20 September 2018
EMA/CHMP/717199/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Venclyxto

International non-proprietary name: venetoclax

Procedure No. EMEA/H/C/004106/II/0008

Note

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

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List of abbreviations

AE	adverse event
ALC	absolute lymphocyte count
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
BCRi	B-cell receptor pathway inhibitor
BR	bendamustine in combination with rituximab
CCOD	clinical cutoff date
CLL	chronic lymphocytic leukemia
CMH	Cochran–Mantel–Haenszel
CR	complete remission
CRi	complete remission with incomplete bone marrow recovery
CT	computed tomography
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOCTR	end of the combination treatment response
EORTC	European Organisation for Research and Treatment of Cancer
E-R	exposure response
FC	fludarabine and cyclophosphamide
FDA	U.S. Food and Drug Administration
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IRC	Independent Review Committee
IV	Intravenous
iwCLL	international workshop on Chronic Lymphocytic Leukemia
K-M	Kaplan-Meier
MDASI	M. D. Anderson Symptom Inventory
MRD	minimal residual disease
MTD	maximum tolerated dose
NHL	non-Hodgkin's lymphoma
nPR	nodular partial remission
OR	overall response
ORR	overall response rate
OS	overall survival

PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetic
popPK	population PK
PR	partial remission
PRO	patient-reported outcome
QD	once daily
QLQ-C30	Quality of Life Questionnaire Core 30
RP2D	recommended phase 2 dose
R/R	replapsed/refractory
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SD	stable disease
SLL	small lymphocytic lymphoma
TLS	tumor lysis syndrome
TTNT	time to next anti-CLL treatment
TTP	time to tumor progression
V+R	venetoclax in combination with rituximab

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 8 January 2018 an application for a variation.

The following variation was requested:

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

Extension of Indication to include Venclyxto in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.
As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

This submission also fulfils the Annex II condition to submit the results of the MURANO study comparing venetoclax plus rituximab to bendamustine plus rituximab in patients with relapsed/refractory CLL. In addition, RMP version 3.0 is submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Venclyxto, was designated as an orphan medicinal product EU/3/12/1080 on 11th November 2012. Venclyxto was designated as an orphan medicinal product in the following indication: Treatment of chronic lymphocytic leukaemia.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The applicant sought Protocol Assistance at the CHMP on clinical aspects.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	8 January 2018
Start of procedure:	27 January 2018
Rapporteur's preliminary assessment report circulated on:	23 March 2018
Co-Rapporteur's preliminary assessment report circulated on:	23 March 2018
Joint Rapporteur's updated assessment report circulated on:	20 April 2018
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 April 2018
MAH's responses submitted to the CHMP on:	20 July 2018
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 August 2018
Rapporteur's updated assessment report on the MAH's responses circulated on:	13 September 2018
PRAC RMP advice and assessment overview adopted by PRAC:	6 September 2018
CHMP opinion:	20 September 2018
The CHMP adopted a report on similarity of Venclyxto with Arzerra (ofatumomab), Gazyvaro (obinutuzumab) and Imbruvica (ibrutinib) on date (Appendix I)	20 September 2018

2. Scientific discussion

2.1. Introduction

Venetoclax is a selective, orally available, small molecule inhibitor designed to bind competitively to B-cell lymphoma-2 (BCL-2), thereby liberating pro-apoptotic proteins to trigger apoptosis in cancer cells. Aberrant expression of BCL-2 is common in chronic lymphocytic leukaemia (CLL) and CLL cells typically rely on BCL-2 for survival.

Chronic lymphocytic leukemia (CLL) is a progressive hematologic disease characterized by an accumulation of monoclonal mature B cells in the blood, bone marrow, and secondary lymph organs,

and diagnosis requires the presence of ≥5000 B-lymphocytes/µL in the peripheral blood for the duration of at least 3 months. It is the most common form of adult leukaemia in the Western world, representing about 30% of leukaemias, with higher incidences in North America and Europe than in Asia, with an incidence of 4 per 100,000 persons per year. In Europe, the age-standardised CLL incidence rate from the United Kingdom Clinical Practice Research Datalink was 6.2/100,000 person years. The median age of diagnosis in the EU is 72 years and only 10% of patients are less than 55 years old. The current WHO classification system recognizes and groups CLL and small lymphocytic lymphoma (SLL) as the same biological entity, with CLL clinically manifesting primarily in bone marrow and peripheral blood, and SLL primarily manifesting in the lymph nodes.

Current treatments for CLL are not curative. Fewer patients obtain responses with each subsequent regimen, and subjects become increasingly resistant to available therapy. Patients who relapse after a disease-free period of over 1 year (2-3 years for chemoimmunotherapy) are considered treatment sensitive and may be candidates for treatment reinitiation. Patients who relapse after a shorter interval, or are refractory to first-line treatment, present a more challenging group, particularly those who are older, have comorbid conditions, and/or harbour high-risk cytogenic abnormalities. A retrospective analysis of patients in the German CLL8 trial found that overall survival after the start of salvage treatment among patients whose disease had progressed within 2 years after the end of chemoimmunotherapy was about 2 years, comparable to that of truly refractory patients. In the EUROCARE-5 registry, the survival rate for patients with CLL at 5 years post diagnosis was 69.0%.

Patients with a genetic mutation with 17p del or a mutation of the tumour suppressor gene TP53 have a poor prognosis, with a median overall survival (OS) of 2 to 5 years. Approximately 5% to 10% of patients with early stage CLL have a 17p del and/or TP53 mutation; this rate increases with treatment lines up to 40% in advanced refractory CLL. Approximately 80% of CLL patients with a 17p del also have a mutation in TP53; sole TP53 mutations in the absence of 17p del have been reported to occur in approximately 4% to 5% of patients.

The monoclonal antibody ofatumumab, is currently approved in the EU in the treatment of CLL in the relapsed or refractory setting as a single agent. The combination of the monoclonal antibody rituximab with chemotherapy (eg, fludarabine and cyclophosphamide) (FCR regimen) is approved in the EU for use in this setting. Marketing authorization for alemtuzumab, which had been indicated for the treatment of CLL in patients for whom fludarabine combination chemotherapy is not appropriate, was withdrawn in the EU in August 2012.

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only treatment option with the potential to cure CLL; however most patients are not fit for HSCT and the benefits must be weighed against the risks for each patient. Historically, the prognosis for 17p del CLL patients has been poor due to the limited efficacy of immunotherapy and chemoimmunotherapy-based regimens. A median progression free survival (PFS) of 14 months has been reported in first-line 17p deletion patients and 6 to 7 months in relapsed/refractory (R/R) 17p del patients; median OS was approximately 24 months.

Recent introduction of targeted therapy, such as BCR inhibitors (BCRi), has improved the treatment options for CLL patients with the 17p del or TP53 mutation. Ibrutinib demonstrates independent review committee (IRC) assessed objective remission rate (ORR) of 48% to 65% (investigator assessed ORR of 83% to 86%) and idelalisib/rituximab demonstrates IRC assessed ORR of 85%. In 2014, Imbruvica (ibrutinib) and Zydelig (idelalisib) in combination with rituximab were approved for treatment of CLL patients that have received at least one prior therapy and first-line treatment in the presence of 17p del or TP53 mutation in patients unsuitable for chemo-immunotherapy.

Venclyxto in monotherapy is currently conditionally licensed for the treatment of CLL:

- in the presence of 17 p 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.

This is an extension of Indication to include: “Venclyxto in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy”.

Venclyxto is orally administered presented as film coated tablets proposed as a starting dose of 20 mg once daily for 7 days, to be gradually increased over a period of 5 weeks up to the recommended daily dose of 400 mg.

The MAH requested scientific advice (protocol assistance) and follow up advice on clinical aspects of this application.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The applicant 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

2.3.2. Pharmacokinetics

Venetoclax observed PK

Pharmacokinetic (PK) measurements were taken in both study M13-365 and study GO28667. The PK samples were collected after the venetoclax dose ramp-up schedule. The pre-dose sample for Cycle 1 was collected prior to the first dose of rituximab, whereas all subsequent PK samples were collected after initiating rituximab therapy. A comparison of cycle 1 and cycle 4 pre-dose steady-state mean venetoclax plasma concentration is shown in **Table 1**.

Table 1: Cross-Study Comparison of Steady-State Mean (± SD) Venetoclax Plasma Pre-dose Concentrations (µg/mL) Following a 400 mg Dose of Venetoclax

Study	Steady-State mean (±SD) Venetoclax Plasma Predose Concentrations (µg/mL) Following a 400 mg Dose of Venetoclax	
	Cycle 1 [a, b]	Cycle 4 [a, b]
M13-365 [c]	0.72±0.49 (n=13)	0.63±0.58 (n=12)
GO28667	0.63±0.54 (n=151)	0.68±0.75 (n=112)

[a] In M13-365 Cycle 1 is Month 1, Cycle 4 is Month 4.
[b] Cycle 1 pre-dose is venetoclax alone, Cycle 4 pre-dose is venetoclax with rituximab.
[c] Cohort 3 and 6.

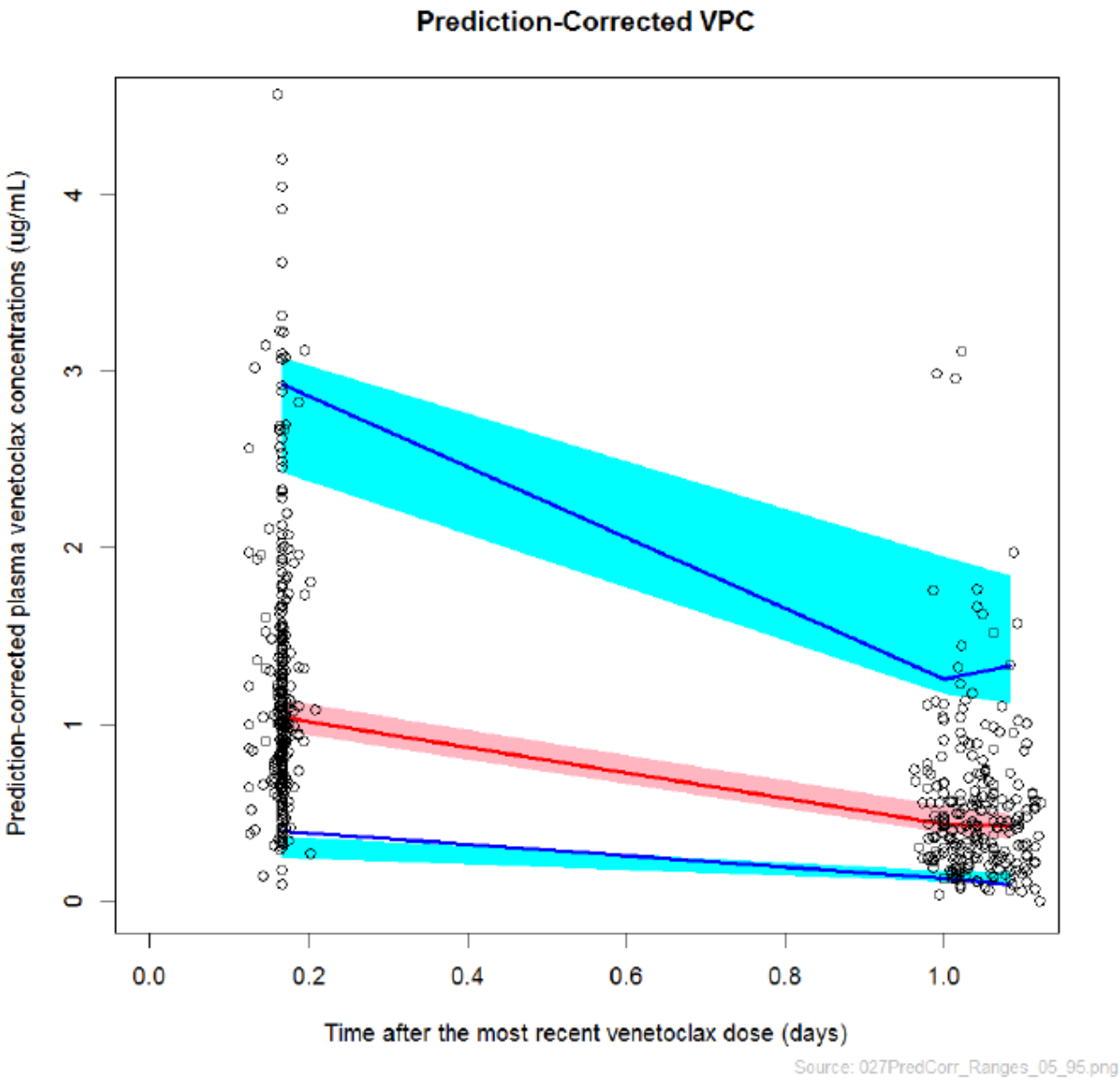
PopPK venetoclax

PK parameters of venetoclax were characterized using a popPK analysis. The popPK analysis assessed whether a previous popPK model structure for venetoclax was able to describe PK of venetoclax in combination with Rituximab in study GO28667. All patients in Arm A (venetoclax + rituximab) in study GO28667 with at least one quantifiable plasma venetoclax concentration value by the pharmacokinetic samples analysis data cut-off date (2/24/2017) were included in the population pharmacokinetic analysis. The analysis included 600 quantifiable venetoclax plasma samples from 182 patients following 400 mg daily dose of venetoclax.

The data were described by the two-compartment population PK model with first-order absorption and elimination. The final model structure was identical to the final model of the previous analysis, with an additional effect of geographical region on apparent clearance. Shrinkage of the inter-individual random effects was moderate to high (31-54%). Rituximab co-administration was estimated to increase CL/F by 7% (95% CI: 2% – 12%). Patients from Central and Eastern Europe and Asia had apparent clearance 30% (95% CI: 21% – 39%) lower and steady state exposure approximately 43% higher compared to patients from other regions.

Figure 1: Prediction-Corrected Visual Predictive Check, Model 027 (Final Model)

Points are prediction-corrected venetoclax concentrations plotted versus time after most recent venetoclax dose. The lines show median (red), and the 5th and 95th percentiles (blue) of the prediction-corrected venetoclax concentrations. The shaded regions show the 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 500 trials with dosing, sampling, and the covariate values of the analysis dataset.



Patients from Central and Eastern Europe and Asia had apparent clearance 30% lower and steady state exposure approximately 43% higher compared to patients from other regions. Only 4 patients were from Asia, thus no conclusion on PK differences for patients from the Asian region can be drawn.

60 patients were from central/eastern Europe. However it does not appear that a link for this geographical region to race can be made that would explain the difference in clearance. In the popPK

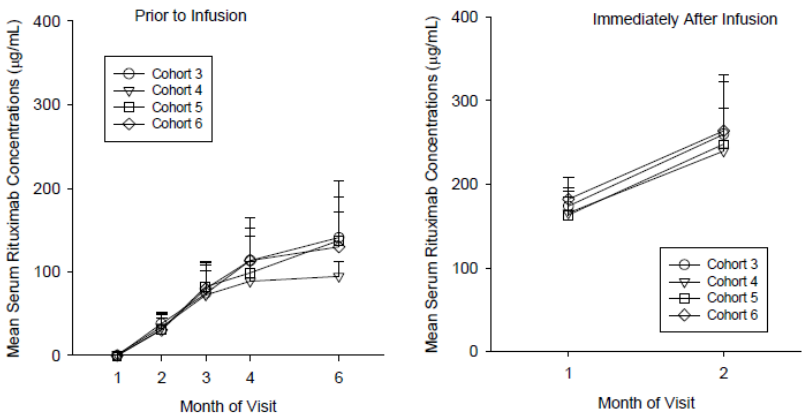
report 176 patients were assigned race *white* while 6 patients were assigned as Asian. No other races were reported.

Both the popPK and the observed data suggest that there is no DDI between venetoclax and rituximab. The similarity in parameter estimates between the previous and the updated popPK models show that PK of venetoclax is similar in study GO28667 compared to what has previously been reported.

Rituximab PK

PK samples for rituximab were not collected in study GO28667 but were collected in study M13-365. The mean (SD) for serum concentration of rituximab for cohorts 3 through 6 obtained at the monthly combination visits prior to and immediately after the infusion are presented in **Figure 2**. Different doses of venetoclax from Cohorts 3 through 6 (200, 300, 400 and 600 mg) did not have any statistically significant impact on rituximab mean concentrations prior to and immediately after infusion at each combination therapy visit (p-value < 0.05). Steady-state (Month 6) mean rituximab trough concentrations ranged from 94.9 - 141 µg/mL, depending on cohort. These are similar to trough values reported in the literature with the same rituximab dosing regimen in R/R CLL patients, with mean rituximab trough concentrations at Month 6 of around 100 µg/mL (Li *et al.*, J Clin Pharmacol. 2012). Mean rituximab trough concentrations at the early cycles, such as at Month 3, are approximately 2 to 3 -fold higher than that reported in the literature, likely due to early reduction of B-cells by venetoclax.

Figure 2: Mean (± SD) Rituximab Serum Concentrations prior to and Immediately after Infusion at Monthly Visits: Cohorts 3 to 6



2.3.3. Pharmacodynamics

No additional studies on pharmacodynamics were submitted.

2.3.4. PK/PD modelling

The post-hoc estimates of venetoclax PK parameters from the final population PK model and the relevant PK covariates for each subject were used to estimate individual exposure measures for each patient. For subjects who did not have evaluable PK data and were not included in the population PK analysis, the PK parameters were imputed using the population estimates and the individual subject's covariate values.

Exposure-efficacy analysis

The exposure-efficacy analysis utilized 194 patients administered venetoclax from V+R arm of Study GO28667. The exposure-efficacy analysis of venetoclax efficacy parameters showed no statistically significant or clinically meaningful relationships with venetoclax exposure, supporting the current QD 400 mg regimen of venetoclax in combination with rituximab in R/R CLL patients.

Exposure-safety analysis

The main exposure-safety analysis, which only analyzed the AE data after the end of the ramp-up phase, utilized 191 patients from V+R arm of Study GO28667 and 48 patients from Study M13-365. The logistic regression analyses in patients from studies M13-365 and GO28667 indicated that there were no statistically significant associations between venetoclax exposure and probability of treatment-emergent Grade ≥ 3 neutropenia and treatmentemergent Grade ≥ 3 infections. The pooled exposure-safety analysis suggested no statistically significant improvement in the safety profile would be expected with lower venetoclax exposure over the tested venetoclax dose range (200 - 600 mg QD). Venetoclax co administration did not appear to impact the delivery of rituximab, and patients with higher venetoclax exposure showed similar tolerability of the study treatment compared to patients with lower venetoclax exposure. There was no apparent correlation between venetoclax exposure and venetoclax or rituximab dose intensity. Overall, the exposure safety/tolerability parameters showed no statistically significant or clinically meaningful relationships with venetoclax exposure, supporting the current QD 400 mg regimen of venetoclax in combination with rituximab in R/R CLL patients.

2.3.5. Discussion on clinical pharmacology

The observed mean steady state pre-dose concentration for venetoclax at cycle 1 (venetoclax alone) and cycle 4 (venetoclax + rituximab) are all similar in both the M13-365 and the GO28667 studies. This suggests that there is no drug-drug interaction (DDI) between venetoclax and rituximab affecting venetoclax PK. This is further supported by the popPK analysis.

The previous popPK model structure, used as a starting point here, has previously been assessed and deemed adequate. The pcVPC for the updated model show that the model structure is adequate also for the new data from the GO28667 study. The parameter estimates between the previous model and the updated model are small. Shrinkage was however relatively high.

Rituximab co-administration was estimated to increase CL/F by 7% which can be considered negligible.

Rituximab exposures at steady state did not appear to be affected by different doses of venetoclax in study M13-365. Mean rituximab trough concentrations at the early cycles were a 2 to 3 -fold higher

than that reported in the literature. The explanation that this is likely due to early reduction of B-cells by venetoclax is accepted. Mean concentrations of rituximab at early cycles are still lower than at steady state, thus this increased exposure at early cycles is not expected to provide any safety concerns.

The reason for lower clearance patients in Central/Eastern Europe is not known and could be a chance finding. Further, the venetoclax dose is titrated up for 5 weeks and a table for dose modifications due to toxicity is provided in section 4.2 of the SmPC. Thus, it does not appear that any changes in posology for patients in Central/Eastern Europe are warranted.

Only one dosing regimen was used in study GO28667 and thus, the usefulness of the exposure-efficacy analysis is limited. Shrinkage from the popPK was relatively high (31-54%) indicating difficulty for the model to estimate individual parameters, further limiting the value of the exposure-efficacy analysis.

As expected, the exposure-response analysis showed no significant relationships with venetoclax exposure.

The information from the exposure-response analyses are of limited value but the venetoclax dosing regimen in combination with rituximab can be supported based on the clinical efficacy data (see Clinical Efficacy section).

Only one dosing regimen was used in study GO28667. For the exposure-safety analyses, data from study M13-365 was also included. While the data from M13-365 was for only around 50 patients, the usefulness of exposure-safety analyses could have been higher than for the exposure-efficacy since several doses were studied in M13-365. For subjects who did not have evaluable PK data and were not included in the population PK analysis, the primary PK parameters were imputed using the population estimates and the individual subject's covariate values. Since data from M13-365 was not included in the popPK model, the exposures for patients in M13-365 is not adequately described by the applicants approach. In addition, high shrinkage from the popPK model is still an issue further limiting the usefulness of the exposure-safety analysis.

The exposure safety/tolerability parameters showed no statistically significant or clinically meaningful relationships with venetoclax exposure. While the exposure-safety has several limitations it suggested that no statistically significant improvement in the safety profile would be expected with lower venetoclax exposure over the tested venetoclax dose range. This would suggest that the approved 400 mg dosing regimen of venetoclaxm which was chosen for study GO28667 was appropriate from an exposure-safety standpoint. (see also Clinical Safety section).

The usefulness of the conducted exposure-efficacy and exposure-safety modeling analyses are limited but using the approved doses of venetoclax and rituximab appear appropriate. This is supported by the pharmacokinetics, no clinically relevant DDI between venetoclax and rituximab was found in the observed data or in the popPK analysis.

2.3.6. Conclusions on clinical pharmacology

Clinical pharmacology aspects have been adequately studied. No relevant changes are needed in section 5.2 in the SmPC.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Study M13-365 A Phase 1b Study Evaluating the Safety and Tolerability of Venetoclax (ABT-199) in Combination with Rituximab in Subjects with Relapsed Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma.

First subject study visit 25 July 2012, ongoing, data cut off 01 July 2016.

The primary objectives of this study were to assess the safety profile, determine the maximum tolerated dose (MTD), and establish the Recommended Phase 2 Dose (RPTD) of venetoclax when administered in combination with rituximab in subjects with relapsed chronic lymphocytic leukemia (CLL).

Ramp up dosing of venetoclax was modified to 20 mg, 50 mg, 100 mg, 200 mg (or additional lead-in steps to designated cohort dose). After a week at the designated cohort dose of venetoclax, the combination of venetoclax and rituximab was started.

Up to 50 subjects with relapsed CLL or SLL were planned. As of the data cutoff for this interim CSR, 49 subjects have been treated with at least 1 dose of venetoclax and are included in the safety population, including 8 subjects in the expanded safety cohort.

For the combination period, rituximab was administered monthly on Day 1 of Months 1 to 6 for an overall duration of approximately 6 months. After discontinuation of rituximab, subjects were allowed to receive venetoclax monotherapy for up to 4 years following the date of the last subject enrolled.

Efficacy Results:

All efficacy analyses were exploratory. The 49 subjects enrolled in the study were included across 5 dose-escalating cohorts, in addition to 1 safety expansion cohort at the RPTD and schedule. The efficacy results are summarized as follows: Overall, the majority of subjects (42 [85.7%]) achieved investigator assessed objective response, 25/49 (51.0%) subjects achieved CR or CRi.

Safety Results:

Analysis of overall safety in Study M13-365 at doses from 200 to 600 mg venetoclax did not convincingly demonstrate a relationship between dose and safety. Incidences of treatment emergent adverse events in the Blood and Lymphatic Disorders, Gastrointestinal Disorders, General Disorders and Administration Site Conditions, Metabolism and Nutrition Disorders, Skin and Subcutaneous Tissue Disorders, Musculoskeletal and Connective Tissue Disorders, and Investigations SOCs and grade 3 or 4 adverse events overall were numerically lowest in the 400 mg dose group compared to total subjects. The selection of 400 mg as the dose to explore further in the safety expansion portion of this study (Cohort 6) was based on the balance of safety and efficacy data.

2.4.2. Main study(ies)

Study MURANO

Methods

This is a multicentre, Phase III, open-label, randomized study in relapsed/refractory patients with chronic lymphocytic leukemia to evaluate the benefit of venetoclax plus rituximab compared with bendamustine plus rituximab.

Study participants

Main inclusion criteria:

- CLL (Hallek et al 2008)
- Relapsed disease: Achieved CR/PR but evidence of progression after 6 months or more.
- Refractory disease: Treatment failure or progression within 6 months or less after last leukaemia therapy.
- At least one, but no more than three lines of therapy. At least one prior standard chemotherapy regimen according to guidelines.
- Prior bendamustine only if DOR > 24 months.
- ECOG 1 or less.
- Adequate bone marrow, renal and hepatic function.

Main exclusion criteria:

- Transformation to aggressive lymphoma (Richter, DLBCL, pro-lymphocyte), CNS involvement.
- Prior allogenic SCTP
- Intolerance etc. to bendamustine, rituximab
- Autoimmune haemolysis, ITP
- Positive tests for HIV, hepatitis B/C
- Cardiovascular instability grade 3 or more.

Treatments

Experimental therapy: Venetoclax 400 mg daily p.o. (after ramp-up over 4-5 weeks according to SPC and to avoid tumour lysis) for up to two years + rituximab 375 mg/m2 cycle 1 and 500 mg/m2 cycles 2-6 (SPC), cycle length 28 days.

Control therapy: Bendamustin 70 mg/m2 day 1 and 2 for 6 cycles and rituximab 375 mg/m2 cycle 1 and 500 mg/m2 cycles 2-6 (SPC), cycle length 28 days.

Objectives

Outcomes/endpoints

Primary endpoint: PFS (in EU investigator assessed, in US IRC)

Secondary endpoints: CR (IRC), ORR (IRC), OS, MRD, and subgroup by 17 p status PFS, CR, (IRC), ORR (IRC), MRD.

Exploratory endpoints: Relationship between Bcl-2 expression and outcome, "other" biomarkers and outcome.

PRO: Treatment-related symptoms by M.D. symptom inventory (MDASi), EORTC QLQ-C30 and module CLL16. Change from baseline QKQ-C30. Interference of disease symptoms and treatment related symptoms on QoL with MDASI.

Stratification 17 p status, risk status, geographic region, stratified log rank (non-stratified log rank for "confirmation)**.**

- Risk status: High risk (17p del, no response to first line therapy, relapse within 12 month after chemotherapy, 24 month after chemo-immuno-therapy). Low risk: complementary set.
- Region: US/Canada, Australia/New/Zealand, Western Europe, Central/Eastern Europe, Asia, Latin America.
- Planned sample size 370 individuals randomized 1:1. Final analysis at 186 investigator assessed PFS events, one interim analysis at 140 events, i.e. 38% of events in the long run (assuming no cure, relative survival).

Sample size

The primary endpoint of PFS was used to determine the sample size for the study based on the following assumptions: Two-sided log-rank test at the 0.05 level of significance, 80% power to detect a hazard ratio (HR) for venetoclax + R versus BR of 0.66, corresponding to an approximate median improvement of 15.2 months to 23 months (34% reduction in risk of a PFS event), Exponential distribution of PFS, an annual dropout rate of 5%, One interim analysis (IA) for efficacy at approximately 75% of total investigator- assessed PFS events (approximately 140 investigator-assessed PFS events). With these assumptions, 186 investigator-assessed PFS events were required to achieve 80% power for the primary analysis of PFS in all patients. It is planned to enroll 370 patients across the two arms with 1:1 randomization ratio. Sample size calculations were performed with Insightful S+ Seq Trial S 2.0.6.

Randomisation

Block stratified randomization procedure using an interactive voice/web based system was used.

Blinding (masking)

The study was open label.

Statistical methods

Analysis sets. The primary analysis of efficacy was based on the set of all randomized patients (cf intention-to-treat population). The primary analysis of safety was based on the set of all treated patients, who received at least one dose of the study treatment.

Planned interim analysis. One IA was planned during the conduct of the study to assess the efficacy of V+R combination treatment compared with B+R treatment, and to allow for release of the results earlier than the planned final analysis in case of significant differences. The IA is performed when approximately 140 investigator-assessed PFS events have occurred in both treatment arms combined (75% of the 186 events required for the final primary efficacy analysis is available). The stopping boundary follows a unified family with parameter P=2 (Kittelson and Emerson 1999). Based on 140 events, the duration of PFS will be tested at the IA, which corresponds to approximately a 2-sided p-value of 2 * 0.0013 = 0.0026.

Primary efficacy endpoint analysis. A two-sided stratified (by 17p deletion status, risk status and geographic region) log-rank test adjusted for interim analysis; a two sided unstratified log-rank test was performed to confirm the primary analysis. Median PFS and 95% confidence limits were estimated using Kaplan-Meier methodology.

The primary endpoint will be tested at the IA with 140 events, which corresponds to approximately a 2-sided p-value of 2 * 0.0013 = 0.0026. In case the observed number of events is not exactly 140, the boundaries will be updated to reflect the number of events based on investigator assessment and IRC assessment, respectively.

Secondary efficacy endpoint analysis. To adjust for multiple testing of the key secondary efficacy endpoints, a fixed sequence hierarchical testing procedure was used for specific key efficacy endpoints. Formal statistical testing of response rates between the two arms was performed at the two-sided significance level of 0.05 using a stratified Cochran-Mantel-Haenszel (CMH) test. Time-to-event endpoints such as OS, EFS, and TTNT were analyzed using the same statistical methods described for the primary analysis of PFS. Additional secondary endpoints were not tested formally.

Secondary endpoints were tested following a multiple testing procedure based on hierarchical testing. To adjust for multiple testing of key secondary efficacy endpoints, a fixed sequence testing procedure was used (Westfall and Krishen 2001). The following endpoints were tested in the following order: 1) IRC-assessed CR rate, 2) IRC-assessed best ORR, 3) OS.

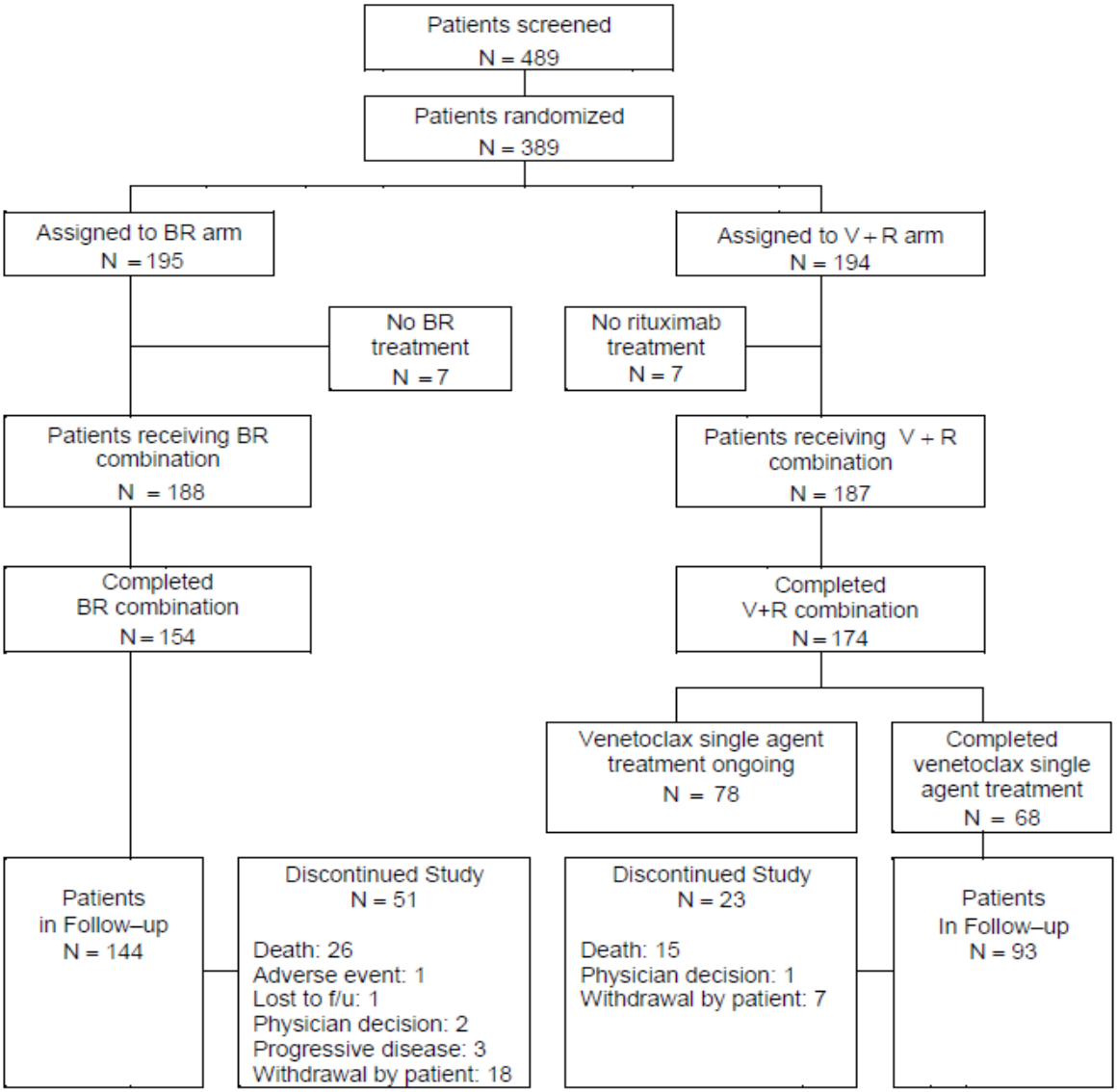
If the study meets its primary efficacy endpoint of prolonged PFS in the treatment arm (V+R) in all randomized patients, then a formal statistical test of IRC-assessed CR rate between the two arms will be performed at the two-sided significance level of 0.05 by using a stratified Cochran-Mantel-Haenszel (CMH) test with stratification factors. If the study does not meet its primary endpoint, then this test will not be performed. The IRC-assessed best ORR will only be tested by the same stratified CMH test once the null hypothesis for IRC-assessed CR rate in all randomized patients has been rejected at a two-sided significance level of 0.05.

If the null hypothesis for IRC-assessed best ORR has been rejected at a two-sided significance level of 0.05, the duration of OS will be analyzed at a nominal alpha spend of 0.0001. Approximately 3 years after the last patient is enrolled, OS will be tested at a two-sided significance level of 0.0499.

Results

Participant flow

Figure 3: Participant flow in Murano study



BR = bendamustine; V + R = venetoclax and rituximab;

Recruitment

Study period: February 2014 (first patient screened) to May 2017 (cut-off for interim analysis)

Study centres: 20 countries (14 EU), 109 centres.

Conduct of the study

A total of 59.9% (233/389) of patients (67.0% [130/194] in the VR arm and 52.8% [103/195] in the BR arm) had at least one major protocol deviation reported. The most common deviations (reported for 66.0% of patients in the VR arm and 50.3% of patients in the BR arm) were procedural deviations, the majority of which were missing individual laboratory assessments at a single response assessment.

None of the major deviations were likely to have an impact on study outcomes.

Baseline data

The median age was 65 years, and about 14% were older than 75, i.e. rather typical for CLL studies with moderately intensive therapies. As expected there was a dominance of males, about 3/4. About half were considered “high risk” and close to 20% had del 17p. About 1/3 enrolled in Western Europe and 1/3 in Central and Eastern Europe.

Table 2: Disease Characteristics

			BR	VR
Time from diagnosis, median, years			7	6
ECOG	0		56 %	57 %
Fludarabine refractory, yes			16%	14%
Bulky disease, lgl largest diameter ≥10 cm			15 %	13 %
Lymphocytes ≥100 10^9/l			28%	26%
B-symptoms	Fever	yes	2%	2%
	Night sweats	yes	21%	22 %
	Weight loss	yes	7%	6%
Del 17 p	yes	Local lab	21%	18%
		Central lab	27%	27%
Del 11 q	yes		27%	27%
Trisomy 12	yes		19%	13%
Del 13 q	yes		76%	83%
Risk status	High*		61%	56%
IgVH unmutated			68%	68%
TP53 mutated			28%	25%
Beta 2 micro > 3.5 mg/l			68%	66%
Prior therapies 1 2 3 FCR FC Chlorambucil +/- prednisolone			 60% 22% 17% 55% 14% 16%	 57% 29% 11% 54% 22% 13%

Fludarabine refractory: no response or progression on therapy or within 6 months.

High risk: 17p del, no response to first line therapy, relapse within 12 month after chemotherapy, 24 month after chemoimmuno-therapy.

FCR: Fludarabine, Cyclophosphamide, Rituximab

Outcomes and estimation

Table 3: Summary (investigator assessment)

Parameter	Bendamustine plus Rituximab (N=195)	Venetoclax plus Rituximab (N=194)
Progression-Free Survival		
Patients with event	114 (58.5%)	32 (16.5%)
Time to Event (months)		
Median [95% CI]	17.0 [15.5, 21.6]	NE
P-value (log-rank test, stratified)	p<0.0001	
Hazard Ratio (stratified), [95% CI]	0.17 [0.11, 0.25]	
Estimate of 1-year PFS rate [95% CI]	72.5% [66.0, 79.1]	92.7% [89.1, 96.4]
Estimate of 2-year PFS rate [95% CI]	36.3% [28.5, 44.0]	84.9% [79.1, 90.6]
PFS in 17p del population[†]	n=46	n=46
Patients with event	27 (58.7%)	7 (15.2%)
Time to Event (months)		
Median [95% CI]	15.4 [10.0, 21.0]	NE [27.6, NE]
P-value (log-rank test, unstratified)	p<0.0001*	
Hazard Ratio (unstratified), [95% CI]	0.13 [0.05, 0.31]	
Estimate of 1-year PFS rate [95% CI]	64.4% [49.4, 79.4]	95.6% [89.5, 100]
Estimate of 2-year PFS rate [95% CI]	27.8% [11.1, 44.4]	81.5% [66.9, 96.1]
Overall Response		
Responders	132 (67.7%)	181 (93.3%)
95% CI	[60.6, 74.2]	[88.8, 96.4]
Difference in Response Rates [95% CI]	25.6% [17.9, 33.3]	
P-value (CMH test)	p<0.0001*	
CR	15 (7.7%)	47 (24.2%)
Cri	1 (0.5%)	5 (2.6%)
nPR	12 (6.2%)	6 (3.1%)
PR	104 (53.3%)	123 (63.4%)
Nonresponders	63 (32.3%)	13 (6.7%)
Stable disease	44 (22.6%)	4 (2.1%)
Progressive disease	6 (3.1%)	3 (1.5%)
Missing or unevaluable	13 (6.7%)	6 (3.1%)
Complete Response Rate		
Complete Responders	16 (8.2%)	52 (26.8%)
95% CI	[4.8, 13.0]	[20.7, 33.6]
Difference in Response Rates [95% CI]	18.6% [11.0, 26.2]	
P-value (CMH test)	p < 0.0001*	
Overall Survival		
Patients with event	27 (13.8%)	15 (7.7%)
Time to event (months)		
Median [95% CI]	NE	NE
P-value (log-rank, stratified)	p=0.0186*	
Hazard Ratio (stratified), [95% CI]	0.48 [0.25, 0.90]	
Estimate of 1-year OS rate [95% CI]	91.1% [86.9, 95.3]	95.9% [93.0, 98.7]
Estimate of 2-year OS rate [95% CI]	86.6% [81.4, 91.7]	91.9% [87.7, 96.1]
Best MRD-negativity Rate in peripheral blood[‡]		
MRD Negative, n (%)	45 (23.1%)	162 (83.5%)
MRD Positive, n (%)	150 (76.9%)	32 (16.5%)
95% CI for MRD negative rates	[17.4, 29.6]	[77.5, 88.4]
Difference in MRD negative rates [95% CI]	60.4% [52.3, 68.6]	
P-value (Chi-square test)	p < 0.0001*	

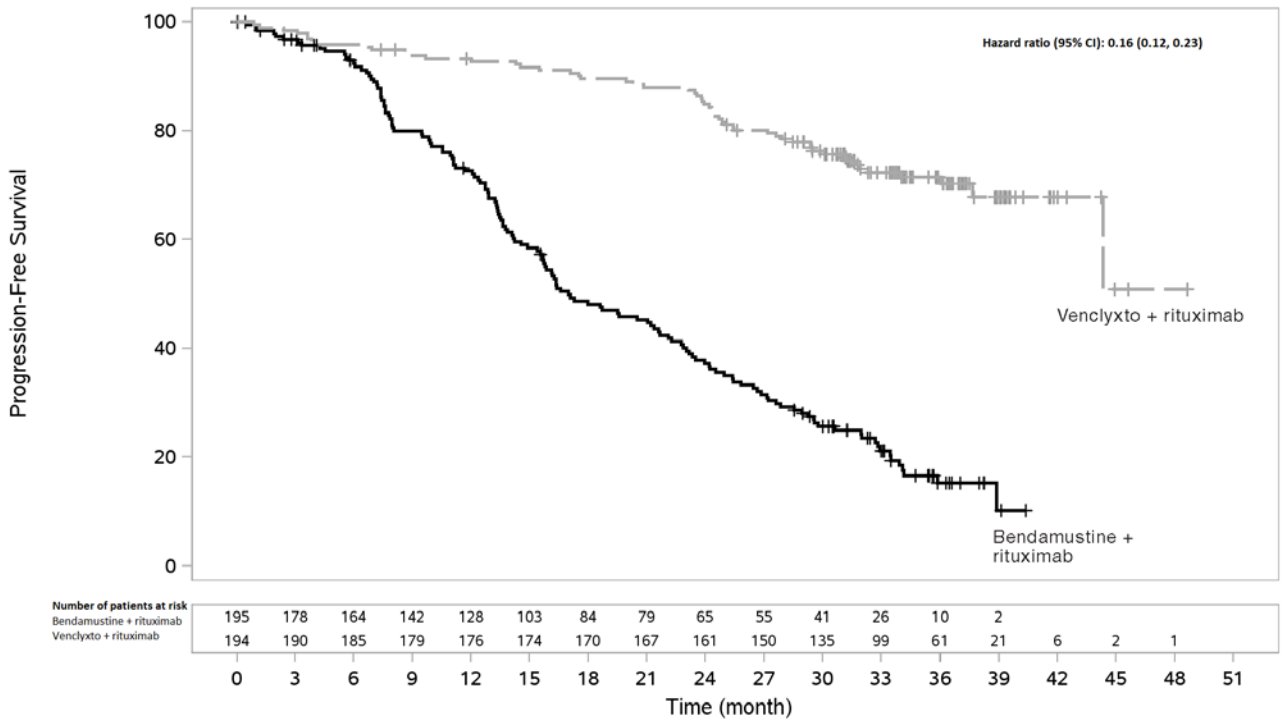
Table 4: Investigator-assessed progression-free survival in patients with previously treated CLL in MURANO (data cut-off date 8 May 2017)

	Venetoclax + rituximab N = 194	Bendamustine + rituximab N = 195
Number of events (%)	32 (16.5)	114 (58.5)
Disease progression	21	98
Death events	11	16
Median, months (95% CI)	NR	17.0 (15.5, 21.6)
Hazard ratio (95% CI)	0.17 (0.11, 0.25)	
P-value[a]	<0.0001	
12-month PFS estimate (95% CI)	92.7 (89.1, 96.4)	72.5 (65.9, 79.1)
24-month PFS estimate (95% CI)	84.9 (79.1, 90.6)	36.3 (28.5, 44.0)

CI = confidence interval; NR = not reached
[a]Stratified P-value.

At an updated efficacy analysis with all patients off treatment (data cut-off date 8 May 2018 and median follow-up of 36 months) the 36-month PFS estimate in the venetoclax + rituximab arm was 71.4% [95% CI: 64.8, 78.1] and in the bendamustine + rituximab arm was 15.2% [95% CI: 9.1, 21].

Figure 4: Kaplan-Meier curves of investigator-assessed progression-free survival (intent-to-treat population) in MURANO (data cut-off date 8 May 2018)



In total, 130 patients in the venetoclax + rituximab arm completed 2 years of venetoclax treatment without progression. Of the 130 patients, 92 patients completed the 6-month post treatment follow-up visit. The estimated PFS rate at 6 months post treatment was 92%.

At 6 months, the VR arm had 8 PFS events compared with 14 PFS events in the BR arm. Also, the BR arm had 18 patients censored within the first six months compared with only one patient censored in the VR arm. Per medical monitor review, the 18 patients censored in the BR arm included 14 who dropped out from the study early and 4 patients who did not have adequate response assessment beyond 6 months.

Table 5: Summary of Sensitivity Analyses for PFS (by Investigator and IRC Assessments, ITT Population)

	Investigator-Assessed PFS		IRC-Assessed PFS	
Analysis	BR N=195	V+R N=194	BR N=195	V+R N=194
Unstratified log-rank test				
Patients with event	114	32	106	35
Median PFS [95% CI], mo	17.0 [15.5, 21.6]	NE	18.1 [15.8, 22.3]	NE
HR (versus BR) [95% CI]	0.17 [0.12, 0.26]		0.20 [0.14, 0.30]	
p-value (log-rank test)	<0.0001		<0.0001	
Censoring for Non Protocol Therapy[a]				
Patients with event	110	31	101	34
Median PFS [95% CI], mo	17.1 [15.7, 21.6]	NE	19.0 [16.2, 22.5]	NE
HR (versus BR) [95% CI]	0.17 [0.11, 0.25]		0.19 [0.13, 0.29]	
p-value (log-rank test)	<0.0001		<0.0001	
Censoring for missing PFS assessments[b]				
Patient with event	106	30	96	35
Median PFS [95% CI], mo	18.0 [15.7, 22.3]	NE	19.6 [16.2, 22.8]	NE
HR (versus BR) [95% CI]	0.16 [0.11, 0.25]		0.20 [0.13, 0.30]	
p-value (log-rank test)	<0.0001		<0.0001	

BR=bendamustine plus rituximab; CI=confidence interval; HR=hazard ratio; INV=investigator; IRC=Independent Review Committee; mo=months; NPT=non-protocol therapy; PFS=progression-free survival; V+R=venetoclax plus rituximab.

[a] Patients who started non-protocol specified anti-CLL treatment before occurrence of PFS event were censored at the time of the new treatment initiation. Two of the 194 patients (1.0%) in the V+R arm and 8/195 patients (4.1%) in the BR arm received new anti-leukemic treatments before progression

[b] Patients with PD or death reported after missing more than one visit consecutively were censored at their last adequate response assessment date before the missed visits.

Efficacy results for the pre-specified primary analysis (data cut-off date 8 May 2017) were also assessed by an Independent Review Committee (IRC) demonstrating a statistically significant 81% reduction in the risk of progression or death for patients treated with venetoclax + rituximab (hazard ratio: 0.19 [95% CI: 0.13, 0.28]; P<0.0001). Additional efficacy results for the pre-specified primary analysis are shown below:

Table 6: Efficacy results in MURANO – Secondary endpoints

	Investigator assessed		IRC assessed	
Endpoint	Venetoclax + rituximab N = 194	Bendamustine + rituximab N = 195	Venetoclax + rituximab N = 194	Bendamustine + rituximab N = 195
Response rate				
ORR, % (95% CI)	93.3 (88.8, 96.4)	67.7 (60.6, 74.2)	92.3 (87.6, 95.6)	72.3 (65.5, 78.5)
CR+CRi, (%)	26.8	8.2	8.2	3.6
nPR, (%)	3.1	6.2	1.5	0.5
PR, (%)	63.4	53.3	82.5[a]	68.2[a]
MRD negativity rate at end of combination treatment[b]				
Peripheral blood, % (95% CI)[c]	62.4 (55.2, 69.2)	13.3 (8.9, 18.9)	NA	NA
Bone marrow, % (95% CI)[d]	15.5(10.7, 21.3)	1.0 (0.1, 3.7)	NA	NA
Overall Survival[e]				
Number of events (%)	15 (7.7)	27 (13.8)		
Hazard ratio (95% CI)	0.48 (0.25, 0.90)			
Time to next anti-leukaemic therapy				
Number of events (%)	23 (11.9)	83 (42.6)	NA	NA
Median, months (95% CI)	NR	26.4	NA	NA
Hazard ratio	0.19 (0.12, 0.31)		NA	

CR = complete remission; CRi = complete remission with incomplete marrow recovery; IRC = independent review committee; MRD = minimal residual disease; nPR = nodular partial remission; NA = not available; NR = not reached; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.

[a]The discrepancy between IRC- and investigator-assessed CR rate was due to interpretation of residual adenopathy on CT scans. Eighteen patients in the venetoclax + rituximab arm and 3 patients in the bendamustine + rituximab arm had negative bone marrow and lymph nodes <2 cm.

[b]Minimal residual disease was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and/or flow cytometry. The cut-off for a negative status was one CLL cell per 10^4 leukocytes.

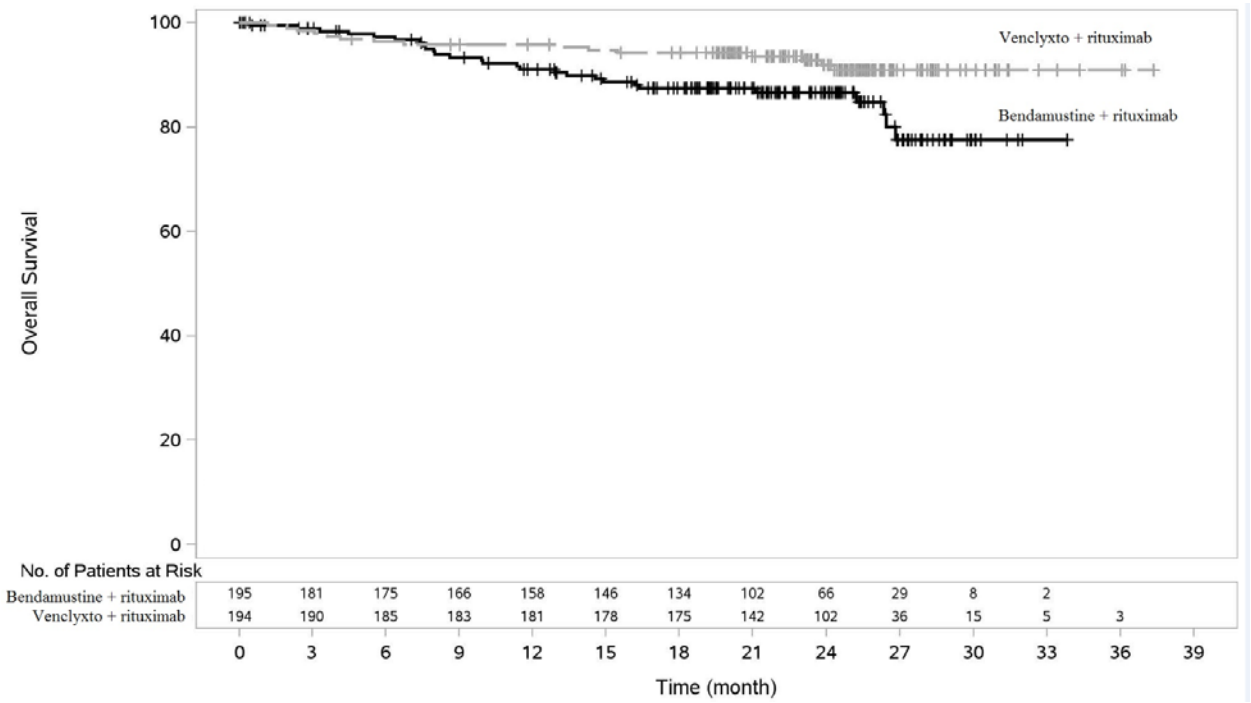
[c]Of those with MRD assay results available in peripheral blood, 72.5% (121/167) in the venetoclax + rituximab arm and 20% (26/128) in the bendamustine + rituximab arm were found to be MRD negative.

[d]Of those with MRD assay results available in bone marrow, 76.9% (30/39) in the venetoclax + rituximab arm and 6.7% (2/30) in the bendamustine + rituximab arm were found to be MRD negative.

[e]Overall survival data are not yet mature.

Median DOR was not reached with median follow up of approximately 23.8 months.

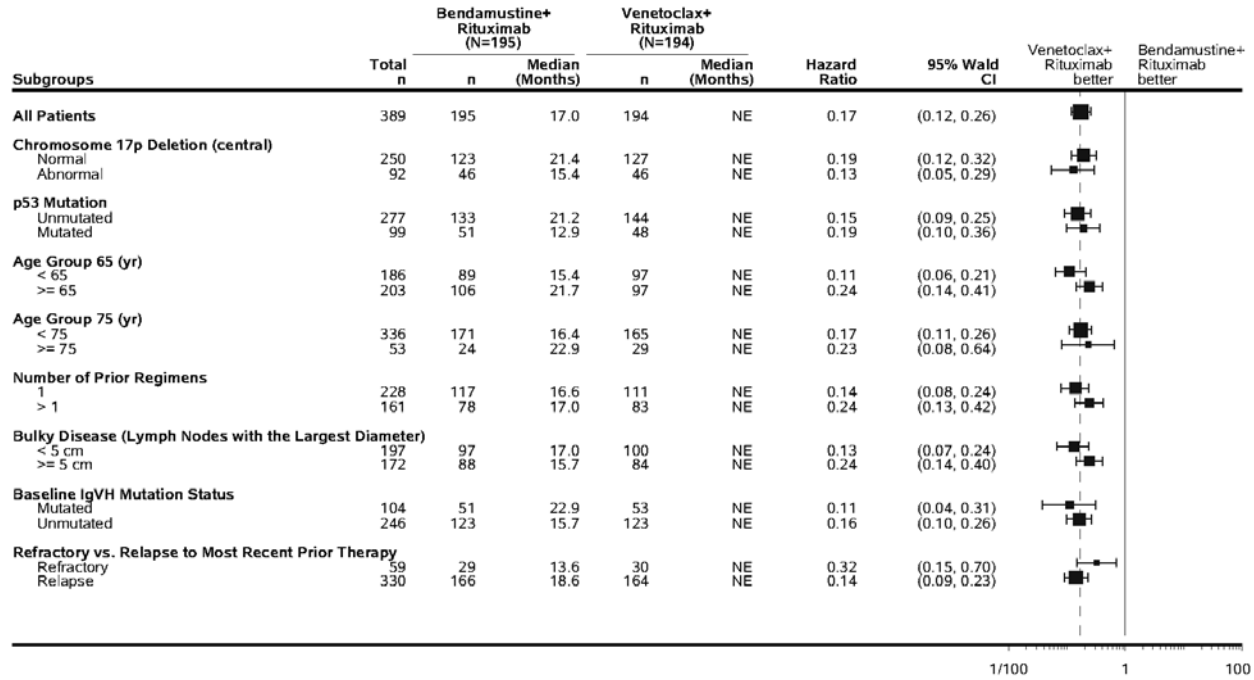
Figure 5: Kaplan-Meier curves of overall survival (intent-to-treat population) in MURANO (data cut-off date 8 May 2017)



Results of subgroup analyses

The observed PFS benefit of venetoclax + rituximab compared with bendamustine + rituximab was consistently observed across all subgroups of patients evaluated, including age (< 65, ≥ 65 years and < 75, ≥ 75 years), prior lines of therapy (1, >1), bulky disease (< 5 cm, ≥ 5 cm), 17p deletion, 11q deletion, *TP53* mutation, *IgVH* mutation, and refractory versus relapse to most recent therapy.

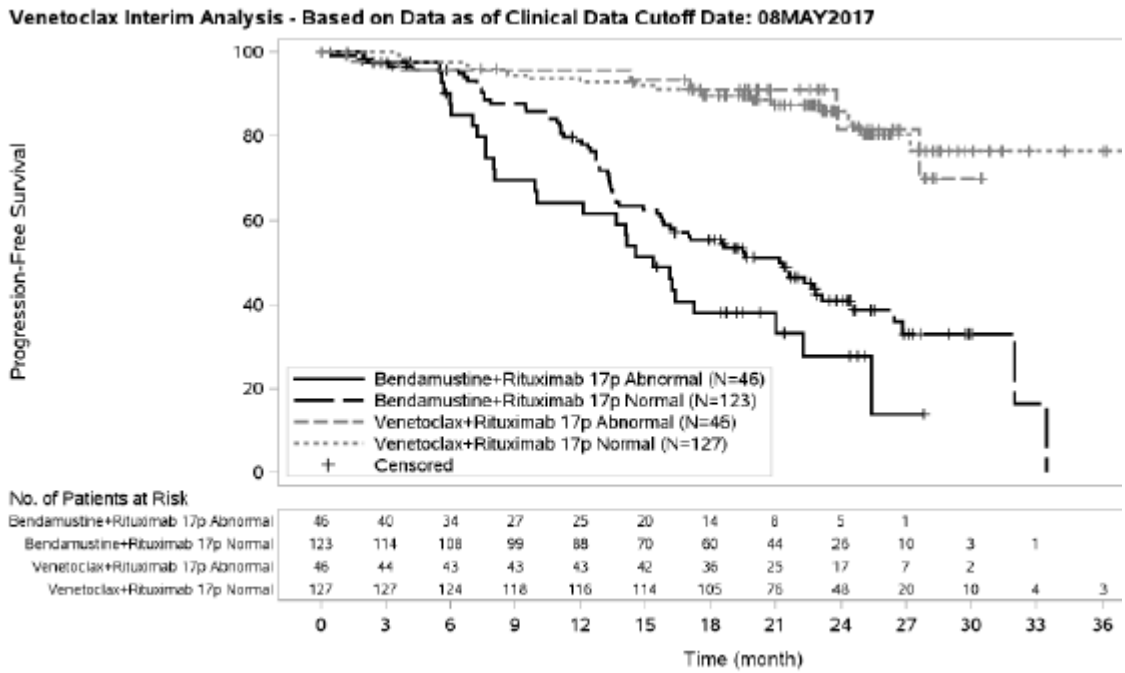
Figure 6: Forest plot of Investigator-Assessed PFS in Subgroups from MURANO



17p deletion status was determined based on central laboratory test results.
Unstratified hazard ratio is displayed on the X-axis with logarithmic scale.
NE=not evaluable.

Ancillary analyses

Figure 7: Kaplan-Meier Plot of Investigator-Assessed Progression-Free Survival by 17p Deletion Status (ITT Population)



Patient 17p deletion status was determined based on central laboratory test results.

Figure 8: Kaplan-Meier Plot of Time to New Anti-CLL Treatment (ITT Population)

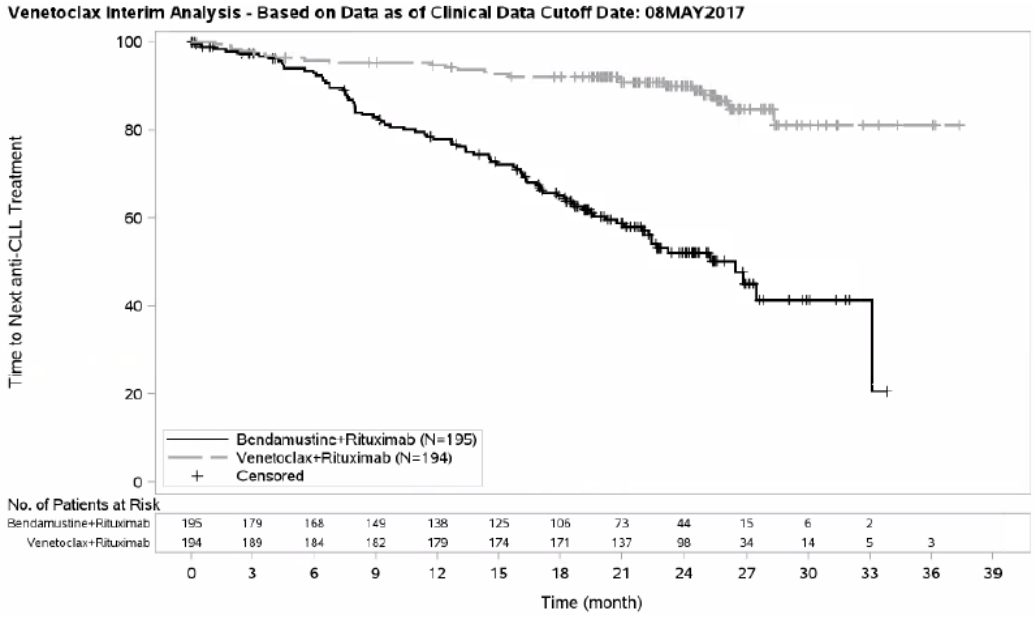


Table 7: Time to New Anti-CLL Treatment (ITT Population) (data cut-off date 8 May 2017)

	Bendamustine+Rituximab (N=195)		Venetoclax+Rituximab (N=194)
Patients with event (%)	83 (42.6%)		23 (11.9%)
Earliest contributing event			
New anti-leukemic treatment	61		10
Death	22		13
Patients without event (%)	112 (57.4%)		171 (88.1%)
Time to Event (Month)			
Median	26.4		NE
95% CI	(21.9, 33.1)		NE
25% and 75%-ile	13.8, 33.1		NE
Range	0.0* to 33.8*		0.3* to 37.4*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.19	
95% CI		(0.12, 0.31)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.19	
95% CI		(0.12, 0.31)	
Time Point Analysis			
1 Year Duration			
Patients remaining at risk	138		179
Event Free Rate (%)	77.90		94.80
95% CI	(71.84, 83.95)		(91.67, 97.94)
2 Year Duration			
Patients remaining at risk	44		98
Event Free Rate (%)	52.09		90.00
95% CI	(43.96, 60.23)		(85.56, 94.44)

* Censored
Summaries of time to event (median, percentiles) are based on Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression model.
Stratification factors: 17p deletion, risk status, geographic region.

Minimal Residual Disease

Peripheral blood MRD response was assessed using iwCLL recommended ASO-PCR and flow cytometry for all patients and across serial timepoints. MRD was considered negative if the result was less than one CLL cell in 10000 leukocytes (MRD value <0.0001, 10-4).

For both ASO-PCR and flow cytometry methods, only samples that had a limit of detection (LOD) below 10-4 were considered for MRD determination. In addition, for flow cytometry, samples were required to have a minimum of 200,000 leukocytes assessed, which adhered to the prior reporting conventions for MRD flow cytometry data in clinical trials.

Unlike peripheral blood MRD assessments that were performed serially throughout the study, MRD assessments in bone marrow were only required for responders (CR or PR) at the end of combination treatment response visit or at any other point during the study that a patient became a responder. A total of 115/389 patients [29.6%] had post baseline BM samples available for MRD assessment (74/194 patients [38.1%] in the VR arm and 41/195 patients [21.0%] in the BR arm).

Comparison of MRD-negativity between the two arms in peripheral blood at the end of the combination treatment response (EOCTR) visit was a secondary endpoint for this study.

Table 8: MRD-Negativity (Peripheral Blood) at the End of Combination Treatment Visit – ITT Population (data cut-off date 8 May 2017)

Visit	Bendamustine+Rituximab (N=195)		Venetoclax+Rituximab (N=194)
End Of Combination Treatment Response Visit			
MRD Negative	26 (13.3%)		121 (62.4%)
MRD Positive	169 (86.7%)		73 (37.6%)
95% CI for MRD negative rates	(8.90, 18.92)		(55.15, 69.21)
Difference in MRD negative rates		49.04	
95% CI		(40.44, 57.64)	
p-value (Chi-square)		<.0001	
Odds Ratio		10.77	
95% CI		(6.50, 17.85)	
MRD Assay Positive	102 (52.3%)		46 (23.7%)
MRD Undetermined	2 (1.0%)		2 (1.0%)
PD or death before visit	23 (11.8%)		9 (4.6%)
Withdrew from study before visit due to to reasons other than death	15 (7.7%)		4 (2.1%)
MRD Missing	27 (13.8%)		12 (6.2%)

MRD blood response status was derived from combining ASO-PCR and flow cytometry results. 95% CI for rates were constructed using Pearson-Clopper method. 95% CI for difference in rates were constructed using Anderson-Hauck method.

The MRD-negativity rate in peripheral blood among investigator-assessed complete responders (CR/CRi) was 94.2% (49/52 patients) in the VR arm compared with 31.3% (5/16 patients) in the BR arm; and among investigator-assessed partial responders (nPR/PR) was 86.0% (111/129 patients) in the VR arm compared with 32.8% (38/116 patients) in the BR arm.

Concordance between the MRD status in peripheral blood and in bone marrow was 84.3% based on 108 pairs of post-baseline samples across both arms; 48 out of 60 (80.0%) patients that had been

measured as MRD negative by blood also measured MRD negative in bone marrow samples while 48 out of 53 (90.6%) patients that measured MRD negative in bone marrow also measured negative in blood.

Subgroup Analyses of Investigator Assessed PFS

Table 9: Subgroup Analysis of PFS By stratification factors (data cut-off date 8 May 2017)

Randomization Strata	Total n	Bendamustine+ Rituximab (N=195) n	Bendamustine+ Rituximab (N=195) Median (Months)	Venetoclax+ Rituximab (N=194) n	Venetoclax+ Rituximab (N=194) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	17.0	194	NE	0.17	(0.12, 0.26)
17p Deletion (IvRS)							
Normal	313	155	19.6	158	NE	0.18	(0.12, 0.28)
Abnormal	76	40	12.2	36	NE	0.14	(0.06, 0.33)
Risk Status (IvRS)							
Low	178	88	21.6	90	NE	0.14	(0.07, 0.28)
High	211	107	15.4	104	NE	0.19	(0.11, 0.30)
Geographic Region (IvRS)							
United States/Canada	34	18	15.8	16	NE	0.29	(0.10, 0.83)
Australia/New Zealand	86	42	24.5	44	NE	0.34	(0.16, 0.72)
Western Europe	131	65	17.1	66	NE	0.11	(0.05, 0.23)
Central and Eastern Europe	130	66	15.5	64	NE	0.13	(0.06, 0.27)
Asia	8	4	13.6	4	NE	0.28	(0.03, 2.69)

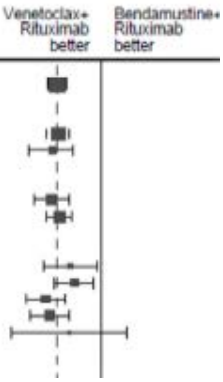


Table 10: Subgroup analysis By demographics (data cut-off date 8 May 2017)

Demographic Subgroups	Total n	Bendamustine+ Rituximab (N=195) n	Bendamustine+ Rituximab (N=195) Median (Months)	Venetoclax+ Rituximab (N=194) n	Venetoclax+ Rituximab (N=194) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	17.0	194	NE	0.17	(0.12, 0.26)
Age Group 65 (yr)							
< 65	186	89	15.4	97	NE	0.11	(0.06, 0.21)
>= 65	203	106	21.7	97	NE	0.24	(0.14, 0.41)
Age Group 75 (yr)							
< 75	336	171	16.4	165	NE	0.17	(0.11, 0.26)
>= 75	53	24	22.9	29	NE	0.23	(0.08, 0.64)
Sex							
Male	287	151	16.4	136	NE	0.19	(0.12, 0.30)
Female	102	44	17.3	58	NE	0.12	(0.05, 0.29)
Race							
White	359	178	17.1	181	NE	0.18	(0.12, 0.27)
Non-White	12	6	16.3	6	NE	0.24	(0.02, 2.30)

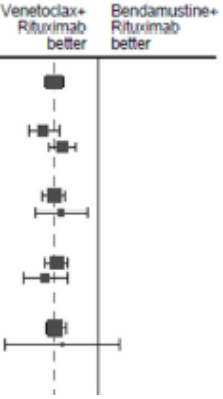


Table 11: Subgroup analysis by prognosis (data cut-off date 8 May 2017)

Biomarker	Total n	Bendamustine+ Rituximab (N=195) n	Bendamustine+ Rituximab (N=195) Median (Months)	Venetoclax+ Rituximab (N=194) n	Venetoclax+ Rituximab (N=194) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	17.0	194	NE	0.17	(0.12, 0.26)
Chromosome 17p Deletion (central)							
Normal	250	123	21.4	127	NE	0.19	(0.12, 0.32)
Abnormal	92	46	15.4	46	NE	0.13	(0.05, 0.29)
Chromosome 11q Deletion							
Normal	217	105	21.7	112	NE	0.22	(0.13, 0.37)
Abnormal	125	64	15.7	61	NE	0.11	(0.05, 0.25)
p53 Mutation							
Unmutated	277	133	21.2	144	NE	0.15	(0.09, 0.25)
Mutated	99	51	12.9	48	NE	0.19	(0.10, 0.36)
Baseline IgVH Mutation Status							
Mutated	104	51	22.9	53	NE	0.11	(0.04, 0.31)
Unmutated	246	123	15.7	123	NE	0.16	(0.10, 0.26)
Baseline Beta-2 Microglobulin							
<= 3.5 mg/L	123	59	16.3	64	NE	0.07	(0.03, 0.18)
> 3.5 mg/L	252	127	18.7	125	NE	0.25	(0.16, 0.39)
p53 Mutation and/or 17p Deletion (central)							
Unmutated	201	95	22.3	106	NE	0.16	(0.08, 0.29)
Mutated	147	75	14.2	72	NE	0.17	(0.10, 0.31)

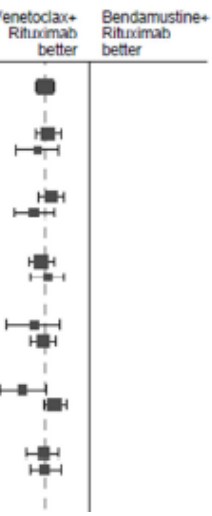


Table 12: Subgroup analysis by prognosis, update May 2018

Biomarker	Total n	Bendamustine+ Rituximab (N=195) n	Bendamustine+ Rituximab (N=195) Median (Months)	Venetoclax+ Rituximab (N=194) n	Venetoclax+ Rituximab (N=194) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	17.0	194	NE	0.19	(0.14, 0.27)
Chromosome 17p Deletion (central)							
Normal	250	123	21.4	127	NE	0.19	(0.13, 0.29)
Abnormal	92	46	15.4	46	NE	0.21	(0.11, 0.39)
Chromosome 11q Deletion							
Normal	217	105	22.1	112	44.3	0.26	(0.17, 0.39)
Abnormal	125	64	15.7	61	NE	0.11	(0.05, 0.21)
p53 Mutation							
Unmutated	276	132	21.2	144	NE	0.16	(0.10, 0.24)
Mutated	99	51	12.9	48	36.0	0.25	(0.15, 0.43)
Baseline IgVH Mutation Status							
Mutated	104	51	24.2	53	NE	0.16	(0.07, 0.33)
Unmutated	246	123	15.7	123	44.3	0.16	(0.11, 0.24)
Baseline Beta-2 Microglobulin							
<= 3.5 mg/L	123	59	16.3	64	NE	0.13	(0.07, 0.24)
> 3.5 mg/L	252	127	19.5	125	44.3	0.25	(0.17, 0.36)
p53 Mutation and/or 17p Deletion (central)							
Unmutated	201	95	22.8	106	NE	0.16	(0.10, 0.27)
Mutated	147	75	14.6	72	NE	0.23	(0.15, 0.37)

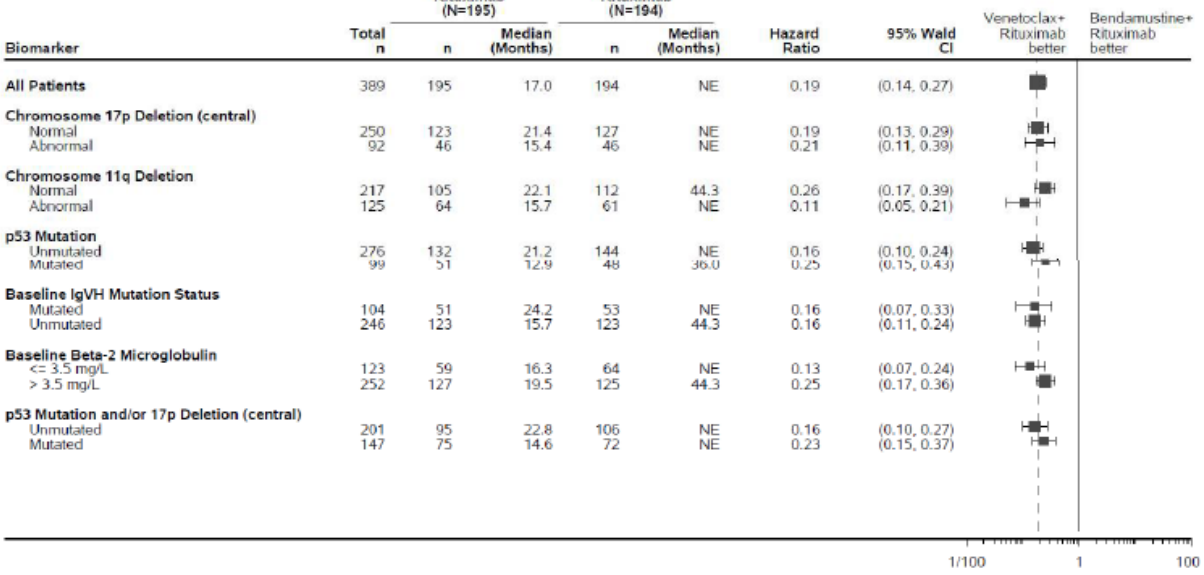


Table 13: Subgroup analysis by disease characteristics (data cut-off date 8 May 2017)

Baseline Characteristics	Total n	Bendamustine+ Rituximab (NE=195) n	Bendamustine+ Rituximab (NE=195) Median (Months)	Venetoclax+ Rituximab (NE=194) n	Venetoclax+ Rituximab (NE=194) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	389	195	17.0	194	NE	0.17	(0.12, 0.26)
Renal Impairment Status							
Normal	157	78	14.2	79	NE	0.17	(0.09, 0.31)
Mild	184	90	21.0	94	NE	0.17	(0.09, 0.31)
Moderate	48	27	22.9	21	NE	0.30	(0.11, 0.85)
Hepatic Impairment Status							
Normal	294	148	17.0	146	NE	0.17	(0.11, 0.27)
Mild	76	39	14.9	37	NE	0.20	(0.08, 0.51)
Moderate	18	7	15.4	11	NE	0.01	(0.01, 1.02)
Severe	1	1	NE		NE	NE	(NE , NE)
Rai Stage							
Stage 0	82	39	17.3	43	NE	0.16	(0.07, 0.38)
Stage 1	102	50	17.5	48	NE	0.13	(0.06, 0.29)
Stage 2	104	56	21.5	48	NE	0.16	(0.07, 0.38)
Stage 3	45	22	22.3	23	NE	0.20	(0.06, 0.73)
Stage 4	51	19	18.0	32	NE	0.30	(0.13, 0.73)
Bulky Disease (Lymph Nodes with the Largest Diameter)							
< 5 cm	197	97	17.0	100	NE	0.13	(0.07, 0.24)
>= 5 cm	172	88	15.7	84	NE	0.24	(0.14, 0.40)
Bulky Disease (Lymph Nodes with the Largest Diameter)							
<10 cm	319	158	17.1	161	NE	0.18	(0.12, 0.27)
>= 10 cm	50	27	13.5	23	NE	0.19	(0.07, 0.52)
Number of Prior Regimens							
1	228	117	16.6	111	NE	0.14	(0.08, 0.24)
2	100	43	21.2	57	NE	0.24	(0.11, 0.50)

Summary of main study(ies)

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 14: Summary of main study, primary analyses of May 2018

Title: Study GO28667: A multicenter, Phase III, open-label, randomized study in relapsed/refractory patients with chronic lymphocytic leukemia to evaluate the benefit of venetoclax (GDC-0199/ABT-199) plus rituximab compared with bendamustine plus rituximab			
Study identifier	EudraCT 2013-002110-12		
Design	ongoing, open-label, international, multicenter, randomized, comparative Phase III study		
	Duration of main phase:		First Patient Screened: 26 Feb 2014 Last Patient Randomized: 23 Sep 2015 Data cut-off: 08 May 2017
	Duration of Run-in phase:		Ramp up of venetoclax for 5 weeks prior to rituximab add-on
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	V+R		Venetoclax+Rituximab followed by venetoclax monotherapy until PD or max 2 years, 194 patients
	B+R		Bendamustin+Rituximab. for six cycles (or PD), 195 patientsx
Endpoints and definitions	Primary endpoint	INV-PFS	Progression-free survival
	Secondary endpoints (with MTP):	1) IRC-CR 2) IRC-ORR 3) OS	1) IRC-assessed complete response rate 2) IRC-assessed best objective response rate 3) overall survival
	Exploratory endpoints (without MTP):	see CSR	see CSR
Database lock	2017-09-09		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT First Patient Screened: 26 Feb 2014 Last Patient Randomized: 23 Sep 2015 Data cut-off: 08 May 2017		
Descriptive statistics and estimate variability	Treatment group	B+R	V+R
	Number of subjects	195	194
	PRIMARY: INV-PFS, (Median, stratified)	17	Not estimated
	CI95%	[15.5, 21.6]	Not estimated
	SECONDARY: IRC-CC	7 (3.6%)	16 (8.2%)
	CI95%	[1.5%, 7.3%]	[4.8%, 13.1%]
	SECONDARY: IRC-ORR	141 (72.3%)	179 (92.3%)
	CI95%	[65.5%, 78.5%]	[87.6%, 95.6%]
	SECONDARY: OS	Not estimated	Not estimated
	CI95%	Not estimated	Not estimated
Effect estimate per comparison	PRIMARY: INV-PFS	Comparison groups	V+R:B+R
		Hazard Ratio, stratified	0.17
		CI95%	[0.11, 0.25]
		P-value	<0.0001
	SECONDARY: IRC-CC	Comparison groups	V+R:B+R
		Difference in Response Rates of Complete Response (IRC)	4.7%
		CI95%	[-0.3%, 9.6%]
		P-value	0.0814
	SECONDARY: IRC-ORR	Comparison groups	V+R:B+R
		Difference in Response Rates of Objective Response Rates (ORR)	20.0%
		CI95%	[12.4%, 27.56%]
		P-value	<0.0001
	SECONDARY: IRC-OS	Comparison groups	V+R:B+R
		Hazard Ratio	Not estimated
		CI95%	Not estimated
		P-value	Not estimated
Notes	The results show superiority of V+R over B+R regarding the primary endpoint in terms of statistical significance and clinical relevance. The secondary endpoints are not-significant, but descriptive statistics are consistent with primary endpoint.		

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

A randomised (1:1), multicenter, open-label phase III study evaluated the efficacy and safety of Venclyxto + rituximab versus BR in patients with previously treated CLL. Patients in the Venclyxto + rituximab arm completed the Venclyxto 5-week dose-titration schedule and then received 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. Rituximab was initiated after the 5-week dose-titration schedule at 375 mg/m^2 for Cycle 1 and 500 mg/m^2 for Cycles 2-6. Each cycle was 28 days. Patients randomised to BR received bendamustine at 70 mg/m^2 on Days 1 and 2 for 6 cycles and rituximab as described above.

The overall study design was accepted by the SAWP/CHMP: Bendamustin + rituximab versus venetoclax + rituximab for six cycles followed by monotherapy with venetoclax until PD with PFS as primary endpoint – highlighting that the benefit of continuing ABT-199 until progression without a placebo control will not only lead to results that are non-interpretable as regards the benefit of ABT-199 "maintenance" treatment, but also to events of progression on-therapy of ABT-199, in contrast to the reference arm where most progression events will occur off-therapy. Also, the MAH was advised to avoid cross-over until informative survival data are available.

Changes/deviations from advice/planned design were: Venetoclax was to be administered for a total of 6 + 18 months not until PD. An interim analysis was undertaken at about 35% of events of PFS in the long run (assuming no cure). The difference between events of progression on and off therapy was not addressed.

A follow-up advice was requested and important and accepted changes included an interim analysis to be conducted "if the number of investigator assessed events of PFS is less than 160 as of 12 months after the enrolment of the last patient. Further time to progression was changed to total duration of therapy 12 months. The possibility of cross-over at time of progression was no longer optional.

Median age was 65 years (range: 22 to 85); 74% were male, and 97% were white. Median time since diagnosis was 6.7 years (range: 0.3 to 29.5). Median prior lines of therapy was 1 (range: 1 to 5); and included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%) and prior purine analogs (81%, including 55% FCR). At baseline, 46.6% of patients had one or more nodes ≥5 cm, and 67.6% had ALC ≥25 x 10^9/l. A 17p deletion was detected in 26.9% of patients, *TP53* mutations in 26.3%, 11q deletion in 36.5%, and unmutated *IgVH* gene in 68.3%. Median follow-up time for primary analysis was 23.8 months (range: 0.0 to 37.4 months).

Enrolled patients with at least one prior adequate treatment regimen (according to clinical guidelines) represent a rather heterogeneous population: median (and mean) time from diagnosis was about 7 years, but the majority of patients had been treated with only one prior regimen. It should be noticed, however, that diagnosis does not imply need for therapy. On the other hand, more than 50% of patients were considered "high risk" and non-adjusted beta 2 microglobulin was above 3.5 mg/dl in close to 70% of patients. Subgroup analysis in terms of PFS, indicate no important relationship between prognosis and HR for PFS, but data may be misleading due to the low event rate in the VR arm.

Progression-free survival (PFS) was assessed by investigators using the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

Efficacy data and additional analyses

Efficacy results for PFS at the time of pre-specified primary interim analysis (data cut-off date 8 May 2017) showed an event rate of 16.5% of the VR combination as compared to 58.5% of the BR combination, with an improvement of the PFS of HR 0.17 (0.11, 0.25). At an updated efficacy analysis with all patients off treatment (data cut-off date 8 May 2018 and median follow-up of 36 months) the 36-month PFS estimate in the venetoclax + rituximab arm was 71.4% [95% CI: 64.8, 78.1] and in the bendamustine + rituximab arm was 15.2% [95% CI: 9.1, 21].

Efficacy results for the pre-specified primary analysis (data cut-off date 8 May 2017) were also assessed by an Independent Review Committee (IRC) demonstrating a statistically significant 81% reduction in the risk of progression or death for patients treated with venetoclax + rituximab (hazard ratio: 0.19 [95% CI: 0.13, 0.28]; P<0.0001). Median DOR was not reached with median follow up of approximately 23.8 months.

In total, 130 patients in the venetoclax + rituximab arm completed 2 years of venetoclax treatment without progression. Of the 130 patients, 92 patients completed the 6-month post treatment follow-up visit. The estimated PFS rate at 6 months post treatment was 92%.

The observed PFS benefit of venetoclax + rituximab compared with bendamustine + rituximab was consistently observed across all subgroups of patients evaluated, including age (< 65, ≥ 65 years and < 75, ≥ 75 years), prior lines of therapy (1, >1), bulky disease (< 5 cm, ≥ 5 cm), 17p deletion, 11q deletion, *TP53* mutation*, IgVH* mutation, and refractory versus relapse to most recent therapy.

In terms of response rate (IRC by convention, no confirmation required, RECIST 1.1), CR rate is borderline 8% vs. 4% (p=0.08). Of note, in the investigator analysis, CR rates are much higher 27% vs. 8% (p<0.0008). This discrepancy was most likely due to the assessment of borderline lymph nodes. MRD negativity at end of dual therapy also favoured the venetoclax arm. According to the analysis plan, ORR should be assessed only if CR is positive: ORR 92% vs. 72% (p<0.0001). MRD data may be used to bridge between the validity of IRC and investigator assessment of CR**.**

Formally PFS (primary endpoint) was highly significant and convincing, HR 0.17 (p< 0.0001). The event rate in the venetoclax arm was only 17%. Furthermore there were two steps in the PFS curves: in the BR arm at about 6 months and in the VT arm at about 2 years, i.e. at time of stopping therapy. In the control arm, PFS is likely to be sufficiently stable, event rate 58% and long follow-up off therapy. The pattern of recurrence in the venetoclax arm is not possible to estimate.

In the updated cutoff of May 2018, altogether 61 patients provided PFS data at 36 months, 12 months after stopping venetoclax. Based on the shapes of the time to event curves it appears possible to conclude that the event rate with respect to progressive disease is not worse, if not better, in the VR arm after end of venetoclax than in the BR arm after month 24.

As a concequence, it also appears possible to conclude that “truncated” time without therapy is longer than 18 months (24 – 6 months), meaning that time without therapy when data become mure mature is highly likely to be longer in the VT arm compared with the BT arm. At the updated analysis, a total of 61 randomized patients had died; 22/194 patients (11.3%) in the V+R arm and 39/195 patients (20.0%) in the BR arm with an exploratory HR of 0.5 (0.3; 0.85).

Section 5.1 of the SmPC has been revised to include information on the results of the MURANO trial.

The recommended dose of venetoclax in combination with rituximab is 400 mg once daily. Rituximab should be adminstered after the patient has completed the dose-titration schedule and has received

the recommended daily dose of 400 mg venetoclax for 7 days. Venetoclax should be taken for 24 months from Cycle 1 Day 1 of rituximab. Section 4.2 of the SmPC has been updated with relevant posology information on the combination with rituximab.

2.4.4. Conclusions on the clinical efficacy

In overall the efficacy of venetoclax in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy has been demonstrated.

The CHMP considers the following measures necessary to address issues related to efficacy:

- Submission of the final CSR of the MURANO study including updated efficacy data.

2.5. Clinical safety

Introduction

The safety profile of Venclyxto, as reflected in the current SPC, is based on pooled, single-arm data of 296 patients with treatment experienced CLL treated with venetoclax 400 mg monotherapy once daily.

The most serious adverse reaction was tumour lysis syndrome (TLS). The most commonly occurring adverse reactions (≥20%) of any grade in patients receiving Venclyxto monotherapy were neutropenia/neutrophil count decreased, diarrhoea, nausea, anaemia, upper respiratory tract infection, fatigue, hyperphosphataemia, vomiting, and constipation. The most frequently reported serious adverse reactions (≥2%) were pneumonia, febrile neutropenia, and TLS.

Based on this experience, AEs of special interest included:

Table 15: AEs of special interest – search criteria

Selected TEAEs	Search Criteria
Tumor Lysis Syndrome (AE)	SMQ – "Tumor Lysis Syndrome" (narrow) *
Grade ≥ 3 neutropenia	PT terms – "neutropenia", "neutrophil count decreased", "febrile neutropenia", "agranulocytosis", "neutropenic infection", and "neutropenic sepsis"
Infection Serious infection Grade ≥ 3 infection	SOC of "Infections and Infestations"
Second primary malignancy	SMQ – "malignant tumours" (narrow) and "myelodysplastic syndromes" (narrow)
Drug-Induced Liver Injury (AE)	PT Term – "drug-induced liver injury"
Grade ≥ 3 thrombocytopenia	PT terms – "thrombocytopenia" and "platelet count decreased"
Grade>3 infusion-related reaction	Roche standard AEGT – "Infusion-related reaction + hypersensitivity"

* Additionally, the assessment of Howard criteria were used to identify laboratory abnormalities consistent with tumour lysis syndrome. This broad search method ensured that all relevant cases were identified using adverse events and/or laboratory data.

AE = adverse events; AEGT=adverse event group term; CRF=case report form; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = Standardized MedDRA Query; SOC = system organ class; TEAEs = treatment-emergent adverse events.

In addition events of Richter transformation were closely monitored (RMP: important potential risk).

Table 16: Laboratory Abnormalities Search Criteria

Laboratory Abnormalities	Search Criteria
Tumor Lysis Syndrome (Howard Criteria;	≥ 2 of the following metabolic abnormalities within 24 hours of each other (applicable to post-dose laboratory values only): • Uric Acid > 476 µmol/L or 8.0 mg/dL • Potassium > 6.0 mmol/L • Inorganic Phosphorus > 1.5 mmol/L or 4.5 mg/dL • Calcium < 1.75 mmol/L or 7.0 mg/dL
Potential Drug-Induced Liver Injury (Hy's Law)	Post-dose laboratory ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN that occur within 72 hours of each other

ALT = alanine aminotransferase; AST = aspartate aminotransferase; L = litre; µmol = micromole; mg/dL = milligram/deciliter; mmol = millimole; mEq = milliequivalent; ULN = upper limit of normal

Patient exposure

Table 17: Venetoclax exposure

	Venetoclax (400 mg) +Rituximab (N=210)
Treatment duration (day)	
n	210
Mean (SD)	598.9 (227.1)
Median	674.0
Min - Max	1 - 1089
Treatment duration (month)	
n	210
0 - 1	5 (2.4%)
>1 - 7	17 (8.1%)
>7 - 12	14 (6.7%)
>12 - 18	12 (5.7%)
>18	162 (77.1%)

As of the 8 May 2017 clinical cut-off date for Study GO28667, patients received a median of 6 cycles of **bendamustine** (range: 0-6). Overall, 70/188 of patients (37.2%) had a bendamustine dose modification due to AEs (62 patients [33.0%]) and/or other reason (12 patients [6.4%]). A total of 26/188 patients (13.8%) in the BR arm experienced 36 AEs that led to reduction of the bendamustine dose.

Table 18: Extent of Exposure to Treatment during the VR Combination Treatment Period and Venetoclax Single Agent Treatment Period (Safety Population) (data cut-off date 8 May 2017)

	V+R Combination Regimen	
	Venetoclax+R Combination Treatment Period (N=194)	Venetoclax Single Agent Treatment Period (N=187)
Treatment duration (day)		
N	194	173
Mean (SD)	202.9 (63.4)	445.4 (129.0)
Median	203.0	475.0
Min - Max	2 - 757	15 - 665
Treatment duration (month)		
n	194	173
0 - 1	3 (1.5%)	2 (1.2%)
>1 - 7	149 (76.8%)	11 (6.4%)
>7 - 12	41 (21.1%)	20 (11.6%)
>12 - 18	0	102 (59.0%)
>18 - 24	0	38 (22.0%)
> 24	1 (0.5%)	0
Dose intensity (%)		
N	189	172
Mean (SD)	91.9 (14.3)	90.6 (18.2)
Median	97.2	99.6
Min - Max	36 - 100	23 - 100
Number of patients with a dose modification		
n	194	173
Yes	119 (61.3%)	57 (32.9%)
No	75 (38.7%)	116 (67.1%)
Was dose ever modified due to AE		
n	194	173
Yes	115 (59.3%)	53 (30.6%)
No	79 (40.7%)	120 (69.4%)
Was dose ever modified due to Med. Error		
n	194	173
Yes	5 (2.6%)	2 (1.2%)
No	189 (97.4%)	171 (98.8%)
Was dose ever modified due to other reason		
n	194	173
Yes	9 (4.6%)	9 (5.2%)
No	185 (95.4%)	164 (94.8%)

Venetoclax+R combination treatment period: starts from the first Venetoclax dose day until 28 days after the last Rituximab exposure.
Venetoclax single agent treatment period: starts from the 29th day after last Rituximab exposure.
Treatment duration is defined as the total number of days with Venetoclax exposure within each period. Dose intensity is calculated as the total dose received by patients divided by the expected total target dose within each period.

Adverse events

Table 19: Overview of adverse events

	Bendamustine+Rituximab (N=188)	Venetoclax (400 mg)+Rituximab (N=210)
Total number of patients with at least one AE	185 (98.4%)	210 (100.0%)
Total number of AEs	1830	2541
Total number of deaths	27 (14.4%)	16 (7.6%)
Total number of patients withdrawn from study due to an AE	1 (0.5%)	0
Total number of patients with at least one		
AE with fatal outcome	11 (5.9%)	11 (5.2%)
Serious AE	81 (43.1%)	98 (46.7%)
Serious AE leading to withdrawal from any treatment	12 (6.4%)	17 (8.1%)
Serious AE leading to withdrawal from Venetoclax	0	16 (7.6%)
Serious AE leading to dose interruption	19 (10.1%)	49 (23.3%)
Serious AE leading to dose reduction	11 (5.9%)	7 (3.3%)
Related Serious AE	51 (27.1%)	45 (21.4%)
AE leading to withdrawal from any treatment	18 (9.6%)	33 (15.7%)
AE leading to withdrawal from Venetoclax	0	27 (12.9%)
AE leading to dose interruption	76 (40.4%)	144 (68.6%)
AE leading to dose reduction	28 (14.9%)	34 (16.2%)
Related AE	170 (90.4%)	185 (88.1%)
Related AE leading to withdrawal from any treatment	15 (8.0%)	21 (10.0%)
Related AE leading to withdrawal from Venetoclax	0	17 (8.1%)
Related AE leading to dose interruption	65 (34.6%)	124 (59.0%)
Related AE leading to dose reduction	26 (13.8%)	31 (14.8%)
Grade 3,4 AE (at greatest intensity)	125 (66.5%)	159 (75.7%)

Overall, the most frequently reported body systems (SOCs≥10%) with AEs considered related to venetoclax by the investigator included Blood and Lymphatic System Disorders (61.0%), Gastrointestinal Disorders (38.6%), Infections and Infestations (24.8%), General Disorders and Administration Site Conditions (17.6%), Metabolism and Nutrition Disorders (17.1%), and Investigations (15.7%).

Table 20: Overview of Adverse Events during VR Combination Treatment Period and Venetoclax Single Agent Treatment Period (data cut-off date 8 May 2017)

	V+R Combination Regimen	
	Venetoclax+R Combination Treatment Period (N=194)	Venetoclax Single Agent Treatment Period (N=171)
Total number of patients with at least one AE	192 (99.0%)	143 (83.6%)
Total number of AEs	1673	589
Total number of deaths	11 (5.7%)	4 (2.3%)
Total number of patients withdrawn from study due to an AE	0	0
Total number of patients with at least one		
AE with fatal outcome	8 (4.1%)	2 (1.2%)
Serious AE	63 (32.5%)	36 (21.1%)
Serious AE leading to withdrawal from any treatment	9 (4.6%)	6 (3.5%)
Serious AE leading to withdrawal from Venetoclax	8 (4.1%)	6 (3.5%)
Serious AE leading to dose reduction	5 (2.6%)	0
Serious AE leading to dose interruption	34 (17.5%)	14 (8.2%)
Related Serious AE	34 (17.5%)	12 (7.0%)
AE leading to withdrawal from any treatment	17 (8.8%)	13 (7.6%)
AE leading to withdrawal from Venetoclax	13 (6.7%)	12 (7.0%)
AE leading to dose reduction	24 (12.4%)	5 (2.9%)
AE leading to dose interruption	125 (64.4%)	47 (27.5%)
Related AE	165 (85.1%)	68 (39.8%)
Related AE leading to withdrawal from any treatment	10 (5.2%)	9 (5.3%)
Related AE leading to withdrawal from Venetoclax	7 (3.6%)	9 (5.3%)
Related AE leading to dose reduction	22 (11.3%)	5 (2.9%)
Related AE leading to dose interruption	112 (57.7%)	30 (17.5%)
Grade 3,4 AE (at greatest intensity)	130 (67.0%)	21 (12.3%)

Treatment Emergent Adverse Events included. Investigator text for AEs is coded using MedDRA v19.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes outcomes that were available in the database as of the snapshot date, for adverse events with onset date on or before the clinical cutoff date.

During the VR combination period, the most frequent Grade ≥3 AEs (in at least 2% of patients) were neutropenia [54.1%], anaemia [8.2%], neutrophil count decreased [5.2%], pneumonia [4.6%], thrombocytopenia [4.6%], febrile neutropenia [3.6%], tumour lysis syndrome [3.1%]), hyperglycaemia [2.1%], and autoimmune haemolytic anaemia [2.1%],

During the venetoclax single agent treatment period the most frequently reported Grade ≥ 3 AEs were neutropenia [11.1%] anaemia [2.9%], thrombocytopenia [2.3%], pneumonia [1.8%], neutrophil count decreased [1.2%], diarrhoea [1.2%], myelodysplastic syndrome [1.2%]), diabetes mellitus [1.2%] and hypertension [1.2%]. All other Grade ≥ 3 AEs were reported as unique events.

Serious adverse event / deaths / other significant events

Table 21: Adverse Events Resulting in Death: Safety-Evaluable Patients

MedDRA SOC and Preferred Term	Bendamustine+Rituximab (N=188)	Venetoclax (400 mg)+Rituximab (N=210)
Total number of deaths	11 (5.9%)	11 (5.2%)
Infections and infestations / Pneumonia	0	3 (1.4%)
Blood and lymphatic system disorders / Thrombocytopenia	0	1 (0.5%)
Cardiac disorders / Cardiac failure	0	1 (0.5%)
Cardiac disorders / Myocardial infarction	0	1 (0.5%)
General disorders and administration site conditions / Sudden cardiac death	0	1 (0.5%)
Infections and infestations / Sepsis	2 (1.1%)	1 (0.5%)
Metabolism and nutrition disorders / Hyperkalaemia	0	1 (0.5%)
Metabolism and nutrition disorders / Tumour lysis syndrome	0	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) / Colorectal cancer	0	1 (0.5%)
Nervous system disorders / Status epilepticus	0	1 (0.5%)
Respiratory, thoracic and mediastinal disorders / Acute respiratory failure	0	1 (0.5%)

MedDRA SOC and Preferred Term	Bendamustine+Rituximab (N=188)	Venetoclax (400 mg)+Rituximab (N=210)
Cardiac disorders / Myocardial ischaemia	0	0
General disorders and administration site conditions / Sudden death	1 (0.5%)	0
Infections and infestations / Listeria sepsis	1 (0.5%)	0
Infections and infestations / Scedosporium infection	1 (0.5%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) / Lung neoplasm malignant	2 (1.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) / Acute myeloid leukaemia	1 (0.5%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) / Lymphoma	1 (0.5%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) / Malignant neoplasm progression	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) / Richter's syndrome	0	0
Nervous system disorders / Haemorrhagic stroke	1 (0.5%)	0
Respiratory, thoracic and mediastinal disorders / Pulmonary embolism	1 (0.5%)	0

Table 22: Serious Adverse Events Occurring in≥1% of Patients: Safety-Evaluable Patient

MedDRA System Organ Class MedDRA Preferred Term	Bendamustine +Rituximab (N=188)	Venetoclax (400 mg) +Rituximab (N=210)
Total number of patients with at least one adverse event	81 (43.1%)	98 (46.7%)
Overall total number of events	151	172
Infections and infestations		
Total number of patients with at least one adverse event		
Total number of events	55	63
Pneumonia	15 (8.0%)	16 (7.6%)
Influenza	2 (1.1%)	4 (1.9%)
Lung infection	0	3 (1.4%)
Upper respiratory tract infection	2 (1.1%)	3 (1.4%)
Appendicitis	0	2 (1.0%)
Cystitis	0	2 (1.0%)
Lower respiratory tract infection	1 (0.5%)	2 (1.0%)
Respiratory tract infection	0	2 (1.0%)
Sinusitis	1 (0.5%)	2 (1.0%)
Sepsis	4 (2.1%)	1 (0.5%)
Bronchitis	2 (1.1%)	0
Pharyngitis	2 (1.1%)	0
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event		
Total number of events	32	27
Febrile neutropenia	16 (8.5%)	8 (3.8%)
Autoimmune haemolytic anaemia	3 (1.6%)	4 (1.9%)
Anaemia	5 (2.7%)	3 (1.4%)
Neutropenia	3 (1.6%)	3 (1.4%)
Thrombocytopenia	2 (1.1%)	2 (1.0%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event		
Total number of events	1	15
Tumour lysis syndrome	1 (0.5%)	5 (2.4%)
Hyperkalaemia	0	3 (1.4%)
Dehydration	0	2 (1.0%)
Hyperphosphataemia	0	2 (1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total number of patients with at least one adverse event		
Total number of events	9	17
Squamous cell carcinoma	1 (0.5%)	3 (1.4%)
Colorectal cancer	0	2 (1.0%)
Myelodysplastic syndrome	0	2 (1.0%)
Lung neoplasm malignant	2 (1.1%)	0
Gastrointestinal disorders		
Total number of patients with at least one adverse event		
Total number of events	4	13
Diarrhoea	0	3 (1.4%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event		
Total number of events	20	8
Pyrexia	13 (6.9%)	5 (2.4%)
Cardiac disorders		
Total number of patients with at least one adverse event		
Total number of events	3	5
Myocardial infarction	0	2 (1.0%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event		
Total number of events	9	3
Infusion related reaction	6 (3.2%)	1 (0.5%)
Vascular disorders		
Total number of patients with at least one adverse event		
Total number of events	8	1
Hypotension	5 (2.7%)	0

Tumour lysis syndrome: Six cases (3%) of TLS were reported in the V+R arm of MURANO, in one case due to a high starting dose, 100 mg instead of 20 mg. All events occurred during the venetoclax ramp-up period and resolved within 2 days. All 6 patients reached the recommended dose of 400 mg. In addition there were two clinical cases not meeting the Howard criteria (laboratory), 1 case in each arm of the study (BR and V+R). No clinical TLS cases were reported in the V+R arm under the current prophylactic and monitoring measures.

Only based on Howard criteria, there were an additional 5 patients in the V+R arm with TLS, but according to the investigator not clinically relevant and not reported as AE. Three of the 5 patients were receiving the former measures for TLS prophylaxis. Four of the 5 patients had abnormal single or multiple laboratory values at baseline, prior to starting venetoclax treatment.

There were two cases of TLS in the BR arm.

Grade 3 or higher events of infections or serious infections: These events were reported in similar frequencies in the VT and BR arms, pneumonia being the most common serious event (about 8%).

There were 4 fatal events in the VR arm, thereof 2 at time of disease transformation (Richter) and 4 in the BR group. In the BR group there were two fatalities due to opportunistic infections (Listeria, Scedosporium).

Table 23: Second primary malignancies (May 2017):

	BR (n=188)	VR (210)
Second primary malignancy		
Total number of patients with at least one adverse event	16	35
Total number of events		
Squamous cell carcinoma	2 (1.1%)	7 (3.3%)
Squamous cell carcinoma of skin	2 (1.1%)	7 (3.3%)
Basal cell carcinoma	2 (1.1%)	5 (2.4%)
Myelodysplastic syndrome	0	3 (1.4%)
Colorectal cancer	0	2 (1.0%)
Malignant neoplasm progression	0	1 (0.5%)
Lung neoplasm malignant	2 (1.1%)	0

	Primary Analysis (08 May 2017)		Updated Analysis (08 May 2018)	
	BR (N = 188)	V+R (N = 194)	BR (N = 188)	V+R (N = 194)
Second Primary Malignancies	13 (6.9%)	21 (10.8%)	16 (8.5%)	25 (12.9%)

Richter transformation: In the MURANO study there were 6 cases of transformation in the VR arm (DLBCL 5, Hodgkin 1) and 5 in the BR arm (DLBCL 3, Non-B cell lymphoma 1, transformation NUD 1).

Drug induced liver injury: No case fulfilling the criteria for DILI was identified in the VR arm (MURANO).

Hy's law: Two cases in the BR arm (MURANO)

Grade ≥3 Infusion-related Reactions: Overall, 6/194 patients (3.1%) in the V+R arm experienced 7 Grade ≥ 3 IRRs and 18/188 patients (9.6%) in the BR arm experienced 22 Grade ≥ 3 IRRs. The majority of these were Grade 3 in severity (7/7 events in the V+R arm; 21/22 events in the BR arm). One Grade 4 infusion related reaction was reported in the BR arm. There were no Grade 5 IRRs.

In the VR arm, 1 patient experienced a serious Grade ≥3 infusion related reaction. The event resolved after 2 days following treatment for the event. Of the 6 patients in the VR arm who experienced a Grade ≥3 IRR, none discontinued rituximab treatment or had a rituximab dose modification.

In the BR arm, 9 patients experienced a serious Grade ≥ 3IRR. Of the 18 patients in the BR arm with a Grade ≥3 IRR, 3 patients discontinued rituximab treatment and 2 patients discontinued bendamustine. Additionally, 5 patients in the BR arm had a rituximab dose interruption due to a Grade ≥ 3 IRR.

Laboratory findings

Haematology

During the study most patients in both treatment arms either exhibited no shift or a worsening by 1 grade in any particular hematology laboratory parameter and there was no marked difference between the V+R and BR treatment arms with regards to the number of patients experiencing a shift from baseline in their haematology laboratory parameters. An exception was neutrophil count (hypo) where patients in the V+R arm who started with neutropenia at baseline were observed to experience a shift to a worse grade during treatment.

Blood Chemistry

During the study most patients in both treatment arms either exhibited no shift or a worsening by 1 grade and there was no marked difference between the VR and BR treatment arms.

The only exception was Grade 3/4 low phosphorus values which were reported in 30/194 patients (15.5%) of patients in the V+R arm and 8/188 patients (4.3%) of patients in the BR arm.

Safety in special populations

Age: Higher rates of SAEs in the VR arm were observed in patients ≥65 years of age as compared to patients < 65 years (51.5% vs. 41.2%) (serious neoplasms (11.3% vs. 2.1%) and serious gastrointestinal disorders (8.2% vs. 1.0%).

There were no differences in the pattern of AEs between male and female patients.

Discontinuation due to adverse events

A numerically higher rate of treatment withdrawals of any study treatment due to an AE was observed in the VR analysis sets compared with the BR analysis set, 15.7% in the VR 400 mg dose analysis set vs. 9.6% in the BR analysis set. Neutropenia, thrombocytopenia, autoimmune haemolytic anaemia, pneumonia, and malignant neoplasm progression (reported as an AE in Study M13-365) were the most frequently reported AEs (≥1% of patients) leading to discontinuation of venetoclax.

Overall, the number of patients with at least one AE leading to venetoclax dose interruption was 141/210 (67.1%) in the VR 400 mg dose analysis set. The most frequent AE that resulted in venetoclax dose interruption was neutropenia (40.5%). Other frequently reported AEs leading to dose

interruption included diarrhoea (4.8%), thrombocytopenia (4.3%), pneumonia and nausea (3.8% each), URTI (3.3%), neutrophil count decreased (2.9%), and bronchitis and influenza (2.4% each).

Post marketing experience

No additional safety signal identified. World-wide cumulative exposure: 778 patient-treatment years.

2.5.1. Discussion on clinical safety

The addition of rituximab to venetoclax results, as expected, in an increase in haematological toxicity. Especially neutropenia led to interruption and sometimes dose reduction. CLL per se is associated with an increase in infectious events and the increase is of similar magnitude as seen for BR.

The overall safety profile of Venclyxto is based on data from 490 patients with CLL treated in clinical trials with venetoclax in combination with rituximab or as monotherapy. The safety analysis included patients from one phase III study (MURANO), two phase 2 studies (M13-982 and M14-032), and one phase 1 study (M12-175). MURANO was a randomised, controlled trial in which 194 patients with previously treated CLL received venetoclax in combination with rituximab. In the phase 2 and phase 1 studies, 296 patients with previously treated CLL, which included 188 patients with 17p deletion and 92 patients who had failed a B-cell receptor pathway inhibitor were treated with venetoclax monotherapy (see section 5.1).

In the open-label, randomised phase III study (MURANO), the incidence of TLS was 3% (6/194) in patients treated with venetoclax + rituximab. After 77/389 patients were enrolled in the study, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures described in Posology (see section 4.2). All events of TLS occurred during the venetoclax dose-titration phase and resolved within two days. All six patients completed the dose titration and reached the recommended daily dose of 400 mg of venetoclax. No clinical TLS was observed in patients who followed the current 5-week dose-titration schedule and TLS prophylaxis and monitoring measures (see section 4.2). The rates of grade ≥3 laboratory abnormalities relevant to TLS were hyperkalemia 1%, hyperphosphatemia 1%, and hyperuricemia 1%.

Neutropenia is an identified risk with Venclyxto treatment. Grade 3 or 4 neutropenia has been reported in patients treated with venetoclax in the combination study with rituximab (GO28667/MURANO) and in the monotherapy studies (see section 4.8). In the MURANO study, neutropenia was reported in 61% (all grades) of patients on the venetoclax + rituximab arm. Forty-three percent of patients treated with venetoclax + rituximab experienced dose interruption and 3% of patients discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 32% of patients and grade 4 neutropenia in 26% of patients. The median duration of grade 3 or 4 neutropenia was 8 days (range: 1-712 days). With venetoclax + rituximab treatment, febrile neutropenia was reported in 4% of patients, grade ≥3 infections in 18%, and serious infections in 21% of patients.

The most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in the combination study with rituximab were neutropenia, diarrhoea, and upper respiratory tract infection. In the monotherapy studies, the most common adverse reactions were neutropenia/neutrophil count decreased, diarrhoea, nausea, anaemia, fatigue, and upper respiratory tract infection.

The most frequently reported serious adverse reactions (≥2%) in patients receiving venetoclax in combination with rituximab or as monotherapy were pneumonia, febrile neutropenia, and TLS.

Richter transformation, in clinical practice observed as rapid progression of transformed lymphoma is expected and was observed in similar incidence in VR and BR.

Second primary malignancies were observed and should be further characterised in relation to duration of exposure and observation, etc. A numerical increase is observed also in the update in the MURANO study and appears driven by non-melanoma skin cancer. Second primaries should remain an important potential risk in the RMP. The likely magnitude of the potential risk does not influence the risk assessment to an important degree.

Discontinuations due to adverse reactions occurred in 16% of patients treated with the combination of venetoclax and rituximab in the MURANO study. In the monotherapy studies with venetoclax, 9% of patients discontinued due to adverse reactions.

Dosage reductions due to adverse reactions occurred in 15% of patients treated with the combination of venetoclax and rituximab in the MURANO study and 12% of patients treated with venetoclax in the monotherapy studies.

In the MURANO study, dose interruptions due to adverse reactions occurred in 71% of patients treated with the combination of venetoclax and rituximab. The most common adverse reaction that led to dose interruption of venetoclax was neutropenia (43%).

Tolerability of 6 cycles of VR as measured by discontinuation and AEs seems to be similar to 6 cycles BR. Monotherapy for 18 months is associated with 7% AEs leading to withdrawal.

Relevant amendments have been introduced in section 4.4 and 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

No new safety concerns related to venetoclax have been identified and add-on of rituximab leads to the expected increase in bone marrow toxicity.

The CHMP considers the following measures necessary to address issues related to safety:

- The submission of the final CSR from Study GO28667 (MURANO) in order to have an update on the overall safety profile with a special focus on the issues of Richter's transformation and secondary primary malignancy.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 3.3 with the following content:

Safety concerns

Summary of the safety concerns:

Summary of Safety Concerns	
Important identified risks	• Tumor lysis syndrome • Neutropenia • Serious infection
Important potential risks	• Embryofetal toxicity • Medication error • Richter's transformation • Second primary malignancy
Missing information	• Carcinogenicity studies • Safety in severe hepatic impairment • Safety in severe renal impairment • Safety in long-term exposure (> 12 months)

Pharmacovigilance plan

Summary Table of Additional Pharmacovigilance Activities

Study Name Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Study M14-032 A Phase 2 Open-label Study of the Efficacy and Safety of ABT-199 (GDC-0199) in Chronic Lymphocytic Leukaemia Subjects with Relapse or Refractory to B-cell Receptor Signaling Pathway Inhibitor Therapy Ongoing	Assess the efficacy and safety of venetoclax monotherapy in subjects with CLL relapsed after or refractory to treatment with ibrutinib or idelalisib	Safety in long-term exposure (> 12 months) of venetoclax Second primary malignancy and Richter's transformation in longer exposure to venetoclax monotherapy	Interim CSR	March 2018
Category 3 - Required additional pharmacovigilance activities				
Study GO28667 (MURANO) Multicenter, Phase III, Open-Label, Randomised Study in Relapsed / Refractory Patients with Chronic Lymphocytic Leukaemia to Evaluate the Benefit of venetoclax	Evaluate the safety and efficacy of venetoclax and rituximab compared with BR in subjects with R/R CLL	Overall safety profile (provide comparator data) Richter's	Primary analysis and interim CSR completed	December 2017

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
(GDC-0199/ ABT-199) Plus Rituximab Compared with Bendamustine Plus Rituximab Ongoing		transformation and secondary primary malignancy	Final report	December 2022
Study M13-982 A Phase 2 Open-Label Study of the Efficacy of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukaemia Harboring the 17p Deletion Ongoing	Evaluate the efficacy of venetoclax monotherapy in subjects with R/R CLL in the presence of 17p del or *TP53* mutations	Safety in long-term exposure (> 12 months) of venetoclax Second primary malignancy and Richter's transformation in longer exposure to venetoclax monotherapy	Interim CSR	June 2018
Study M12-175 A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukaemia and Non-Hodgkin Lymphoma Ongoing	Assess the safety profile; characterize PK; determine MTD, RPTD, and lead-in period regimen of venetoclax monotherapy in subjects with R/R CLL (Arm A) or NHL (Arm B)	Safety in long-term exposure (> 12 months) of venetoclax Second primary malignancy and Richter's transformation in longer exposure to venetoclax monotherapy	Interim CSR	September 2019
Study M15-342 A Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment Ongoing	To assess the safety and pharmacokinetics of venetoclax following oral administration of a single dose of venetoclax in subjects with various degrees of hepatic impairment	Use in patients with severe hepatic impairment	Final CSR	December 2018

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P16-562 Prospective Observational Cohort Study to Assess the Safety of Venetoclax in the Swedish Cohort of Chronic Lymphocytic Leukaemia Patients Planned	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 o Other autoimmune hemolytic anemia o Idiopathic thrombocytopenic purpura • Tumor Lysis syndrome • Hematologic adverse event o Anemia o Thrombocytopenia o Neutropenia • Pneumonia • Febrile Neutropenia • Diarrhea • Nausea/Vomit • Upper respiratory tract infection • Fatigue • Hyperphosphatemia • Constipation	Interim CSR Final report	Every second year over a study period of 8 years Planned December 2025
Study M16-185 Clinical drug-drug interaction study	Open-label study to assess the effect of venetoclax on the pharmacokinetics of oral	Potential DDIs with oral contraceptives	Study planned	Date for submission cannot

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
with an oral contraceptive Planned	contraceptive in hematologic malignancy patients			be specified since the Agency agreed to conduction of this study when the indication is potentially widened to a younger population

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Tumor lysis syndrome (TLS)	Routine risk minimization measures: SmPC sections 4.2;4.4;4.5;4.8 Other routine risk minimization measures: • 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 • Package leaflet Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: AE follow-up questionnaire for TLS Additional pharmacovigilance activities: None
Neutropenia	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	SmPC sections 4.2;4.4;4.8 Other routine risk minimization measures: • Prescription only medicine. • Use of treatment should be initiated and supervised by specialist • Package leaflet Additional risk minimization measures: None	reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Serious infection	Routine risk minimization measures: SmPC sections 4.2;4.4;4.5;4.8 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist • Package leaflet Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Questionnaire for infections Additional pharmacovigilance activities: None
Embryofetal toxicity	Routine risk minimization measures: SmPC sections 4.6; 5.3 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	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Questionnaire for pregnancies Additional pharmacovigilance activities: None
Medication error	Routine risk minimization measures: SmPC sections 4.2;4.9 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Each carton will be dispensed weekly to the patient during the first 4 weeks of the dose titration • Labeling and packaging layout (immediate and outer packaging) has	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	been designed to minimize medication errors • Package leaflet Additional risk minimization measures: None	
Richter's transformation	Routine risk minimization measures: SmPC sections 4.2 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional Pharmacovigilance Activities: Studies GO28667 (MURANO), M14-032, M13-982, and M12 175.
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	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional Pharmacovigilance Activities: Studies M14-032, M13-982, M12 175 and P16-562.
Carcinogenicity studies	Routine risk minimization measures: SmPC section 5.3 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in severe hepatic impairment	Routine risk minimization measures: SmPC section 4.2	Routine pharmacovigilance activities beyond adverse reaction reporting and signal

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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	detection: None Additional Pharmacovigilance Activities: Study M15-342
Safety in severe renal impairment	Routine risk minimization measures: SmPC section 4.2 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	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in long-term exposure (> 12 months)	Routine risk minimization measures: SmPC section 5.1 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional Pharmacovigilance Activities: Studies M14-032, M13-982, M12-175, and Study P16-562

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The condition for which Venclyxto in combination with rituximab is applied for is the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

Based on single arm studies showing impressive activity in hard to treat patients with CLL, Venclyxto is currently licensed 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.
- Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or *TP5* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

3.1.2. Available therapies and unmet medical need

Current treatments for CLL are not curative. Fewer patients obtain responses with each subsequent regimen, and subjects become increasingly resistant to available therapy. Patients who relapse after a disease-free period of over 1 year (2-3 years for chemoimmunotherapy) are considered treatment sensitive and may be candidates for treatment reinitiation. Patients who relapse after a shorter interval, or are refractory to first-line treatment, present a more challenging group, particularly those who are older, have comorbid conditions, and/or harbour high-risk cytogenic abnormalities. Overall, there is a long expected survival (from time of diagnosis, 5-year relative survival rate about 75%). In the EUROCARE-5 registry, the survival rate for patients with CLL at 5 years post diagnosis was 69.0%. Due to the licensure of highly active new treatment options (venetoclax, ibrutinib, idelalisib), therapy in B-cell malignancies is in a dynamic phase.

3.1.3. Main clinical studies

The MURANO study was a randomised study comparing bendamustine + rituximab (BR) with venetoclax + rituximab (VR), both for six cycles followed by venetoclax versus no treatment up to a total study duration of 2 years in R/R CLL after at least one, but not more than three lines of therapy, thereof at least one “guideline compliant” regimen.

The MA of Venclyxto was conditional to the reporting of study M14-032, whilst reporting of the current study MURANO was an annex IIE obligation.

3.2. Favourable effects

The primary endpoint (ITT), PFS, showed a HR 0.17, with event rates 59% for the BR arm and 17% in the VR arm, p< 0.0001 (investigator assessment). At an updated efficacy analysis with all patients off treatment (data cut-off date 8 May 2018 and median follow-up of 36 months) the 36-month PFS

estimate in the venetoclax + rituximab arm was 71.4% [95% CI: 64.8, 78.1] and in the bendamustine + rituximab arm was 15.2% [95% CI: 9.1, 21].

The observed PFS benefit of venetoclax + rituximab compared with bendamustine + rituximab was consistently observed across all subgroups of patients evaluated, including age (< 65, ≥ 65 years and < 75, ≥ 75 years), prior lines of therapy (1, >1), bulky disease (< 5 cm, ≥ 5 cm), 17p deletion, 11q deletion, *TP53* mutation, *IgVH* mutation, and refractory versus relapse to most recent therapy. The HR for PFS (17p del) was HR 0.13, event rates 59% (BR) and 15% (VR) p< 0.0001 (investigator assessment) (predefined subgroup).

With regard to the secondary endpoint CR+Cri (hierarchical testing), this was 3.6% (BR) vs. 8.2% (VT), p=0.08 (IRC).

Efficacy results for the pre-specified primary analysis (data cut-off date 8 May 2017) were also assessed by an Independent Review Committee (IRC) demonstrating a statistically significant 81% reduction in the risk of progression or death for patients treated with venetoclax + rituximab (hazard ratio: 0.19 [95% CI: 0.13, 0.28]; P<0.0001). Median DOR was not reached with median follow up of approximately 23.8 months.

3.3. Uncertainties and limitations about favourable effects

Additional information on the long term outcome, would be needed as OS is still immature (20% and 11% events). The exploratory HR was 0.5 (0.3; 0.85). Data will be obtained through the final CSR of MURANO study (see RMP).

3.4. Unfavourable effects

The safety profile of VR is manageable in the clinic with standard measures and adherence to Venclyxto (see SmPC section 4.2). Dose reductions/interruptions, mainly for neutropenia, were undertaken in about 2/3 patients. In the combination phase, neutropenia was also more pronounced in the VR arm. There was no difference in infectious events.

The most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in the combination study with rituximab were neutropenia, diarrhoea, and upper respiratory tract infection. The most frequently reported serious adverse reactions (≥2%) in patients receiving venetoclax in combination with rituximab or as monotherapy were pneumonia, febrile neutropenia, and TLS.

Altogether 16% discontinued the combination phase and 9% the monotherapy phase.

Second primary malignancies are included in the RMP as an important potential risk that should be monitored.

3.5. Uncertainties and limitations about unfavourable effects

3.6. Effects Table

Table 24: Effects of venetoclax

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Primary endpoint	HR 0.19 P<0.0001			Updated analyses indicate that the event pattern is comparable VR vs. BR	
CR	First secondary e.p.	%	8	4	IRC analysis (see above)	
OS	Immature	HR 0.5 (0.3; 0.85)	Events 11%	Events 20%		
Unfavourable Effects						
Discontinuation of any treatment due to related AE		%	10	8		
AE with fatal outcome		%	6	5		
SAE		%	46	43		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

B-cell malignancies is in a dynamic phase as highly active new treatment options (venetoclax, ibrutinib, idelalisib), are approved. Licensure was conditional to the reporting of study M14-032, whilst reporting of the current study MURANO was an annex IIE obligation.

In studies comparing induction + maintenance vs. induction only, endpoints beyond first time to progression or deaths are expected to support licensure according to the current NfG. In this case an established standard of care regimen (BR) over 6 months is compared with an experimental regimen (VR) over 2 years, i.e. two regimens of different durations were compared. This may justify a partly different approach from an assessment perspective, not least as CLL is an indolent disease with durable responses also in the R/R stage and beyond.

In the interim analysis submitted to support licensure of the VR regimen, the primary endpoint and all supportive measures of efficacy clearly indicated that VR is superior to BR. The pattern of recurrence after end of therapy in the VR arm, a highly relevant outcome measure from a clinical perspective, provided too limited information for an assessment. Based on the update, it appears clear that the recurrence pattern off-therapy in the VR arm is not worse than the pattern in the BR. As the roughly estimated “truncated” mean time to next line of therapy appears longer than 18 months (24 – 36 months) a benefit of VR over BR also from the perspective of “time off-therapy” is likely, but not proven yet.

The safety profile of VR is manageable, dose reductions/interruptions, mainly for neutropenia were undertaken in about 2/3 patients. In the combination phase, neutropenia was also more pronounced in

the VR arm. There was no difference in infectious events. Altogether 16% discontinued the combination phase and 9% the monotherapy phase. Altogether the intensity of treatment is rather high, but clinically clearly manageable by standard measures.

CLL in response may be viewed as an essentially symptom-free disease and next-line therapy is normally instituted in case of symptomatic disease. A delay in the initiation of next-line therapy has been shown to be achievable with an HR of 0.2, corresponding to a roughly estimated truncated mean of more than 18 months. These data are immature, and assuming that there are no major differences in duration of next-line therapies, the VR regimen despite its longer duration, is unlikely to result in a totality of more time on therapy with associated side effects than the use of BR in treatment experienced patients with CLL. At this early time point, besides the benefit of higher response rates and longer estimated PFS, OS data also look favourable to the experimental regimen.

3.7.2. Balance of benefits and risks

Altogether benefit – risk is found to be favourable, but there are outstanding issues that should be addressed in the final study report. Apart from updates of OS, PFS (e.g. reported as restricted mean time) and, e.g. comparative time on/off therapy, an update of MRD data is of clear interest. This may enable a more detailed analysis of pattern of recurrence in responding patients off therapy, e.g. recurrence in relation to depth of response (by quantitative data, not only dichotomized) and the possible additional relevance of study therapy.

Final safety data for the monotherapy phase will be reported (see RMP).

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Venetoclax in combination with rituximab in the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy is concluded to be positive.

4. Recommendations

Outcome

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

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

Extension of Indication to include Venclyxto in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated.
The Package Leaflet is updated in accordance.

This submission also fulfils the Annex II condition to submit the results of the MURANO study comparing venetoclax plus rituximab to bendamustine plus rituximab in patients with relapsed/refractory CLL.

In addition, RMP version 3.3 (in version 2 of the RMP template) is being approved.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Venclyxto is not similar to Arzerra (ofatumomab), Gazyvaro (obinutuzumab) and Imbruvica (ibrutinib) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix I

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include Venclyxto in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.
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Summary

Please refer to the Scientific Discussion – Venclyxto II-08.

6. Attachments

1. SmPC, Annex II, Package Leaflet (changes highlighted) of Venclyxto, film-coated tablets as adopted by the CHMP on 20 September 2018.

7. Appendix

1. CHMP AR on similarity dated 20 September 2018