30 January 2020
EMA/166265/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of variations including an extension of indication assessment report

Invented name: Venclyxto

International non-proprietary name: venetoclax

Procedure No. EMEA/H/C/004106/II/0023/G

Marketing authorisation holder (MAH) AbbVie Deutschland GmbH & Co. KG

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

1L	first line/previously untreated
AE	adverse event
AESI	adverse event of special interest
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
BCL-2	B-cell lymphoma-2
BR	bendamustine+rituximab
CHMP	Committee for Medicinal Products for Human Use
CIRS	Cumulative Illness Rating Scale
Clb	Chlorambucil
CLL	chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
CR	complete response
CrCl	creatinine clearance
CRi	complete response with incomplete bone marrow recovery
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DI	Dose Intensity
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EFD	embryo-foetal development
EFS	Event free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	end of treatment
EQ-5D-3L	EuroQoL 5-Dimension questionnaire
ESMO	European Society for Medical Oncology
EU	European Union
EuroQoL	European Quality of Life
FCR	fludarabine+cyclophosphamide+rituximab
FDA	US Food and Drug Administration
G	obinutuzumab (GAZYVA®/Gazyvaro®)
GCP	Good Clinical Practice
GClb	obinutuzumab in combination with chlorambucil
GD	Gavage day
HR	hazard ratio
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IgVH/IGHV	immunoglobulin heavy chain variable region
IRC	Independent Review Committee
IRR	infusion-related reaction
ITT	intent-to-treat

iwCLL	international workshop on Chronic Lymphocytic Leukemia
K-M	Kaplan-Meier
MDASI-CLL	M.D. Anderson Symptom Assessment Inventory—CLL
MRD	minimal residual disease
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
OR	overall response
ORR	overall response rate
OS	overall survival
PCR	Polymerase Chain Reaction
PFS	progression-free survival
PIP	Pediatric Investigation Plan
PK	Pharmacokinetics
popPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QLQ-C30	Quality of Life Questionnaire-Core 30
R/R	relapsed or refractory
RMP	Risk management plan
SAE	serious adverse event
SLL	small lymphocytic lymphoma
SOC	System Organ Class
TLS	tumor lysis syndrome
VEN	Venetoclax
VEN+G	venetoclax in combination with obinutuzumab

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 28 June 2019 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Extension of indication to include, in combination with an anti-CD20 antibody (obinutuzumab), treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for Venclyxto based on the results of the pivotal CLL14/BO25323 phase 3 study; consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC and corresponding sections of the PL have been revised. The updated RMP version 5.1 has been submitted. Additionally, the SmPC section 5.3 has been updated based on the results of a 4-week dose ranging study, a 6-month carcinogenicity study and two embryo-foetal development (EFD) studies in mice. Minor editorial changes have been introduced throughout the Product Information.

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0246/2019 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0246/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific Advice from the CHMP on 9 November 2017 (EMA/CHMP/SAWP/716506/2017).

The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Filip Josephson

Timetable	Actual dates
Submission date	28 June 2019
Start of procedure:	20 July 2019
CHMP Rapporteur Assessment Report	13 September 2019
CHMP Co-Rapporteur Assessment Report	13 September 2019
PRAC Rapporteur Assessment Report	19 September 2019
PRAC members comments	25 September 2019
Updated PRAC Rapporteur Assessment Report	26 September 2019
PRAC Outcome	3 October 2019
CHMP members comments	7 October 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2019
Request for supplementary information (RSI)	17 October 2019
CHMP Rapporteur Assessment Report	20 December 2019
PRAC Rapporteur Assessment Report	3 January 2020
PRAC members comments	8 January 2020
Updated PRAC Rapporteur Assessment Report	9 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	20 January 2020
Updated CHMP Rapporteur Assessment Report	23 January 2020
Opinion	30 January 2020
The CHMP adopted a report on similarity on date (Appendix I)	30 January 2020

2. Scientific discussion

2.1. Introduction

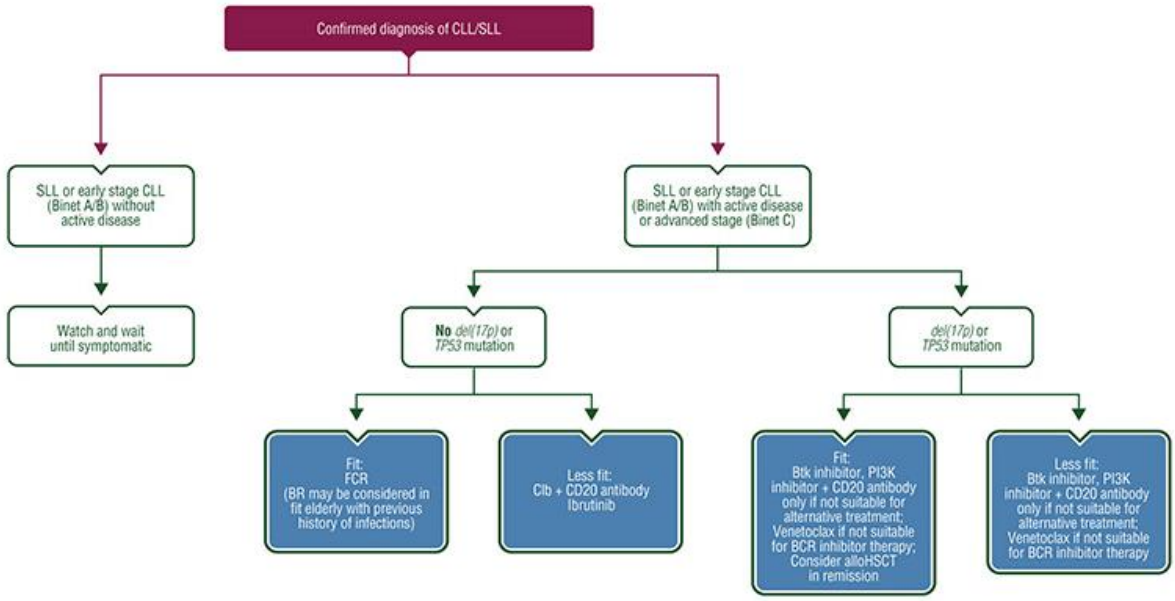
CLL remains the most prevalent chronic leukaemia in clinical practice. The treatment landscape for first-line CLL is evolving. Deep remissions and clinically significant PFS can be achieved with chemo-immunotherapy combinations, such as fludarabine-based regimens, but these intensive regimens cannot be used for the majority of newly diagnosed patients with CLL who are older and/or have comorbidities. Such patients require more effective but less toxic regimens. More tolerable regimens, such as anti-CD20 antibodies plus chlorambucil have improved outcomes of patients with CLL and comorbidities compared with previous standard-of-care (chlorambucil). Chlorambucil + obinutuzumab has shown improved PFS and OS (Goede et al. 2014, 2018), and is now the standard of care in older patients with comorbidities. However, many only achieve a partial response and no MRD negativity.

The current International Working Group for CLL (iwCLL) 2018 guidelines recommend active surveillance until disease-related symptoms develop. The prognostic factors in CLL are largely based on recurrent molecular and cytogenetic abnormalities. The role of MRD negativity in achieving deeper remissions and longer PFS (and ultimately overall survival) is taking centre stage in clinical trials.

Both NCCN (latest version:2020) and ESMO (2015, with an update in 2017) segregate patients with and without del(17p)/TP53mut and fit from unfit:

Figure 1

» Algorithm for Front-line Treatment



About the product

Venetoclax is a selective, orally bioavailable, small molecule, B-cell lymphoma-2 (BCL-2) inhibitor that restores programmed cell death (apoptosis) in cancer cells. BCL-2 over expression is a major contributor to the pathogenesis of some types of lymphoid malignancies, including chronic lymphocytic laeukemia (CLL).

The approved indications are:

Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

Venclyxto monotherapy is indicated for the treatment of CLL:

• in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or

• in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

The proposed indication is: Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

Venetoclax is given for a total of 12 cycles, each cycle consisting of 28 days: 6 cycles in combination with obinutuzumab, followed by 6 cycles of venetoclax as a single agent.

2.2. Non-clinical aspects

2.2.1. Introduction

The subject of this grouped type II variation application is to extend the approved indication of venclyxto, in combination with the anti-CD20 antibody obinutuzumab, as a frontline treatment of CLL.

Further, the MAH submitted new non-clinical carcinogenicity and embryo foetal development (EFD) data. An overview of the new non-clinical studies is presented below.

Table 1: Overview of new non-clinical toxicology studies with venetoclax and M27

Study type/duration	Species/strain	Route of administration	Dose (mg/kg/day)	GLP	Reference
Repeat-dose toxicity					
4-week repeat-dose toxicity study with M27	Mouse/ CByB6F1-Tg(HRAS)2Jic wild type	Oral	M27: 0, 30, 100, 300	Yes	R&D/16/0143
Carcinogenicity					
26-week carcinogenicity study with venetoclax and M27	Mouse/ Taconic Model 001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic	Oral	Venetoclax: 0, 40, 130, 400 M27: 0, 250 N-nitroso-N-methylurea (positive control) 75 single dose	Yes	R&D/18/0248
Reproductive and developmental toxicity					
DRF EFD with M27, 10 days (GD 6-15)	Mouse/CD1	Oral	M27: 0, 30, 100, 250	No	R&D/18/0477
EFD with M27, 10 days (GD 6-15)	Mouse/CD1	Oral	M27: 0, 30, 250	Yes	R&D/18/0648

2.2.2. Pharmacology

No new non-clinical pharmacology studies have been submitted (see discussion on non-Clinical aspects).

2.2.3. Toxicology

Single dose toxicity

No new single-dose toxicity studies have been submitted (see discussion).

Repeat dose toxicity

Table 2: 4-week repeat-dose toxicity study with M27

Report number/GLP /Duration	Species/Sex/ Number/Group	Dose (mg/kg/day)/ Route	NOAEL (mg/kg/day)
R&D/16/0143 GLP 4-weeks	Mouse wild-type (non-transgenic littermates) CByB6F1-Tg(HRAS)2Jic 10/sex/group 10/sex/group TK	0 (control), M27: 30, 100, 300 Oral gavage *Control: copovidone in 0,1% antifoam C in purified water.*	300 mg/kg/day

Mortality: none

Food consumption/body weight: ≥30 mg/kg/day; decreased food consumption in males (ranging from -7,2 to -12,6% compared to control). Body weight gain in males at 30 and 300mg/kg/day was less than that of control (-36.4% and -58.2%, respectively).

Haematology: ≥30mg/kg/day; decrease in mean lymphocyte count in males (-24% to -40% compared to control). 300mg/kg/day; minimal decrease in haemoglobin in females (-4%).

There were no M27-related clinical observations and no M27-related changes in clinical chemistry, organ weight, gross or histopathology.

Genotoxicity

No new genotoxicity studies have been submitted (see discussion).

Carcinogenicity

Table 3: 6-month carcinogenicity study with venetoclax and M27

Report number/GLP /Duration	Species/Sex/ Number/Group	Dose (mg/kg/day)/ Route
R&D/18/0248 GLP 6-months	Tg-rasH2 transgenic mice (Mouse Taconic Model 001178-T(hemizygous), CByB6F1-Tg(HRAS)2Jic) 25/sex/group 18/sex/group TK (non-transgenic littermates)	0 (control), Venetoclax: 0, 40, 130, 400 M27: 250 N-nitroso-N-methylurea (MNU) (positive control): 75 single dose IP Oral gavage *Control item 1: Water+ 0,1% antifoam* *Control item 2: Milled placebo*

Mortality: Incidence of unscheduled deaths was similar in control or test item groups (≤2 animals/sex/group). In the positive control group 0/15 males and 6/15 females died early. The deaths in positive control females were attributed to tumours of the skin, lymphoid tissue, lung and uterus.

Survival (%):

Control item 1: 96 males, 96 females

Control item 2: 100 males, 100 females

Venetoclax 40mg/kg/day: 92 males, 92 females

Venetoclax 130mg/kg/day: 92 males, 100 females

Venetoclax 400mg/kg/day: 96 males, 100 females

M27 250mg/kg/day: 96 males, 92 females

MNU 75mg single dose: 100 males, 60 females

Clinical signs: Venetoclax: ≥40mg/kg/day; Hair discoloured grey/white in all animals at all doses. M27: Hair discoloured grey in 1 female.

Body weight, food consumption: All groups gained body weight, but females given venetoclax gained less weight (5-8%) than controls. No significant differences in food consumption were found.

Macroscopic pathology: Venetoclax 400mg/kg/day; Slight increased incidence of glandular stomach swollen/thickened in females.

Histopathology:

Neoplastic lesions: none

Non-neoplastic lesions: Venetoclax ≥40mg/kg/day; Generalised decrease in lymphocytes in Gut associated lymphoid tissue (GALT), lymph nodes, thymus and spleen, increased extramedullary haematopoiesis in spleen, and liver vacuolation (in males only). Venetoclax 400mg/kg/day; Inflammation and hyperplasia of the glandular stomach (in males only).

M27 250mg/kg/day: Liver vacuolation (in males only), Decrease in lymphocytes in lymph nodes, spleen and thymus.

Table 4: Summary of toxicokinetics for venetoclax and M27

Daily dose (mg/kg/day)	**40** (ven) males	**130** (ven) males	**400** (ven) males	**250** (M27) males	**40** (ven) females	**130** (ven) females	**400** (ven) females	**250** (M27) females
Number of TK animals	18	18	18	18	18	18	18	18
Day 91: Mean C_{max} (µg/mL)	2,58	3,48	5,44	8,35	2,97	4,12	6,45	13,6
Day 91: Mean AUC (µg•hr/mL)	20,6	34,8	52,4	64,7	20,4	37,2	77,8	103

Daily dose M27 (mg/kg/day)	**30** males	**100** males	**300** males	**30** females	**100** females	**300** females
Number of TK animals	9	9	9	9	9	9
Day 1: Mean C_{max} (µg/mL)	1,34	3,7	7,57	3,13	9,02	24,6
Day 1: Mean AUC (µg•hr/mL)	8,81	28	62,2	19,2	65,6	179
Day 28: Mean C_{max} (µg/mL)	1,37	3,23	12,1	2,79	7,46	25,2
Day 28: Mean AUC (µg•hr/mL)	7,26	24,5	88,7	15,5	54,8	271

Reproduction toxicity

The applicant has conducted two new EFD studies (one DRF and one pivotal GLP study) to evaluate the potential of embryo-foetal toxicity of the major human metabolite M27. Both studies were performed in CD1-mice and are summarised below.

Table 5: Embryo-Foetal DRF study

Study ID /GLP/ Duration	**Species/Sex/ Number/Group**	**Dose (mg/kg/day)**	**NOAEL (mg/kg/day)**
R&D18/0477 DRF, Non-GLP Treatment GD6-15	Mouse Crl:CD1 Pregnant dams Age: ~11w of age. 10 females/group 3-15 pregnant females used for TK	0 (Control) M27: 30, 100, 250 Dose volume: 10 mL/kg/dose *Control: copovidone in 0,1% antifoam C in purified water.*	F_0 females: 250 F_1 litters: 250

Maternal mortality: One mouse in the 100mg/kg/day dose group was euthanised on GD10 due to adverse clinical signs (decreased activity, hunched posture, cold to touch and abnormal breathing sounds). This mouse lost 10% of body weight from GD9 to GD10. At necropsy the mouse had a perforation in the trachea and the applicant considered this unscheduled death to be unrelated to treatment and due to gavage error.

One mouse receiving 30mg/kg/day was euthanised on GD11 due to adverse clinical signs (decreased activity, cold to touch, swollen forelimbs and thorax, erected fur and eye discharge). This mouse lost 19% of body weight from GD9 to GD11. At necropsy the mouse had a perforation in the esophagus and accumulation of gritty, tan material in the right axilla and the applicant considered this unscheduled death to be unrelated to treatment and due to gavage error.

Maternal performance: No M27 related effects detected

Litters: The number of late resorptions was increased in the 250mg/kg/day dose group compared to control (0,3 resorptions/litter vs 0,0 in controls). This increase was considered to be unrelated to the treatment because the incidence was within the historical range of the testing facility.

Toxicokinetics

Toxicokinetics on GD 15				
M27 Dose (mg/kg/day)	**Cohort**	**Cmax (µg/mL)**	**Tmax (h)**	**AUC (µg•hr/mL)**
30	Maternal	8,66	3,0	40,1
	Foetal	0,60	6,0	6,72
100	Maternal	17,0	3,0	121
	Foetal	1,13	6,0	15,9
250	Maternal	20,4	6,0	135
	Foetal	1,59	12,0	26,0

Embryo-foetal GLP study

Study ID /GLP/ Duration	**Species/Sex/ Number/Group**	**Dose (mg/kg/day)**	**NOAEL (mg/kg/day)**
R&D18/0648 GLP Treatment GD6-15	Mouse Crl:CD1 Pregnant dams Age: ~11w of age. 25 females/group 6-30 pregnant females used for TK	0 (Control) M27: 30, 250 Dose volume: 10 mL/kg/dose *Control: copovidone in 0,1% antifoam C in purified water.*	**Applicant** F_0 females: 250 F_1 litters: 250 **Rapporteur** F_0 females: 250 F_1 litters: 30

Maternal mortality: No mortality or cases of moribund condition leading to termination.

Maternal clinical signs: None reported.

Maternal body weight and food consumption: No effects of M27 on maternal body weight or food consumption. Mean maternal body weight and mean maternal body weight gain for M27 treated animals on GD18 were ~98 % of controls. Mean maternal food consumption was ~106% of controls.

Table 6: Summary of Maternal performance and litters outcomes

M27 Dose (mg/kg/day)	**0**	**30**	**250**
No. of dams	25	25	25
No. of pregnant dams	25	25	24
Mortality	0	0	0
No. aborted or with total resorption of litters	0	0	0
Mean no. of Corpora Lutea	15,8	15,4	17
Mean no. of implantations	15	14,6	15,2
Mean % preimplantation loss	4,69	4,65	8,7

M27 Dose (mg/kg/day)	**0**	**30**	**250**
No. of litters evaluated	25	25	25
Total no. of foetuses examined	362	336	328
Mean total no. of foetuses	14,6	13,5	13,7
No. of dead foetuses	2	2	0
Mean no. of resorptions/litter (early)	0,3	0,9	1,2*
Mean no. of resorptions/litter (late)	0,1	0,2	0,3
Mean no. of total resorptions/litter (late)	0,4	1,1	1,5*
Mean % postimplantation loss	3	7,87	9,72*
Mean foetal bodyweight (g) (both sexes)	1,352	1,374	1,336
Foetal sex ratios (% males)	51,88	48,32	47,42

*= $p<0,05$

Table 7: Foetal external examination

Summary of external foetal abnormalities (Incidental or Malformations) Foetuses N (%) Litters N (%)			
M27 Dose (mg/kg/day)	**0**	**30**	**250**
No. of foetuses examined	362	336	328
Eye, open	1 (0,27) 1 (4,0)	0 (0) 0 (0)	3 (0,74) 1 (4,2)
Cleft palate	1 (0,27) 1 (4,0)	2 (0,56) 2 (8,0)	0 (0) 0 (0)
Head/neck exencephaly	1 (0,27) 1 (4,0)	0 (0) 0 (0)	0 (0) 0 (0)
Hindlimb malrotated	1 (0,24) 1 (4,0)	0 (0) 0 (0)	2 (0,61) 2 (8,3)
Hindpaw, hyperflexion	0 (0) 0 (0)	0 (0) 0 (0)	1 (0,28) 1 (4,2)
Tail, bent	0 (0) 0 (0)	2 (0,50) 2 (8,0)	0 (0) 0 (0)

Table 8: Foetal visceral and skeletal examination

Summary of visceral foetal abnormalities (Incidental, Malformations or Variations) Foetuses N (%) Litters N (%)			
M27 Dose (mg/kg/day)	**0**	**30**	**250**
No. of foetuses examined	175	162	159
Diaphragm, hernia	0 (0) 0 (0)	1 (0,67) 1 (4,0)	0 (0) 0 (0)
Eye, lens discoloured	2 (1,14) 2 (8,0)	0 (0) 0 (0)	2 (1,39) 1 (8,3)
Eye, retina fold	1 (0,57) 1 (4,0)	0 (0) 0 (0)	2 (1,39) 1 (4,2)
Kidney, absent	0 (0) 0 (0)	1 (0,57) 1 (4,0)	0 (0) 0 (0)
Liver, lobe malpositioned	0 (0) 0 (0)	1 (0,67) 1 (4,0)	0 (0) 0 (0)
Lung, small	0 (0) 0 (0)	1 (0,67) 1 (4,0)	0 (0) 0 (0)
Cleft palate	0 (0) 0 (0)	2 (1,11) 2 (8,0)	0 (0) 0 (0)
Ureter, absent	0 (0) 0 (0)	1 (0,57) 1 (4,0)	0 (0) 0 (0)

Summary of skeletal foetal abnormalities (Incidental, Malformations or Variations) Foetuses N (%) Litters N (%)			
M27 Dose (mg/kg/day)	**0**	**30**	**250**
No. of foetuses examined	187	174	169
Skeletal mechanical damage	3 (1,71) 2 (8,0)	6 (3,90) 3 (12,0)	12 (8,66) 7 (29,2)
Skull, frontal misshapen	1 (0,50) 1(4,0)	0 (0) 0 (0)	0 (0) 0 (0)
Skull, palatine cleft	1 (0,50) 1 (4,0)	0 (0) 0 (0)	0 (0) 0 (0)
Skull, parietal misshapen	1 (0,50) 1 (4,0)	0 (0) 0 (0)	0 (0) 0 (0)
Skull, supraoccipital absent	1 (0,50) 1 (4,0)	0 (0) 0 (0)	0 (0) 0 (0)
Skull, suture bone present	34 (18,1) 14 (56,0)	33 (20,1) 15 (60,0)	33 (19,5) 19 (79,2)
Skull, zygoatic arch incomplete ossification	0 (0) 0 (0)	0 (0) 0 (0)	1(0,69) 1 (4,2)
Sternebra, asymmetric	6 (3,3) 5 (20,0)	3 (1,81) 2 (8,0)	0 (0) 0 (0)
Sternebra, bipartite ossification	4 (2,29) 3 (12,0)	2 (1,24) 2 (8,0)	0 (0) 0 (0)
Sternebra, fused	2 (1,02) 2 (8,0)	1 (0,57) 1 (4,0)	0 (0) 0 (0)
Sternebra incomplete ossification	1 (0,57) 1 (4,0)	1 (0,57) 1 (4,0)	0 (0) 0 (0)
Sternebra misshapen	2 (1,14) 2 (8,0)	1 (0,57) 1 (4,0)	0 (0) 0 (0)
Supernumerary rib, cervical short	46 (23,72) 17 (68,0)	21 (12,16) 14 (56,0)	28 (15,5) 13 (54,2)
Vertebra, Cervical arch incomplete ossification	3 (1,52) 3 (12,0)	3 (1,72) 1 (4,0)	1 (0,52) 1 (4,2)

Foetal ossification site averages

There were no statistically significant or biologically important differences compared to control in the average numbers of ossification sites per foetus for the hyoid, vertebrae, ribs, sternum, forelimbs or hindlimbs.

Table 9: Toxicokinetics

Mean toxicokinetic parameters for M27 in maternal mouse plasma						
	GD6			GD15		
Dose (mg/kg/day)	**Cmax (µg/mL)**	**Tmax (hr)**	**AUC (µg•hr/mL)**	**Cmax (µg/mL)**	**Tmax (hr)**	**AUC (µg•hr/mL)**
30	2,77	3,0	14,8	5,71	3,0	35,2
250	13,7	3,0	75,3	14,7	3,0	131

Mean M27 ratios of foetal to maternal AUC			
	GD15		
Dose (mg/kg/day)	**Foetal (µg/mL)**	**Maternal (µg/mL)**	**AUC ratio (Foetal/Maternal)**
30	14,0	35,2	0,398
250	70	131	0,534

Toxicokinetic data

Toxicokinetic data are presented in the description of the individual studies.

Local tolerance

No new local tolerance studies have been submitted (see discussion).

Other toxicity studies

The applicant has provided juvenile toxicity study for venetoclax performed in mice, however since this variation application only concerns only adult population, the juvenile toxicity study has not been assessed within this application.

2.2.4. Ecotoxicity/environmental risk assessment

The applicant has provided an updated ERA dated March 2019. Only the new information and its consequences have been considered in this assessment.

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

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

Table 10: Summary of PEC/PNEC ratio and outcome

Endpoint	PEC/PNEC (mg/L)	PEC/PNEC value	PEC/PNEC evaluation	Outcome
Water	0,000096/0,00073	0,13	<1	No further testing necessary
Groundwater	0,000024/0,00073	0,033	<1	No further testing necessary
Microorganisms	0,000096/100	0,00000096	<0,1	No further testing necessary
Sediment	0,29/5,56	0,052	<1	No further testing necessary
Soil	0,0308/17,9	0,0017	<1	No further testing necessary

2.2.5. Discussion on non-clinical aspects

The present procedure concerns a grouped type II variation application to extend the approved indication of venclyxto (venetoclax) in combination with the anti-CD20 antibody obinutuzumab, as frontline treatment of CLL. Since the new proposed indication does not fall within the scope of ICH S9, the applicant has performed new non-clinical studies. The choice of studies were endorsed in a scientific advice provided in 2017 by the CHMP (EMA/CHMP/SAWP/716506/2017) and include: a 6 month-transgenic mouse carcinogenicity study, which includes dosing of venetoclax and the human metabolite M27; a 4-week mouse repeat-dose toxicity study with M27 and; two mouse embryo-foetal development (EFD) studies with M27. All studies were performed in mice which is considered to be a relevant species.

4-week repeat-dose toxicity study (R&D/16/0143) with M27 in mice

The M27 human metabolite is similar to venetoclax in structure but has notably less potency (approx. 170-fold less). M27 is observed at exposures greater than 10% of total venetoclax related exposures and at significantly greater levels in humans than the maximum exposure seen in animals. M27 represents up to around 30% of venetoclax+M27 exposure at steady state. By contrast, steady state plasma levels of M27 in mice and dogs were ≤ 5% of human exposure. M27 is thought to be formed via mono-oxidation of venetoclax on the 6-position of the cyclohexenyl moiety to give M5, followed by enzyme-mediated cyclization at the α-carbon of piperazine. For testing purposes, M27 (A-1621332) was synthetized.

In a 4-week repeat-dose toxicity study, mice (wild-type rasH2 mice) were dosed orally with synthesised M27 up to doses of 300mg/kg/day. Plasma (AUC) exposures to M27 at and above those at the venetoclax maximum recommended human dose (400mg/day) were achieved.

All mice survived throughout the study and no adverse findings were reported. Similar to venetoclax, M27 exposure resulted in haematological toxicity manifested by a decrease in lymphocyte count and haemoglobin.

There were no M27-related clinical observations and no M27-related changes in clinical chemistry, organ weight, gross- or histopathology.

A minimal non-dose related decrease in food intake was recorded in males but not in females. The decrease in food intake was coupled to a decrease in percent mean body weight gain in males at 30 and 300mg/kg/day but not at 100mg/kg/day. However, since the differences in the absolute mean body weight gain can be considered small (0,35g and 0,23g vs 0,55g in controls) and there was no correlation with mean body weight and food consumption, the relevance of this finding is uncertain.

A 6-month carcinogenicity study of venetoclax and M27 in transgenic mice evaluated the carcinogenicity of venetoclax and the major human metabolite M27 (synthesized and dosed) in orally administered Tg-rasH2 transgenic mice. The top dose of venetoclax (400mg/kg/day) and M27 (250mg/kg/day) was the maximum feasible dose (based on dose volume and viscosity limitations) and resulted in an exposure margin to clinical AUC of around 2-fold for venetoclax and 5,8-fold for M27. Venetoclax and the M27 major human metabolite were not carcinogenic in this study at oral doses up to 400 mg/kg/day of venetoclax and at a single dose level of 250 mg/kg/day of M27.

As observed in previous repeat-dose studies performed in CD1 mice prior the initial MAA, non-neoplastic microscopical findings related to venetoclax were seen in the lymphoid system (GALT, lymph nodes and thymus) and spleen in both sexes and included a generalised decrease in lymphocytes and increased extramedullary haematopoiesis in the spleen. In general, similar but lower incidence/severity of venetoclax-related changes in the lymphoid system and liver were present in mice given M27 at 250mg/kg/day, consistent with the weaker pharmacologic potency of M27 as a Bcl-2 inhibitor.

The MAH's rationale for not performing a 2-year rat study, has been accepted in the CHMP scientific advice EMA/CHMP/SAWP/716506/2017 and the rationale is based on results obtained from a 13-week GLP dose-selection study in rat in which decreases in haemoglobin and RBC levels were observed. In the rat study there were toxic effects in female rats resulting in moribundity and early termination at high dose (400mg/kg/day) and adverse decreases in RBC mass at 150 mg/kg/day, corresponding to clinical exposure. The MTD in females was set to 8mg/kg/day. Although not as pronounced, similar effects were observed in male rats were a more than 10% decrease in body weight gain resulted in an MTD of 150mg/kg/day, corresponding to an exposure margin of 0,8x to clinical exposure. These results indicate that even at sub-therapeutic exposure levels, female rats would not survive for 2-years and the survival of male rats would be uncertain and therefore omission of the 2-year rat study is acceptable.

In conclusion, the absence of carcinogenic effects of venetoclax or M27 in the 6-month transgenic mouse carcinogenicity study, in combination with previously reported negative genotoxicity findings with venetoclax and M27 and the absence of neoplastic lesions in chronic venetoclax toxicity studies in CD1 mice (6-months) and dogs (9-months), suggest a low carcinogenic risk to patients treated with venetoclax.

In the Embryo-foetal studies study performed for the initial MAA, venetoclax was associated with post-implantation loss and decreased foetal body weight in mice and maternal toxicity in rabbits. Only one species (mouse) was used to assess for M27-related maternal and embryo-foetal toxicity. The approach was considered acceptable in the CHMP scientific advice (EMA/CHMP/SAWP/716506/2017).

The applicant performed two new EFD studies (one DRF and one pivotal GLP study), both performed in CD1 mice, with the major human metabolite M27. In the pivotal GLP study the high dose of 250 mg/kg/day (dosed from GD6 to GD15) was the maximum feasible dose (based on dose volume and viscosity limitations) and resulted in an exposure margin of maternal to clinical AUC of around 8-fold and a mean foetal to maternal M27 concentration ratio of 0,534.

The major human metabolite M27 was associated with post-implantation loss and resorptions at exposures approximately 9-times the human M27-AUC exposure at a 400 mg dose of venetoclax. In rabbits, venetoclax produced maternal toxicity, but no foetal toxicity at exposures of 0.1 times the human AUC exposure at a 400 mg dose.

There were no mortalities at any doses tested. Compared to the concurrent controls, there were signs of M27-related adverse effects on embryo-foetal development, based on the increase in resorptions (control:0,4; 30mg:1,1; 250mg:1,5) and post-implantation losses (control:3%; 30mg:7,87%; 250mg: 9,72%). The proposed maternal NOAEL of 250mg/kg/day is agreed. The wording the SmPC section 4.6 where use of venetoclax is not recommended during pregnancy and breast-feeding remains unchanged.

The applicant has provided juvenile toxicity study for venetoclax performed in mice, however since this variation application only concerns only adult population, the juvenile toxicity study has not been assessed within this application.

Ecotoxicity/environmental risk assessment

Due to the change in indication, the applicant has provided an updated ERA based on new Fpen value (0,48%) which has been taken from the Orphanet portal for rare diseases. This approach is considered acceptable. PEC/PNEC ratio values were all <1. In line with previous assessment of venetoclax and based on the updated data submitted in this application, the new indication does not lead to a significant increase in environmental exposure further to the use of venetoclax.

2.2.6. Conclusion on the non-clinical aspects

The non-clinical aspects in support of this extension of indication are adequately studied. The new non-clinical studies assessed in this application do not indicate an increased risk of carcinogenicity of either venetoclax or the M27 major human metabolite. M27 produced embryo-foetal toxicity at exposures approximately 8-times the human margins.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of venetoclax.

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

Tabular overview of clinical studies

Study ID	Study Design	Study Population	Endpoints[b]	Treatment Regimen	Data Cutoff
Pivotal Study					
BO25323/ CLL14	Open-label, multicenter, randomized	1L CLL (n [enrolled] = 445:13 in Safety Run-In[a]; 432 in main phase of study)	Primary Efficacy: PFS by investigator assessment (PFS assessed by IRC for US regulatory decision making)[c] Key Secondary Efficacy: ORR[d], CR rate[d], MRD negativity rate[d,e,f], OS Other endpoints: Safety, PK/PD, PRO	**Arm A** (venetoclax+obinutuzumab) Venetoclax (12 cycles): • Cycle 1: 20 mg daily (Day 22 – 28) • Cycle 2: 50 mg daily (Day 1 – 7), 100 mg daily (Day 8 – 14), 200 mg daily (Day 15 – 21), 400 mg daily (Day 22 – 28) • Cycles 3–12: 400 mg daily Obinutuzumab (6 cycles): • Cycle 1: 100 mg or 1000 mg on Day 1 (if 100 mg, then 900 mg on Day 2), and 1000 mg at Day 8 and Day 15 • Cycles 2 – 6: 1000 mg on Day 1 **Arm B** (obinutuzumab+chlorambucil) Chlorambucil (12 cycles): • Cycles 1 – 12: 0.5 mg/kg on Day 1 • Cycles 1 – 12: 0.5 mg/kg on Day 15 Obinutuzumab (6 cycles): Same as above	17 Aug 2018
Supportive Study					
GP28331	Multicenter, dose-finding, safety	1L CLL (n [enrolled] = 32) R/R CLL (n [enrolled] = 50)	Primary: MTD, safety and tolerability of the combination Secondary: PK, PD, ORR[g], DOR, CR rate, PFS Exploratory: MRD negativity rate	Venetoclax + obinutuzumab, followed by venetoclax single agent **Schedule A**: venetoclax introduced before obinutuzumab (obinutuzumab initiated following venetoclax ramp-up) **Schedule B**: venetoclax introduced after obinutuzumab (venetoclax initiated on Day 22 following obinutuzumab loading-dose period)	21 May 2018

1L = first line (previously untreated); CLL = chronic lymphocytic leukemia; CR = complete response; DOR = duration of response; ID = identification; IRC = Independent Review Committee; iwCLL = international workshop on Chronic Lymphocytic Leukemia; MRD = minimal residual disease; MTD = maximum tolerated dose; ORR = overall response rate (CR + PR); OS = overall survival; PD = pharmacodynamics; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; PRO = patient-reported outcome; R/R = relapsed or refractory

a Enrollment into the safety run-in phase was completed in April 2015 with 13 patients. One patient was withdrawn from treatment per protocol due to an infusion-related reaction following the first administration of obinutuzumab and before any venetoclax was given and was excluded from the efficacy analysis, but remained in the safety population.

b Measures of disease response performed by investigator assessment according to 2008 iwCLL Guidelines.

c Although this is an open-label study, assessments by the IRC are blinded to the treatment arm.

d Three months after completion of treatment (EOT assessment).

e Measured by ASO-PCR in both bone marrow and peripheral blood.

f Investigator-assessed MRD response rate (measured by ASO-PCR) in patients with CR in both bone marrow and peripheral blood at EOT assessment

g From Cycle 2 of treatment during anytime if CR or PR was determined.

2.3.2. Pharmacokinetics

The new clinical pharmacology information includes venetoclax PK, efficacy, and safety data from patients with 1L and R/R CLL participating in the following two clinical studies:

- Pivotal Phase III Study BO25323, is an ongoing trial evaluating the efficacy and safety of venetoclax + obinutuzumab (VEN+G), Arm A compared with obinutuzumab + chlorambucil

(GClb), Arm B in patients with previously untreated CLL patients and coexisting medical conditions. The study included: pre- and 4 hours post-dose PK sampling for venetoclax, pre- and end of infusion PK sampling for obinutuzumab (approximately four PK samples per VEN+G treated patient) on a single visit of Day 1 in Cycle 4 from 194 patients in Arm A. A summary of PK concentrations for venetoclax and obinutuzumab from the primary CSR are provided in this document. A PopPK analysis of the venetoclax PK data using a Bayesian approach and the E-R (efficacy/safety/tolerability) analysis for patients randomized to VEN+G arm was performed.

- Updated data from the supportive Phase Ib Study GP28331, which is an ongoing Phase Ib, multicenter, open-label, dose-finding and safety study of venetoclax administered in combination with obinutuzumab. A total of 82 patients were enrolled in the study, 50 R/R and 32 previously untreated CLL patients. This study is a dose-escalation study with venetoclax doses ranging from 100 mg to 400mg. The study includes venetoclax and obinutuzumab PK sampling from 81 patients and was included in the original submission. The venetoclax PK data from this study was also included in the PopPK analysis.

Analytical Methods

Details of specific and sensitive bioanalytical assays using high performance liquid chromatography tandem mass spectrometry (LC-MS/MS) developed and validated for the quantitative determination of venetoclax in human plasma were provided in the original application.

During sample analysis, the assay reproducibility was demonstrated at least once per assay using an incurred samples reanalysis (ISR) approach. There was no change in analytical methods for venetoclax assays that were provided in the original application and subsequent filings.

Details of the specific and sensitive bioanalytical assays for the quantitation of obinutuzumab using an enzyme-linked immunosorbent assay (ELISA) platform validated at PPD and a titer-based bridging ELISA for the quantitation of anti-obinutuzumab antibodies developed at PPD were provided to the agency during the registration of Gazyva®. The method validations were conducted in compliance with internal standard operating procedures. The assay reproducibility for the quantitation of obinutuzumab was demonstrated using an ISR approach during sample analysis.

Table 11.Summary of Bioanalytical Methods for Quantitation of Venetoclax and Obinutuzumab

Compound	Method (Matrix)	LLOQ	Assay Range	Inter-Run		Long Term Stability	ISR
				Accuracy %Bias	Precision %CV		
Venetoclax (A-1195425)	LC-MS/MS (plasma)	2.05 ng/mL	2.05 to 2050 ng/mL	–1.5 to 3.7	1.6 to 3.2	1500 d (~–20°C) 210 d (~–70°C)	passed
		2.11 ng/mL	2.11 to 2030 ng/mL	–1.6 to 0.0	1.6 to 5.5		
Obinutuzumab (RO5072759)	ELISA (serum)	4.05 ng/mL[a]	4.05 to 400 ng/mL[a]	–2.72 to 3.58	3.55 to 12.4	1126 d (~–25°C and ~–80°C)	passed

LLOQ = Lower limit of quantitation; CV = Coefficient of variation; ISR = Incurred samples reanalysis; LC-MS/MS = Liquid chromatography tandem mass spectrometry; ELISA = Enzyme-linked immunosorbent assay; d = Day

a. Concentration in 100% serum (Minimum Required Dilution (MRD) 1:10).

Table 12. Summary of Bioanalytical Method for Detection of Anti-Drug Antibodies (Anti-Obinutuzumab Antibodies)

Method (Matrix)	MRD	Sensitivity	Drug Tolerance	Intra-Run Precision %CV	Inter-Run Precision %CV	Selectivity
ELISA (serum)	1:10	18.4 ng/mL	500 ng/mL PC detected in presence of 47.8 µg/mL	1.88 to 4.87	10.9 to 18.7	100% of LPC samples above CP were within < 100% of Control response

MRD = Minimum required dilution; CV = Coefficient of variation; ELISA = Enzyme-linked immunosorbent assay; PC = Positive control; LPC = Low positive control; CP = Cut point

Pharmacokinetics

Population PK

Methods

The PopPK of venetoclax in R/R CLL/SLL, NHL, and healthy subjects was characterized in support of the filing of venetoclax used as monotherapy in patients with R/R CLL. The current PopPK analysis used the PopPK model structure (a two-compartment PK model with first-order absorption and elimination) from the initial MAA with the parameters implemented as informative Bayesian priors. This model was then fit to the Studies GP28331 and BO25323 PK data to yield the final PopPK model and parameters.

Model parameters were estimated with the new data, and additional covariates (not previously evaluated) were tested in the model. These covariates were obinutuzumab co-administration and Binet stage. Bayesian prior distributions were not used for these additional covariates. Covariate effects were added to the model multiplicatively and tested with alpha=0.01 significance level. The final model was evaluated using diagnostic plots, visual predictive check, and normalized prediction distribution errors (NPDE) plots. Correlations of apparent clearance with previously tested covariates (that were found not to be significant in the previous model) and the additional covariates (not previously evaluated) were investigated by diagnostic plots. Individual post-hoc estimated PK parameters were computed from the final model and used to calculate steady state exposures. These PK parameters and exposures were summarized overall and stratified by study. The non-linear mixed-effects modelling software, NONMEM Version 7.4.3, utilizing PRIOR subroutine and the first-order conditional estimation method with interaction was used for the analysis.

Results

Among 216 patients randomized to Arm A in study BO25323, 13 patients in the safety run-in phase from Study BO25323, and 82 patients enrolled in Study GP28331, a total of 274 patients (194 from Study BO25323 and 80 from Study GP28331) had at least one quantifiable PK sample and were included in the analysis. A total of 1,563 quantifiable samples from 274 patients were used in the analysis. A total of 2.6% of samples were below limit of quantification and were excluded from the analysis.

The final model was structurally identical to the model of the previous analysis. The data were described by the two-compartment popPK model with first-order absorption and elimination. The parameter estimates were very similar to the estimates of the previous analysis.

Table 13. Parameter Estimates for the Final Model

Parameter		Estimate	RSE(%)	95%CI		
CL/F (L/day)	θ_1	446	2.48	425 - 468		
V_2/F (L)	θ_2	116	13.2	86.2 - 146		
Q/F (L/day)	θ_3	98.8	4.95	89.1 - 108		
V_3/F (L)	θ_4	121	3.74	112 - 130		
k_a	θ_5	3.76	3.76	3.48 - 4.04		
$F_{1,fasting}$	θ_6	0.338	0.952	0.332 - 0.344		
$F_{1,moderate\ fat}$	θ_7	1.4	8.00	1.18 - 1.62		
$F_{1,high\ fat}$	θ_8	1.44	1.28	1.41 - 1.48		
$F_{1,fed}$	θ_9	1.29	3.85	1.19 - 1.39		
$F_{1,DOSE}$	θ_{10}	-0.150	2.16	-0.157 - -0.144		
CL_{RTX}	θ_{11}	1.24	2.90	1.17 - 1.32		
$CL_{C3AHIB=2}$	θ_{12}	0.861	4.08	0.793 - 0.930		
$CL_{C3AHIB=3}$	θ_{13}	0.178	5.95	0.157 - 0.199		
$V_{2,PTOP>0}$	θ_{14}	1.73	12.0	1.33 - 2.14		
$V_{2,SEX=1}$	θ_{15}	0.703	5.65	0.625 - 0.781		
$CL_{OATP1B3}$	θ_{16}	0.864	2.41	0.823 - 0.905		
Parameter		**Estimate**	**RSE(%)**	**RSE(%)**	**Variability**	**Shrinkage**
ω^2_{CL}	$\Omega(1,1)$	0.164	7.85	0.139 - 0.189	CV=40.5%	21.3%
ω^2_{V2}	$\Omega(2,2)$	0.153	6.11	0.135 - 0.171	CV=39.1%	53.4%
ω^2_{F1}	$\Omega(3,3)$	0.0834	12.6	0.0628 - 0.104	CV=28.9%	46.8%
σ^2_{prop}	$\Sigma(1,1)$	0.222	1.47	0.216 - 0.229	CV=47.1%	9.5%
σ^2_{add}	$\Sigma(2,2)$	$3.03 \cdot 10^{-7}$	39.5	$6.88 \cdot 10^{-8}$-$5.38 \cdot 10^{-7}$	SD=$5.51 \cdot 10^{-4}$	9.5%
Derived parameters						
$t_{1/2}$ (day)		1.08				

SE: Standard Error: RSE: Relative Standard Error, %RSE=100·SE/PE, where PE is a parameter estimate;. 95% CI=95% confidence interval. SD=Standard Deviation; CV=coefficient of variation, CV=100*SD %.

Table 14. Summary of Conditional Predictions for Model Parameters, Overall and by Study

Study	Number of Patients	F_1	CL/F (L/day)	V_2/F (L)	CL/F/F_1 (L/day)	$t_{1/2}$ (day)
		Geometric Mean (CV)				
All patients	274	0.993 (0.154)	443 (0.32)	182 (0.241)	447 (0.44)	1.13 (0.119)
Study BO25323 (CLL14)	194	0.976 (0.139)	458 (0.308)	183 (0.204)	469 (0.43)	1.12 (0.102)
Study GP28331	80	1.03 (0.179)	411 (0.336)	180 (0.313)	397 (0.446)	1.16 (0.15)
		Mean (SD)				
All patients	274	1.00 (0.158)	466 (147)	187 (45.1)	491 (220)	1.14 (0.158)
Study BO25323 (CLL14)	194	0.986 (0.139)	480 (151)	186 (36.6)	514 (229)	1.12 (0.126)
Study GP28331	80	1.05 (0.19)	433 (133)	189 (61.3)	436 (188)	1.18 (0.213)

The covariate factors and patients' individual random effects were used to compute PK parameters in each group, assuming 400 mg dose. CV was computed as standard deviation of the log-transformed data.

Table 15. Difference in Parameter Estimates between the Previous Model and The Final Model

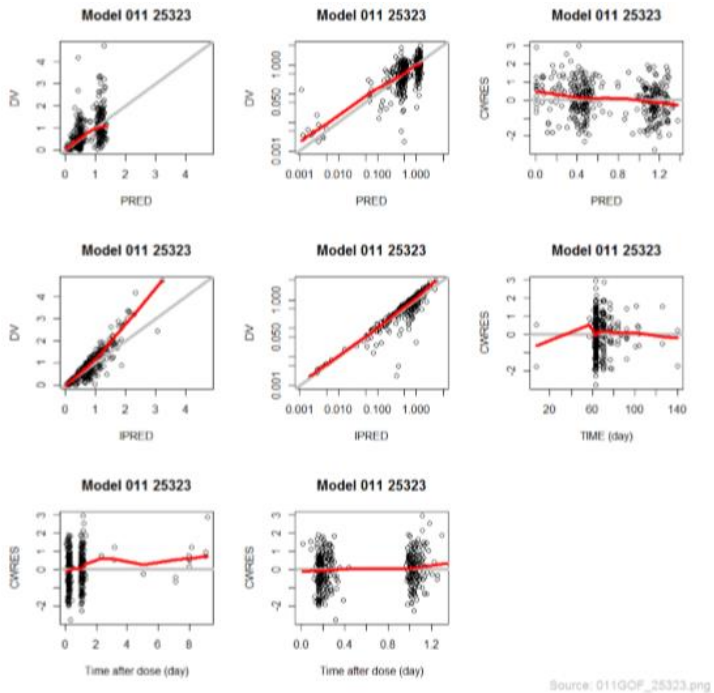
Parameter		Previous Model Estimate	Final Model Estimate	Percent Difference
CL/F (L/day)	θ_1	447	446	-0.1
V_2/F (L)	θ_2	118	116	-1.3
Q/F (L/day)	θ_3	97.2	98.8	1.6
V_3/F (L)	θ_4	119	121	2.0
k_a	θ_5	3.72	3.76	1.0
$F_{1,fasting}$	θ_6	0.335	0.338	1.0
$F_{1,moderate\ fat}$	θ_7	1.31	1.4	7.3
$F_{1,high\ fat}$	θ_8	1.43	1.44	1.0
$F_{1,fed}$	θ_9	1.23	1.29	5.0
$F_{1,DOSE}$	θ_{10}	-0.18	-0.15	-16.7
CL_{RTX}	θ_{11}	1.22	1.24	1.8
$CL_{C3AHIB=2}$	θ_{12}	0.842	0.861	2.3
$CL_{C3AHIB=3}$	θ_{13}	0.184	0.178	-3.2
$V_{2,PTOP>0}$	θ_{14}	1.71	1.73	1.4
$V_{2,SEX=1}$	θ_{15}	0.68	0.703	3.4
$CL_{OATP1B3}$	θ_{16}	0.853	0.864	1.3
ω^2_{CL}	$\Omega(1,1)$	0.153	0.164	7.3
ω^2_{V2}	$\Omega(2,2)$	0.205	0.153	-25.5
ω^2_{F1}	$\Omega(3,3)$	0.0972	0.0834	-14.2
σ^2_{prop}	$\Sigma(1,1)$	0.223	0.222	-0.2
σ^2_{add}	$\Sigma(2,2)$	$3.07 \cdot 10^{-07}$	$3.03 \cdot 10^{-07}$	-1.2

SE=Standard Error; RSE=Relative Standard Error, %RSE=100·SE/PE, where PE is a parameter estimate;. 95% CI=95% confidence interval, SD=Standard Deviation; CV=coefficient of variation, CV=100*SD %.
Source: 002_vs_011.csv

Analysis of covariates

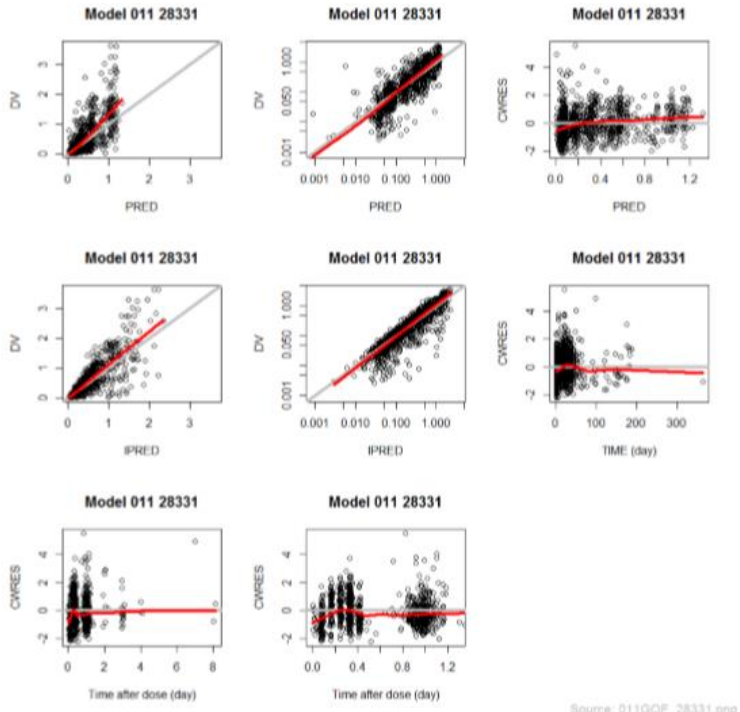
Obinutuzumab co-administration and Binet stage did not influence venetoclax apparent clearance. In agreement with the previous model, no relationship was observed between venetoclax apparent clearance and body weight, age, sex, mild and moderate hepatic and renal impairment, CrCL, AST, ALT, bilirubin, albumin and co-administration of P-glycoprotein (P-gp) inhibitors or weak CYP3A inhibitors.

Figure 2. Goodness of Fit for the Final Model: Study BO25323



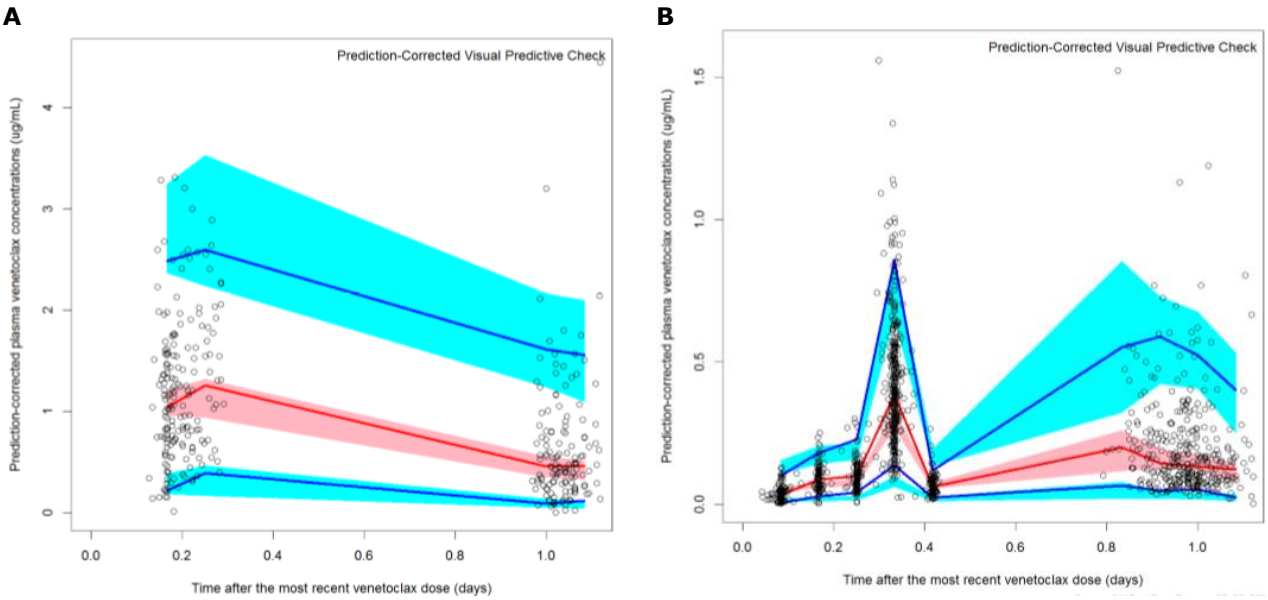
DV: Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions of the model; **CWRES**: conditional weighted residuals; **TIME**: time after the first dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines. Plots of CWRES versus time after dose are shown for the intervals of 10 days and 1.2 days, to magnify the time interval of interest.

Figure 3. Goodness of Fit for the Final Model: Study GP28331



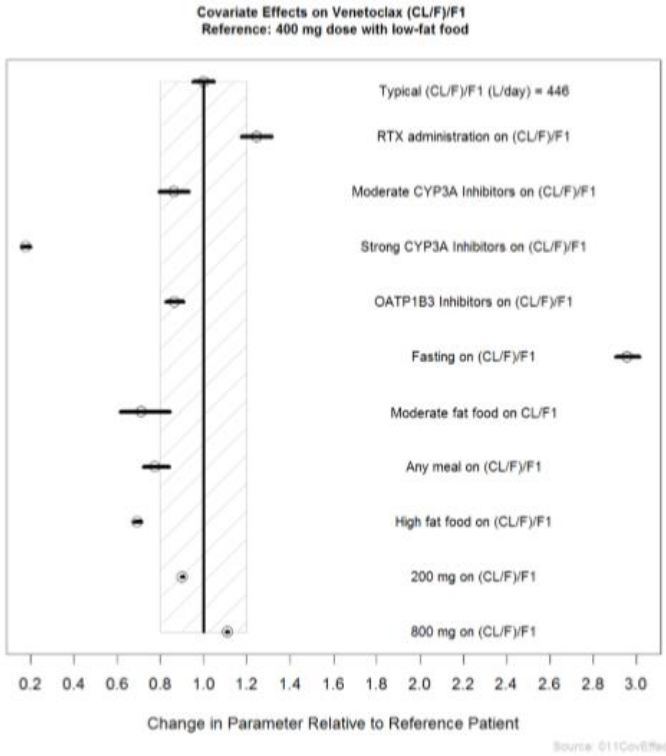
DV: Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions of the model; **CWRES**: conditional weighted residuals; **TIME**: time after the first dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines. Plots of CWRES versus time after dose are shown for the intervals of 10 days and 1.2 days, to magnify the time interval of interest.

Figure 4. Prediction-corrected Visual Predictive Check, Final Model: Study BO25323 (A) and Study GP28331 (B)



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.

Figure 5. Covariate Effects on (CL/F)/F1 for Final Model



Ratio of the typical parameter and its 95% CI for subpopulations to the typical parameter of a reference patient is illustrated. Standard errors of the parameter estimates were used to compute confidence intervals. For categorical covariates and for continuous covariates with a specific value, point estimates are represented by open circles, and 95% CIs are represented by horizontal bars. The hatched area represents typical value ± 20%.
Administration of rituximab (RTX), moderate or strong CYP3A inhibitors, or OATP1B3 transporter inhibitors affected venetoclax apparent clearance (CL/F). Food and dose affected venetoclax relative bioavailability (F_1). The plot shows effects of these covariates on CL/F/F_1 ratio as this ratio directly affects venetoclax exposure.

2.3.3. Pharmacodynamics

Methods

A Bayesian PopPK approach was used to characterize the PK properties of venetoclax in Studies GP28331 and BO25323 and to provide the individual subject exposure metrics for an assessment of the exposure-efficacy, exposure-safety and exposure-tolerability relationships for Study BO25323 only.

- **Analysis of Exposure-Safety and Exposure-Tolerability Relationships**

The objectives were to investigate the relationships between venetoclax exposure and

- probability of treatment-emergent Grade ≥ 3 neutropenia;
- probability of treatment-emergent Grade ≥ 3 thrombocytopenia;
- probability of treatment-emergent Grade ≥ 3 infections (including opportunistic infections);
- probability of treatment-emergent serious adverse events;
- venetoclax dose intensity;
- obinutuzumab dose intensity.

For each AE type, logistic regression models were implemented to assess correlation of the probability of AE occurrence with venetoclax exposure. Covariate modeling was implemented using the forward selection procedure with α = 0.01 significance level. The evaluated covariates were: demographics (body weight, sex, age, race), geographic region, and baseline disease characteristics (ECOG score, Binet stage, CLL risk group, presence of B-symptoms, CIRS score, and somatic mutations [17p deletion, 11q deletion, 13q deletion, 12t trisomy, TP53 mutation, IgVH mutation]). The resulting full model was used to evaluate the exposure-response relationship. Significance levels of covariate effects (associated p-values) were also presented. As the main purpose of the analysis was to evaluate the effect of exposure, backward elimination from the full model was not implemented.

Dose intensity (DI) was used to characterize treatment tolerability. Correlations of venetoclax and obinutuzumab DI with $C_{meanSS,nominal}$ were explored graphically and were summarized by tertials of $C_{meanSS,nominal}$.

- **Analysis of Exposure-Efficacy Relationships**

The objectives were to assess the relationships between venetoclax exposure and

- investigator-assessed (INV) progression-free survival (PFS);
- independent review committee (IRC) -assessed PFS

For each endpoint, graphical time-to-event analyses (KM plots) stratified by quartiles or tertials of $C_{meanSS,nominal}$ and Cox Proportional Hazard (CPH) modelling were conducted. $C_{meanSS,nominal}$ was used as a measure of exposure; continuous and categorical (tertials of exposure) variables were tested. Covariate CPH modelling was implemented using the forward selection procedure with α = 0.01 significance level and the same covariates as for the exposure-safety analysis. The resulting full model was used to evaluate the exposure response relationship. Significance levels of covariate effects (associated p-values) were also presented.

- ***Data***

The exposure-safety and exposure-efficacy analyses were conducted with data collected from patients of Study BO25323/CLL14 randomized to venetoclax + obinutuzumab arm. The data from the safety run-in part of the study were not used.

The empirical Bayes post-hoc estimates of venetoclax primary PK parameters (apparent clearance [CL/F] and relative bioavailability [F1]) estimated using the final population PK model and the relevant PK covariates for each subject, were used to estimate an individual exposure measure, the nominal venetoclax exposure at steady state ($C_{meanSS,nominal}$), as follows:

$C_{meanSS,nominal} = D_{nom}*F_1/(CL/F)/\tau$,

where D_{nom} was the nominal target dose assigned to a patient at randomization (400 mg), and τ was inter-dose interval (1 day). Since the PK model predicted dependence of bioavailability on dose, the nominal dose (D_{nom}) was used to compute the relative bioavailability parameter for the exposure measures. Values of covariates at the time of the first obinutuzumab dose were used to compute apparent clearance.

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.

Results

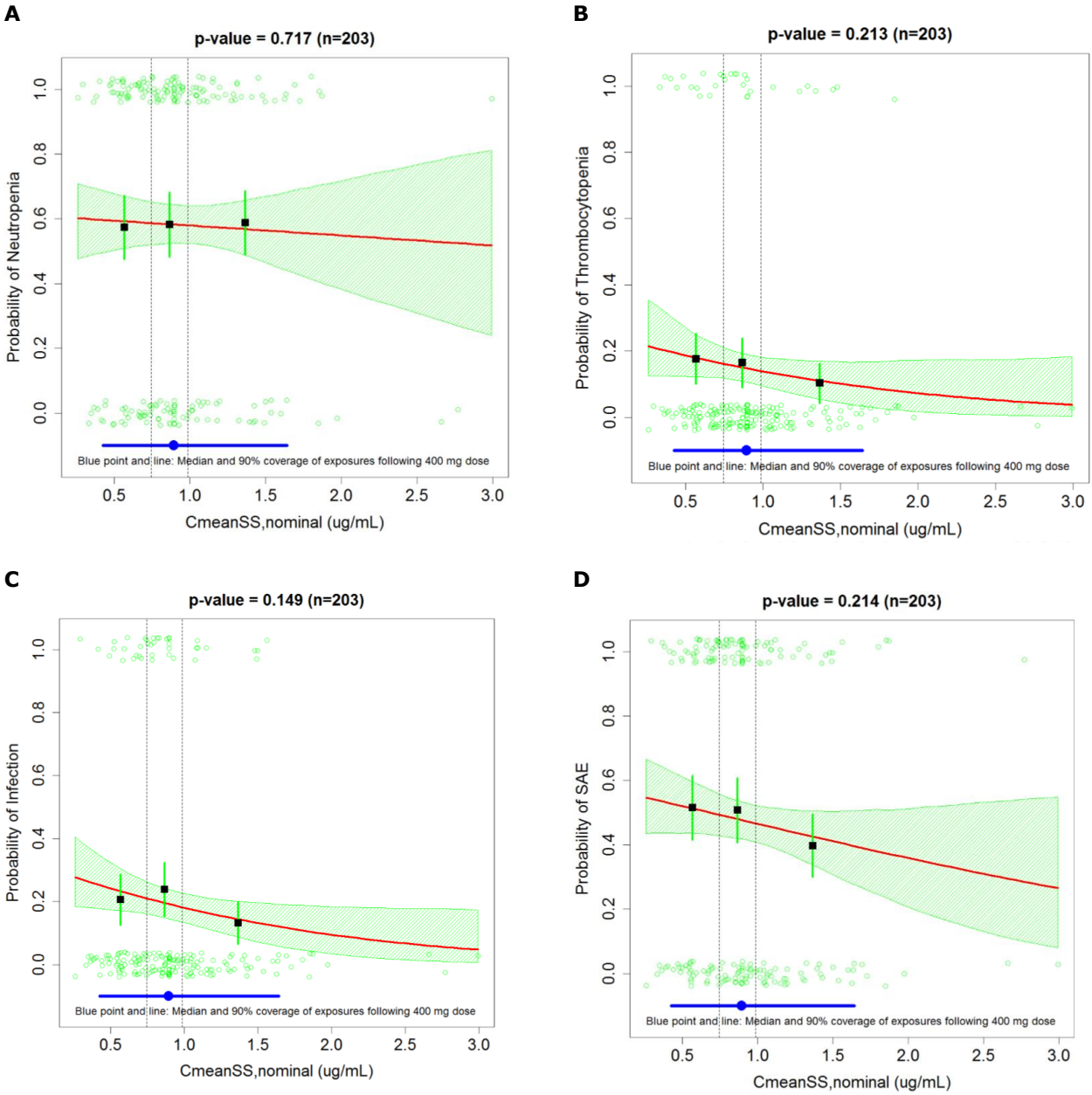
The analyses included 203 patients from venetoclax + obinutuzumab arm of the study (excluding safety run-in patients).

- **Exposure-Safety Analyses**

A total of 118 (58.1%) patients had a treatment-emergent Grade ≥ 3 neutropenia; 30 (14.8%) patients had treatment-emergent Grade ≥ 3 thrombocytopenia; 39 (19.2%) patients had treatment-emergent Grade ≥ 3 Infections, and 96 (47.3%) patients had treatment-emergent serious adverse events. For all investigated types of AE, there were no statistically significant relationships between venetoclax exposure and the probability of AE occurrence.

The logistic regression analysis of exposure-safety relationships in patients from StudyBO25323 indicated that there was no statistically significant relationship between venetoclax exposure and the probability of developing TEAEs of Grade ≥ 3 neutropenia, Grade ≥ 3 thrombocytopenia, Grade ≥ 3 infections or SAEs.

Figure 6. Logistic Regression for Grade ≥3 Neutropenia (A), Grade ≥3 Thrombocytopenia (B), Grade ≥3 Infections (C), Serious Adverse Events (D)



The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p = 1) and without events (p = 0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Blue line and point indicate point estimate and 95% coverage interval of steady-state exposure following 400 mg QD doses. P-value is provided by *glm()* function.

Subjects with ECOG score ≥ 2 were estimated to have significantly lower probability of Grade ≥3 neutropenia ($p < 0.01$) while subjects with Binet Stage C have significantly higher probability of Grade ≥3 neutropenia ($p < 0.01$). Probability of Grade ≥3 neutropenia decreased with increase of baseline bilirubin concentrations ($p = 0.012$). Subjects with Binet Stage C (BINET =3) were estimated to have significantly higher probability of Grade ≥3 thrombocytopenia ($p < 0.001$). No covariates had significant effects on the probability of Grade ≥3 infections at $\alpha = 0.01$ level. Subjects from Central or Eastern Europe (REGION = 4) were estimated to have a significantly lower probability of serious adverse events ($p = 0.006$).

Table 16. Logistic Regression Analyses for Adverse Events: Final Models

Parameter	Estimate	SE	RSE (%)	95%CI	p
Grade ≥ 3 Neutropenia					
Intercept	0.7538	0.4542	60.25	–0.1364; 1.644	
Slope of $C_{meanSS,nominal}$	0.0393	0.3613	919.28	–0.6688; 0.7474	0.910
ECOG = 2 effect[a]	–1.278	0.4701	36.79	–2.199; –0.3563	0.0066
BINET=3 effect[b]	0.9339	0.3231	34.6	0.3006; 1.567	0.0038
Bilirubin effect	–0.9994	0.4001	40.03	–1.784; –0.2152	0.0120
Grade ≥ 3 Thrombocytopenia					
Intercept	–2.127	0.6704	31.52	–3.441; –0.8128	
Slope of $C_{meanSS,nominal}$	–0.5497	0.6305	114.7	–1.785; 0.6861	0.38
Binet Stage = 3 effect[b]	1.579	0.4441	28.14	0.7081; 2.449	0.00038
Serious Adverse Events					
Intercept	0.4833	0.3742	77.43	–0.2501; 1.217	
Slope of $C_{meanSS,nominal}$	–0.3808	0.3674	96.46	–1.101; 0.3392	0.30
Region = 4 effect[c]	–0.9167	0.3364	36.7	–1.576; –0.2573	0.0064

Estimate: estimate of the coefficient on a model parameter; SE = standard error of the estimate; RSE = relative standard error of the parameter estimate (%); 95%CI = 95% confidence interval on the parameter estimate, Δ OF = change of the objective function value relative to the null model that does not include any parameters.

[a]ECOG = 2 represents patients with ECOG score ≥ 2 and in the covariate analysis were compared to those with ECOG score < 2.

[b]BINET = 3 represents patients with Binet stage C and in the covariate analysis were compared to those with Binet stage A.

[c]Region = 4 represent patients from Central/Eastern Europe and in the covariate analysis were compared to those from the other regions (US/Canada, Australia/New Zealand, Western Europe and Latin America).

- **Exposure-Dose Intensity Analyses**

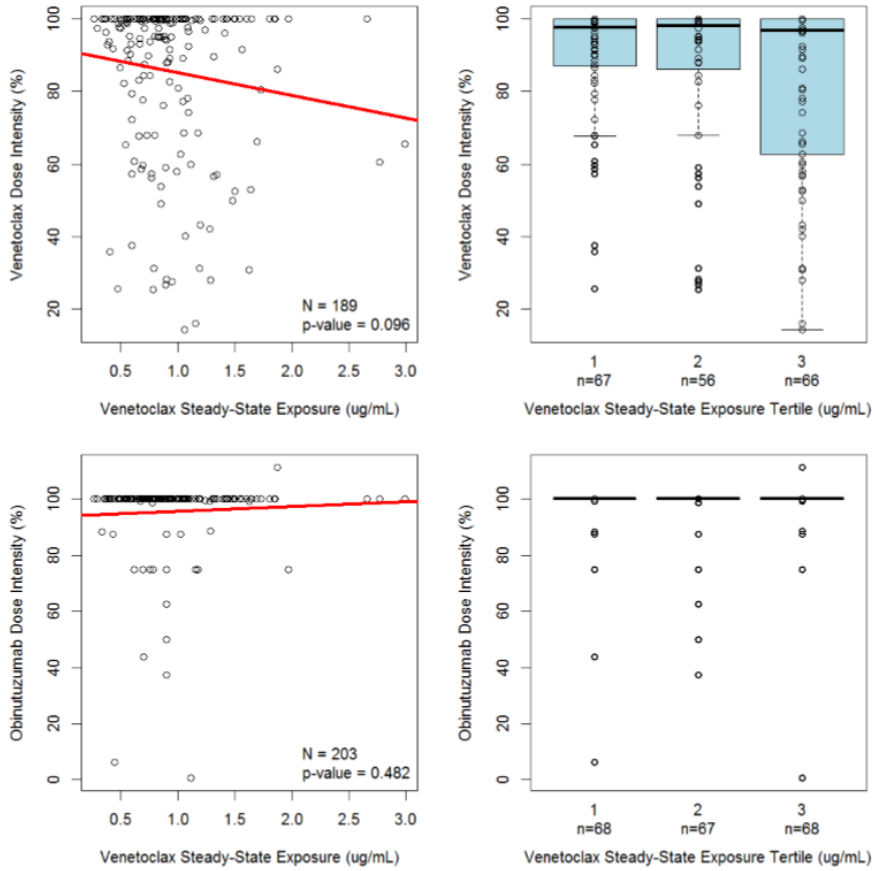
Dose intensity was calculated as the total cumulative dose actually received divided by the cumulative planned dose. The planned (target) dose of venetoclax was 400 mg and the cumulative planned dose was calculated from the day when a patient first received the 400 mg dose of venetoclax (Cycle 2, Day 22) until the last actual dose of venetoclax received. The maximum total planned duration of venetoclax treatment after reaching target dose in this approach for calculating dose intensity was 287 days (9.6 months).

The median duration of exposure to venetoclax, from first venetoclax dose, was 315.0 days (10.5 months) (range: 1-406 days [13.5 months]). After reaching the target dose, the median dose intensity for venetoclax was 97.5% (range: 14%-100%).

Obinutuzumab mean dose intensities in venetoclax + obinutuzumab arm were comparable across venetoclax exposure tertials and were between 92.5% and 97.2% for all tertials of venetoclax exposure. Venetoclax mean dose intensities in venetoclax + obinutuzumab arm were comparable across venetoclax exposure tertials and were between 81.1% and 89.3% for all tertials of venetoclax exposure.

Figure 7. Venetoclax and Obinutuzumab Dose Intensity versus Venetoclax Exposure

Circles correspond to individual dose intensity values. $C_{meanSS,nominal}$ defined by Eq. 1 was used as a measure of exposure. **Left**: Red lines are the lowess trend lines. **Right**: The distributions of venetoclax and obinutuzumab dose intensity using box and whisker plots. Median values are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR.

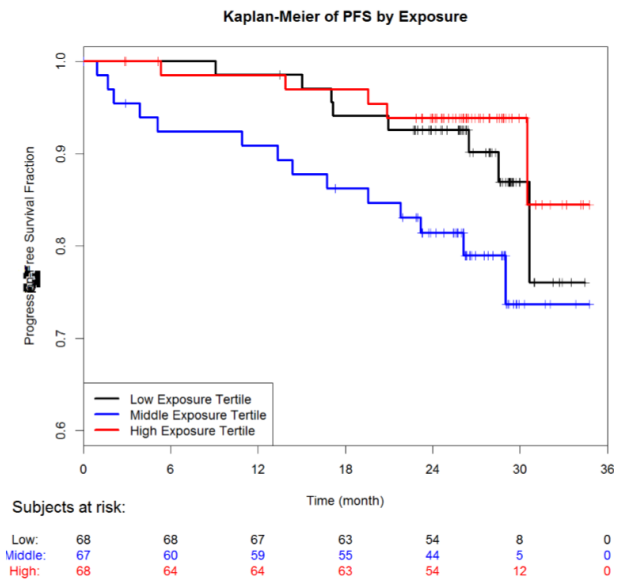


- **Exposure-Efficacy Analyses**

A total of 27 (13.3%) and 26 (12.8%) patients had INV and IRC- assessed progression events, respectively. The KM plots stratified by tertials and quartiles of venetoclax exposure and CPH models indicated no venetoclax exposure-PFS relationships. Risk of progression or death was lower in patients with t12 trisomy ($p < 0.01$). None of the covariates were significant at $\alpha = 0.01$ level.

Figure 8. Kaplan-Meier Analysis of Time to Progression (Investigator Data) (A; tertials, B; quartiles) and Time to Progression (IRC Data) (C; tertials, D; quartiles)

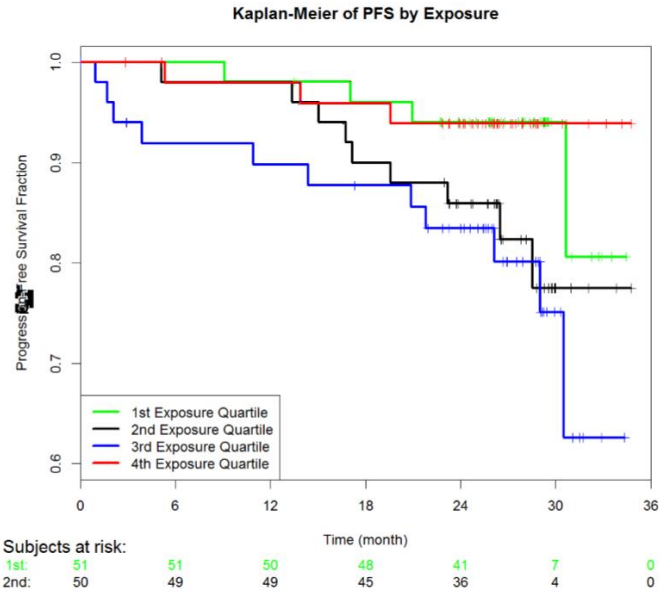
A



Subjects at risk:

Low:	68	68	67	63	54	8	0
Middle:	67	60	59	55	44	5	0
High:	68	64	64	63	54	12	0

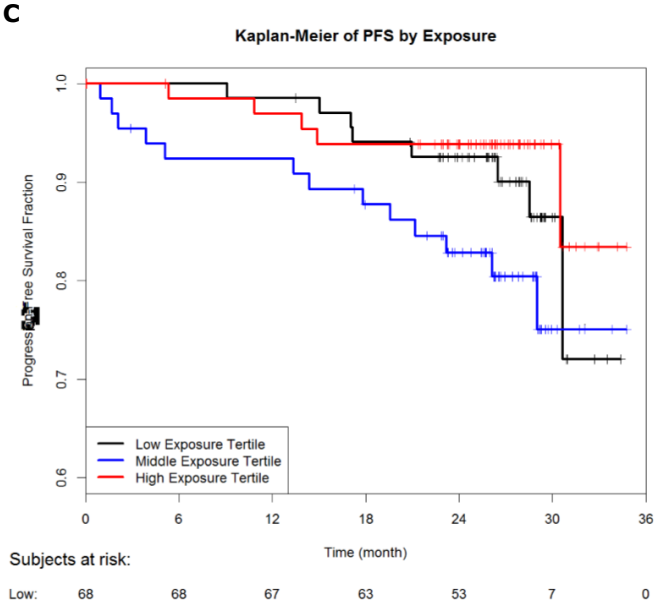
B



Subjects at risk:

1st:	51	51	50	48	41	7	0
2nd:	50	49	49	45	36	4	0
3rd:	51	44	43	41	36	7	0
4th:	51	48	48	47	39	7	0

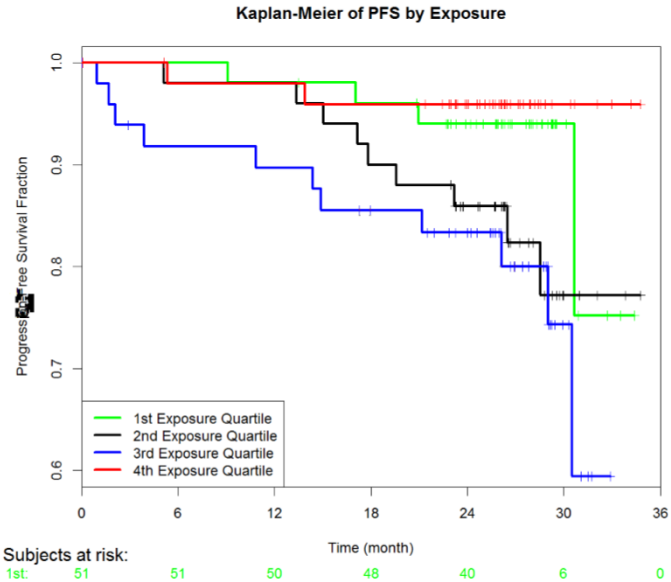
C



Subjects at risk:

Low:	68	68	67	63	53	7	0
Middle:	67	60	60	55	44	5	0
High:	68	64	63	61	50	11	0

D



Subjects at risk:

1st:	51	51	50	48	40	6	0
2nd:	50	49	49	45	36	4	0
3rd:	51	44	43	39	34	6	0
4th:	51	48	48	47	37	7	0

Table 17. Final CPH Models for PFS

Parameter	β	SE	RSE (%)	p-value
Investigator Data: $C_{meanSS,nominal}$ + factor(T12=1)				
$C_{meanSS,nominal}$	–0.5053	0.5346	105.79	0.34
T12 = 1	–18.29	4099	22412.19	[a]0.0020
IRC Data: $C_{meanSS,nominal}$ + factor(T12=1)				
$C_{meanSS,nominal}$	–0.59	0.5531	93.75	0.29
T12 = 1	–18.29	4197	22951.99	[b]0.0026

[a] p-value was computed based on the chi-square distribution (OF drop of 9.51 points).
[b] p-value was computed based on the chi-square distribution (OF drop of 9.05 points).
SE = standard error of β estimate; RSE = relative standard error of β estimate (%); NE = not estimable.
Source: Type_1_Stage1ModelTablePFS.csv, Type_2_ Stage1ModelTablePFS.csv,

2.3.4. Discussion on clinical pharmacology

The bioanalysis methods for both venetoclax and obinutuzumab were not changed since their respective original application and were therefore not re-assessed. The same is true for the ADA method.

QCs and calibration curves were within the acceptance criteria in the analytical runs for studies BO25323 and GP28331, for both venetoclax and obinutuzumab. ISR was performed and passed in all studies where it was required. No ISR was performed in study BO25323 for venetoclax, but ISR was passed (95.1% of 41 study samples were within ±30%) for obinutuzumab. During the analysis of study GP28331 samples, the sample preparation for venetoclax was changed from solid phase extraction to liquid/liquid extraction. This change of method was adequately validated using the ISR with 16 samples, where all met the acceptance criteria. 130 samples were reanalyzed for obinutuzumab and 80.8% of them passed the ISR acceptance criteria. ADA analysis (screening, confirmation & titration) was performed only in study GP28331. No ADAs were detected in the patients´ samples. No NAb analysis was performed.

The purpose of the PopPK model was to confirm that PK of venetoclax did not change with co-administration of obinutuzumab, and to provide the individual subject exposure metrics for an assessment of the exposure-efficacy, exposure-safety and exposure-tolerability relationships for Study BO25323.

The population pharmacokinetic analysis was in general well performed and adequately reported. The methods applied were according to general standards. The goodness-of-fit plots and the dose-normalised visual predictive checks for the final model reveal a reasonable prediction of lower concentrations, however the high concentrations (8 hours post dose samples) are under-predicted. This is also visible in the Goodness of Fit plots.

The diagnostic plots of the model did not indicate any model deficiencies. The model evaluation procedures (prediction-corrected visual predictive check [pc-VPC]) confirmed good predictive abilities of the model and there were no dependencies unaccounted for by the model.

Overall, the PopPK model adequately characterized venetoclax plasma concentrations over time in Studies GP28331 and BO25323. The PK of venetoclax was similar when co-administered with obinutuzumab. The model is sufficient to use for simulations and to evaluate the E-R relationships of venetoclax for Study BO25323. The parameters from the updated model do not differ greatly from the previous estimation.

Venetoclax is a small-molecule Bcl-2 family protein inhibitor that binds with high affinity to Bcl-2 and with much lower affinity to other Bcl-2 family proteins like Bcl-XL, Bcl-w. Venetoclax can restore programmed

cell death (apoptosis) in cancer cells where it has been blocked by high level expression of Bcl-2. Obinutuzumab is a novel, humanized, type II glycoengineered MAb directed against the CD20 antigen, which is found on most malignant and benign cells of B-cell origin. Obinutuzumab has the following characteristics: high-affinity binding to the CD20 antigen, low complement-dependent cytotoxicity activity, high direct cell death induction, and high antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.

The objective was to investigate exposure-safety, tolerability and efficacy relationships for venetoclax when co-administered with obinutuzumab. Individual subject CL/F and F1 were derived from the PopPK model and used to calculate $C_{meanSS,nominal}$ for a 400 mg dose. Dose adjustment were not taken into account analysis, therefore the conclusions made are not supported.

The logistic regression analysis of exposure-safety relationships indicated that there was no statistically significant relationship between venetoclax exposure and the probability of developing Grade ≥ 3 neutropenia, Grade ≥ 3 thrombocytopenia, Grade ≥ 3 infections or serious adverse events. The trend indicated that the probability is lower with increasing exposure, however, these subjects may have reduced their dose, thereby giving arise to this trend

The obinutuzumab dose intensities were comparable across venetoclax exposure tertiles, with the medians equal to 100% for all exposure groups. Venetoclax co-administration did not impact the delivery of obinutuzumab. Some trends are observed for lower venetoclax dose intensities with increasing venetoclax exposures, however, this was not considered clinically relevant given the lack of apparent E-R relationships with the primary efficacy endpoints and the key AEs of interest.

2.3.5. Conclusions on clinical pharmacology

Overall, the PopPK model adequately characterised venetoclax plasma concentrations over time in Studies GP28331 and BO25323. The PK of venetoclax was similar when co-administered with obinutuzumab. The model is sufficient to use for simulations and to evaluate the E-R relationships of venetoclax for Study BO25323.

The Applicant investigated exposure-safety, tolerability and efficacy relationships for venetoclax when co-administered with obinutuzumab. The clinical pharmacology aspects of the proposed indication are adequately studied.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Study GP28331, *A phase Ib multicenter dose-finding and safety study of venetoclax and obinutuzumab in patients with relapsed or refractory or previously untreated CLL.*

The rationale for selection of the recommended dose and regimen for venetoclax in combination with obinutuzumab in the treatment of previously untreated CLL patients with coexisting medical conditions in the Pivotal StudyBO25323 was based on available information, from the Phase I dose-escalation Study M12-175 and is further supported by the Phase Ib dose-finding/safety Study GP28331 of venetoclax in combination with obinutuzumab in patients with R/R or previously untreated chronic lymphocytic leukemia.

2.4.2. Main study

Study BO25323/CLL14

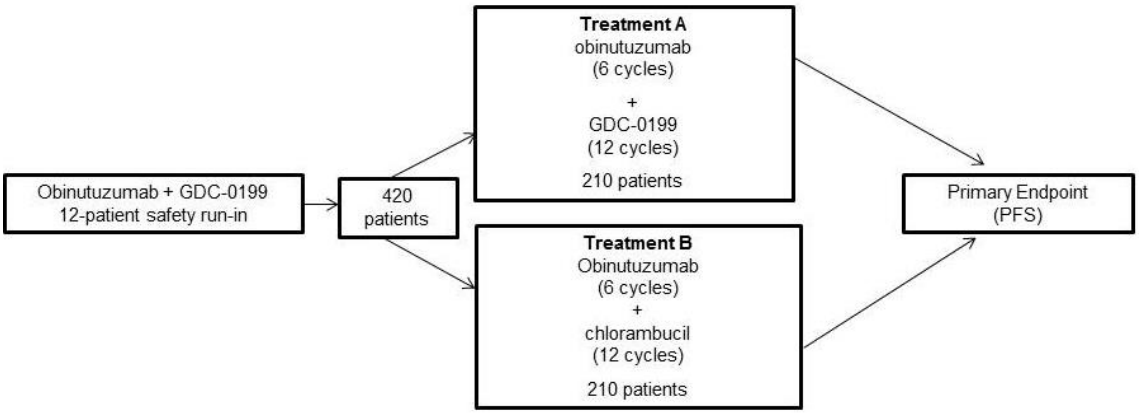
A prospective, open-label, randomized phase III trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax versus obinutuzumab and chlorambucil in previously untreated patients with CLL and coexisting medical conditions.

Cutoff date: August 2018.

Methods

The study had a safety run-in with 12 patients. The stopping criteria (i.e. one treatment-related death or one gr4 AE related to a clinical TLS despite protocol-specified prophylaxis, either following the administration of the first dose of venetoclax or during dose escalation) were not met and the Applicant proceeded to the randomized portion.

Figure 9: Study design



Study participants

Main inclusion criteria

- Previously untreated CLL (iwCLL criteria) requiring treatment
- Total Cumulative Illness Rating Score (CIRS)>6 or CrCl<70 mL/min
- Adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening as follows, unless cytopenia was due to marrow involvement of CLL:
- Absolute neutrophil count>1.0 x 10^9/L
- Platelet counts>30 x 10^9/L; in cases of thrombocytopenia clearly due to marrow involvement of CLL (per the discretion of the investigator); platelet count had to be >10 x 10^9/L if there was bone marrow involvement
- Total hemoglobin>9 g/dL without transfusion support, unless anemia was due to marrow involvement of CLL
- Adequate liver function

Main exclusion criteria

- Transformation of CLL to aggressive NHL (Richter's transformation or pro-lymphocytic leukemia)
- Known central nervous system involvement
- Patients with a history of confirmed progressive multifocal leukoencephalopathy

- An individual organ/system impairment score of 4 as assessed by the CIRS definition limiting the ability to receive the treatment regimen with the exception of eyes, ears, nose, throat organ system
- Patients with uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Inadequate renal function: CrCl<30 mL/min
- Patients with infections requiring IV treatment within the last 2 months prior to enrolment
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products

Treatments

The safety run-in included 13 patients (VEN+G). Once the twelfth patient had reached the end of cycle 3 the randomized portion began. A total of 432 patients were randomized.

The treatment duration in both groups (VEN+G vs GClb) consisted of 12 cycles lasting 28 days each. No crossover was allowed. Obinutuzumab was administered iv for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6. Chlorambucil was administered orally at 0.5 mg per kilogram of body weight on days 1 and 15 of each cycle until completion of 12 cycles. The daily oral venetoclax regimen was initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of cycle 12. The risk of tumor lysis syndrome (TLS) was assessed on the basis of the absolute lymphocyte count and lymph-node size to guide prophylactic measures. Criteria for dose modifications were specified in the study protocol.

Objectives

Efficacy
Primary: to determine efficacy by investigator-assessed PFS
Secondary efficacy objective: to determine efficacy as assessed by PFS (IRC), overall response, complete response, and MRD response rate as measured by allele-specific oligonucleotide polymerase chain reaction [ASO-PCR])
Note: IRC-assessed PFS was primary endpoint for United States regulatory purposes.

Safety
Nature, frequency, and severity AEs and SAEs.

Patient-reported outcomes
To compare disease and treatment-related symptoms following study treatments as measured by M.D. Anderson Symptom Inventory (MDASI-CLL) and to evaluate changes in physical functioning, role functioning, and global health status/quality of life following study treatments as measured by EORTC QLQ-C30.

Health economics
To compare the health utility effect of study treatments as measured by EQ-5D-3L.

Outcomes/endpoints

Primary endpoint: PFS, investigator-assessed defined as time from randomization to the first occurrence of progression or relapse (determined using standard iwCLL guidelines or death from any cause, whichever occurred first).

Key secondary endpoints:

- PFS-IRC
- ORR defined as rate of a clinical response of CR, CRi, or PR at the completion of treatment assessment (EOT assessment i.e., 3 months after treatment completion/early termination), as determined by the investigator
- CR rate: CR Rate is defined as rate of a clinical response of CR or CRi at the completion of treatment assessment (EOT assessment i.e., 3 months after treatment completion/early termination), as determined by the investigator
- MRD negativity: MRD response rate (determined as the proportion of patients with MRD negativity – where MRD negativity was defined as $< 10^{-4}$ [less than 1 cell in 10,000 leukocytes]) measured in both peripheral blood and bone marrow at the completion of treatment assessment (EOT assessment i.e., 3 months after treatment completion/early termination), both measured by ASO-PCR.
- ORR at the completion of combination treatment
- MRD at the completion of the combination treatment
- MRD response rate in patients with CR
- OS: The time between the date of randomization and the date of death due to any cause. Patients who were alive (including lost to follow-up) at the time of the analysis were censored at the date when they were last known to be alive.
- DOR: The time from the first occurrence of a documented overall response (CR, CRi, or PR, as assessed by the investigator) to the first occurrence of progression or relapse as determined by the investigator or death from any cause.
- Time to next line therapy: time between the date of randomization and the date of first intake of next line therapy or death from any cause.
- PROs

Sample size

The sample size for the study was determined given the requirements to perform a hypothesis test for clinically relevant statistical superiority in the primary endpoint of PFS.

Estimates of the number of events required to demonstrate efficacy with regard to PFS were based on the following assumptions:

- Log-rank test at the two-sided 0.05 level of significance
- Median PFS for GClb control arm (27 months)
- 80% power to detect $HR = 0.65$ for the comparison of $VEN + G$ experimental arm versus GClb, with median PFS for $VEN + G$ increased to 41.5 months
- Exponential distribution of PFS
- Annual drop-out rate of 10%

One interim analysis for efficacy after 75% of PFS events, utilizing a stopping boundary according to the γ family error spending function with parameter $\gamma = -9.21$.

The addition of an optional early interim analysis (performed after 85 events [50% of PFS events] as per Protocol amendment 7 required no adjustment to the sample size, as the impact on the statistical power calculation was negligible.

Based on these assumptions, a total of 170 PFS events is required for the final PFS analysis of PFS.

Randomisation

Patients were assigned in 1:1 ratio to one of the two treatment arms (VEN + G or GClb) through a block stratified randomization procedure. The randomization scheme ensured approximately equal sample sizes in the two treatment groups with regards the following stratification factors:

- Binet stage (3 levels): A, B, or C
- Geographic region (US/Canada/Central America; Australia/New Zealand; Western Europe; Central and Eastern Europe; or Latin America)

Blinding (masking)

This was an open-label study. The IRC and the sponsor were blinded to treatment arm.

Statistical methods

Treatment comparisons were made using a two-sided log-rank test (at 0.05 significance level, adjusted for the interim analyses), stratified by Binet stage and Geographic Region. If the null hypothesis was rejected and the observed HR was favourable for the VEN + G experimental arm, then it was to be concluded that VEN + G significantly lowered the risk of PFS events more than GClb. A two-sided non-stratified log-rank test was performed to support the primary analysis.

Median PFS and the 95% confidence limits will be estimated using Brookmeyer Crowley method, with the Kaplan-Meier survival curve presented to provide a visual description. PFS rates for 1, 2, and 3 years after randomization with 95% CIs using Brookmeyer Crowley method will be reported. Estimates of the treatment effect will be expressed as HR including 95% confidence limits estimated through a Cox proportional-hazards analysis stratified by Binet stage and Geographic Region.

For patients who were alive and had not had disease progression or relapse, PFS data were censored on the date of the last disease assessment. In the analysis of MRD negativity and response to treatment, patients without a sample or response assessment that could be evaluated were counted as not being negative for residual disease or as not having a response, respectively.

If the study meets the primary efficacy endpoint of investigator assessed PFS, then the formal statistical testing procedure for the key secondary endpoints will be performed using alpha-splitting and recycling of alpha. To adjust for multiple testing, the pre-specified hierarchical testing of eight key secondary efficacy endpoints was used in the following order:

1. Independent review committee-assessed PFS
2. Minimal residual disease in bone marrow 3 months after treatment completion
3. Complete response rate [investigator-assessed] 3 months after treatment completion
4. Minimal residual disease in peripheral blood 3 months after treatment completion
5. Minimal residual disease in complete response in bone marrow 3 months after treatment completion
6. Minimal residual disease in complete response in peripheral blood 3 months after treatment completion
7. Overall response rate [investigator-assessed] 3 months after treatment completion
8. Overall survival

The α-spending boundary of each endpoint at the interim analysis is given as follows:

	Endpoint	α Spend at Interim Analysis
1	Independent review committee–assessed PFS	0.0019
2	Minimal residual disease in bone marrow 3 months after treatment completion	0.0019
3	Complete response rate [investigator-assessed] 3 months after treatment completion	0.05
4	Minimal residual disease in peripheral blood 3 months after treatment completion	0.05
5	Minimal residual disease in complete response in bone marrow 3 months after treatment completion	0.05
6	Minimal residual disease in complete response in peripheral blood 3 months after treatment completion	0.05
7	Overall response rate [investigator-assessed] 3 months after treatment completion	0.05
8	Overall survival	0.007

To check robustness of the primary analysis of PFS and underlying assumptions, the following sensitivity analyses for PFS (both investigator-assessed and IRC-assessed) will be performed on the ITT population:

- An unstratified log-rank test for the primary PFS comparison between treatment arms will be conducted.
- The impact of patients' initiation of non-protocol specified anti-CLL therapy without meeting the criteria of disease progression/relapse on PFS will be assessed by censoring these patients at the start date of the non-protocol specified anti-CLL treatment. Stopping only one component of the randomized study treatment will not be considered a reason for censoring patients.
- To assess the impact of missing assessments on PFS, an analysis on PFS will be performed by censoring those patients who progressed, relapsed or died after missing more than one visit consecutively at their last adequate response assessment date before the missed visits.

The primary and secondary analyses were based on the ITT population, defined as all randomized patients. Subgroup analyses of investigator-assessed PFS, IRC-assessed PFS, MRD, ORR, CR and OS were performed to assess internal consistency using the ITT population. The odds ratios of response and their 95% confidence intervals, HR of time-to-event endpoints and their 95% confidence intervals (based on similar analyses to the primary endpoint), as well as the sample sizes were reported separately for each level of the following subgroups in forest plots by baseline characteristics and stratification factors (Binet stage and Region).

Originally an interim analysis for efficacy were planned once a minimum of 110 PFS events have occurred. PFS were to be tested at the significance level determined using the gamma family error spending function with parameter $\gamma=-9.21$ so that the overall two-sided type I error rate will be maintained at the 0.05 level. In protocol amendment 7 an optional early interim analysis (at a minimum of 85 events) was included, if this was performed and passed, this later original interim analysis was not to be undertaken.

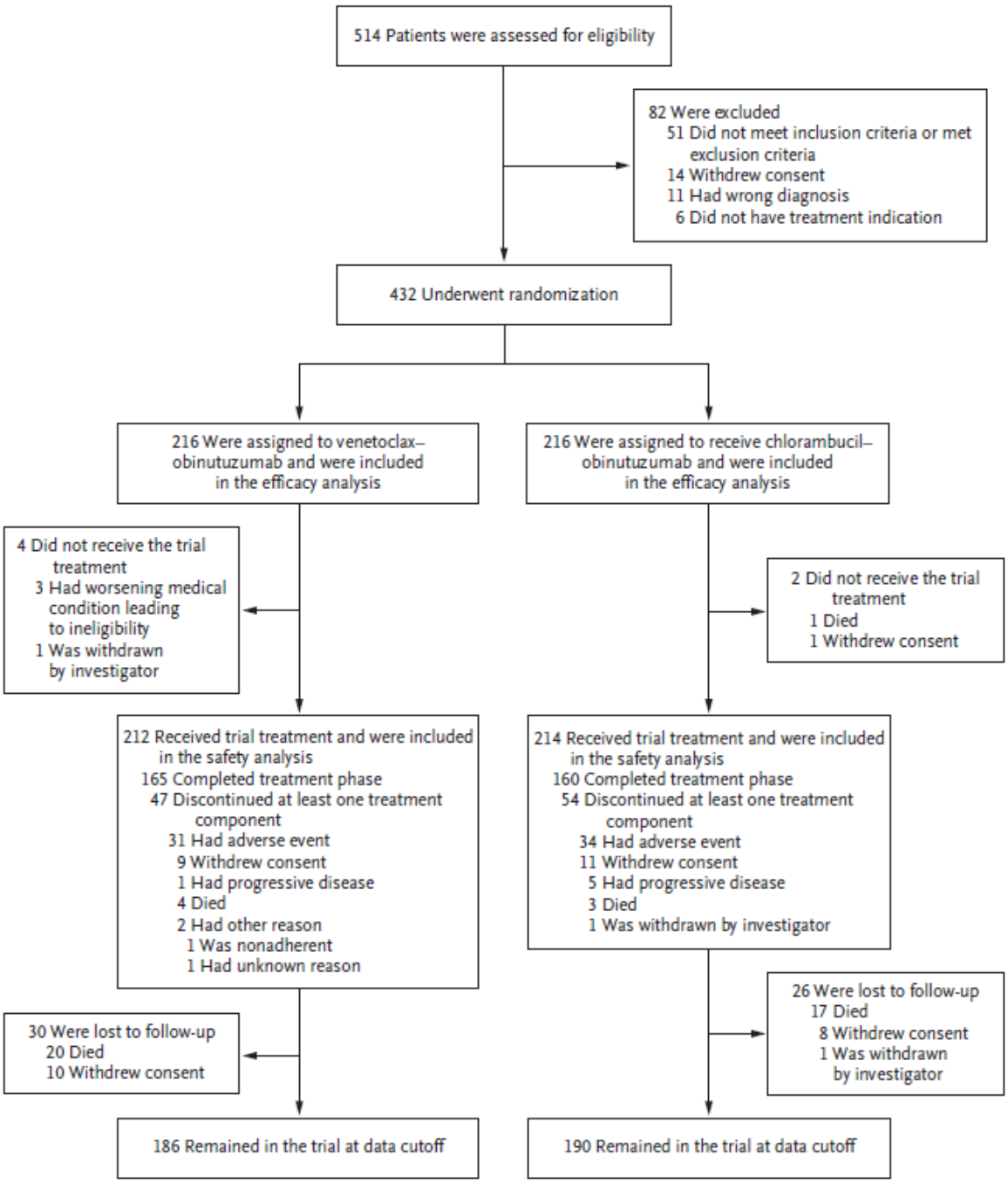
The final analysis was designed to be conducted after 170 events have occurred. venetoclax dose, then the interim analysis may be conducted once a minimum of 85 PFS events have occurred.

Also, exploratory analyses were performed, including graphical analyses, of the relationship between MRD (on the basis of peripheral blood results by ASO-PCR) and PFS.

Results

Participant flow

Figure 10 Participant flow



Recruitment

Out of 514 patients assessed for eligibility in the main study, 432 were enrolled, 216 in each arm; 186/216 patients in VEN+G and 190/216 in GClb were ongoing at cutoff (Aug. 2018).

Conduct of the study

There were 6 protocol amendments.

Baseline data

Characteristic	Venetoclax–Obinutuzumab (N=216)	Chlorambucil–Obinutuzumab (N=216)
Age ≥75 yr — no. (%)	72 (33.3)	78 (36.1)
Male sex — no. (%)	146 (67.6)	143 (66.2)
Binet stage — no. (%)†		
A	46 (21.3)	44 (20.4)
B	77 (35.6)	80 (37.0)
C	93 (43.1)	92 (42.6)
Tumor lysis syndrome risk category — no. (%)		
Low	29 (13.4)	26 (12.0)
Intermediate	139 (64.4)	147 (68.1)
High	48 (22.2)	43 (19.9)
Total CIRS score >6 — no. (%)‡	186 (86.1)	177 (81.9)
Calculated creatinine clearance <70 ml/min — no./total no. (%)	128/215 (59.5)	118/213 (55.4)
Cytogenetic subgroup — no./total no. (%)§		
Deletion in 17p	17/200 (8.5)	14/193 (7.3)
Deletion in 11q	36/200 (18.0)	38/193 (19.7)
Trisomy 12	36/200 (18.0)	40/193 (20.7)
No abnormalities	50/200 (25.0)	42/193 (21.8)
Deletion in 13q alone	61/200 (30.5)	59/193 (30.6)
IGHV mutational status — no./total no. (%)		
Mutated	76/200 (38.0)	83/208 (39.9)
Unmutated	121/200 (60.5)	123/208 (59.1)
Could not be evaluated	3/200 (1.5)	2/208 (1.0)
TP53 mutational status — no./total no. (%)		
Mutated	19/171 (11.1)	13/157 (8.3)
Unmutated	152/171 (88.9)	144/157 (91.7)

* There were no significant differences between the groups at baseline. Percentages may not total 100 because of rounding.
† Binet stages indicate the degree of advancement of chronic lymphocytic leukemia and are based on organ and lymph-node involvement, hemoglobin levels, and platelet counts.
‡ Scores on the Cumulative Illness Rating Scale (CIRS) range from 0 to 56, with higher scores indicating more impaired function of organ systems.
§ Cytogenetic subgroups were determined according to the hierarchical model of Döhner at al.[18]

The patients were elderly (median age, 72 years; range: 41 to 89; 34.7% were aged over 75 years) and white (89.4%). Approximately two-thirds of patients (66.9%) were male. The majority of patients were enrolled in Europe, 69.7%. Overall, the median time from first diagnosis of CLL to randomization was 2.5 years (0-20.4 years). The majority of patients were Binet stage B or C (79.1%) at baseline and approximately half (49.8%) were experiencing B symptoms at baseline, with night sweats (43.5%) being the most frequent B symptom. TLS risk was categorized as low, medium or high and the risk categories were balanced between groups: 43 patients (20%) in the GClb arm and 48 (22.2%) in the VEN+G arm belonged to the high- risk category). The majority of patients (66.2%) were considered as intermediate risk.

The proportion of patients with *unmutated IGVH* mutational status (based on central assessment) was 57% in the GClb arm and 56% in the VEN+G arm; 10 patients in the GClb arm (4.6%) and 19 in the VEN+G arm (8.8%) either had missing samples or were not evaluable for IGVH mutational status. The *TP53* mutation was carried by 13 patients (6%) in the GClb arm and 19 patients (8.8%) in the VEN+G arm. The mutational status was unknown for 59 patients (27.3%) in the GClb arm and 45 (20.8%) in the VEN+G arm. The *17p* deletion was present in 14 patients (7.3%) in the GClb arm and 17 patients (8.5%) in the VEN+G arm.

The median CIRS score was numerically higher in the VEN+G arm (9 vs 8 in the GClb arm), and the proportion of patients with CIRS score of >6 was 86.1% compared with 81.9%, respectively. The proportion of patients with creatinine clearance <70 mL/min was 55.4% in the GClb arm and 59.5% in the VEN+G arm.

In terms of prognosis, the CLL-IPI scores were similar for the two treatment arms; 60% in the GClb arm and 60.4% in the VEN+G arm had a high score.

CIRS: 177 patients (81.9%) in the GClb arm and 186 (86.1%) in the VEN+G arm had a CIRS score >6. Most patients in each treatment arm had comorbidities in 4-8 organ systems (179 patients [82.9%] in both arms). A higher percentage of patients in the VEN+G group had involvement of cardiac systems and hypertension, followed by respiratory organ system.

As for concurrent diseases, vascular disorders were the most frequent type of concurrent medical condition: GClb 155 (71.8%) compared with 175 (81%) in the experimental arm, mainly due to hypertension; COPD: 11 patients (5.1%) in the GClb arm vs 18 (8.3%) in the VEN+G arm; asthma 6 (2.8%) vs 10 (4.6%), respectively.

Numbers analysed

Outcomes and estimation

Table 18 Efficacy outcomes

Parameter[a]	GClb (N=216)	VEN+G (N=216)
Progression-Free Survival (Investigator Assessment)		
Patients with event	77 (35.6%)	30 (13.9%)
Time to event (months)		
Median [95% CI]	NE [31.1, NE]	NE [NE]
P-value (log-rank test, stratified)	p<0.0001	
Hazard ratio (stratified), [95% CI]	0.35 [0.23, 0.53]	
Estimate of 1-year PFS rate % (95% CI)	92.11 (88.40, 95.82)	94.62 (91.53, 97.71)
Estimate of 2-year PFS rate % (95% CI)	64.10 (57.39, 70.81)	88.15 (83.69, 92.60)
Progression-Free Survival (IRC Assessment)		
Patients with event	79 (36.6%)	29 (13.4%)
Time to event (months)		
Median [95% CI]	NE [31.1, NE]	NE [NE]
P-value (log-rank test, stratified)	p<0.0001	
Hazard ratio (stratified), [95% CI]	0.33 [0.22, 0.51]	
Estimate of 1-year PFS rate % (95% CI)	91.16 (87.27, 95.06)	94.60 (91.50, 97.71)
Estimate of 2-year PFS rate % (95% CI)	63.70 (56.99, 70.42)	88.59 (84.20, 92.98)
Overall Response Rate (Investigator Assessment)[b] (EOT)		
Responders	154 (71.3%)	183 (84.7%)
95% CI	[64.77, 77.23]	[79.22, 89.24]
Difference in response rates [95% CI]	13.43 [5.47, 21.38]	
P-value (CMH test)	p=0.0007	
Complete Response Rate(Investigator Assessment)[b] (EOT)		
Responders	50 (23.1%)	107 (49.5%)
95% CI	[17.70, 29.35]	[42.68, 56.40]
Difference in response rates [95% CI]	26.39 [17.41, 35.36]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate–Peripheral Blood[b] (EOT)		
MRD negative (at 10^{-4})	76 (35.2%)	163 (75.5%)
95% CI	[28.83, 41.95]	[69.17, 81.05]
Difference in MRD negative rates [95% CI]	40.28 [31.45, 49.10]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate–Bone Marrow [b] (EOT)		
MRD negative (at 10^{-4})	37 (17.1%)	123 (56.9%)
95% CI	[12.36, 22.83]	[50.05, 63.64]
Difference in MRD negative rates [95% CI]	39.81 [31.27, 48.36]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate in CR[c] Patients–Peripheral Blood (EOT)		
Responders	31 (14.4%)	91 (42.1%)
95% CI	[9.96, 19.75]	[35.46, 49.02]
Difference in MRD responder rates [95% CI]	27.78 [19.45, 36.10]	
P-value (CMH test)	p<0.0001	

EOT = at end of treatment (i.e., 3 months after treatment completion/early termination); MRD: minimum residual disease; [a] Key secondary response rates were also compared using a stratified test (according to the hierarchical testing approach),[b] By ASO-PCR, [c] CR status is assessed by investigator, [d] As of clinical cut-off, the overall survival data were immature to be meaningful.

Table 19: PFS (inv. assessed)

	GClb (N=216)		VEN+G (N=216)
Patients with event (%)	77 (35.6%)		30 (13.9%)
Earliest contributing event			
Disease Progression	69		14
Death	8		16
Patients without event (%)*	139 (64.4%)		186 (86.1%)
Time to Event (Month)			
Median	NE		NE
95% CI	(31.1, NE)		NE
25% and 75%-ile	18.5, NE		NE
Range	0.0* to 35.9*		0.0* to 34.7*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.35	
95% CI		(0.23, 0.53)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.34	
95% CI		(0.22, 0.51)	
Time Point Analysis			
6 Month Duration			
Patients remaining at risk	194		195
Event Free Rate (%)	95.59		96.10
95% CI	(92.78, 98.41)		(93.45, 98.75)
12 Month Duration			
Patients remaining at risk	184		192
Event Free Rate (%)	92.11		94.62
95% CI	(88.40, 95.82)		(91.53, 97.71)
18 Month Duration			
Patients remaining at risk	152		183
Event Free Rate (%)	76.55		91.16
95% CI	(70.68, 82.42)		(87.26, 95.06)
24 Month Duration			
Patients remaining at risk	110		153
Event Free Rate (%)	64.10		88.15
95% CI	(57.39, 70.81)		(83.69, 92.60)
30 Month Duration			
Patients remaining at risk	21		25
Event Free Rate (%)	60.37		83.75
95% CI	(53.28, 67.47)		(77.67, 89.82)

* 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: Binet and Geographic region.

At the interim analysis (specified at 110 events, with 107 actual events), the number of PFS events in the control arm was low, 35.6%. Despite a median follow-up of approximately 29 months for each arm, the PFS data can be considered immature. From around month 23 and on, extensive censoring is observed.

Figure 11 K-M of PFS (investigator assessed)

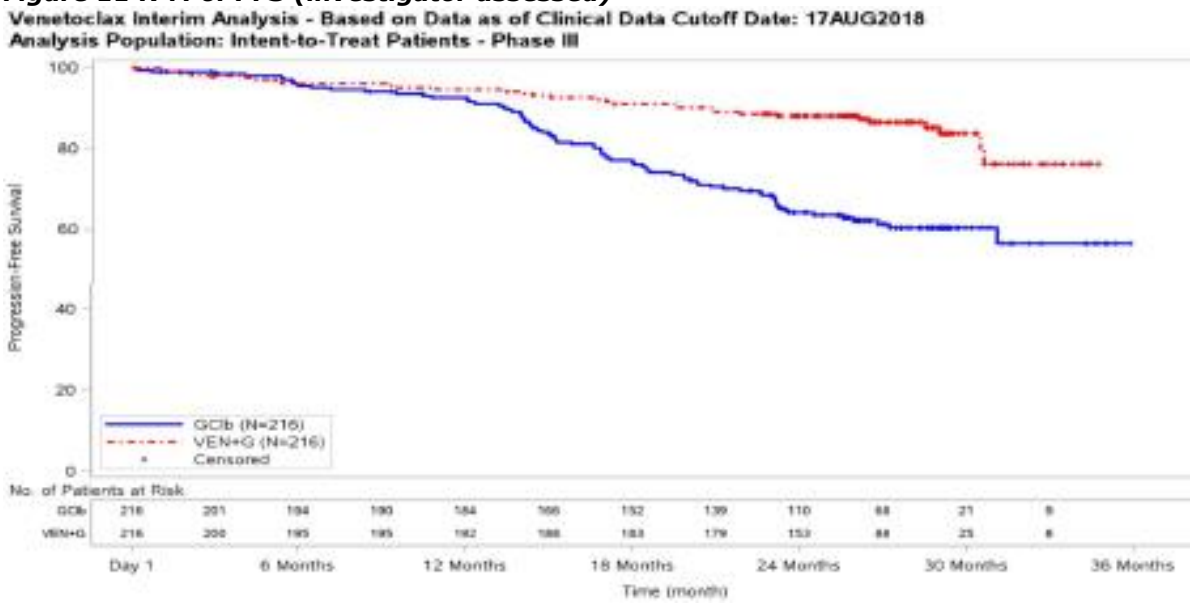
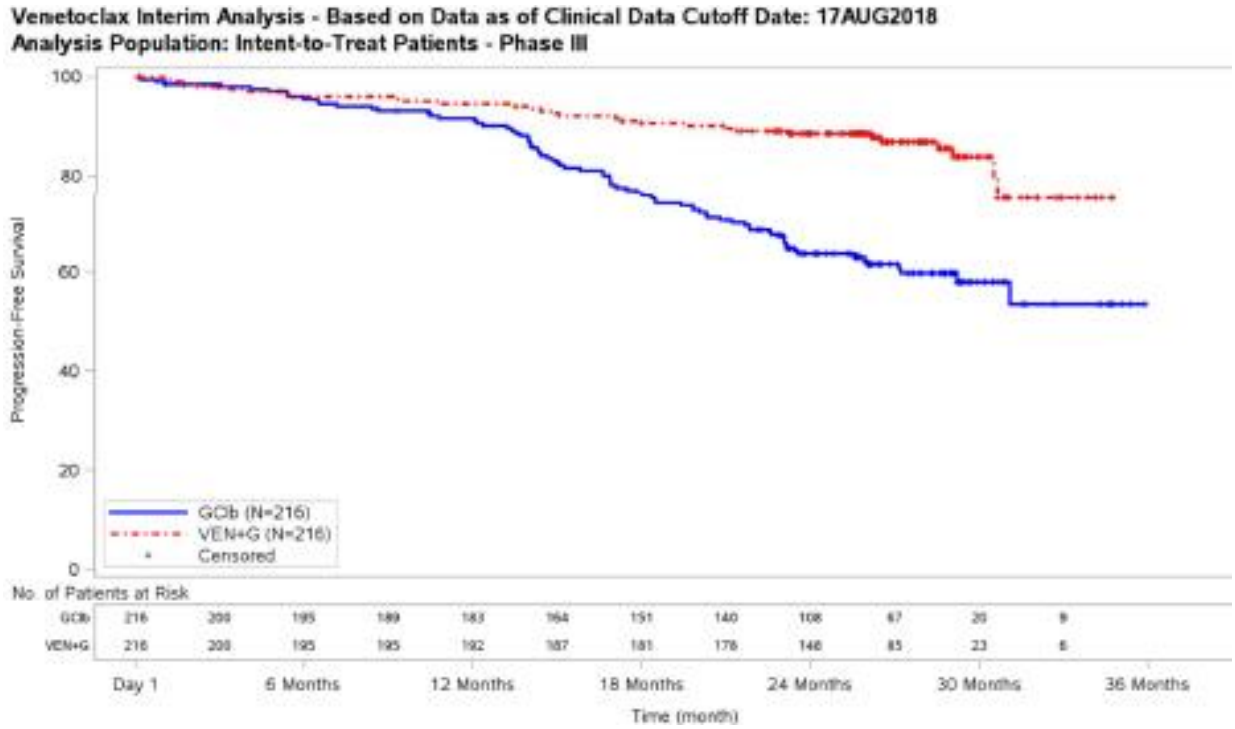


Figure 12: PFS by IRC



The reported concordance between investigator and IRC is very high (98.1%).

Sensitivity analyses for PFS

Three sensitivity analyses of investigator-assessed PFS were conducted to test for the potential impact of differences in modelling or censoring approaches:

1. A non-stratified log-rank test
2. PFS analyses with censoring at initiation of non-protocol-specified anti-CLL therapy before meeting disease progression criteria to assess potential confounding of treatment effect estimates by subsequent therapy
3. PFS analyses with censoring of death or disease progression after more than one missed response assessment at the date of last adequate response assessment

Table 20 Sensitivity analyses for PFS

Analysis	INV-Assessed PFS		IRC-Assessed PFS	
	GClb arm	VEN+G arm	GClb arm	VEN+G arm
Censoring for More Than One Missed Response Assessment[a]				
Patients with event	75 (34.7%)	28 (13.0%)	77 (35.6%)	27 (12.5%)
Median Time to Event (months)	NE (31.1, NE)	NE (NE)	NE (31.1, NE)	NE (NE)
Stratified P-value (log-rank)	<.0001		<.0001	
Stratified HR (CI 95%)	0.33 (0.22, 0.52)		0.32 (0.21, 0.50)	
Unstratified P-value (log-rank)	<.0001		<.0001	
Unstratified HR (CI 95%)	0.32 (0.21, 0.50)		0.30 (0.20, 0.47)	
Censoring for new anti-CLL Treatment[b]				
Patients with event	77 (35.6%)	29 (13.4%)	78 (36.1%)	28 (13.0%)
Median Time to Event (months)	139 (64.4%)	187 (86.6%)	NE (31.1, NE)	NE (NE)
Stratified P-value (log-rank)	<.0001		<.0001	
Stratified HR (CI 95%)	0.34 (0.22, 0.52)		0.33 (0.21, 0.50)	
Unstratified P-value (log-rank)	<.0001		<.0001	
Unstratified HR (CI 95%)	0.33 (0.21, 0.50)		0.31 (0.20, 0.48)	

Secondary endpoints

A higher number of patients treated with VEN+G had an Overall Response in comparison to the GClb arm per investigator assessment (84.7% vs 71.3% where a difference of 13.43% seen in the response rates (95% CI:5.47,21.38) p value = 0.0007 stratified Cochran-Mantel-Haenszel test.

Likewise for CR/CRi, patients treated with VEN+G achieved a higher rate of CR/Cri compared with patients in the GClb arm as per investigator assessment (49.5% vs 23.1%,difference in response rate:26.39,95% CI 17.41,35.36 [p value <0.0001,stratified Cochran-Mantel-Haenszel test

ORR and CR

Table 21: ORR and CR results

	GCIb (N=216)		VEN+G (N=216)
Responders	154 (71.3%)		183 (84.7%)
Non Responders	62 (28.7%)		33 (15.3%)
95% CI for Response Rates	(64.77, 77.23)		(79.22, 89.24)
Difference in Response Rates		13.43	
95% CI		(5.47, 21.38)	
p-value (Cochran-Mantel-Haenszel)		0.0007	
Odds Ratio		2.25	
95% CI		(1.40, 3.63)	
Combined Response (CR/CRi)	50 (23.1%)		107 (49.5%)
Complete Response (CR)	47 (21.8%)		100 (46.3%)
Complete Response with Incomplete Bone Marrow Recovery (CRi)	3 (1.4%)		7 (3.2%)
Partial Response (PR)	104 (48.1%)		76 (35.2%)

Derived as first response on or after end of treatment. Responders is defined as clinical response of CR, CRi, or PR.
P-value is from the Cochran-Mantel-Haenszel (CMH) test stratified by the IvRS randomization stratification factors.
95% CI for rates were constructed using Pearson-Clopper method. 95% CI for difference in rates were contructed using Anderson-Hauck method. Odds ratio was estimated using logistic regression model. 95% CI for odds ratio was constructed using Wald test.

MRD

MRD responses comprised 1) peripheral blood MRD assessment in all patients and 2) bone marrow MRD assessment in responders (CR+PR). ASO-PCR MRD was assessed 3 months after treatment completion/early termination for all patients (PB and BM) and across pre-specified time-points for PB (every 3 mo for 18 months from EOT and thereafter every 6 months until 5 years from last patient enrolled). The patients for whom no post-baseline MRD assessment was available at a specific time-point were considered MRD positive for that particular time-point. The status recorded for missing bone marrow biopsies or missing computed tomographic scans was partial response or stable disease, respectively.

Table 22 MRD negativity in bone marrow at the EOT visit (ITT)

	GClb (N=216)		VEN+G (N=216)
MRD Negative*	37 (17.1%)		123 (56.9%)
MRD Positive**	179 (82.9%)		93 (43.1%)
95% CI for MRD negative rates	(12.36, 22.83)		(50.05, 63.64)
Difference in MRD negative rates		39.81	
95% CI		(31.27, 48.36)	
p-value (Chi-square)		<.0001	
Odds Ratio		6.40	
95% CI		(4.10, 9.98)	
MRD Negative	37 (17.1%)		123 (56.9%)
MRD Assay Positive	112 (51.9%)		33 (15.3%)
MRD Sample Missing - PD/Death	13 (6.0%)		5 (2.3%)
MRD Sample Missing - W/d from Study	3 (1.4%)		5 (2.3%)
MRD Sample Missing - Other	51 (23.6%)		50 (23.1%)

95% CI for rates were constructed using Pearson-Clopper method. 95% CI for difference in rates were constructed using Anderson-Hauck method.
* MRD Negative < 10^-4.
** Includes MRD Missing and Non-Evaluable Samples.

Table 23 MRD negativity in peripheral blood at the EOT visit (ITT)

	GClb (N=216)		VEN+G (N=216)
MRD Negative*	76 (35.2%)		163 (75.5%)
MRD Positive**	140 (64.8%)		53 (24.5%)
95% CI for MRD negative rates	(28.83, 41.95)		(69.17, 81.05)
Difference in MRD negative rates		40.28	
95% CI		(31.45, 49.10)	
p-value (Chi-square)		<.0001	
Odds Ratio		5.67	
95% CI		(3.73, 8.60)	
MRD Negative	76 (35.2%)		163 (75.5%)
MRD Assay Positive	106 (49.1%)		24 (11.1%)
MRD Sample Missing - PD/Death	9 (4.2%)		5 (2.3%)
MRD Sample Missing - W/d from Study	3 (1.4%)		5 (2.3%)
MRD Sample Missing - Other	22 (10.2%)		19 (8.8%)

MRD and clinical outcome

Table 24 MRD negativity (bone marrow) at EOT assessment (ITT population)

	GClb (N=216)		VEN+G (N=216)
MRD Responder*	23 (10.6%)		73 (33.8%)
MRD Non-Responder	193 (89.4%)		143 (66.2%)
95% CI for MRD responder rates	(6.87, 15.55)		(27.52, 40.53)
Difference in MRD responder rates		23.15	
95% CI		(15.37, 30.93)	
p-value (Chi-square)		<.0001	
Odds Ratio		4.28	
95% CI		(2.56, 7.18)	

95% CI for rates were constructed using Pearson-Clopper method. 95% CI for difference in rates

Table 25 MRD negativity (peripheral blood) at EOT assessment (ITT population)

	GClb (N=216)		VEN+G (N=216)
MRD Responder*	31 (14.4%)		91 (42.1%)
MRD Non-Responder	185 (85.6%)		125 (57.9%)
95% CI for MRD responder rates	(9.96, 19.75)		(35.46, 49.02)
Difference in MRD responder rates		27.78	
95% CI		(19.45, 36.10)	
p-value (Chi-square)		<.0001	
Odds Ratio		4.34	
95% CI		(2.72, 6.93)	

DOR

Overall, 197/216 in GClb and 200/216 in VEN+G arm responded to treatment.

	GClb (N=216)		VEN+G (N=216)
Patients included in analysis	197 (100.0%)		200 (100.0%)
Patients with event (%)	67 (34.0%)		24 (12.0%)
Earliest contributing event			
Disease Progression	64		12
Death	3		12
Patients without event (%)*	130 (66.0%)		176 (88.0%)
Time to Event (Month)			
Median	NE		NE
95% CI	(28.1, NE)		NE
25% and 75%-ile	17.3, NE		NE
Range	0.0+ to 32.9+		0.0+ to 31.9+
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.31	
95% CI		(0.20, 0.50)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.30	
95% CI		(0.19, 0.48)	

Figure 13: EFS

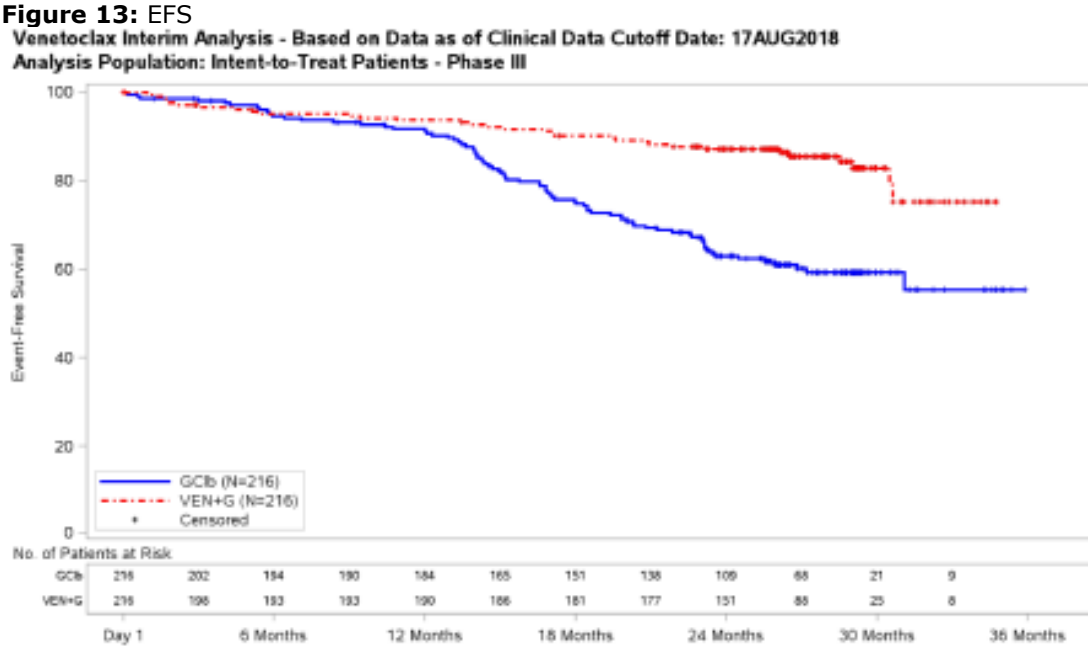
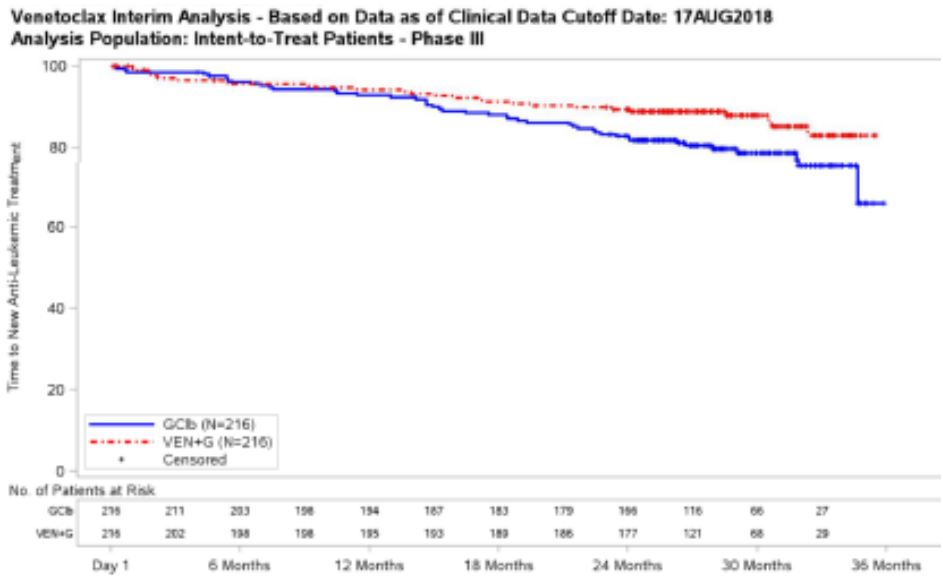


Table 26: time to next therapy

	GClb (N=216)		VEN+G (N=216)
Patients with event (%)	45 (20.8%)		27 (12.5%)
Earliest contributing event			
New anti-leukemic treatment	32		10
Death	13		17
Patients without event (%)*	171 (79.2%)		189 (87.5%)
Time to Event (Month)			
Median	NE		NE
95% CI	(34.6, NE)		NE
25% and 75%-ile	34.6, NE		NE
Range	0.0* to 35.9*		0.0* to 35.4*
Stratified Analysis			
p-value (log-rank)		0.0340	
Hazard Ratio		0.60	
95% CI		(0.37, 0.97)	
Unstratified Analysis			
p-value (log-rank)		0.0285	
Hazard Ratio		0.59	
95% CI		(0.37, 0.95)	
Time Point Analysis			
6 Month Duration			
Patients remaining at risk	203		198
Event Free Rate (%)	96.24		95.67
95% CI	(93.69, 98.80)		(92.91, 98.44)
12 Month Duration			
Patients remaining at risk	194		195
Event Free Rate (%)	92.91		94.22
95% CI	(89.44, 96.37)		(91.05, 97.40)
18 Month Duration			
Patients remaining at risk	183		189
Event Free Rate (%)	88.09		91.32
95% CI	(83.71, 92.48)		(87.49, 95.15)
24 Month Duration			
Patients remaining at risk	166		177
Event Free Rate (%)	82.30		89.38
95% CI	(77.12, 87.48)		(85.19, 93.58)
30 Month Duration			
Patients remaining at risk	66		68
Event Free Rate (%)	78.71		87.96
95% CI	(72.83, 84.58)		(83.36, 92.57)

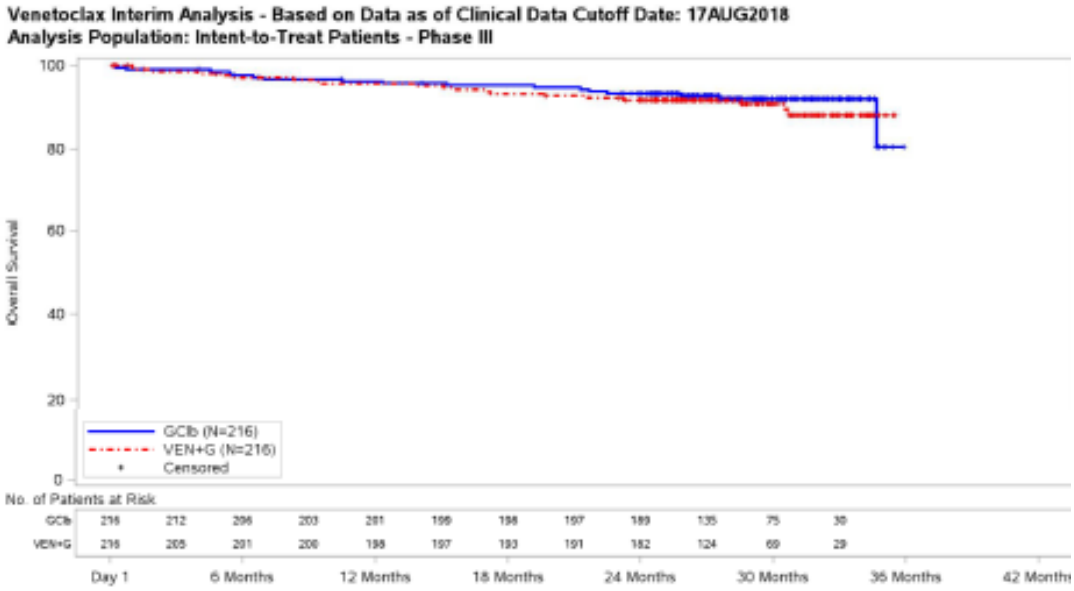
Figure 14: Time to next line therapy



OS

At the data cut-off less than 10% of enrolled patients had died: 7.9% (17/216) OS events in GClb and 9.3% (20/216) in VEN+G.

Figure 15: Overall Survival



PROs

MDASI-CLL, EORTC QLC-C30 and EQ-5D-3L analyses did not show a difference between treatments.

Ancillary analyses

Pre-specified subgroup analyses of investigator-assessed PFS and MRD negativity in peripheral blood 3 months after treatment completion were performed to assess internal consistency using the ITT population.

Pre-specified subgroups included: Binet stage at screening (A, B, C), Age (<75, ≥75), Gender (male, female), Cytogenetic factors (deletion 17p, 11q and 13q, and trisomy 12), *TP53* status (deletion and/or mutation, none), IGVH mutational status (unmutated, mutated)

Since the study was powered for the ITT population, all subgroup analyses were exploratory.

Figure 16: Investigator-assessed PFS by prognostic subgroup

			Chlorambucil–obinutuzumab			Venetoclax–obinutuzumab				
Category	Subgroup	Total n	n	Events	PFS rate month 24 (%)	n	Events	PFS rate month 24 (%)	Hazard ratio	95% Wald CI
All		432	216	77	64.1	216	30	88.1	0.34	0.23–0.53
Binet stage at screening	A	90	44	18	56.6	46	3	95.7	0.13	0.04–0.42
	B	157	80	30	62.5	77	9	86.9	0.26	0.12–0.55
	C	185	92	29	69.1	93	18	83.4	0.56	0.32–1.05
Age groups (years)	<75	282	138	49	63.5	144	17	89.7	0.28	0.16–0.48
	≥75	150	78	28	65.1	72	13	84.9	0.48	0.25–0.93
Gender	Male	289	143	49	65.4	146	21	87.7	0.37	0.22–0.61
	Female	143	73	28	61.4	70	9	89.1	0.29	0.13–0.60
Cytogenetic subgroups as per hierarchy	del(17p)	31	14	10	23.1	17	7	64.7	0.33	0.12–0.89
	del(11q)	74	38	20	41.3	36	4	91.2	0.11	0.03–0.36
	Trisomy 12	76	40	17	55.6	36	0	100.0	NE	NE
	No abnormalities	92	42	8	82.1	50	9	67.2	0.93	0.36–2.41
	del(13q)	120	59	16	78.3	61	8	88.1	0.45	0.19–1.05
TP53 deletion and/or mutation	Present	46	22	15	32.7	24	7	70.9	0.31	0.13–0.76
	Not present	287	139	49	65.0	148	14	92.1	0.23	0.13–0.42
IGHV mutational status	Unmutated	244	123	57	51.0	121	16	89.4	0.22	0.12–0.38
	Mutated	159	83	15	85.6	76	9	90.3	0.64	0.28–1.46

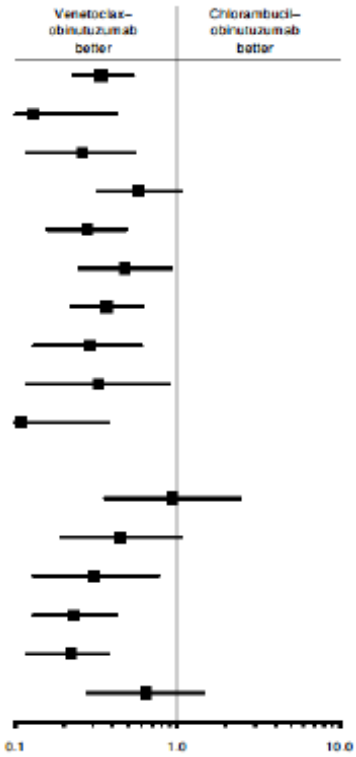
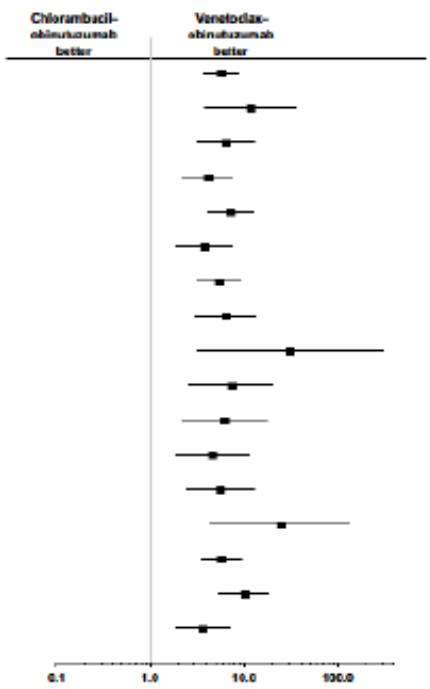


Figure 17: MRD negativity by ASO-PCR in peripheral blood 3 months after completion of treatment by prognostic subgroup

			Chlorambucil–ebinutuzumab		Venetoclax–obinutuzumab			
Category	Subgroup	Total n	n	MRD negative (%)	n	MRD negative (%)	Odds ratio	95% CI
All		432	216	35.2	216	75.5	5.67	3.74–8.64
Binet stage at screening	A	90	44	40.9	46	89.1	11.84	3.92–35.80
	B	157	80	33.8	77	76.6	6.40	3.19–12.89
	C	185	92	33.7	93	67.7	4.13	2.26–7.63
Age groups (years)	<75	282	138	31.9	144	77.1	7.19	4.24–12.19
	≥75	150	78	41.0	72	72.2	3.74	1.88–7.42
Gender	Male	289	143	35.7	146	74.7	5.31	3.20–8.82
	Female	143	73	34.2	70	77.1	6.48	3.19–13.55
Cytogenetic subgroups as per hierarchy	del(17p)	31	14	7.1	17	76.6	31.20	3.17–306.84
	del(11q)	74	38	26.3	36	72.2	7.26	2.61–20.32
	Trisomy 12	76	40	40.0	36	80.6	6.21	2.26–17.08
	No abnormalities	92	42	38.1	50	74.0	4.63	1.91–11.23
	del(13q)	120	59	42.4	61	80.3	5.56	2.49–12.39
TP53 deletion and/or mutation	Present	46	22	9.1	24	70.8	24.39	4.44–132.84
	Not present	287	139	36.0	148	76.4	5.75	3.44–9.60
IGHV mutational status	Unmutated	244	123	27.6	121	75.2	10.05	5.58–18.16
	Mutated	159	83	43.4	76	73.7	3.66	1.87–7.15



The available PFS and MRD data support an effect across cytogenetic subgroups and mutational status.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27 Summary of Efficacy for trial BO25323/CLL14

A prospective, open-label, randomized phase III trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax versus obinutuzumab and chlorambucil in previously untreated patients with CLL and coexisting medical conditions.			
Study identifier	BO25323/CLL14		
Design	Randomized, open-label		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		2015- (ongoing) 2014-2015 NA
Hypothesis	Superiority		
Treatments groups	VEN+G (experiment)		12 cycles, n=216
	GClb (control)		12 cycles, n=216
Endpoints and definitions	Primary	PFS	Inv-assessed
	Secondary	PFS IRC, ORR, CR, MRD, PROs	PFS IRC was the primary endpoint in the US.
Database lock	17 August 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT		

Effect estimate per comparison

Parameter[a]	GCIb (N=216)	VEN+G (N=216)
Progression-Free Survival (Investigator Assessment)		
Patients with event	77 (35.6%)	30 (13.9%)
Time to event (months)		
Median [95% CI]	NE [31.1, NE]	NE [NE]
P-value (log-rank test, stratified)	p<0.0001	
Hazard ratio (stratified), [95% CI]	0.35 [0.23, 0.53]	
Estimate of 1-year PFS rate % (95% CI)	82.11 (88.40, 95.82)	94.62 (91.53, 97.71)
Estimate of 2-year PFS rate % (95% CI)	64.10 (57.39, 70.81)	88.15 (83.69, 92.60)
Progression-Free Survival (IRC Assessment)		
Patients with event	79 (36.6%)	29 (13.4%)
Time to event (months)		
Median [95% CI]	NE [31.1, NE]	NE [NE]
P-value (log-rank test, stratified)	p<0.0001	
Hazard ratio (stratified), [95% CI]	0.33 [0.22, 0.51]	
Estimate of 1-year PFS rate % (95% CI)	91.16 (87.27, 95.06)	94.60 (91.50, 97.71)
Estimate of 2-year PFS rate % (95% CI)	83.70 (56.99, 70.42)	88.59 (84.20, 92.98)
Overall Response Rate (Investigator Assessment)[b] (EOT)		
Responders	154 (71.3%)	183 (84.7%)
95% CI	[64.77, 77.23]	[79.22, 89.24]
Difference in response rates [95% CI]	13.43 [5.47, 21.38]	
P-value (CMH test)	p=0.0007	
Complete Response Rate(Investigator Assessment)[b] (EOT)		
Responders	50 (23.1%)	107 (49.5%)
95% CI	[17.70, 29.35]	[42.68, 56.40]
Difference in response rates [95% CI]	26.39 [17.41, 35.36]	
P-value (CMH test)	p<0.0001	
Complete Response Rate(Investigator Assessment)[b] (EOT)		
Responders	50 (23.1%)	107 (49.5%)
95% CI	[17.70, 29.35]	[42.68, 56.40]
Difference in response rates [95% CI]	26.39 [17.41, 35.36]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate–Peripheral Blood[b] (EOT)		
MRD negative (at 10^{-4})	76 (35.2%)	163 (75.5%)
95% CI	[28.83, 41.95]	[69.17, 81.05]
Difference in MRD negative rates [95% CI]	40.28 [31.45, 49.10]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate–Bone Marrow[b] (EOT)		
MRD negative (at 10^{-4})	37 (17.1%)	123 (56.9%)
95% CI	[12.36, 22.83]	[50.05, 63.64]
Difference in MRD negative rates [95% CI]	39.81 [31.27, 48.36]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate in CR[c] Patients–Peripheral Blood (EOT)		
Responders	31 (14.4%)	91 (42.1%)
95% CI	[9.96, 19.75]	[35.46, 49.02]
Difference in MRD responder rates [95% CI]	27.78 [19.45, 36.10]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate in CR[c] Patients–Bone Marrow (EOT)		
Responders	23 (10.6%)	73 (33.8%)
95% CI	[6.87, 15.55]	[27.52, 40.53]
Difference in MRD responder rates [95% CI]	23.15 [15.37, 30.93]	
P-value (CMH test)	p<0.0001	
Overall Survival[d]		
Patients with event	17 (7.9%)	20 (9.3%)
Time to event (months)		
Median [95% CI]	NE [NE]	NE [NE]
P-value (log-rank, stratified)	p=0.5216	
Hazard ratio (stratified), [95% CI]	1.24 [0.64, 2.40]	
Estimate of 1-year OS rate % (95% CI)	96.22 (93.66, 98.79)	95.67 (92.90, 98.44)
Estimate of 2-year OS rate % (95% CI)	93.34 (89.97, 96.71)	91.79 (88.05, 95.53)

CMH=Cochran-Mantel-Haenszel; CR=complete remission; EOT = At end of treatment (i.e., 3 months after treatment completion/early termination); MRD=minimum residual disease; NE=not evaluable.

[a] Key secondary response rates were also compared using a stratified test (according to the hierarchical testing approach). [b] By ASO-PCR. [c] CR status is assessed by investigator [d] As of the clinical cut-off date, the overall survival data were too immature to be meaningful.

Supportive study

Study GP28331, *A phase Ib multicenter dose-finding and safety study of venetoclax and obinutuzumab in patients with relapsed or refractory or previously untreated CLL.*

GP28331 (Phase Ib) (CCOD: 21 May 2018)	Open-label, multicenter, dose-finding and safety study	Adult patients with previously untreated CLL or with relapsed/refractory CLL	• To estimate the maximum tolerated dose (MTD) of venetoclax in combination with obinutuzumab in patients with R/R CLL & patients with previously untreated CLL. • To evaluate the safety and tolerability of venetoclax in combination with obinutuzumab in patients with R/R CLL & patients with previously untreated CLL	50 R/R patients and 32 1L patients who received at least 2 cycles of combination treatment (venetoclax and obinutuzumab) – (22 patients [16 R/R and 6 1L patients] in dose-finding stage, 56 patients [30 R/R and 26 1L patients] in safety-expansion stage)	Venetoclax[c]: Orally once daily, starting at 20 mg/day for 1 week, then 50 mg/day for 1 week, and continuing sequentially through each cohort each week until the target cohort dose was reached (100, 200, 400 mg/day), then daily dosing until disease progression. Obinutuzumab[c]: IV infusion at 1000 mg at the clinic, with three doses given during Cycle 1 on Days 1, 8, and 15 (first dose split: 100 mg on Day 1 and 900 mg on Day 2), and thereafter on Day 1 of each subsequent cycle for up to six cycles (each cycle is 28 days).

CCOD- clinical cutoff date; CLL- chronic lymphocytic leukemia; IV- intravenous; PFS-progression-free survival; PO- per oral; R/R- relapsed or refractory

[a] Enrollment into the safety run-in phase was completed in April 2015 with 13 patients. One patient was withdrawn from treatment per protocol due to an infusion-related reaction (IRR) following the first administration of obinutuzumab and before any venetoclax was given and was excluded from the efficacy analysis, but remained in the safety population.

[b] Each cycle is 28 days

[c] On Cycle 1 Day 1, start obinutuzumab administration at 1000 mg (dose may be split as 100 mg and 900 mg on Days 1 and 2). Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of five subsequent cycles (total of 6 cycles, 28 days each).

[d] 400 mg venetoclax daily / oral tablet / 12 cycles (28 days each cycle). Patients underwent a ramp-up period, first dose 20 mg starting Day 22 of Cycle 1 and reaching 400 mg daily on Day 22 of Cycle 2.

Primary objective: safety and tolerability

Secondary objectives: to estimate OR, DOR, CR, PFS, OS

Results

- All 1L patients responded to treatment; 25/32 (78.1%) achieved a CR/CRi.
- Consistent overall response rates and deep remissions were observed in all patient subgroups, regardless of cytogenetic factors and/or physical fitness status. Responses were similar among patients with del(17p)/*TP53* mutation or IgVH mutational status.
- The median duration of response was not reached in 1L patients (range: 10.2-33.3 months). At 1 and 2 years after their first response, the percentage of patients remaining in response to treatment was 93.75% and 90.63%, respectively.
- After a median follow-up of 26.7 months for 1L patients (range: 16-39 months), the 12-month PFS was 100% and at 24 months, the PFS rate was 90.63%.
- Progression of disease occurred in 4 1L patients, 3 of whom had 17p del and/or *TP53* mutation at baseline. Among the 22 1L fit patients, 3 (13.6%) had disease progression. Among the subset of 1L fit patients who did not have venetoclax treatment extended beyond 1 year, 1 patient out of 13 (7.7%) had disease progression.
- MRD was negative (e.g., undetectable at a threshold < 1 CLL cell per 10000 leukocytes) in peripheral blood of 90.6% (29/32) of 1L patients at least 3 months after the last obinutuzumab dose. Specifically, after at least 3 months from the last venetoclax dose, the rate of undetectable peripheral blood MRD was sustained at 71.9% (23/32) in the 1L patient population, 68.2% in the 1L fit population and 84.6% in the 1L fit population who did not have venetoclax treatment extended beyond 1 year. MRD responses were consistent regardless of cytogenetic subgroups and clinical fitness status. MRD-negativity was reported in bone marrow assessment in 78.1% (25/32) of 1L patients.

The efficacy outcomes (ORR and MRD negativity) were similar in all 1L group of patients analysed, including the 22 1L patients considered to be 'fit' and to have been potentially eligible to receive chemo-immunotherapy (FCR or BR) as treatment prior to study entry.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal trial CLL14 was a randomized, multicenter, open label, phase 3 study that evaluated the efficacy and safety of venclyxto in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) for patients with previously untreated CLL with coexisting medical conditions (total Cumulative Illness Rating Scale [CIRS] score > 6 or CLcr < 70 mL/min, but not inferior to 30 mL/min). All the patients included required therapy (Binet stage C or symptomatic disease). Patients with Richter's transformation or any individual organ/system impairment score of 4 by CIRS were excluded. Since new treatment options were approved during the recruitment period, patients with *TP53* deletion or mutation were enrolled at the investigator's discretion. Patients in the study were assessed for risk of TLS and received prophylaxis accordingly prior to obinutuzumab administration. All patients received obinutuzumab at 100 mg on Cycle 1 Day 1, followed by 900 mg which could have been administered on Day 1 or Day 2, then 1000 mg doses on Days 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle, for a total of 6 cycles. On Day 22 of Cycle 1, patients in the venetoclax + obinutuzumab arm began the 5-week venetoclax dose-titration schedule, continuing through Cycle 2 Day 28. Upon completion of the dose-titration schedule, patients continued venetoclax 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12. Each cycle was 28 days. Patients randomised to the obinutuzumab + chlorambucil arm received 0.5 mg/kg oral chlorambucil on Day 1 and Day 15 of Cycles 1-12. Patients continued to be followed for disease progression and overall survival after completing therapy.

After a separate safety run-in, 432 patients were randomized 1:1. Cross-over was not allowed. All patients received obinutuzumab at 1000 mg on d1 (the first dose could be split as 100 mg and 900 mg on d1 and 2), and on d8 and 15 of cycle 1, and on d1 of each subsequent cycle, for a total of 6 cycles. Patients in the VEN+G arm began the 5-week venclyxto ramp-up schedule on d22 of cycle 1 and received venclyxto 400 mg once daily from cycle 3 d1 until the last day of cycle 12. Patients randomized to the GClb arm received 0.5 mg/kg oral chlorambucil on d1 and d15 of cycles 1 to 12. Each cycle was 28 days.

The primary endpoint was investigator-assessed PFS. The key secondary endpoints were IRC PFS, minimal residual disease negativity (allele-specific oligonucleotide polymerase-chain-reaction with a cut-off of 10^{-4}) in peripheral blood and bone marrow, overall and complete response, MRD negativity in patients with complete response in PB and marrow (all assessed 3 months after treatment completion), and OS. Other secondary endpoints included DOR, EFS and time to new antileukemic treatment.

Disease was assessed in all patients at baseline and at similar time points in both treatment groups during the trial, including an assessment of the response to therapy 3 months after the completion of treatment, with CR and PR defined in accordance with iwCLL 2008. After the completion of treatment, patients were followed for progression and safety every 3 months for 2 years, and then every 6 months. MRD PB was performed at baseline and at cycles 7, 9, and 12, and then every 3 months. In patients with a treatment response, minimal residual disease in bone marrow was assessed at cycle 9 and 3 months after completion of treatment.

An interim analysis was planned as per protocol to be performed after 110 progression events (65% of total planned events) had occurred. After IA data review (cut-off August 2018), IDMC recommended conducting the primary analysis of the primary and secondary endpoints.

Efficacy data and additional analyses

The baseline demographic and disease characteristics were similar between the study arms. The median age was 72 years (range: 41 to 89 years), 89% were white, 67% were male; 36% and 43% were Binet stage B and C, respectively and approximately half (49.8%) were experiencing B symptoms at baseline, with night sweats (43.5%) being the most frequent B symptom. The 88% of patients had ECOG performance status <2. The median CIRS score was 8 (range: 0 to 28) and 58% of patients had CLcr <70 mL/min. A 17p deletion was detected in 8% of patients, *TP53* mutations in 7%, 11q deletion in 19%, and unmutated *IgVH* in 59.8%. The mutational status was unknown for 59 patients (27.3%) in the GClb arm and 45 (20.8%) in the VEN+G arm. Overall, the median time from first diagnosis of CLL to randomization was 2.5 years (0-20.4 years). TLS risk was categorized as low, medium or high and the risk categories were balanced between groups: 43 patients (20%) in the GClb arm and 48 (22.2%) in the VEN+G arm belonged to the high risk category). The majority of patients (66.2%) were considered as intermediate risk. In terms of prognosis, the CLL-IPI scores were similar for the two treatment arms; 60% in the GClb arm and 60.4% in the VEN+G arm had a high score.

Progression-free survival (PFS) was assessed by investigators and by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

At the interim analysis, all patients were off-treatment for about 17 months. The PFS data can be considered immature, as the number of events in the control arm was low, 35.6% (13.9% in the experimental arm). The HR for progression or death is 0.35 (0.23-0.53). From around month 23 and on, extensive censoring is observed in the KM curves; a KM plot of time in study (from randomization to data cut-off) has been provided. The time in study is similar between the treatment arms, with the majority of patients having a follow-up over 39 months. The robustness of the primary efficacy analysis however is supported by sensitivity analyses related to the censoring mechanism for PFS, unstratified analyses, and subgroup analyses (including *TP53* mutations, deletions or both; and unmutated *IgVH*).

At end of treatment visit, 123 patients (56.9%) in the VEN+G arm had achieved bone marrow MRD negativity and 163 (75.5%) peripheral blood MRD negativity, compared with 37 patients (17.1%) and 76 patients (35.5%), respectively, in the GClb arm. Twelve months after the completion of treatment, MRD negativity rates in peripheral blood were 58% (126/216) in patients treated with VEN+G and 9% (20/216) in patients treated with GClb. In CR/CRi patients, the MRD-negativity rates at end of treatment were higher for VEN+G than for GClb: bone marrow 73 (33.8%) vs 23 (10.6%); peripheral blood: 91 (42.1%) vs 31 (14.4%). In the MURANO study (RR CLL), the MRD status was similar regardless of clinical response; for completeness, data on MRD in PR were presented for study CLL14 and are similar to MURANO findings.

In both arms of study CLL14, the patients who had reached PB MRD negativity at EOT had a longer duration of PFS compared with MRD positive patients. Dimier *et al.* published a model for predicting the effect of treatment on PFS using PB-MRD as a surrogate endpoint in treatment-naïve patients from studies CLL8, CLL10, and CLL11 (Blood. 2018 Mar 1;131(9):955-962). The model demonstrated a statistically significant relationship between treatment effect on PB-MRD and treatment effect on PFS. As the difference between treatment arms in PB-MRD response rates increased, a reduction in the risk of progression or death was observed; for each unit increase in the (log) ratio of MRD^- rates between arms, the log of the PFS hazard ratio decreased by -0.188 (95% CI -0.321 to -0.055). A similar approach, i.e. evaluation of the relationship between treatment effect on PB-MRD and treatment effect on PFS for study CLL14 was presented by the MAH. The available PFS and MRD data support an effect across cytogenetic subgroups and mutational status. The ORR (CR+CRi+PR) was 183 (84.7%) for VEN+G and 154 (71.3%) for GClb. The complete response rate (CR+CRi) was 107 (49.5%) vs 50 (23.1%).

At the time of analysis, median overall survival had not been reached, with fewer than 10% of patients in the study experiencing an event. The median duration of follow-up for OS was 29 months.

The PFS benefit with venetoclax + obinutuzumab versus obinutuzumab + chlorambucil treatment was observed across the following subgroups: sex; age; Binet stage at screening; estimated CrCL; del(17p)/*TP53* mutation; *IgVH* mutational status.

Although exploratory, the efficacy outcomes from study GP28331 (a 32 first-line patient subgroup) support the findings of the pivotal study CLL14. Noteworthy, the trial included 22 1L ¨fit¨ patients, who otherwise could have received a fludarabine-based regimen.

At an updated efficacy analysis (data cut-off date 23 August 2019 and median follow-up of 40 months), the median PFS had not been reached in the venetoclax + obinutuzumab arm and was 35.6 months [95% CI: 33.7,40.7] in the obinutuzumab + chlorambucil arm with a HR of 0.31 [95% CI: 0.22, 0.44]. The 36-month PFS estimate in the venetoclax + obinutuzumab arm was 81.9% [95% CI: 76.5, 87.3] and in the obinutuzumab + chlorambucil arm was 49.5% [95% CI: 42.4, 56.6].

The applicant is seeking an indication for first-line treatment of CLL regardless of fitness, including suitability for FCR. While the patients included in study CLL14, with a median age of 72 and a median CIRS score of 8, might be regarded as representative for most CLL patients, the comparator as well as the inclusion criteria exclude more fit patients. However, based on the precedent set for Imbruvica (ibrutinib), the extrapolation of efficacy also to younger and more fit patients is considered acceptable. This is since the safety profile in such patients is not anticipated to be less favourable; furthermore, the effect size, although not directly compared with FCR, is considered sufficient to make venetoclax + obinutuzumab a reasonable first-line treatment alternative, where the differential safety profile comparted to chemotherapy is notable. The inclusion criteria for the pivotal study (i.e. patients with coexisting conditions) are reflected in section 5.1 of the SPC and study GP28331 did include a small number of fit patients.

2.4.4. Conclusions on the clinical efficacy

Venclyxto and obinutuzumab combination followed by venclyxto monotherapy offer longer progression-free survival compared to chlorambucil and obinituzumab in a first-line CLL population that are either older than 65 years of age or have co-morbidities. The relevance of the efficacy demonstration can be extrapolated to more fit patients with CLL.

2.5. Clinical safety

Introduction

Patient exposure

VEN+G was completed by 159 of the 203 who received both agents while VEN single agent treatment was completed by 166 of the 198 patients who started the single-agent period. The median duration of exposure to venetoclax, from first venetoclax dose, was 315 days (10.5 months). After reaching the target dose, the median dose intensity for venetoclax was 97.5% (range: 14%-100%).

Adverse events

Overview of all AEs (safety population)

	GClb (N=214)	VEN+G (N=212)	All Patients (N=426)
Total number of patients with at least one AE	213 (99.5%)	200 (94.3%)	413 (96.9%)
Total number of AEs	2074	2448	4522
Total number of deaths	16 (7.5%)	20 (9.4%)	36 (8.5%)
Total number of patients withdrawn from study due to an AE	1 (0.5%)	4 (1.9%)	5 (1.2%)
Total number of patients with at least one			
AE with fatal outcome	8 (3.7%)	16 (7.5%)	24 (5.6%)
Serious AE	90 (42.1%)	104 (49.1%)	194 (45.5%)
Serious AE leading to withdrawal from any treatment	18 (8.4%)	14 (6.6%)	32 (7.5%)
Serious AE leading to withdrawal from Venetoclax	0	11 (5.2%)	11 (2.6%)
Serious AE leading to dose interruption from any treatment	29 (13.6%)	48 (22.6%)	77 (18.1%)
Serious AE leading to dose reduction from any treatment	1 (0.5%)	1 (0.5%)	2 (0.5%)
Related Serious AE	56 (26.2%)	56 (26.4%)	112 (26.3%)
AE leading to withdrawal from any treatment	33 (15.4%)	34 (16.0%)	67 (15.7%)
AE leading to withdrawal from Venetoclax	0	27 (12.7%)	27 (6.3%)
AE leading to dose interruption from any treatment	146 (68.2%)	156 (73.6%)	302 (70.9%)
AE leading to dose reduction from any treatment	18 (8.4%)	44 (20.8%)	62 (14.6%)
Related AE	200 (93.5%)	190 (89.6%)	390 (91.5%)
Related AE leading to withdrawal from any treatment	25 (11.7%)	29 (13.7%)	54 (12.7%)
Related AE leading to withdrawal from Venetoclax	0	23 (10.8%)	23 (5.4%)
Related AE leading to dose interruption from any treatment	135 (63.1%)	147 (69.3%)	282 (66.2%)
Related AE leading to dose reduction from any treatment	18 (8.4%)	39 (18.4%)	57 (13.4%)
Grade 3,4 AE (at greatest intensity)	157 (73.4%)	151 (71.2%)	308 (72.3%)
Grade 3,4 AE	164 (76.6%)	167 (78.8%)	331 (77.7%)

All-cause mortality: 9.3% VEN+G vs 7.9% GClb.

Adverse Events with a reporting rate of at least 10%

MedDRA Preferred Term	GClb (N=214)	VEN+G (N=212)	All Patients (N=426)
Total number of patients with at least one adverse event	213 (99.5%)	200 (94.3%)	413 (96.9%)
Total number of events	2074	2448	4522
Neutropenia	122 (57.0%)	122 (57.5%)	244 (57.3%)
Infusion related reaction	110 (51.4%)	95 (44.8%)	205 (48.1%)
Thrombocytopenia	50 (23.4%)	51 (24.1%)	101 (23.7%)
Diarrhoea	32 (15.0%)	59 (27.8%)	91 (21.4%)
Nausea	46 (21.5%)	40 (18.9%)	86 (20.2%)
Pyrexia	33 (15.4%)	48 (22.6%)	81 (19.0%)
Anaemia	40 (18.7%)	35 (16.5%)	75 (17.6%)
Fatigue	30 (14.0%)	32 (15.1%)	62 (14.6%)
Cough	25 (11.7%)	34 (16.0%)	59 (13.8%)
Constipation	19 (8.9%)	28 (13.2%)	47 (11.0%)
Headache	21 (9.8%)	24 (11.3%)	45 (10.6%)

In the VEN+G arm, the most frequently reported (>5%) venetoclax-related AEs were neutropenia (102 patients [48.1%]) and thrombocytopenia (23 patients [10.8%]); diarrhoea (31 patients [14.6%]) and nausea (20 patients [9.4%]); and fatigue (13 patients [6.1%]).

AEs by severity (CTCAE)

MedDRA System Organ Class / MedDRA Preferred Term		GClb (N=214)	VEN+G (N=212)	All Patients (N=426)
- Any adverse events -	n	213 (99.5%)	200 (94.3%)	413 (96.9%)
	1	10 (4.7%)	8 (3.8%)	18 (4.2%)
	2	38 (17.8%)	25 (11.8%)	63 (14.8%)
	3	88 (41.1%)	74 (34.9%)	162 (38.0%)
	4	69 (32.2%)	77 (36.3%)	146 (34.3%)
	5	8 (3.7%)	16 (7.5%)	24 (5.6%)

Grade 3-4 PTs reported with an incidence at least 2% higher in the VEN+G arm were neutropenia (112 patients [52.8%] vs 103 [48.1%] in the GClb arm), hyperglycemia (8 [3.8%] vs 3 [1.4%], respectively), diarrhea (9 [4.2%] compared with 1 [0.5%], respectively) and hypertension (6 [2.8%] compared with 1 [0.5%], respectively).

Dose reduction or interruption

Venetoclax

- Interruption: 334 AEs leading to dose interruption of venetoclax were reported in 121 patients (57.1%). The most common AE that resulted in dose interruption of venetoclax was neutropenia (86 patients [40.6%]). No other AE leading to venetoclax dose interruption was reported in more than 5% of the patients in the VEN+G arm.
- Reduction: dose reductions due to AEs were reported in 43 patients (20.3%). The most common AEs (reported in 3 or more patients) that resulted in dose reduction of venetoclax were neutropenia (28 patients [13.2%]), neutrophil count decreased (4 patients [1.9%]), thrombocytopenia (4 patients [1.9%]).

Obinutuzumab

- Interruption: overall, 247 and 259 AEs leading to obinutuzumab dose interruption, respectively, were reported in 112 patients (52.3%) in the GClb arm and 119 (56.1%) in the VEN+G arm. The most common AEs that resulted in dose interruption of obinutuzumab were neutropenia (49 patients [22.9%] in the GClb arm and 56 [26.4%] in the VEN+G arm) and infusion-related reaction (57 patients [26.6%] and 50 [23.6%], respectively). No other AE leading to obinutuzumab dose interruption was reported in more than 5% of patients in either arm.
- Reduction: obinutuzumab dose reductions were not allowed according to the protocol, but were reported in 2 patients (0.9%) in the GClb arm (due to AEs of IRR and neutropenia) and 3 (1.4%) in the VEN+G arm (due to AEs of IRR, nausea, fatigue and neutrophil count decreased).

Chlorambucil

- Interruption: 266 AEs leading to dose interruption of chlorambucil were reported in 121 patients (56.5%). The most common AEs that resulted in dose interruption of chlorambucil were neutropenia (83 patients [38.8%]) and thrombocytopenia (12 patients [5.6%]). No other event was reported in more than 5% of the patients.
- Reduction: Chlorambucil dose reductions due to AEs were reported in 17 patients (7.9%). The most common AEs (reported in 2 or more patients) that resulted in dose reduction of chlorambucil were neutropenia (13 patients [6.1%]), neutrophil count decreased (2 patients [0.9%]), and thrombocytopenia (2 patients [0.9%]).

Discontinuation due to adverse events

Patients were withdrawn from venetoclax when toxicity could not be managed by dose interruption and dose reduction: 27 patients (12.7%) withdrew from venetoclax treatment due to AEs. The most common AEs that resulted in withdrawal of venetoclax were neutropenia (5 patients [2.4%]), sepsis (2 patients [0.9%]), and asthenia (2 patients [0.9%]).

The percentage of patients who withdrew from obinutuzumab treatment was balanced between treatment arms (16 patients [7.5%] in the GClb arm and 15 [7.1%] in the VEN+G arm). The only AEs reported more than once in either treatment arm that resulted in withdrawal of obinutuzumab were neutropenia (2 patients [0.9%] in the GClb arm and 1 [0.5%] in the VEN+G arm), thrombocytopenia (1 patient [0.5%] and 2 [0.9%], respectively), anaemia (2 patients [0.9%] and none, respectively), and infusion-related reaction (2 patients [0.9%] in both arms).

Thirty-one patients (14.5%) withdrew from chlorambucil because of an AE. The most common AEs that resulted in withdrawal of chlorambucil were neutropenia (5 patients [2.3%]), neutrophil count decreased (2 patients [0.9%]), and infusion-related reaction (2 patients [0.9%]).

Adverse events of special interest (AESI)

Neutropenia, gr 3-4

MedDRA System Organ Class MedDRA Preferred Term	GClb (N=214)	VEN+G (N=212)	All Patients (N=426)
Total number of patients with at least one adverse event	112 (52.3%)	119 (56.1%)	231 (54.2%)
Overall total number of events	250	327	577
Blood and lymphatic system disorders			
Total number of patients with at least one adverse event	103 (48.1%)	112 (52.8%)	215 (50.5%)
Total number of events	224	306	530
Neutropenia	103 (48.1%)	112 (52.8%)	215 (50.5%)
Investigations			
Total number of patients with at least one adverse event	10 (4.7%)	9 (4.2%)	19 (4.5%)
Total number of events	26	21	47
Neutrophil count decreased	10 (4.7%)	9 (4.2%)	19 (4.5%)

Thrombocytopenia, gr 3-4

MedDRA System Organ Class MedDRA Preferred Term	GClb (N=214)	VEN+G (N=212)	All Patients (N=426)
Total number of patients with at least one adverse event	33 (15.4%)	32 (15.1%)	65 (15.3%)
Overall total number of events	43	51	94
Blood and lymphatic system disorders			
Total number of patients with at least one adverse event	32 (15.0%)	29 (13.7%)	61 (14.3%)
Total number of events	42	47	89
Thrombocytopenia	32 (15.0%)	29 (13.7%)	61 (14.3%)
Investigations			
Total number of patients with at least one adverse event	1 (0.5%)	4 (1.9%)	5 (1.2%)
Total number of events	1	4	5
Platelet count decreased	1 (0.5%)	4 (1.9%)	5 (1.2%)

Infections > grade 3

MedDRA System Organ Class MedDRA Preferred Term	GClb (N=214)	VEN+G (N=212)	All Patients (N=426)
Total number of patients with at least one adverse event	35 (16.4%)	41 (19.3%)	76 (17.8%)
Overall total number of events	51	58	109
Infections and infestations			
Total number of patients with at least one adverse event	35 (16.4%)	41 (19.3%)	76 (17.8%)
Total number of events	51	58	109
Pneumonia	9 (4.2%)	9 (4.2%)	18 (4.2%)
Sepsis	2 (0.9%)	7 (3.3%)	9 (2.1%)
Bronchitis	2 (0.9%)	2 (0.9%)	4 (0.9%)
Urinary tract infection	3 (1.4%)	1 (0.5%)	4 (0.9%)
Cellulitis	1 (0.5%)	2 (0.9%)	3 (0.7%)
Infection	1 (0.5%)	2 (0.9%)	3 (0.7%)
Respiratory tract infection	1 (0.5%)	2 (0.9%)	3 (0.7%)
Septic shock	2 (0.9%)	1 (0.5%)	3 (0.7%)
Upper respiratory tract infection	2 (0.9%)	1 (0.5%)	3 (0.7%)
Urosepsis	1 (0.5%)	2 (0.9%)	3 (0.7%)
Atypical pneumonia	1 (0.5%)	1 (0.5%)	2 (0.5%)
Device related infection	0	2 (0.9%)	2 (0.5%)
Erysipelas	1 (0.5%)	1 (0.5%)	2 (0.5%)
Gastroenteritis	2 (0.9%)	0	2 (0.5%)
Hepatitis viral	2 (0.9%)	0	2 (0.5%)
Infectious pleural effusion	1 (0.5%)	1 (0.5%)	2 (0.5%)
Lung infection	1 (0.5%)	1 (0.5%)	2 (0.5%)
Pneumocystis jirovecii pneumonia	1 (0.5%)	1 (0.5%)	2 (0.5%)
Pyelonephritis	1 (0.5%)	1 (0.5%)	2 (0.5%)
Abscess limb	0	1 (0.5%)	1 (0.2%)
Amoebiasis	0	1 (0.5%)	1 (0.2%)
Bronchiolitis	1 (0.5%)	0	1 (0.2%)
Bronchopulmonary aspergillosis	1 (0.5%)	0	1 (0.2%)
Candida infection	0	1 (0.5%)	1 (0.2%)
Chronic sinusitis	1 (0.5%)	0	1 (0.2%)
Eczema infected	1 (0.5%)	0	1 (0.2%)
Endocarditis	0	1 (0.5%)	1 (0.2%)
Enteritis infectious	0	1 (0.5%)	1 (0.2%)
Gastrointestinal infection	0	1 (0.5%)	1 (0.2%)
Hepatitis E	0	1 (0.5%)	1 (0.2%)
Herpes zoster	1 (0.5%)	0	1 (0.2%)
Infective exacerbation of chronic obstructive airways disease	1 (0.5%)	0	1 (0.2%)
Influenza	1 (0.5%)	0	1 (0.2%)
Listeriosis	0	1 (0.5%)	1 (0.2%)
Localised infection	1 (0.5%)	0	1 (0.2%)
Lower respiratory tract infection	0	1 (0.5%)	1 (0.2%)
Muscle abscess	0	1 (0.5%)	1 (0.2%)
Ophthalmic herpes zoster	0	1 (0.5%)	1 (0.2%)
Pneumonia fungal	0	1 (0.5%)	1 (0.2%)
Pneumonia haemophilus	1 (0.5%)	0	1 (0.2%)
Pneumonia respiratory syncytial viral	1 (0.5%)	0	1 (0.2%)
Pseudomembranous colitis	0	1 (0.5%)	1 (0.2%)
Sinusitis	0	1 (0.5%)	1 (0.2%)
Sinusitis aspergillus	0	1 (0.5%)	1 (0.2%)
Skin infection	0	1 (0.5%)	1 (0.2%)
Soft tissue infection	0	1 (0.5%)	1 (0.2%)
Staphylococcal infection	1 (0.5%)	0	1 (0.2%)
Staphylococcal sepsis	1 (0.5%)	0	1 (0.2%)
Tooth abscess	1 (0.5%)	0	1 (0.2%)
Tooth infection	0	1 (0.5%)	1 (0.2%)
Varicella zoster virus infection	0	1 (0.5%)	1 (0.2%)
Wound infection fungal	1 (0.5%)	0	1 (0.2%)

Second primary malignancies

The incidence of second primary malignancies was 22 patients [10.3%] in the GClb arm compared with 29 [13.7%] in the VEN+G arm.

TLS

There were 8 patients with AEs reported as TLS by the investigator, 5 (2.3%) in the GClb arm and 3 (1.4%) in the VEN+G arm. All AEs in the VEN+G arm occurred prior to the first dose of venetoclax and were associated with obinutuzumab treatment.

Richter's transformation

One patient in the GClb arm (timing not known) and 2 in the VEN+G arm (within 2 months of starting tx) developed Richter's transformation. All 3 transformations were to DLBCL.

Infusion-related reactions grade 3-4 (obinutuzumab)

The incidence of gr 3-4 IRR was balanced between treatment arms: 10.7% in the GClb arm vs 11.8% in the VEN+G arm. No fatal IRRs were reported. Treatment for IRR was administered to 19 patients in each arm; 13 patients in each arm required interruption; 1 had an obinutuzumab dose reduction. Obinutuzumab was withdrawn due to IRRs in 2 patients in the GClb arm and 2 in the VEN+G arm. All but 2 patients recovered with sequelae. One patient was recovering at the time of the cut-off.

Serious adverse events

MedDRA System Organ Class MedDRA Preferred Term	GClb (N=214)	VEN+G (N=212)	All Patients (N=426)
Total number of patients with at least one adverse event	90 (42.1%)	104 (49.1%)	194 (45.5%)
Overall total number of events	179	202	381
Infections and infestations			
Total number of patients with at least one adverse event	30 (14.0%)	40 (18.9%)	70 (16.4%)
Total number of events	44	56	100
Pneumonia	9 (4.2%)	10 (4.7%)	19 (4.5%)
Sepsis	2 (0.9%)	6 (2.8%)	8 (1.9%)
Bronchitis	2 (0.9%)	2 (0.9%)	4 (0.9%)
Infection	2 (0.9%)	2 (0.9%)	4 (0.9%)
Cellulitis	0	3 (1.4%)	3 (0.7%)
Influenza	2 (0.9%)	1 (0.5%)	3 (0.7%)
Respiratory tract infection	1 (0.5%)	2 (0.9%)	3 (0.7%)
Septic shock	2 (0.9%)	1 (0.5%)	3 (0.7%)
Urosepsis	1 (0.5%)	2 (0.9%)	3 (0.7%)
Device related infection	0	2 (0.9%)	2 (0.5%)
Gastroenteritis	2 (0.9%)	0	2 (0.5%)
Lung infection	2 (0.9%)	0	2 (0.5%)
Injury, poisoning and procedural complications			
Total number of patients with at least one adverse event	22 (10.3%)	16 (7.5%)	38 (8.9%)
Total number of events	22	19	41
Infusion related reaction	13 (6.1%)	9 (4.2%)	22 (5.2%)
Limb injury	2 (0.9%)	0	2 (0.5%)
Blood and lymphatic system disorders			
Total number of patients with at least one adverse event	17 (7.9%)	19 (9.0%)	36 (8.5%)
Total number of events	20	24	44
Febrile neutropenia	8 (3.7%)	11 (5.2%)	19 (4.5%)
Thrombocytopenia	5 (2.3%)	2 (0.9%)	7 (1.6%)
Neutropenia	1 (0.5%)	3 (1.4%)	4 (0.9%)
Anaemia	1 (0.5%)	2 (0.9%)	3 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Total number of patients with at least one adverse event	12 (5.6%)	15 (7.1%)	27 (6.3%)
Total number of events	13	15	28
Squamous cell carcinoma of skin	3 (1.4%)	2 (0.9%)	5 (1.2%)
Prostate cancer	0	2 (0.9%)	2 (0.5%)
General disorders and administration site conditions			
Total number of patients with at least one adverse event	9 (4.2%)	12 (5.7%)	21 (4.9%)
Total number of events	10	13	23
Pyrexia	7 (3.3%)	8 (3.8%)	15 (3.5%)
Respiratory, thoracic and mediastinal disorders			
Total number of patients with at least one adverse event	9 (4.2%)	12 (5.7%)	21 (4.9%)
Total number of events	10	20	30
Chronic obstructive pulmonary disease	2 (0.9%)	3 (1.4%)	5 (1.2%)
Pleural effusion	2 (0.9%)	1 (0.5%)	3 (0.7%)
Dyspnoea	0	2 (0.9%)	2 (0.5%)

Cardiac disorders			
Total number of patients with at least one adverse event	12 (5.6%)	8 (3.8%)	20 (4.7%)
Total number of events	17	9	26
Atrial fibrillation	3 (1.4%)	1 (0.5%)	4 (0.9%)
Cardiac failure	1 (0.5%)	3 (1.4%)	4 (0.9%)
Myocardial infarction	3 (1.4%)	1 (0.5%)	4 (0.9%)
Acute myocardial infarction	0	2 (0.9%)	2 (0.5%)
Atrial flutter	2 (0.9%)	0	2 (0.5%)
Supraventricular tachycardia	2 (0.9%)	0	2 (0.5%)
Metabolism and nutrition disorders			
Total number of patients with at least one adverse event	7 (3.3%)	7 (3.3%)	14 (3.3%)
Total number of events	8	7	15
Tumour lysis syndrome	4 (1.9%)	1 (0.5%)	5 (1.2%)
Hyperglycaemia	2 (0.9%)	1 (0.5%)	3 (0.7%)
Nervous system disorders			
Total number of patients with at least one adverse event	5 (2.3%)	9 (4.2%)	14 (3.3%)
Total number of events	6	10	16
Syncope	2 (0.9%)	1 (0.5%)	3 (0.7%)
Gastrointestinal disorders			
Total number of patients with at least one adverse event	4 (1.9%)	8 (3.8%)	12 (2.8%)
Total number of events	5	8	13
Inguinal hernia	1 (0.5%)	2 (0.9%)	3 (0.7%)
Diarrhoea	0	2 (0.9%)	2 (0.5%)
Investigations			
Total number of patients with at least one adverse event	4 (1.9%)	4 (1.9%)	8 (1.9%)
Total number of events	7	5	12
Aspartate aminotransferase increased	4 (1.9%)	0	4 (0.9%)
Alanine aminotransferase increased	3 (1.4%)	0	3 (0.7%)
Vascular disorders			
Total number of patients with at least one adverse event	3 (1.4%)	5 (2.4%)	8 (1.9%)
Total number of events	3	5	8
Aortic stenosis	0	2 (0.9%)	2 (0.5%)
Hypotension	2 (0.9%)	0	2 (0.5%)
Musculoskeletal and connective tissue disorders			
Total number of patients with at least one adverse event	4 (1.9%)	1 (0.5%)	5 (1.2%)
Total number of events	4	1	5
Intervertebral disc protrusion	2 (0.9%)	0	2 (0.5%)
Ear and labyrinth disorders			
Total number of patients with at least one adverse event	0	2 (0.9%)	2 (0.5%)
Total number of events	0	2	2
Vertigo	0	2 (0.9%)	2 (0.5%)

The frequency of patients with SAEs was numerically higher in the experimental arm (104 patients [49.1%]) compared with the GClb arm (90 patients [42.1%]).

The SOC with the most SAEs was *Infections and infestations*, with a numerically higher incidence in the VEN+G arm (40 patients [18.9%]) compared with the GClb arm (30 patients [14.0%]). By individual PT within this SOC, the largest difference occurred for sepsis (6 patients [2.8%] in the VEN+G arm and 2 patients [0.9%] in the GClb arm).

SAEs in the *Blood and lymphatic system disorders* SOC were reported in 17 patients (7.9%) in the GClb arm and 19 (9%) in the VEN+G arm. The 3 most frequent AEs in this SOC were febrile neutropenia (reported in 8 patients [3.7%] and 11 [5.2%], respectively), thrombocytopenia (5 patients [2.3%] and 2 [0.9%], respectively), and neutropenia (1 patient [0.5%] and 3 [1.4%], respectively).

SAEs in the *Neoplasms benign, malignant and unspecified* SOC were reported in 12 patients (5.6%) in the GClb arm and 15 (7.1%) in the VEN+G arm.

The most frequently reported individual PTs were infusion-related reaction, 13 patients (6.1%) in the GClb arm and 9 (4.2%) in the VEN+G arm; pneumonia (9 [4.2%] and 10 [4.7%], respectively); febrile neutropenia (8 [3.7%] and 11 [5.2%], respectively) and pyrexia (7 [3.3%] and 8 [3.8%], respectively). The only SAE by grouped PT occurring in more than 5% of the patients in either arm was pneumonia (11 patients [5.1%] in the GClb arm and 13 [6.1%] in the VEN+G arm).

Deaths

Status	GClb (N=216)	VEN+G (N=216)	All Patients (N=432)
Death	17 (7.9%)	20 (9.3%)	37 (8.6%)
Cause of Death	17 (7.9%)	20 (9.3%)	37 (8.6%)
Adverse Event	8 (3.7%)	16 (7.4%)	24 (5.6%)
Acute myeloid leukaemia	1 (0.5%)	0	1 (0.2%)
Bladder cancer	0	1 (0.5%)	1 (0.2%)
Cardiac arrest	1 (0.5%)	1 (0.5%)	2 (0.5%)
Cardiac failure	0	1 (0.5%)	1 (0.2%)
Cerebral ischaemia	0	1 (0.5%)	1 (0.2%)
Immune thrombocytopenic purpura	1 (0.5%)	0	1 (0.2%)
Infection	0	1 (0.5%)	1 (0.2%)
Metastatic malignant melanoma	0	1 (0.5%)	1 (0.2%)
Myelodysplastic syndrome	0	1 (0.5%)	1 (0.2%)
Myocardial infarction	0	1 (0.5%)	1 (0.2%)
Pneumonia	1 (0.5%)	0	1 (0.2%)
Pneumonia fungal	0	1 (0.5%)	1 (0.2%)
Pulmonary embolism	0	1 (0.5%)	1 (0.2%)
Sarcoma of skin	1 (0.5%)	0	1 (0.2%)
Sepsis	0	5 (2.3%)	5 (1.2%)
Septic shock	1 (0.5%)	0	1 (0.2%)
Squamous cell carcinoma of skin	1 (0.5%)	0	1 (0.2%)
Upper gastrointestinal haemorrhage	1 (0.5%)	0	1 (0.2%)
Urosepsis	0	1 (0.5%)	1 (0.2%)
Progression of Disease	5 (2.3%)	3 (1.4%)	8 (1.9%)
PROGRESSION OF DISEASE	5 (2.3%)	3 (1.4%)	8 (1.9%)
Other	4 (1.9%)	1 (0.5%)	5 (1.2%)
CARDIOGENIC SHOCK AND SEPTIC	1 (0.5%)	0	1 (0.2%)
NATURAL CARDIAC DEATH	0	1 (0.5%)	1 (0.2%)
RESPIRATORY SEPSIS	1 (0.5%)	0	1 (0.2%)
SEPSIS	1 (0.5%)	0	1 (0.2%)
UNKNOWN	1 (0.5%)	0	1 (0.2%)

Period in Which Death Occurred:	Number of Patients	
	GClb	VEN+G
Total number during study (safety-evaluable)	**16**	**20**
Any time during study (overall)		
Disease progression	5	3
Fatal AEs	8	16
Other	3	1
During treatment (within 28 days after last dose of study drug)		
Disease progression	0	1
Fatal AEs	3	4
Other	0	0
Total during treatment	**3**	**5**
After treatment (after 29 days after the last dose of study drug)		
Disease progression	5	2
Fatal AEs	5	12
Other[a]	3	1
Total after treatment	**13**	**15**

During the treatment period (or within 28 days of last study drug) there were 3 deaths in the GClb arm and 5 patients in the VEN+G arm. After the end of the study treatment period: 13 in the GClb arm and 15 in the VEN+G arm. Of the 13 post-treatment deaths in the GClb arm, 5 were due to disease progression, 5 to fatal AEs, and 3 were attributed to 'other' causes (respiratory sepsis, sepsis and unknown). Of the 15 post-treatment deaths in the VEN+G arm, 2 deaths were attributed to disease progression, 12 to fatal AEs and 1 to 'other' causes (reported as natural cardiac death). 'Other' causes refer to deaths that were reported as a reason for study discontinuation; after patients had discontinued study treatment for other

reasons (i.e. disease progression or discontinued due to another AE).

Fatal AEs

The frequency of fatal AEs was numerically higher in the VEN+G arm (n=16 [7.5%]) than in the GClb arm (n=8 [3.7%]). The most frequently reported AE leading to death was sepsis (1 patient in the GClb arm and 5 patients in the VEN+G arm). Cardiac arrest was reported in 1 patient in each arm.

Of the 16 patients who experienced Grade 5 AEs in the VEN+G arm, 2 patients (myelodysplastic syndrome and pneumonia fungal) discontinued obinutuzumab prior to receiving the first administration of venetoclax. In both cases, the investigator attributed a causal relationship to obinutuzumab. The other 3 fatal events with onset during the treatment period were sepsis (2 patients) and infection (1 patient). The onset of the remaining 11 fatal AEs occurred in the posttreatment period, that is, 29 days or more after the last study drug administration: one case was attributed to venetoclax.
In the GClb arm, of 8 patients with fatal AEs, 4 had onset during the treatment period, and 4 had onset in the post-treatment period.

- Fatal infections

In the experimental arm, 8 patients experienced fatal infection; of these, one did not receive venetoclax. In 4 patients, the fatal AEs occurred during the treatment period. One of them had Richter's transformation after event onset and died after salvage treatment with RCHOP and allogeneic stem cell transplant. In the other 4 patients, onset of the fatal events was after the end of the treatment period: onset 73, 156, 235 and 346 days after the last dose of venetoclax, respectively. One of these patients died after diagnosis and treatment of T-cell lymphoma (with CHOP therapy).
In the GClb arm, 3 patients experienced fatal events of infection, all of them with onset during the treatment period.

- Cardiovascular deaths

Four patients in the VEN+G arm and 1 patient in the GClb arm experienced fatal cardiovascular AEs. All of these AEs after the treatment period and all patients had a relevant medical history.

- Deaths due to second primary malignancies

Description of Fatal and Second Primary Malignancies

GCIb	VEN+G
Deaths due to Second Primary Malignancy with Onset of AE Occurring During Treatment	
(PT **Squamous cell carcinoma**): This 75-year-old male (initial CIRS 14) had a biopsy of right axilla which showed diffused carcinoma infiltrates in extranodal adipose tissue on study day 128; the patient was diagnosed with squamous cell carcinoma. On study day 313, the patient died due to pneumonia secondary to pulmonary metastasis, which was caused by squamous cell carcinoma of skin.	(PT **Myelodysplastic syndrome**): This 73-year-old male (initial CIRS 10) developed thrombocytopenia on study day 10, and was diagnosed with myelodysplastic syndrome on study day 22. He discontinued obinutuzumab, and died on study day 285. He had never received venetoclax.
Deaths due to Second Primary Malignancy With Onset of AE Occurring After the Treatment Period[a]	
(PT **Sarcoma of skin**): This 83-year-old male (initial CIRS 8) had a history of squamous cell carcinoma and radical surgery of planocellular carcinoma (left antehelix) in 2012. The patient completed obinutuzumab on study day 141, but discontinued chlorambucil due to Staphylococcal infection on study day 169. On study day 426, the patient was suspected to have pleomorphic dermal sarcoma (left side of the neck). On study day 441, CLL tumor assessment showed disease progression (increasing lymphocyte count). On study day 596, biopsy confirmed sarcoma of skin with metastasis. On study day 656, the patient died.	(PT **Metastatic malignant melanoma**): This 73-year-old male (initial CIRS 11) had a medical history of malignant melanoma (1987), basal cell carcinoma and skin neoplasm excision (2011). He received the last dose of venetoclax on study day 342, and later developed metastatic BRAF mutant melanoma on study day 406. He was treated with trametinib and dabrafenib. This event became serious on study day 507, when he was hospitalized with decreased consciousness; he died on study day 513.
(PT **Acute myeloid leukaemia**): This 75-year-old male (initial CIRS 12) discontinued study treatment with chlorambucil and obinutuzumab on study day 57 due to hemolytic anemia. On study day 119, CLL response tumor assessment showed disease progression (increasing/new hepatomegaly or splenomegaly). A bone marrow aspirate and biopsy was performed and on study day 451; the patient was diagnosed with acute myeloid leukemia. Treatment included decitabine. On study day 578, the patient died due to acute myeloid leukaemia.	(PT **Bladder cancer**): This 75-year-old female (initial CIRS 11) with ongoing urinary tract infections since 2007, received the last dose of venetoclax on study day 392. She had never smoked. She was diagnosed with bladder cancer on study day 492, following positive bladder biopsy; the tumour was resected. She later died on study day 867.

[a]More than 28 days after the last study drug administration

Laboratory findings

Grade 4 laboratory abnormalities developing in ≥2% of patients treated with VEN+G included neutropenia (32%), leukopenia and lymphopenia (10%), thrombocytopenia (8%), hypocalcaemia (8%), hyperuricemia (7%), blood creatinine increased (3%), hypercalcemia (3%), and hypokalaemia (2%).

Post-marketing experience

No additional safety signals have been identified based on post-marketing data of venetoclax for the treatment of patients with CLL (from Periodic Safety Update Report for Venetoclax dated 3 August 2018). Between the international birth date (11 April 2016) and 04 June 2018, the estimated cumulative patient exposure from company-sponsored interventional clinical trials for venetoclax is 3,505 patients. The estimated cumulative post-marketing patient exposure since first approval is 3,244.7 patient-treatment

years. The MAH continues to actively monitor safety as part of the ongoing global pharmacovigilance program.

2.5.1. Discussion on clinical safety

A total of 426 patients were treated (212 with VEN+G, 214 with GClb). The median duration of exposure to venclyxto was 10.5 months (range: 0 to 13.5 months). The median number of cycles was 6 for obinutuzumab and 12 for chlorambucil.

In the VEN+G arm, fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 4/212 of patients vs. 2 /216 in GClb arm (all infections). Serious adverse reactions were reported in 49% of patients in the VEN+G arm and 42% in the GClb arm.

In the VEN+G arm, adverse reactions led to treatment discontinuation in 16% of patients (15.4 in GClb), dose reduction in 21% (8.4% in GClb), and dose interruption in 74% (68% in GClb). In the VEN+G arm, neutropenia led to dose interruption of venclyxto in 41% of patients, reduction in 13%, and discontinuation in 2%.

During treatment with single agent venclyxto after completion of VEN+G combination treatment, the most common all grade adverse reaction (≥10% patients) reported was neutropenia (26%). The most common grade ≥3 adverse reactions (≥2% patients) were neutropenia (23%) and anaemia (2%).

An analysis of gr≥3 SAEs in order to explore a possible relationship between organ/system morbidities at baseline and the risk of severe toxicity events in study CLL14 did not reveal any clear relationship.

Grade 3 or 4 neutropenia has been reported in patients treated with venetoclax in combination studies with rituximab or obinutuzumab and in monotherapy studies (see section 4.8). Complete blood counts should be monitored throughout the treatment period. Dose interruptions or reductions are recommended for patients with severe neutropenia (see section 4.2).

Serious infections, including sepsis with fatal outcome, have been reported (see section 4.8). Monitoring of any signs and symptoms of infection is required. Suspected infections are to receive prompt treatment, including antimicrobials and dose interruption or reduction as appropriate (see section 4.2).

Dosage reductions due to adverse reactions occurred in 21% of patients treated with the combination of venetoclax and obinutuzumab in the CLL14 study

Deaths due to infection occurred in 1.9% of patients while on treatment and 1.9% of patients following treatment discontinuation.

Dose interruptions due to adverse reactions occurred in 74% of patients treated with the combination of venetoclax and obinutuzumab in the CLL14 study In the open-label, randomised phase 3 study (CLL14), the incidence of TLS was 1.4% (3/212) in patients treated with venetoclax + obinutuzumab. All three events of TLS resolved and did not lead to withdrawal from the study. Obinutuzumab administration was delayed in two cases in response to the TLS events.

2.5.2. Conclusions on clinical safety

No new safety concerns for venclyxto were identified during in the pivotal and the supportive trial, respectively. However, the proposed regimen is not less toxic than chlorambucil and obinutuzumab, the current standard of care in previously untreated CLL patients with coexisting conditions. Neutropenia, leading to severe infections, dominates the safety profile of the venclyxto and obinutuzumab combination. A higher rate of fatal infections was observed for patients randomized to VEN+G. Section 4.4 of the SPC

was amended to emphasize that neutropenic patients require constant monitoring for prompt identification of infection and aggressive treatment.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 5.1 with this application.

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

The PRAC considered that the risk management plan version 5.4 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 5.4 with the following content:

Table 28. Safery 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 • Toxicity in patients with severe hepatic impairment
Missing information	• Safety in severe renal impairment • Safety in long-term exposure (> 12 months)

Pharmacovigilance plan

Table 29.On-Going and Planned 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				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
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	Interim CSR Final CSR	Report submitted March 2018 December 2022
Study GO28667 (MURANO) Multicenter, Phase III, Open-Label, Randomised Study in Relapsed / Refractory Patients with Chronic Lymphocytic Leukaemia to Evaluate the Benefit of venetoclax (GDC-0199/ ABT-199) Plus Rituximab Compared with Bendamustine Plus Rituximab Ongoing	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 transformation and secondary primary malignancy	Primary analysis and interim CSR completed Final CSR	December 2017 December 2022
Study M13-982 A Phase 2 Open-Label Study of the	Evaluate the safety and efficacy of venetoclax monotherapy in subjects with R/R CLL in the	Safety in long-term exposure (> 12 months) of venetoclax	Interim CSR	Report submitted June 2018

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Efficacy of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukaemia Harboring the 17p Deletion Ongoing	presence of 17p del or *TP53* mutations	Second primary malignancy and Richter's transformation	Final CSR	May 2021
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	Interim CSR Final CSR	September 2019 May 2021
Study P16-562 Prospective Observational Cohort Study to Assess the Safety of Venetoclax in the Swedish Cohort of Chronic Lymphocytic Leukaemia Patients Ongoing	To characterize long term safety of venetoclax including determining the incidence of select adverse events in CLL patients exposed to venetoclax.	Safety in long-term exposure (> 12 months) of venetoclax Select list of adverse events: • 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	Interim CSR Final report	Every second year over a study period of 8 years Planned December 2025

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
		○ Anemia ○ Thrombocytopenia ○ Neutropenia • Pneumonia • Febrile Neutropenia • Diarrhea • Nausea/Vomit • Upper respiratory tract infection • Fatigue • Hyperphosphatemia • Constipation		
Study M16-185 Clinical drug-drug interaction study with an oral contraceptive Planned	Open-label study to assess the effect of venetoclax on the pharmacokinetics of oral contraceptive in hematologic malignancy patients	Potential DDIs with oral contraceptives	Study planned	Date for submission cannot be specified since the Agency agreed to conduction of this study when the indication is potentially widened to a younger population

Risk minimisation measures

Table 30. Summary Table of Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures
Tumour lysis syndrome (TLS)	<u>Routine risk minimisation measures:</u> Posology and method of administration, including prophylactic measures for TLS, are described in Section 4.2 of the SmPC. Warnings and precautions for TLS are listed in Section 4.4 of the SmPC. Interaction with other medicinal products is described in Section 4.5 of the SmPC. TLS is described in Section 4.8 of the SmPC. <u>Other routine risk minimisation measures:</u> Prescription only medicine

Safety Concern	Risk Minimisation Measures
	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 minimisation measures: None
Neutropenia	Routine risk minimisation measures: Posology and method of administration are described in Section 4.2 of the SmPC. Warnings and precautions for neutropenia are listed in Section 4.4 of the SmPC. Neutropenia is listed as a very common adverse reaction in Section 4.8 of the SmPC. Other routine risk minimisation measures: • Prescription only medicine. • Use of treatment should be initiated and supervised by specialist • Package leaflet Additional risk minimisation measures: None
Serious infection	Routine risk minimisation measures: Posology and method of administration are described in Section 4.2 of the SmPC. Supportive measures for infections associated with neutropenia are described in Section 4.4 of the SmPC. Observed infections and infestations are tabulated in Section 4.8. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist • Package leaflet Additional risk minimisation measures: None
Embryofetal toxicity	Routine risk minimisation measures: Language concerning embryofetal toxicity is included in Section 4.6 and Section 5.3 of the SmPC. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet Additional risk minimisation measures: None
Medication error	Routine risk minimisation measures:

Safety Concern	Risk Minimisation Measures
	Posology and method of administration are described in Section 4.2 of the SmPC. Language concerning overdose is included in Section 4.9 of the SmPC. Other routine risk minimisation 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 been designed to minimize medication errors • Package leaflet Additional risk minimisation measures: None
Richter's transformation	Routine risk minimisation measures: Posology and method of administration are described in Section 4.2 of the SmPC. Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist Additional risk minimisation measures: None
Second primary malignancy	Routine risk minimisation measures: None • Other routine risk minimisation measures: Prescription only medicine • Use of treatment should be initiated and supervised by specialist Additional risk minimisation measures: None
Toxicity in Patients with severe hepatic impairment	Routine risk minimisation measures: Posology and method of administration of dose adjustments in patients with severe hepatic impairment are described in Section 4.2 of the SmPC. PK study results pertaining to hepatic impairment are described in Section 5.2 of the SmPC Other routine risk minimisation measures: • Prescription only medication • Use of treatment should be initiated and supervised by specialist Additional risk minimisation measures: None
Safety in severe renal impairment	Routine risk minimisation measures: Section 4.2 of the SmPC advises that safety and efficacy have not yet been established in certain populations. Other routine risk minimisation measures: • Prescription only medicine

Safety Concern	Risk Minimisation Measures
	• Use of treatment should be initiated and supervised by specialists • Package leaflet Additional risk minimisation measures: None
Safety in long-term exposure (> 12 months)	Routine risk minimisation measures: Median duration of treatment is included in Section 5.1 of the SmPC Other routine risk minimisation measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists Additional risk minimisation measures: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the SmPC section 5.3 has been updated based on the results of a 4-week dose ranging study, a 6-month carcinogenicity study and two embryo-foetal development (EFD) studies in mice. Minor editorial changes have been introduced throughout the Product Information.

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, because the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

CLL remains the most prevalent chronic leukaemia in clinical practice. The current International Working Group for CLL (iwCLL) 2018 guidelines recommend active surveillance until disease-related symptoms develop. The prognostic factors in CLL are largely based on recurrent molecular and cytogenetic abnormalities.

3.1.2. Available therapies and unmet medical need

The field is evolving, with a number of drugs entering the relapsed/refractory setting and moving towards first-line, moreover with changes of recommendation category within previously untreated CLL. The role of MRD negativity in achieving deeper remissions and longer PFS (and ultimately overall survival) is taking centre stage in clinical trials. Both NCCN (latest version: 2020) and ESMO (2015, with an update in

2017) segregate patients with and without del(17p)/TP53mut and fit from unfit. It is often said that elderly patients, who usually have a number of coexisting conditions of varying degrees of severity, require an effective, yet less toxic, treatment than the already available therapies. In 2019, FDA approved venclyxto in combination with obinutuzumab (Gazyvaro) for previously untreated CLL (based on CLL14 trial), as well as ibrutinib + obinutuzumab for treatment-naïve CLL/SLL patients (based on the iLLUMINATE trial).

3.1.3. Main clinical studies

The pivotal trial BO25323/CLL14 was a randomized, multicenter, open label, phase 3 study that evaluated the efficacy and safety of venclyxto in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) for patients with previously untreated CLL with coexisting medical conditions (total Cumulative Illness Rating Scale [CIRS] score > 6 or CLcr < 70 mL/min, but not inferior to 30 mL/min). All the patients included required therapy (Binet stage C or symptomatic disease). After a separate safety run-in, 432 patients were randomized 1:1. Cross-over was not allowed. All patients received obinutuzumab at 1000 mg on d1 (the first dose could be split as 100 mg and 900 mg on d1 and 2), and on d8 and 15 of cycle 1, and on d1 of each subsequent cycle, for a total of 6 cycles. Patients in the VEN+G arm began the 5-week venclyxto ramp-up schedule on d22 of cycle 1 and received venclyxto 400 mg once daily from cycle 3 d1 until the last day of cycle 12. Patients randomized to the GClb arm received 0.5 mg/kg oral chlorambucil on d1 and d15 of cycles 1 to 12. Each cycle was 28 days.

The primary endpoint, Progression-free survival (PFS) was assessed by investigators and by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

3.2. Favourable effects

At data cutoff, 30 (13.9%) PFS inv. events were registered in VEN+G arm vs 77 (35.6%) in GClb arm. Of those, 14, compared with 69, were events of disease progression. The HR for PFS-inv. was 0.35 (0.23-0.53).

At end of treatment visit, 123 patients (56.9%) in the VEN+G arm had achieved bone marrow MRD negativity and 163 (75.5%) peripheral blood MRD negativity, compared with 37 patients (17.1%) and 76 patients (35.5%), respectively, in the GClb arm. Twelve months after the completion of treatment, MRD negativity rates in peripheral blood were 58% (126/216) in patients treated with VEN+G and 9% (20/216) in patients treated with GClb. In CR/CRi patients, the MRD-negativity rates at end of treatment were higher for VEN+G than for GClb: bone marrow 73 (33.8%) vs 23 (10.6%); peripheral blood: 91 (42.1%) vs 31 (14.4%).

The available PFS and MRD data support an effect across cytogenetic subgroups and mutational status. The CR was 107 (49.5%) vs 50 (23.1%); ORR 183 (84.7%) vs 154 (71.3%). At the time of the cut-off, less than 10% of the study population had an OS event.

3.3. Uncertainties and limitations about favourable effects

Although the maturity of PFS events is relatively low, and time-related secondary endpoints including OS are yet not informative, the treatment effect is adequately robust and consistent among subgroups; there are no uncertainties on the favourable effects.

3.4. Unfavourable effects

In the VEN+G arm, fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 4/212 of patients vs. 2 /216 in GClb arm (all infections).

Serious adverse reactions were reported in 49% of patients in the VEN+G arm and 42% in the GClb arm.

In the VEN+G arm, adverse reactions led to treatment discontinuation in 16% of patients (15.4 in GClb), dose reduction in 21% (8.4% in GClb), and dose interruption in 74% (68% in GClb).

In the VEN+G arm, neutropenia led to dose interruption of venclyxto in 41% of patients, reduction in 13%, and discontinuation in 2%.

3.5. Uncertainties and limitations about unfavourable effects

There were no uncertainties about the unfavourable effects

3.6. Effects Table

Effects Table for Venclyxto (data cut-off: August 2018)

Effect	Short description	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects				
		VEN+G n=216	**GClb** n=216	
PFS inv.				
	no. of events	30 (13.9%)	77 (35.6%)	Immature PFS data, however 17 months of off-treatment follow-up in both arms.
	-DP	14	69	
	-death	16	8	
	median (mo)	NE	NE	
	HR	0.35 (0.23-0.53)		PFS IRC 0.33
ORR		183 (84.7%)	154 (71.3%)	Diff 13.43% (5.47-21.38)
CR		107 (49.5%)	50 (23.1%)	Diff 26.39% (17.41-35.36)
MRD	PB	163 (75.5%)	76 (35.2%)	
	Marrow	123 (56.9%)	37 (17.1%)	
	PB in CR patients	91 (42.1%)	31 (14.4%)	MRD correlation with PFS
Unfavourable Effects				
Observe that in clinical praxis GClb is administered for 6 cycles, with no chlorambucil monotherapy for another 6 cycles, as done in CLL14 for regulatory purposes (to obtain same duration of treatment in both arms).				
		n=212	n=214	
Interruption		73.6%	68.2%	VEN+G: 41% were due to neutropenia
Dose reduction		20.8%	8.4%	VEN+G: 13% were due to neutropenia
Discontinuation		16%	15.4%	VEN+G: 2% were due to neutropenia

Effect	Short description	Treatment	Control	Uncertainties / Strength of evidence
AEs>10% (all grades/Gr≥3)		%		
	Neutropenia	60/56	62/52	Gr 3-4 febrile neutropenia 5.2 vs 3.7 Gr 3-4 infections 17.5 vs 15 GCSF 43.5 vs 45.8
	Anemia	17/8	20/7	
	Diarrhea	28/4	15/1	
	Nausea	19/0	22/1	
	Constipation	13/0	9/0	
	Vomiting	10/1	8/1	
	Fatigue	21/2	23/1	
	upper resp. tract infection	17/1	17/1	
SAEs		104 (49.1%)	90 (42.1%)	Infection: 18.9% vs 14%
Deaths	all-cause mortality	20 (9.4%)	16 (7.5%)	
	fatal AEs	16 (7.5%)	8 (3.7%)	Treatment-related infection: 4 vs 2 patients
	-on treatment	5	4	
	-after completion of treatment	11	4	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CLL patients, who usually have a number of coexisting conditions of varying degrees of severity, require an effective, yet less toxic, treatment than the already available therapies. In the pivotal study CLL14, PFS outcomes were supported by MRD results and other secondary endpoints. A fixed duration of one year of treatment seems sufficient to allow deep and prolonged control of disease. However, the proposed regimen is not less toxic than GClb. Although no new safety concerns for venclyxto were identified, neutropenia, leading to severe infections, some fatal, dominate the safety profile of the VEN+G combination. Nevertheless, as most infections can be managed adequately in the clinical setting if promptly identified and treated, the effect of the combination of venclyxto and obinutuzumab is considered to outweigh the risk of infection.

3.7.2. Balance of benefits and risks

The applicant is seeking an indication for first-line treatment of CLL regardless of age or comorbidities. While the patients included in study CLL14, with a median age of 72 and a median CIRS score of 8, might be regarded as representative for most CLL patients, patients considered fit for e.g. FCR were not studied. However, extrapolation of efficacy also to younger and more fit patients is considered acceptable. This is since the safety profile in such patients is not anticipated to be less favourable; furthermore, the effect size demonstrated, although not directly compared with FCR, is considered sufficient to make venetoclax + obinutuzumab a reasonable first line treatment alternative, where the differential safety profile comparted to chemotherapy is notable. The inclusion criteria for the pivotal study (i.e. patients with coexisting conditions) are reflected in section 5.1 of the SPC.

3.8. Conclusions

The overall B/R of Venclyxto in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) is positive.

4. Recommendations

Outcome

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

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include, in combination with an anti-CD20 antibody (obinutuzumab), treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for Venclyxto based on the results of the pivotal CLL14/BO25323 phase 3 study; consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC and corresponding sections of the PL have been revised. The updated RMP version 5.4 has been agreed. Additionally, the SmPC section 5.3 has been updated based on the results of a 4-week dose ranging study, a 6-month carcinogenicity study and two embryo-foetal development (EFD) studies in mice. Minor editorial changes have been introduced throughout the Product Information.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Venclyxto is not similar to Gazyvaro (obinutuzumab) and Imbruvica (ibrutinib) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Venclyxto-H-C-4106-II-23-G