancies during the entire study period were reported for 29 (9.0%) subjects. Non-skin cancer occurred in 10 (3.1%) subjects and included prostate cancer (3 [0.9%] subjects), myelodysplastic syndrome (2 [0.6%] subjects), and invasive ductal breast carcinoma, lung adenocarcinoma, renal oncocytoma, breast cancer, and renal cancer (1 [0.3%] subject, each). Non-melanoma skin cancer occurred in 16 (5.0%) subjects and included basal cell carcinoma (13 [4.0%] subjects) and squamous cell carcinoma (4 [1.2%] subjects). Melanoma skin cancer occurred in 7 (2.2%) subjects and included malignant melanoma (6 [1.9%] subjects) and malignant melanoma *in situ* (1 [0.3%] subject). Overall, other malignancies of Grade 3 or 4 severity occurred in 5 (1.5%) subjects (events: malignant melanoma in 2 subjects, basal cell carcinoma, lung adenocarcinoma, renal oncocytoma, and myelodysplastic syndrome in 1 subject each).

Other malignancies reported as treatment-emergent events were reported in 16 (5.0%) subjects in the FD cohort + the first 16 cycles of the MRD cohort.

Hypertension

In Study CLL3011, hypertension events (identified by hypertension narrow MedDRA SMQ) were reported for 15 (14.2%) subjects in the Ibr+Ven arm and 5 (4.8%) subjects in the Clb+Ob arm. Overall, Grade 3 or 4 hypertension was reported in 9 (8.5%) subjects in the Ibr+Ven arm and 2

(1.9%) subjects in the Clb+Ob arm. Two (1.9%) subjects in the Ibr+Ven arm had serious hypertension TEAEs. No subjects had ibrutinib discontinued and no dose reductions were reported as a result of treatment-emergent hypertension in either treatment arm.

In Study 1142, hypertension events were reported for 16.4% of subjects in the FD cohort + the first 16 cycles of the MRD cohort. Grade 3 or 4 hypertension was reported in 23 (7.1%) subjects. One (0.3%) subject had a serious hypertension TEAE. No subjects had treatment discontinued and no dose reductions were reported as a result of treatment-emergent hypertension.

Hepatoxicity including hepatic failure

Treatment-emergent adverse events of any grade within the SOC of Hepatobiliary Disorders were reported in 7 (6.6%) subjects in the Ibr+Ven arm and 4 (3.8%) subjects in the Clb+Ob arm. Grade 3 or 4 events were reported for 4 (3.8%) subjects in the Ibr+Ven arm and 1 (1.0%) subject in the Clb+Ob arm. One subject (1.0%) in the Clb+Ob arm had a fatal hepatic TEAE of cholestasis.

In the FD cohort + the first 16 cycles of the MRD cohort of Study 1142, hepatic TEAEs were reported for 4.3% of subjects. Grade 3 or 4 hepatic events were observed in 1.9% of subjects. No subjects had a fatal hepatic TEAEs.

Diarrhoea

In Study CLL3011, treatment-emergent diarrhoea was reported in 50.9% of subjects in the Ibr+Ven arm and 12.4% of subjects in the Clb+Ob arm. Grade 3 diarrhoea was reported in 10.4% of subjects in the Ibr+Ven arm and 1.0% of subjects in the Clb+Ob arm. There were no Grade 4 or fatal events. Most subjects who experienced diarrhoea only had one event (30.2% of subjects in the Ibr+Ven arm and 9.5% of subjects in the Clb+Ob arm). The median time to resolution or improvement of Grade 3 event was 9.0 days in the Ibr+Ven arm and 8.0 days in the Clb+Ob arm. Treatment-emergent diarrhoea led to ibrutinib dose reduction in 7 (6.6%) subjects and to venetoclax dose reduction in 6 (5.7%) subjects. In the Clb+Ob arm, diarrhoea led to chlorambucil dose reduction in 1 (1.0%) subject. In the Ibr+Ven arm, diarrhoea led to ibrutinib and venetoclax dose interruption in 11 (10.4%) and 7 (6.6%) subjects, respectively. In the Clb+Ob arm, diarrhoea led to obinutuzumab dose interruption (i.e., infusion interrupted, delayed, or skipped) in 2 (1.9%) subjects. For 3 (2.8%) subjects in the Ibr+Ven arm, diarrhoea led to study treatment discontinuation.

In Study 1142, diarrhoea was reported for 66.6% of subjects for the FD cohort + the first 16 cycles of the MRD cohort, with 4.0% of subjects experiencing diarrhoea of Grade 3 or 4 severity. Diarrhoea led to ibrutinib dose reduction in 8 (2.5%) subjects, and no diarrhoea events led to ibrutinib discontinuation.

Embryofoetal toxicity

No TEAEs of embryofoetal toxicity were reported in Study CLL3011 or for the FD cohort + the first 16 cycles of the MRD cohort in Study 1142.

Laboratory findings

Haematology

Study CLL3011

In Ven + Ibr arm, treatment-emergent decreases to Grade 3 or 4 low absolute neutrophil count (ANC), hemoglobin, and platelets were observed for 41.5%, 0%, and 13.2% of subjects, respectively; in the Clb + Ob arm, treatment-emergent decreases to Grade 3 or 4 low ANC, hemoglobin, and platelets were observed for 54.3%, 0%, and 31.4% of subjects, respectively.

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort in Study 1142, treatment emergent Grade 3 or 4 decreases in haemoglobin, platelets, and ANC were observed for 0.3%, 11.1%, and 37.5% of subjects, respectively.

Clinical chemistry

Laboratory Tumour Lysis Syndrome per Howard Criteria

Study CLL3011

Review of laboratory data obtained prior to the initiation of and up to 7 days after starting venetoclax identified 4 (4.3%) subjects in the Ven + Ibr arm had observed laboratory values that met Howard criteria for laboratory TLS. None of the subjects had TEAEs of TLS.

Study 1142

One (0.3%) subject in the FD cohort + first 16 cycles of the MRD cohort receiving Ven + Ibr had laboratory values that met Howard criteria for laboratory TLS.

Hepatic abnormalities

In Study CLL3011 (Ibr+Ven and Clb+Ob arms) and Study 1142, the majority of subjects maintained normal serum levels (Grade 0) of ALT, AST, ALP, and bilirubin post-baseline. Most post-baseline increases in ALT, AST, ALP, and bilirubin were mild (Grade 1). In Study 1142, 1 subject (0.3%) met the requisite laboratory criteria for potential Hy's Law based on ALT/AST, alkaline phosphatase, and bilirubin toxicities post-baseline, and none met the requisite laboratory criteria for potential Hy's Law in Study CLL3011.

Serum Electrolyte Abnormalities

Study CLL3011

The majority of subjects in the Ven + Ibr and Clb + Ob arms maintained normal (Grade 0) serum levels of sodium, potassium, and phosphate post-baseline. Post-baseline increase in serum sodium was infrequent and most shifts were limited to Grade 1. Treatment-emergent worsening to Grade 3 or 4 in > 5% of subjects was reported for sodium decreased (worst on-treatment toxicity of Grade 3) in 10.4% of subjects in the Ven + Ibr arm and 1.9% of subjects in the Clb + Ob arm).

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, treatment-emergent Grade 3 or 4 decreases in potassium, sodium, and corrected calcium were observed for 1.2%, 1.2%, and 0.3% of subjects, respectively. Treatment emergent Grade 3 or 4 increases in potassium, sodium, and corrected calcium were observed for 1.9%, 0%, and 0% of subjects, respectively.

Safety in special populations

Intrinsic Factors

The overall incidence of TEAEs of any grade was similar for subjects in subgroups, including age, gender, baseline CrCl, and baseline NCI-ODWG liver function status. Due to the small number of subjects in some of the subgroups (e.g., numbers of non-white subjects, subjects aged < 65 years, and subjects with abnormal NCI-ODWG liver function), additional data interpretation for these subgroups is limited.

Extrinsic Factors

An overview of TEAEs in the Ven + Ibr arm for subgroups with or without concomitant use of a moderate/strong CYP3A inhibitor is provided in the Study CLL3011 Primary Analysis CSR Attachment TSFAE16E and Attachment TSFAE16F. The overall incidence of TEAEs of any grade was similar for subjects with or without concomitant use of a moderate/strong CYP3A inhibitor; the number of subjects in the subgroup with concomitant use of strong inhibitors was small (n = 5) to provide meaningful interpretation. No other subgroups analyses for extrinsic factors were performed for Study CLL3011 or Study 1142.

Discontinuation due to adverse events

Study CLL3011

TEAEs leading to ibrutinib or venetoclax discontinuation were reported in 20.8% of subjects in the Ven + Ibr arm, with 19.8% and 11.3% of subjects discontinuing ibrutinib and venetoclax, respectively. Adverse events listed as a reason for study drug discontinuation in > 2 subjects were cardiac failure (5 [4.7%] subjects) and diarrhoea (3 [2.8%] subjects) for ibrutinib and diarrhoea (4 [3.8%] subjects) for venetoclax. TEAEs leading to chlorambucil or obinutuzumab discontinuation were reported in 7.6% of subjects in the Clb + Ob arm, with 5.7% and 3.8% of subjects discontinuing chlorambucil and obinutuzumab, respectively. All adverse events listed as a reason for study drug discontinuation were reported for only 1 subject, except neutropenia (2 [1.9%] subjects).

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, TEAEs leading to ibrutinib or venetoclax discontinuation were reported in 19 (5.9%) subjects and 9 (2.8%) subjects, respectively. TEAEs leading to the study drug discontinuation in ≥ 2 subjects were cardiac arrest and neutropenia (2 [0.6%] subjects, each) for ibrutinib and cardiac arrest and vomiting (2 [0.6%] subjects, each) for venetoclax.

Adverse events leading to dose reduction

Study CLL3011

The number of subjects with TEAEs leading to ibrutinib and/or venetoclax dose reduction was 28 (26.4%) in the Ven + Ibr arm. TEAEs leading to ibrutinib dose reduction were reported in 19 (17.9%) subjects; TEAEs listed as the primary reason for ibrutinib dose reduction in > 2 subjects were diarrhoea (7 [6.6%] subjects) and neutropenia (3 [2.8%] subjects). TEAEs leading to venetoclax dose reduction were reported in 18 (17.0%) subjects; TEAEs listed as the primary reason for venetoclax dose reduction in > 2 subjects were neutropenia (8 [7.5%] subjects) and diarrhoea (6 [5.7%] subjects). TEAEs leading to chlorambucil dose reduction were reported in 22 (21.0%) subjects in the Clb + Ob arm. Dose reduction was not permitted for obinutuzumab. TEAEs listed as the primary reason for chlorambucil dose reduction in > 2 subjects were neutropenia (12 [11.4%] subjects), anaemia (4 [3.8%] subjects), and thrombocytopenia and aspartate aminotransferase increased (3 [2.9%] subjects each).

Study 1142

For the FD cohort + the first 16 cycles of the MRD cohort, TEAEs leading to the dose reduction of ibrutinib and venetoclax were reported in 12.1% and 12.4% of subjects, respectively. TEAEs leading to the dose reduction of ibrutinib in > 2 subjects were diarrhoea (8 [2.5%] subjects), arthralgia (6 [1.9%] subjects), neutropenia and rash maculo-papular (3 [0.9%] subjects, each); TEAEs leading to the dose reduction of venetoclax in > 2 subjects were neutropenia (12 [3.7%] subjects), diarrhoea (11 [3.4%] subjects), and platelet count decreased (3 [0.9%] subjects).

Adverse Drug Reactions

The specific methodology for determination and assessment of ADRs was performed based on integration of data from Study CLL3011 and 1142 with that from previous studies forming the basis of the ADR information in the currently approved SmPC.

ADRs for CLL patients were updated to include new information from Study CLL3011 and Study 1142, are listed in Table 8 in the SmPC by SOC and frequency grouping. Only the highest frequency observed in the studies is reported.

Important differences versus the adverse reaction table in the currently approved SmPC include:

- Within the Infections and infestations SOC, the frequency category for Urinary tract infection (all grades) was changed from "Common" to "Very common"
- Within the Gastrointestinal disorders, Diarrhoea (Grade ≥3) was changed from Common to Very Common.

Post marketing experience

Venetoclax was first approved for use in 2016 and has been approved for use in 83 countries for patients with AML and in 84 countries for patients with CLL, as of 04 December 2023. Venetoclax is currently approved for the treatment of CLL, SLL, and AML, and is being investigated in Phase 1 to Phase 3 oncology studies as monotherapy and in combination with a variety of agents for the treatment of these and other hematologic malignancies.

As of the most recent Periodic Safety Update Report (PSUR; reporting interval, 05 December 2022 through 04 December 2023), the cumulative estimated subject exposure from company-sponsored interventional clinical trials for venetoclax is 5,632 subjects. The estimated cumulative post marketing patient exposure since the first approval (11 April 2016) through 30 November 2023 is 149,057 patient treatment years (PTY).

The following continue to be considered important identified risks associated with venetoclax: TLS, Neutropenia and Serious Infections.

2.7.1. Discussion on clinical safety

The safety data in support of this application to extend the existing indication in first line CLL with combination therapy with ibrutinib and venetoclax is based on 2 studies: Study CLL3011 and Study 1142.

The treatment regimen in the Ibr+Ven arm in both studies consisted of 3 cycles of ibrutinib monotherapy, followed by 12 cycles of ibrutinib in combination with venetoclax; except for the

treatment duration, posology for ibrutinib and venetoclax was according to the SmPC for both products. Treatment in the Clb+Ob arm consisted of 6 cycles.

Patient exposure

At the time of the primary analysis data cut-off (Study CLL3011: 26 February 2021; Study 1142: 12 November 2020), none of the patients in either study was still on treatment. In study CLL3011, median treatment duration was 2.7 times longer in the Ibr+Ven arm (13.8 months) vs. the Clb+Ob arm (5.1 months), reflecting the fixed duration of treatment in both arms. Median treatment duration in the Ibr+Ven cohort in study 1142 was 14.1 months. Median relative dose intensity for ibrutinib treatment in the Ibr+Ven cohorts was 97.7% and 98.8% in study CLL3011 and 1142, respectively. Median relative dose intensity for venetoclax was 97.6% in study CLL3011 and 99.4% and 99.3% in the FD and MRD cohort, respectively, in study 1142. Also, median dose intensity based on the cumulative total dose received/planned was high (98.4%).

Demographics

Patient characteristics were balanced in both arms of study CLL3011. In the Ibr+Ven arm in study CLL3011, median age was 71 years (range 47-93 years) with 84.9% of patients ≥65 years of age; 54.7% of patients had an ECOG performance status of 1 and 12.3% with ECOG 2. In study 1142, median age was 59 years (range 28-71 years) with 26.6% of patients ≥65 years of age; 66.6% had ECOG 0; no patients with ECOG 2 were included in the study. Generally, the patient population in the Ibr+Ven arms enrolled in studies CLL3011 and 1142 differed in terms of age and ECOG performance status with patients in study CLL3011 being older and with a worse ECOG performance status compared with those in study 1142.

TEAEs

In study CLL3011, the frequency of patients with any TEAE (Ibr+Ven vs. Clb+Ob: 99.1% vs. 94.3%) and any grade ≥3 TEAE (Ibr+Ven vs. Clb+Ob: 75.5% vs. 69.5%) was similar between treatment arms. Higher frequencies (Ibr+Ven vs. Clb+Ob) were noted for SAEs (46.2% vs. 27.6%; grade ≥3: 38.7% vs. 21.9%) and fatal TEAEs leading to death within 30 days of last dose (6.6% vs. 0). In study 1142, lower frequencies were noted for grade ≥3 TEAE (64.7%), SAEs (21.7%; grade ≥3: 18.3%) and fatal TEAEs (0.3%) compared with the Ibr+Ven arm of study CLL3011. Data on treatment discontinuations are discussed below.

The most common TEAEs (≥20% of patients) in the Ibr+Ven arms were diarrhoea, neutropenia and nausea (reported in both studies); in study 1142, also arthralgia, headache, upper respiratory tract infection, fatigue, muscle spasms, increased tendency to bruise, and vomiting were reported in ≥20% of patients. The reported common TEAEs in the Ibr+Ven arms in both studies were generally consistent with the known safety profile for ibrutinib and/or venetoclax.

In study CLL3011, grade 3 or 4 TEAEs were reported at similar frequency (Ibr+Ven vs. Clb+Ob: 68.9% vs. 67.6%). The most common grade 3 or 4 TEAEs (≥5% of patients) in the Ibr+Ven arm for study CLL3011 were neutropenia, diarrhoea, neutrophil count decreased, hypertension, atrial fibrillation, pneumonia, hyponatremia and thrombocytopenia. In study 1142, grade 3 or 4 TEAEs (64.4%) were reported at a similar frequency as in the Ibr+Ven arm of study CLL3011. The most common grade 3 or 4 TEAEs were neutropenia (34.1%), and hypertension (6.8%).

Compared with the Clb+Ob arm, a higher frequency in grade 3 or 4 TEAEs (>5% difference) in the Ibr+Ven arm was noted for diarrhoea (10.4% vs. 1.0%), hyponatraemia (5.7% vs. 0%), hypertension (7.5% vs. 1.9%) and atrial fibrillation (6.6% vs. 0%). A lower frequency in grade 3 or 4 TEAEs (>5% difference) in the Ibr+Ven arm vs. the Clb+Ob arm was noted for neutropenia (28.3% vs. 44.8%), thrombocytopenia (5.7% vs. 20.0%) and tumour lysis syndrome (0% vs. 5.7%).

SAEs

In study CLL3011, the frequency of SAEs was higher in the Ibr+Ven arm (46.2%) compared with the Clb+Ob arm (27.6%).

The most common SAEs (≥2% of subjects) in the Ibr+Ven arm were atrial fibrillation, pneumonia, anaemia, cardiac failure and diarrhoea. The most common SAEs in the Clb+Ob arm were pneumonia, febrile neutropenia, infusion-related reaction and TLS. During the first 6 cycles of study CLL3011, the most common SAEs reported in both study arms (pneumonia, anaemia and diarrhoea) did not show a difference in incidence rate between study arms or a difference in trend over time. For atrial fibrillation SAEs reported with Ibr+Ven, incidence rates remained stable over time during the first 6 cycles.

SAEs in the Ibr+Ven arm in study 1142 were generally reported at a lower frequency compared with study CLL3011.

Deaths due to TEAEs

In study CLL3011, fatal TEAEs (death within 30 days of last dose) were reported for 7 patients (6.6%) in the Ibr+Ven arm vs. no patients in the Clb+Ob arm. Of the 7 deaths in the Ibr+Ven arm, 4 deaths occurred during ibrutinib lead-in therapy and 3 during ibrutinib and venetoclax combination therapy.

PTs were as follows: pneumonia, malignant neoplasm and cardiac arrest (1 patient each) and 1 patient with cardiac failure, pneumonia and sinus node dysfunction during ibrutinib lead-in; 1 case of ischaemic stroke and 2 cases of sudden death during ibrutinib + venetoclax treatment. In both cases of sudden death reported during Ibr+Ven treatment, the data is not sufficient to assess if venetoclax might indirectly contribute to the fatal cardiac events.

In 4 of the 7 cases, the fatal events were cardiac in nature and assessed as possibly related to ibrutinib. Baseline factors in these 4 cases were as follows: age 63-80 years, CIRS score of 5-13, ECOG PS of 1 or 2 and cardiac risk factors (hypertension, hypercholesterolaemia, atrial fibrillation, myocardial ischaemia, myocardial infarction and diabetes mellitus).

In study 1142, sudden death was reported in 1 patient (0.3%) during ibrutinib lead-in. The cause of sudden death was due to cardiomegaly and coronary artery disease as per the autopsy report. Causality was assessed as possibly related to ibrutinib. This patient had baseline risk factors (hypertension, hyperlipidaemia and congenital heart disease (atrioventricular malformation)); ECOG performance status was 0.

AEs of clinical interest and other safety observations

With regard to the AEs of special interest (haemorrhage, TLS, cardiac arrythmias hepatotoxicity, hypertension, infections, including viral reactivation and other malignancies) no new concerns were identified. The TEAEs reported for these safety topics were consistent with the established safety profiles for ibrutinib and/or venetoclax.

Discontinuation due to adverse events

In study CLL3011, treatment discontinuations due to TEAEs for either study drug were reported at a higher rate in the Ibr+Ven arm (20.8%) compared with the Clb+Ob arm (7.6%). In study 1142, treatment discontinuations due to TEAEs for either study drug were reported in 6.5% of patients over the total treatment period.

Dose reductions

In the Ibr+Ven arms of studies CLL3011 and 1142, dose reductions for ibrutinib were reported in 19 patients (17.9%) and 39 patients (12.1%), respectively.

SmPC

ADRs for CLL patients were updated to include new information from Study CLL3011 and Study 1142. The most notable changes were changes in the frequency category for urinary tract infection (all grades) and diarrhoea (Grade ≥3) which were both changed from "Common" to "Very common"

2.7.2. Conclusions on clinical safety

The first-line treatment of CLL patients with ibrutinib in combination with venetoclax in study CLL3011 indicates a more pronounced toxicity profile in terms of higher incidence rates of SAEs and fatal TEAEs in comparison with chlorambucil and obinutuzumab treatment. The TEAEs reported with ibrutinib/venetoclax combination treatment were generally consistent with the known safety profile for either ibrutinib or venetoclax.

Comparison of the general safety profile for the ibrutinib/venetoclax arms across studies CLL3011 and 1142, indicated a similar incidence rate for grade 3 or 4 TEAEs and lower incidence rates for SAEs and fatal TEAEs in study 1142, possibly reflecting a younger and more fit patient population.

The safety profile of ibrutinib in combination with venetoclax in the first line treatment of CLL is largely consistent with the known safety profiles of ibrutinib and venetoclax.

2.7.3. 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.

2.8. 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 Medication error Richter's transformation (for CLL only) Second primary malignancy 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
Prospective Observational Cohort Study to Assess the Long Term Safety of Venetoclax in the Swedish Cohort of Chronic Lymphocytic Leukaemia Patients
 	
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
		<u>Select list of adverse events:</u>
		• Second primary malignancies
		• Richter's transformation (DLBCL, HL)
		• Opportunistic serious infections
		• Autoimmune hematological event
		  ○ Other autoimmune hemolytic anemia
		  ○ Idiopathic thrombocytopenic purpura
		• Tumor Lysis syndrome
			Interim CSR
			
			Final report
				Every second year over a study period of 8 years
				
				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> Posology and method of administration, including prophylactic measures for TLS, are described in section 4.2 of the SmPC (CLL and AML). Warnings and precautions for TLS are listed in section 4.4 of the SmPC (CLL and AML). Interaction with other medicinal products is described in section 4.5 of the SmPC (CLL and AML). TLS is described in section 4.8 of the SmPC (CLL and AML). <u>Other routine risk minimization measures:</u> • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Packaging design and language to facilitate adherence to the dose-titration schedule • Pack size and package leaflet <u>Additional risk minimization measures:</u>

Safety Concern	Risk Minimization Measures
	• Distribution of DHPC in European countries (CLL only) (activity completed in 2021 and effectiveness evaluation completed in 2025) • Distribution of a patient card in European countries (CLL only)
Embryofetal toxicity	Routine risk minimization measures: Language concerning embryofetal toxicity is included in section 4.6 and section 5.3 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet Additional risk minimization measures: None
Medication error	Routine risk minimization measures: Posology and method of administration are described in section 4.2 of the SmPC (CLL and AML). Description of contents of venetoclax container, including dose strength, shape and color of tablets, in section 3 and section 6.5 of SmPC (CLL). Language concerning overdose is included in section 4.9 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine
	• Use of treatment should be initiated and supervised by specialists • In CLL, each carton will be dispensed weekly to the patient during the first 4 weeks of the dose titration • In AML, only 100 mg tablets will be dispensed to minimize medication errors • Labeling and packaging layout (immediate and outer packaging) has been designed to minimize medication errors • Pack size and package leaflet Additional risk minimization measures: None
Richter's transformation (for CLL only)	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist Additional risk minimization measures: None
Second primary malignancy	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist Additional risk minimization measures: None

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

2.9. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to the increase in exposure of venetoclax when administrated in combination with ibrutinib has been added to the product information. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Malta and Iceland.

2.9.1. 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 addition of limited venetoclax and ibrutinib combination specific information to the CLL indication does not change the format or layout of the approved package leaflets and thus no additional consultation with target population groups is warranted.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication for venetoclax in this application is: for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) in combination with ibrutinib.

3.1.2. Available therapies and unmet medical need

Therapy for patients with previously untreated CLL includes agents with distinct mechanisms of action such as BTK inhibitors, chemotherapy, anti-CD20 monoclonal antibodies, Pi3K inhibitor, and BCL-2 inhibitor (venetoclax).

Several different treatment strategies are available for first-line therapy including continuous treatment with BTKis until progression, or time-limited therapies such as venetoclax plus obinutuzumab or venetoclax plus ibrutinib.

Since 2022, ibrutinib in combination with venetoclax is already approved in EU for the treatment of previously untreated CLL, following the submission of a variation from Janssen-Cilag International NV (Janssen), which is the MAH for Imbruvica (ibrutinib, see EPAR EMEA/H/C/003791/II/0070 and Imbruvica SmPC).

3.1.3. Main clinical studies

Study 3011 (GLOW)

This was an open label study randomizing previously untreated subjects older than 64 years or with comorbidities, excluding those with del17p/TP53 mutated disease, 1:1 between the experimental regimen and the approved chlorambucil + obinutuzumab (clb+obi) regimen. Stratification factors were IGHV and del11q status.

The primary endpoint was PFS assessed by IRC, stratified test. Secondary endpoints included MRD negativity rate in bone marrow and OS.

Ibrutinib was administrated for a total of 15 cycles (15x28=420 days, corresponding to approximately 14 months) and venetoclax was introduced after 3 cycles of ibrutinib monotherapy as an attempt to reduce frequency/severity of tumour lysis syndrome (TLS), and continued for 12 cycles.

The ITT analysis set consisted of 211 subjects, 106 in the experimental arm and 105 in the control arm. The primary analysis was event-driven, planned after 71 observed events, and based on a cut-off on 26 February 2021 with a median follow-up of ~28 months. An analysis with 6-months extended follow-up, cut-off 19 August 2021 with a median follow-up of ~34 months, was also provided in the primary CSR.

An updated CSR dated 1 August 2024, with 36-month extended follow-up from primary analysis and a median time on study for all subjects of 64.0 months (range: 1.7 to 69.7) at DCO 24 February 2024, was also submitted in this procedure.

Study 1142 (CAPTIVATE), FD cohort

This was a single-arm trial enrolling previously untreated subjects 18-70 years old with or without del17p/TP53 mutation, i.e., a more fit population compared to that enrolled in the 3011 study.

The primary endpoint was CRR (CR/CRi) per investigator in the non-del17p population, testing ≤37% *vs* >37%. Secondary endpoints included ORR, DOR, MRD and OS.

The analysis set used for the primary analysis consisted of 159 subjects whereof 27 with del17p/TP53 mutation. The primary analysis was planned when the last enrolled subject had the opportunity to be followed for at least 30 cycles (15 cycles of treatment + 15 cycles of posttreatment follow-up) and based on a data extract on 12 November 2020, with a median follow-up of ~28 months. An analysis

with 9-months extended follow-up, cut-off 4 August 2021 with a median follow-up of ~39 months, was also provided in the primary analysis CSR.

An updated CSR dated 21 August 2024 with the final analysis and a median follow-up duration of 69.0 months (range 0.8 to 73.2) in the FD cohort (database lock date 21 May 2024) was submitted in this procedure.

3.2. Favourable effects

Study 3011 (GLOW)

PFS

The experimental regimen was statistically superior over control in terms of PFS, HR=0.216 (95% CI: 0.131, 0.357); p<0.0001, at the primary analysis by IRC, with an event rate of 64% for the control arm. This is supported by presented alternative analyses, and a generally consistent treatment effect across predefined subgroups.

At the time of the 36-months extended follow-up, with a median time on study of 64 months, the PFS by INV showed a continued benefit with fixed duration ibrutinib plus venetoclax vs. chlorambucil plus obinutuzumab (HR: 0.267; 95%CI: 0.182, 0.393), nominal p<0.0001, not type 1 error controlled.

MRD

With sample rates of 87% in the experimental arm and 80% in the control arm, the primary analysis of best MRD response in bone marrow (BM) assessed by NGS showed a response rate of 55.7% in the experimental arm and 21.0% in the control arm, rate ratio 2.65 (95% CI: 1.75, 3.99); p<0.0001.

At 3 months post-treatment, the MRD negativity rates in the experimental arm *vs* the control arm were 52% *vs* 17% in BM (sample rates 80% *vs* 77%) and 55% *vs* 39% in peripheral blood (PB) (sample rates 83% *vs* 84%), respectively. At 12 months post treatment, corresponding to 26 months after randomisation, and with a sampling rate of 77%, the MRD negativity rate in PB was 49% in the experimental arm vs 12% (sampling rate 50%) in the control arm.

OS

At the primary analysis, 11 (10.4%) death events were observed in the experimental arm and 12 (11.4%) in the control arm; HR=1.048 (95% CI: 0.454, 2.419).

Based on the data cut-off of 24 February 2024, with a median time on study of 64.0 months and a maturity of 38% in the control arm and 19% in the experimental arm, the HR for OS was 0.462 (95% CI: 0.269, 0.791).

Study 1142 (CAPTIVATE), FD cohort

CRR

At the primary analysis, the CRR per investigator for all subjects was 55.3% (95% CI: 47.6, 63.1) and 55.9% (95% CI: 47.5, 64.2) for subjects without del 17p. The CR rate for subjects without del 17p was significantly higher than the study-assumed minimum rate of 37% (1-sided p-value < 0.0001) as well as the 40% rate achieved in this population with FCR. CRR in del 17p/TP53 mutated disease (n=27) was similar to the complement, 56%. The CR rate per IRC was 61% (95% CI: 52.8, 69.2) for subjects without del 17p and 59.7% (95% CI: 52.1, 67.4)) for all subjects.

ORR

At the primary analysis, the ORR per investigator assessment as well as IRC was 96.2% for all subjects and 95.6% for subjects without del 17p. For subjects with del 17p/TP53 mutated disease, the ORR was 96.3%. No change in ORR per investigator assessment was observed after 9-months extended follow-up.

DOR

At the primary analysis, the median DOR per investigator assessment were not reached for all subjects or for subjects without del 17p; the 24-month landmark estimates were 94.7% for all subjects and 96.1% for subjects without del 17p based on an overall median follow-up of 28 months. With 9-months extended follow-up, similar outcomes in DOR were observed for all subjects and subjects without del 17p (median not reached for both populations; 30-month landmark estimates of 88.6% and 89.8%, respectively). At the primary analysis, the 24-month landmark estimate for DOR was 84% for the del17p/TP53 population.

In the final analysis, with a median follow-up duration of 69 months, the median DOR was still not reached for all-treated subjects and subjects without del 17p.

MRD

At the primary analysis, with MRD assessed by flow cytometry in the all-treated population, the overall negativity rate was 60% in BM and 77% in PB, and the corresponding figures 52% and 57% for MRD negativity rate 3 months post-treatment. The outcomes were similar at 9-months extended follow-up.

The overall MRD negativity rate in PB in the del17p/TP53 population was 82% at the primary analysis, 59% at 3 months post-treatment, and 37% at 12 months post-treatment. The corresponding figures for BM were 41%, 41% and not applicable.

OS

Regarding OS, the K-M point estimates at 24 months were 98.1% for all subjects and 97.7% for non-del 17p subjects. For subjects with del 17p/TP53 mutated disease, the K-M point estimate at 24 months was 96.2%.

In the final analysis, with a 69-month median follow-up, the K-M point estimate for OS at 66 months was > 95% for all-treated subjects and the subjects without del 17p. The median OS was also not reached for subjects with del 17p/TP53 and the K-M point estimate of OS rate at 66 months for these subjects was 88.1%.

3.3. Uncertainties and limitations about favourable effects

Data on del17p/TP53 mutated disease is scarce with the entire dataset consisting of only 27 subjects in the 1142 single arm trial.

3.4. Unfavourable effects

Study CLL3011

The frequency of patients with any TEAE (Ibr+Ven vs. Clb+Ob: 99.1% vs. 94.3%) and any grade ≥3 TEAE (Ibr+Ven vs. Clb+Ob: 75.5% vs. 69.5%) was similar between treatment arms. Higher frequencies (Ibr+Ven vs. Clb+Ob) were noted for SAEs (46.2% vs. 27.6%; grade ≥3: 38.7% vs. 21.9%) and fatal TEAEs leading to death within 30 days of last dose (6.6% vs. 0).

A higher frequency in grade 3 or 4 TEAEs (>5% difference) in the Ibr+Ven arm vs. the Clb+Ob arm was noted for diarrhoea (10.4% vs. 1.0%), hyponatraemia (5.7% vs. 0%), hypertension (7.5% vs. 1.9%) and atrial fibrillation (6.6% vs. 0%). A lower frequency in grade 3 or 4 TEAEs (>5% difference) in the Ibr+Ven arm vs. the Clb+Ob arm was noted for neutropenia (28.3% vs. 44.8%), thrombocytopenia (5.7% vs. 20.0%) and tumour lysis syndrome (0% vs. 5.7%).

The frequency of SAEs was higher in the Ibr+Ven arm (46.2%) compared with the Clb+Ob arm (27.6%). The most common SAEs (≥2% of subjects) in the Ibr+Ven arm were atrial fibrillation, pneumonia, anaemia, cardiac failure, and diarrhoea. The most common SAEs in the Clb+Ob arm were pneumonia, febrile neutropenia, infusion-related reaction, and TLS.

Fatal TEAEs (death within 30 days of last dose) were reported for 7 patients (6.6%) in the Ibr+Ven arm vs. no patients in the Clb+Ob arm. Of the 7 deaths in the Ibr+Ven arm, 4 deaths occurred during ibrutinib lead-in therapy and 3 during ibrutinib and venetoclax combination therapy.

Tumour lysis syndrome TEAEs were reported in the Clb+Ob arm only (5.7%; all grade 3 or 4). In the Ibr+Ven arm in study CLL3011, 55.7% of patients were hospitalised for TLS prophylaxis after ibrutinib lead-in. Based on laboratory data, 4 patients met the Howard criteria for subclinical TLS.

Treatment discontinuations for either study drug were reported at a higher rate in the Ibr+Ven arm (20.8%) compared with the Clb+Ob arm (7.6%).

Study 1142

Lower frequencies were noted for grade ≥3 TEAE (64.7%), SAEs (21.7%; grade ≥3: 18.3%) and fatal TEAEs (0.3%) compared with the Ibr+Ven arm of study CLL3011. The fatal event was reported as sudden death in 1 patient (0.3%) during ibrutinib lead-in. Grade 3 or 4 TLS was reported in 1 patient (0.3%).

Treatment discontinuations for either study drug were reported in 6.5% of patients over the total treatment period.

3.5. Uncertainties and limitations about unfavourable effects

There was an imbalance in treatment associated deaths which were only reported in the Ibr+Ven arm in study CLL3011. However, there is uncertainty on the magnitude of any difference, especially given the relatively small sample size of study CLL3011. Notably, data with 36 months extended follow-up after the primary analysis, are not indicative of any overall detrimental effect on OS for the Ibr+Ven combination.

The precise impact of each agent in the combination on the safety profile cannot be ascertained in the absence of single agent treatment arms. Given the few cases of fatal cardiac death during ibrutinib/venetoclax combination treatment, there is uncertainty regarding a potential indirect role of venetoclax. The effect of increased exposure of venetoclax on the safety profile of venetoclax when given in combination with ibrutinib cannot be assessed but information to this effect has been added in the SmPC.

3.6. Effects Table

Table 45. Effects Table for venetoclax in combination with ibrutinib for the for the treatment of adult patients with previously untreated CLL

Effect	Short description	Unit	Ven+Ibr	Clb+Obi	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Time from date of randomisation to date of first observation per investigator assessment of progressive disease or death due to any cause, whichever occurs first according to the IWCLL 2008 criteria	Median, months (95% CI)	NE (31.2, NE)	21 (16.6, 24.7)	HR (95% CI): 0.22 (0.13, 0.36), p-value<0.0001 Consistent results with extended follow-up	CLL3011
MRD negativity rate	In bone marrow measured by NGS	n (%) (95 % CI)	59 (55.7) (46.2, 65.1)	22 (21) (13.2, 28.7)	Consistent results with measurements post treatment	
CRR (CR/Cri) by IRC	All subjects Non-del17p	% (95 % CI)	59.7 (52.1, 67.4) 61.0 (52.8,69.2)	NA	In patients with del 17p/TP53 mutation (n = 27) complete response rate based on IRC assessment was 55.6%.	1142

Unfavourable Effects			Any grade	Grade 3-4	Any grade	Grade 3-4		
AEOSI	Haemorrhage	%	34.9	3.8	7.6	1.0	Lack of monotherapy arm makes difficult to ascertain contribution of individual components to observed effects	CLL3011
			60.7	0.9	NA	NA		1142
	Tumour lysis syndrome	%	0	0	5.7	5.7		CLL3011
			0.3	0.3	NA	NA		1142
	Hepatotoxicity	%	6.6	3.8	3.8	1.0		CLL3011
			4.3	1.9	NA	NA		1142
	Atrial fibrillation	%	14.2	6.6	1.9	0		CLL3011
			5.9	1.5	NA	NA		1142

	Other cardiac arrhythmias	%	14.2	2.8	10.5	1.9		CLL3011
			17.3	2.2	NA	NA		1142
	Cardiac failure	%	4.7	2.8	1.0	1.0		CLL3011
			0.3	0.3	NA	NA		1142
	Hypertension	%	14.2	8.5	4.8	1.9		CLL3011
			16.4	7.1	NA	NA		1142
	Infections	%	60.4	15.1	48.6	10.5		CLL3011
			69.7	8.4	NA	NA		1142
	Other malignancies	%	7.5	NA	9.5	NA		CLL3011
			5.6	NA	NA	NA		1142
Death	Due to AE		6.6	NA	1.9	NA	OS after extended follow-up not indicative of detrimental effect	CLL3011
			0	NA	NA	NA		1142

Abbreviations: AE: Adverse event; AEOSI: Adverse event of special interest; CI: confidence interval; CLL: chronic lymphocytic leukaemia; CR: complete response; CRi: complete response with incomplete marrow recover; CRR: complete response rate; HR: hazard ratio; IRC: independent review committee; IWCLL: International Workshop in CLL ;MRD: minimal residual disease; NA: not applicable; NE: not estimable; NGS: next generation sequencing; OS: overall survival; PFS: progression free survival;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the randomised 3011 study, enrolling previously untreated subjects older than 64 years or with comorbidities, excluding those with del17p/TP53 mutated disease, the experimental regimen combining two distinct and complementary mechanisms of action, was significantly and robustly superior to clb+obi in terms of PFS, with a HR point estimate of 0.216 in the primary analysis. This outcome is supported by significantly higher best MRD response in BM and CRR in the experimental arm.

A high CRR in study 1142 of 56% was noted, independently of del17p, supported by an ORR of 96% and overall MRD negativity rates of 60% in BM and 77% in PB. Persistence of effect is supported by the long term outcomes after a median follow-up duration of 69 months. Data investigating the ibr+ven regimen in fit patients is derived in the 1142 SAT and compatible with a highly efficient treatment regimen in terms of activity and a high fraction of durable complete responses.

From a safety perspective, the imbalance in fatal events in study CLL3011 is mainly driven by cardiac related deaths in 4 patients. The 4 cardiac deaths reported in the Ibr+Ven arm of study CLL3011 as

well as the death in study 1142 were assessed as possibly related to ibrutinib and occurred in patients with baseline risk factors. As of today, it is well known that ibrutinib increases the risk of fatal and serious cardiac arrhythmias and cardiac failure. However, the overall OS outcome of the study is reassuring, as there is no indication of an overall detrimental effect on survival.

The oral ven+ibr treatment, intended for a limited treatment duration, further provides convenience and the possibility of a drug holiday, and is currently included in the ESMO Guidelines as one of several reasonable treatment options for 1L CLL patients who are sufficiently fit for its use.

3.7.2. Balance of benefits and risks

The benefits of venetoclax in combination with ibrutinib for a limited treatment duration regimen in 1L CLL outweigh the risks.

3.8. Conclusions

The overall B/R of Venclyxto in combination with ibrutinib 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 ibrutinib, the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for VENCLYXTO based on the results of the phase 3 study 54179060CLL3011 (GLOW) and phase 2 study PCYC-1142-CA (CAPTIVATE). GLOW is a randomized, open-label, phase 3 study of the combination of ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab for the first-line treatment of subjects with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). CAPTIVATE study is a phase 2, multicentre, international, efficacy and safety study assessing treatment with venetoclax plus ibrutinib in subjects with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 12.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor changes to the PI and to update the list of local representatives in the Package Leaflet.

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 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/0000322237.