The Lancet Oncology

Efficacy of venetoclax in patients with relapsed/refractory chronic lymphocytic leukaemia: analysis of the international single-arm phase 3b trial VENICE-1

--Manuscript Draft--

Manuscript Number:	THELANCETONCOLOGY-D-23-01042R4
Article Type:	FAST-TRACK Article (Clinical Trials)
Keywords:	Chronic Lymphocytic Leukaemia; Venetoclax; relapsed/refractory
Corresponding Author:	Francesco Forconi Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK; Haematology Department, Cancer Care Directorate, University Hospital Southampton NHS Trust, Southampton, UK UNITED KINGDOM
First Author:	Arnon P. Kater
Order of Authors:	Arnon P. Kater
	Önder Arslan
	Fatih Demirkan
	Yair Herishanu
	Burhan Ferhanoglu
	Marcos Gonzalez Diaz
	Brian Leber
	Marco Montillo
	Panayiotis Panayiotidis
	Davide Rossi
	Alan Skarbnik
	Adrian Tempescul
	Mehmet Turgut
	Clemens H. Mellink
	Anne-Marie F. van der Kevie-Kersemaekers
	Stuart Lanham
	Ben Sale
	Luis Del Rio
	Relja Popovic
	Brenda J. Chyla
	Todd Busman
	Viktor Komlosi
	Xifeng Wang
	Kavita Sail
	German E. Pena
	Tamas Vizkelety
	Francesco Forconi
Manuscript Region of Origin:	UNITED KINGDOM

Abstract:	Background: Most patients with chronic lymphocytic leukaemia (CLL) progress following (re)treatment with targeted- or chemoimmuno-therapy and have limited subsequent treatment options. Response levels to single-agent venetoclax in the relapsed setting were unknown. This study aimed to assess venetoclax efficacy in B-cell receptor-associated kinase inhibitors (BCRi)-naïve or prior BCRi-treated patients. Methods: The phase 3b VENICE-I trial (NCT02756611) assessed efficacy and safety of venetoclax monotherapy in adults with relapsed/refractory (R/R) CLL, stratified by previous exposure to a BCRi. Eligible participants were aged ≥18 years with previously treated R/R CLL. Presence of del17p or TP53 aberrations and prior BCRi treatment were permitted. Patients received 5-week ramp-up to 400 mg of oral venetoclax and were treated for ≤108 weeks with 2 years follow-up after discontinuation, or optional extended access. The primary efficacy endpoint was complete remission (CR) rate (CR + CR with incomplete marrow recovery [CRi]) in BCRi-naïve patients. Analyses used the intent-to-treat population. Findings: This study enrolled 258 patients (first patient first visit June 22, 2016; last patient last visit March 11, 2022 [study completion]) with R/R CLL; 191 were BCRi-naïve and 67 were BCRi-experienced. Overall, 70% (180) of patients were male. Median (IQR) follow-up in the overall cohort, and BCRi-naïve and -experienced groups was 49·5 (47·2, 54·1), 49·2 (47·2, 53·2), and 49·7 (47·4, 54·3) months, respectively. Of 191 BCRi-naïve patients, 66 (35%) achieved CR + CRi; 18/67(27%) BCRi-experienced patients achieved CR + CRi. Grade ≥3 TEAEs and SAEs were reported in 79% (n=203/258) and 53% (n=136/258) of patients, respectively. The most common TEAE and SAE was neutropenia (37%; n=96/258). and pneumonia (8%; n=21/258), respectively. There were 13 (5%) deaths reported due to AEs. No new safety signals were identified. Interpretation: These data demonstrate deep and durable responses with venetoclax monotherapy in patients with R/R CLL, including BCRi-experienced patients. Funding: AbbVie-sponsored study.

Manuscript ID: THELANCETONCOLOGY-D-23-01042R3

Prof Francesco Forconi
Email: F.forconi@soton.ac.uk

Dr Cheryl Reeves
Senior Editor, *The Lancet Oncology*

January, 2024

Dear Dr Reeves,

On behalf of my co-authors, I am pleased to submit for your further review a revision of our submitted Letter to the Editor, titled “Efficacy of venetoclax in patients with relapsed/refractory chronic lymphocytic leukaemia: analysis of the international phase 3b trial VENICE-1” (manuscript ID: THELANCETONCOLOGY-D-23-01042R3).

We thank the editor for their constructive critique. We are now submitting a revised version of the manuscript that addresses their comments and suggestions. We believe that these revisions now ensure that it meets the approval of the editorial board.

We would like to express our gratitude to the editorial team and the expert reviewers for their time and consideration. We look forward to hearing from you in due course.

Yours sincerely,
Francesco Forconi

Responses to Journal Comments

Manuscript ID: THELANCETONCOLOGY-D-23-01042R2

Efficacy of venetoclax in patients with relapsed/refractory chronic lymphocytic leukaemia: analysis of the international phase 3b trial VENICE-1

Arnon P. Kater, Önder Arslan, Fatih Demirkan, Yair Herishanu, Burhan Ferhanoglu, Marcos Gonzalez Diaz, Brian Leber, Marco Montillo, Panayiotis Panayiotidis, Davide Rossi, Alan Skarbnik, Adrian Tempescul, Mehmet Turgut, Clemens H. Mellink, Anne-marie F. van der Kevie-Kersemaekers, Stuart Lanham, Ben Sale, Luis Del Rio, Relja Popovic, Brenda J. Chyla, Todd Busman, Viktor Komlosi, Xifeng Wang, Kavita Sail, German E. Pena, Tamas Vizkelety, Francesco Forconi

Please note that page numbers refer to pages in the **TRACKED** version of the manuscript.

Editor's comments:

1. ***The Research in Context Panel:*** Please amend as requested.
   Evidence before this study: Authors should state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search, ie, articles published between month/day/year and month/day/year), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.
   Response: *On page 3, the Research in Context Panel has been updated as requested.*

2. **Methods:** You have not moved this sentence from study design to the procedures section as preiously requested, as per Lancet style: The starting dose for venetoclax was 20 mg orally once daily, increased weekly to 50 mg, 100 mg, 200 mg, up to the target of 400 mg once daily, which was the dose administered.
   Response: *The sentence was located within both subsections. The text has been updated to retain the sentence within the procedures subsection while removing it from the study design subsection.*

3. **Methods (Outcomes):** We do require a full definition of the primary efficacy endpoint of complete remission rate to be added please. Ie. defined as the proportion of subjects achieving a CR or CRi as their best response (per the investigator assessment) based on IWCLL NCI-WG criteria.
   Response: *The language related to the primary efficacy endpoint has been adjusted starting on page 8 line 196.*

4. **Methods (Outcomes):** Please add definition for your exploratory efficacy endpoints of assessment of MRD and rate of MRD negativity in peripheral blood (PB) and bone marrow (BM) and for Patient-reported quality of life (QoL).
   Response: *The language related to the exploratory efficacy endpoints has been adjusted starting on page 8 line 203.*

5. **Table 2:** Please change objective response rate to overall response rate as it still says objective response rate.
   Response: *We confirm that this update has been made.*

6. **Table 3:** The adverse events table for adverse events of grade 1 or 2, any occurring in ≥10% of patients is not currently in the correct format. It should be stratified by grades 1-2, 3, 4 and 5 which are the columns. You **can** have both BCRi-naïve and BCRi experienced. The rows show be the specific adverse events eg. Neutropenia, nausea etc. should be reported. All grade 3, 4, and 5 events should be reported. Please see our website for guidance and here is a link to a paper https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00479-5/fulltext
   Response: *Table 3 has been updated per the instructions above.*

Efficacy of venetoclax in patients with relapsed/refractory chronic lymphocytic leukaemia: analysis of the international single-arm phase 3b trial VENICE-1

Author list:

Arnon P. Kater, MD[1], Önder Arslan, MD[2], Fatih Demirkan, MD[3], Yair Herishanu, MD[4], Burhan Ferhanoglu, MD[5], Marcos Gonzalez Diaz, MD[6], Brian Leber, MD[7], Marco Montillo, MD[8], Panayiotis Panayiotidis, MD[9], Davide Rossi, PhD[10,11], Alan Skarbnik, MD[12,13], Adrian Tempescul, PhD[14], Mehmet Turgut, MD[15], Clemens H. Mellink, PhD[16], Anne-Marie F. van der Kevie-Kersemaekers, PhD[17], Stuart Lanham, PhD[18], Ben Sale, MSc[18], Luis Del Rio, MSc[18], Relja Popovic, MD [19], Brenda J. Chyla, PhD[19], Todd Busman, MS[19], Viktor Komlosi, PhD[19], Xifeng Wang, PhD[19], Kavita Sail, PhD[19], German E. Pena, MD [19], Tamas Vizkelety, MD[19], Francesco Forconi, MD[18,20]

Author affiliations:

[1]Department of Hematology, Cancer Center Amsterdam, Lymphoma and Myeloma Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands [AP Kater, MD].

[2]Department of Hematology, Ankara University, Faculty of Medicine, Ankara, Turkey [Ö Arslan, MD].

[3]Department of Hematology, Dokuz Eylül University, Faculty of Medicine, İzmir, Turkey [F Demirkan, MD].

[4]Department of Hematology, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel [Y Herishanu, MD].

[5]Department of Hematology, Koç University Medical Faculty, Istanbul, Turkey [B Ferhanoglu, MD].

[6]Department of Hematology, Center for Cancer Research-IBMCC (USAL-CSIC), PI of CIBERONC, IBSAL-University Hospital, Salamanca, Spain [M Gonzalez Diaz, MD].

[7]Division of Hematology and Thromboembolism, Department of Medicine, McMaster University, Hamilton, Canada [B Leber, MD].

[8]Department of Haematology, Niguarda Cancer Center, Niguarda Hospital, Milan, Italy [M Montillo, MD].

[9]First Department of Propedeutic Internal Medicine, National and Kapodistrian University of Athens, Laikon University Hospital, Athens, Greece [P Panayiotidis, MD].

[10]Institute of Oncology Research, Università della Svizzera Italiana, Bellinzona, Switzerland [D Rossi, PhD].

[11]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland [D Rossi, PhD].

[12]Lymphoproliferative Disorders Program, Novant Health Cancer Institute, Charlotte, NC, USA [A Skarbnik, MD].

[13]John Theurer Cancer Center, Hackensack, NJ, USA [A Skarbnik, MD].

[14]Department of Clinical Hematology, University Teaching Hospital Brest, Brest, France [A Tempescul, PhD].

[15]Department of Hematology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey [M Turgut, MD].

[16]Department of Human Genetics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands [C Mellink, PhD].

[17]Department of Genetics, UMC Utrecht, Utrecht, The Netherlands [AMF van der Kevie-Kersemaekers, PhD].

[18]Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK [S Lanham, PhD; B Sale, MSc; L Del Rio, MSc; F Forconi, MD].

[19]AbbVie Inc., North Chicago, IL, USA [R Popovic, MD; BJ Chyla, PhD; T Busman, MS; V Komlosi, PhD; X Wang, PhD; K Sail, PhD; GE Pena, MD; T Vizkelety, MD].

[20]Haematology Department, Cancer Care Directorate, University Hospital Southampton NHS Trust, Southampton, UK [F Forconi, MD].

Corresponding author:

Name of Author: Francesco Forconi

Address: Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

Tel.: +44-2381205780

Email: f.forconi@soton.ac.uk

Target journal: ***Lancet Oncology***

Word count: 3545~~498~~/3500

Tables/figures: 3 tables, 3 figures

References: 24/30

Research in context

Evidence before this study: We searched PubMed using the search terms "chronic lymphocytic leukemia", "clinical trials", "relapsed chronic lymphocytic leukemia", "refractory chronic lymphocytic leukemia", and "CLL and BCL-2" for studies published between Jan 1, 2011, and Dec 31, 2015. At the time this study was initiated in 2016, venetoclax had received its first approval by the United States Food and Drug Administration (FDA) as monotherapy in patients with chronic lymphocytic leukaemia (CLL) with the 17p deletion (as detected by an FDA-approved test) who have received ≥1 prior therapy; venetoclax was also nearing approval for similar indications in the EU and Canada. The efficacy and safety data supporting approval of venetoclax monotherapy was derived from the following phase I–II studies in relapsed/refractory CLL (R/R CLL) patients: [1] the first-in-human (FIH) study (NCT01328626) that enrolled 116 patients with R/R CLL who received target dosages of 150–1200 mg/day, in which patients had an overall objective response rate (ORR) of 79% with 20% of patients achieving either complete response (CR) or complete response with incomplete count recovery (CRi); [2] a single arm phase II trial (NCT01889186; Clinicaltrials.gov) that enrolled 107 patients with R/R CLL, with 17p deletion, who received the eventual venetoclax label-dose of 400 mg/day, that resulted in an ORR of 79% and CR/CRi rate of 8%; [3] and a phase II trial (NCT02141282; Clinicaltrials.gov) that again evaluated 400 mg/day of venetoclax in patients with CLL that had relapsed or were refractory to the B-Cell receptor targeted agents ibrutinib (n=41) or idelalasib (n=13), that resulted in an ORR of 61% and 50% and CR rate of 8% and 0%, respective to each prior therapy. The findings were broadly similar regardless of patient characteristics, including those often associated with poor chemoimmunotherapy outcomes, such as the presence of the 17p deletion or fludarabine resistance; however, there was a slightly lower ORR among the patients with prior B-cell receptor-associated kinase inhibitors (BCRi) therapy. Since venetoclax therapy in R/R CLL was, at that time, being further developed as a combination regimen with CD20 antibodies, this study (VENICE-I) was intended to provide data across a large population of R/R CLL patients with diverse molecular features and prior treatment experience.

Added value of this study: This phase 3b trial of venetoclax monotherapy is the largest and has the longest follow-up for any trial evaluating venetoclax monotherapy and demonstrated deep and durable responses and prolonged overall survival, irrespective of prior BCRi. With dose modifications, the safety profile of venetoclax was manageable even given this extended period of follow-up, and many patients transitioned to an extension study to continue receiving venetoclax therapy.

Implications of all the available evidence: These data suggest that patients with R/R CLL, including those with prior BCRi experience, can derive significant clinical benefit from venetoclax monotherapy, even over extended periods of time.

Abstract (299/300 words)

Background: Most patients with chronic lymphocytic leukaemia (CLL) progress following (re)treatment with targeted- or chemoimmuno-therapy and have limited subsequent treatment options. Response levels to single-agent venetoclax in the relapsed setting were unknown. This study aimed to assess venetoclax efficacy in B-cell receptor-associated kinase inhibitors (BCRi)-naïve or prior BCRi-treated patients.

Methods: The phase 3b VENICE-I trial (NCT02756611) assessed efficacy and safety of venetoclax monotherapy in adults with relapsed/refractory (R/R) CLL, stratified by previous exposure to a BCRi. Eligible participants were aged ≥18 years with previously treated R/R CLL. Presence of del17p or *TP53* aberrations and prior BCRi treatment were permitted. Patients received 5-week ramp-up to 400 mg of oral venetoclax and were treated for ≤108 weeks with 2 years follow-up after discontinuation, or optional extended access. The primary efficacy endpoint was complete remission (CR) rate (CR + CR with incomplete marrow recovery [CRi]) in BCRi-naïve patients. Analyses used the intent-to-treat population.

Findings: This study enrolled 258 patients (first patient first visit June 22, 2016; last patient last visit March 11, 2022 [study completion]) with R/R CLL; 191 were BCRi-naïve and 67 were BCRi-experienced. Overall, 70% (180) of patients were male. Median (IQR) follow-up in the overall cohort, and BCRi-naïve and -experienced groups was 49·5 (47·2, 54·1), 49·2 (47·2, 53·2), and 49·7 (47·4, 54·3) months, respectively. Of 191 BCRi-naïve patients, 66 (35%) achieved CR + CRi; 18/67(27%) BCRi-experienced patients achieved CR + CRi. Grade ≥3 TEAEs and SAEs were reported in 79% (n=203/258) and 53% (n=136/258) of patients, respectively. The most common TEAE and SAE was neutropenia (37%; n=96/258). and pneumonia (8%; n=21/258), respectively. There were 13 (5%) deaths reported due to AEs. No new safety signals were identified.

Interpretation: These data demonstrate deep and durable responses with venetoclax monotherapy in patients with R/R CLL, including BCRi-experienced patients.

Funding: AbbVie-sponsored study.

Introduction

Treatment with targeted agents, including B-cell receptor-associated kinase inhibitors (BCRi) has improved survival outcomes of chronic lymphocytic leukaemia (CLL).[1-3] However, BCRi need to be taken until progression, ~~which will occur in many patients,~~ and are associated with long-term toxicities.[4,5] B-cell lymphoma-2 (BCL-2) protein, ~~-~~another therapeutic target, is overexpressed in CLL ~~and is another therapeutic target~~.[6,7] Venetoclax, ~~is~~ a first-in-class orally bioavailable BCL-2 inhibitor approved for the treatment of CLL,[8] ~~which~~ acts by inducing rapid apoptosis in CLL cells.[6,9] It has demonstrated deep and durable responses in patients with relapsed/refractory (R/R) CLL, including those with poor prognostic features.[10-12] Single-agent venetoclax can induce overall response rates (ORR) ≥65% in these patients, with ~~and has~~ a manageable safety profile.[3,10,13] Although BCRi refractoriness can impact rate and duration of response (DoR) to venetoclax, data indicate venetoclax is efficacious even after BCRi failure.[3,13-15] The efficacy and safety of fixed-duration venetoclax combinations has been established in R/R and previously untreated CLL,[16-18] but long-term data on single-agent venetoclax treatment in R/R CLL, including BCRi R/R CLL, are sparse.

VENICE-I (NCT02756611) is the largest, multicentre, phase 3b trial designed to assess venetoclax monotherapy efficacy and safety ~~of venetoclax monotherapy~~ in BCRi-naïve and BCRi-experienced patients with R/R CLL, irrespective of 17p deletion or *TP53* mutation status. Here, we report the VENICE-I primary efficacy analyses ~~of venetoclax in BCRi-naïve or prior BCRi-treated patients,~~ and minimal residual disease (MRD) responses. ~~, which are known to be strongly associated with progression-free survival (PFS).[16,19]~~

Methods

Study design and participants

This open-label, single arm, phase 3b study (NCT02756611) was conducted at 59 sites across 21 countries in Europe and North America (**Appendix page 16**).

The starting dose for venetoclax was 20 mg orally once daily, increased weekly to 50 mg, 100 mg, 200 mg, up to the target of 400 mg once daily, which was the dose administered for up to 108 weeks, unless earlier discontinuation occurred due to unacceptable toxicity, disease progression, or lack of tolerability. Dose interruptions and/or dose reductions were applied for haematological and other toxicities related to venetoclax (details in the **Appendix page 5**). In countries where venetoclax was not commercially available, patients who continued to derive benefit after 2 years' treatment were able to extend treatment for ≤3 additional years in the extension phase of the trial. Patients were followed for disease progression and survival for 2 years after venetoclax discontinuation.

The review boards of participating institutions approved the study protocol, which was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Eligible participants were aged ≥18 years with previously treated R/R CLL (progression on prior treatment determined by investigator medical assessment), had a creatinine clearance rate of ≥50 mL/min, and required treatment according to International Workshop on Chronic Lymphocytic Leukaemia 2008 criteria. Presence of del17p or *TP53* aberrations and prior BCRi treatment were permitted. Patients who had developed Richter transformation or prolymphocytic leukaemia, and those who had received prior venetoclax were not eligible. Prior to the start of venetoclax, patients could not have received antineoplastic biologic agents ≤30 days; any anticancer therapy (except BCRi) or radiotherapy within five half-lives or 14 days; steroids or strong/moderate Cytochrome P450 3A (CYP3A) inducers ≤7 days; or strong/moderate CYP3A inhibitors or BCRi ≤3 days. Full inclusion and exclusion criteria are listed in **Appendix pages 2 and 3**. Disease response was assessed at screening, and Weeks 24, 36, and 48. Assessment was conducted by study investigator according to the 2008 modified iwCLL criteria. Laboratory tests were conducted at screening to assess eligibility and included full blood chemistry/haematology panel.

Procedures

Patient sex, race, and ethnicity were provided by the individual investigators.

The starting dose for venetoclax was 20 mg orally once daily (tablet form), increased weekly to 50 mg, 100 mg, 200 mg, then to the target dose of 400 mg once daily. Computed tomography imaging was performed on all patients at screening and also at Week 48, alongside BM biopsy and aspirate to confirm response in patients with CR/CRi.

Blood chemistry/haematology tests were also performed at 6–8 and 24 hours following the first dose increase in patients with low to high risk of TLS.

Each patient could withdraw from the study at any time. Investigators could also discontinue a patient from study drug treatment at any time if the investigator considered it necessary for any reason, including: unsatisfactory response to therapy requirement for other cancer treatment during the study period; unacceptable toxicity; the patient became pregnant while on study; drug protocol non-compliance, and determination that it is in the patient's best interest.

QoL was assessed using the EuroQol 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L), the Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) questionnaire, and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale (detailed in **Appendix page 4**).

Detailed methods for MRD and molecular assessments can be found in **Appendix page 3.** Array-based genomic complexity (GC) status was defined by numbers of copy number aberrations (CA): non-complex (0–2); low (3–4); or high (≥5) as has been previously defined.[17]

Adverse events (AEs) were monitored and recorded throughout the study. Recommended dose modifications are listed in **Appendix page 5**. Safety analyses were performed on patients who received ≥1 dose of venetoclax. Safety evaluations included drug exposure, AEs, serious AEs, deaths, and laboratory parameters. AE analyses only included treatment emergent AEs (TEAEs) with onset on or after first dose and ≤30 days after last dose. AE severity was rated according to NCI Common Terminology Criteria for Adverse Event (NCI CTCAE v4·03).

Outcomes

The primary efficacy endpoint was complete remission (CR) rate (defined as the proportion of patients achieving a CR or~~+~~ CR with incomplete marrow recovery [CRi] as their best response [per investigator assessment] based on iwCLL NCI-WG criteria) in BCRi-naïve patients~~, as defined by iwCLL NCI-WG criteria~~.

Secondary efficacy endpoints included CR/CRi in BCRi-experienced patients, progression-free survival (PFS [~~(~~days from first dose to earliest disease progression or death]), ~~overall response rate~~ORR (~~ORR;~~ CR+CRi+nPR+PR rates), DoR (days from first response to earliest recurrence or progressive disease), time to progression (TTP; days from first dose to earliest disease progression), and overall survival (OS; days from first dose to death). Exploratory efficacy endpoints included assessment of MRD and rate of MRD negativity (defined as the proportion of ~~subject~~patients ~~who had MRD negativity status~~with <1 CLL cell per 10,000 leukocytes ($<10^{-4}$) in peripheral blood (PB) and bone marrow (BM). Patient-reported quality of life (QoL), assessed through the FACT-Leu, FACIT-F, and EQ-5D-5L instruments, was an additional efficacy endpoint; scores for all QoL assessments were calculated according to their respective scoring manuals.

Statistical analysis

The study is registered with ClinicalTrials.gov (NCT02756611). At protocol initiation a sample size of 250 patients was calculated to provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favour of an alternative hypotheses that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate). Prior to readout, the primary hypothesis was revised and a sample size of 190 patients who had not previously received BCRi therapy was required to reject the null hypothesis of a CR/CRi rate ≤6% at approximately 80% power based on an exact test for single proportions using a two-sided alpha of 5%. As the study aimed to enrol approximately 250 patients, up to 60 patients with BCRi

experience could be included allowing descriptive reporting of outcomes for this subgroup within the trial population.

Analyses were performed on the overall cohort and prespecified subgroups (~~of~~ BCRi-naïve and BCRi-experienced). Primary efficacy analysis was conducted once all patients had completed a Week 48 disease assessment. All patients who received ≥1 dose of venetoclax were included ~~and~~; patients who had not achieved CR/CRi at Week 48 were considered nonresponders in the calculation of CR rate. CR/CRi rate and ORR and were evaluated using point estimates and corresponding 95% confidence intervals (CI) were calculated based on binomial distribution.

All time-to-event endpoints were analysed for the whole study period using Kaplan–Meier methodology; patients who did not experience an event (progressive disease or death, where appropriate) were censored at their last adequate disease assessment date (or last known alive date for OS). Descriptive statistics were calculated for baseline demographics and clinical characteristics, QoL, and safety events.

Additional post hoc efficacy analyses (univariate and multivariable) were conducted to assess prominent prognostic factors (*IGHV* status~~,~~ *TP53* status, del17p status, or GC), on outcomes. These were conducted in patients with available baseline molecular results (patients without a specimen or inconclusive results were excluded). Odds ratios (ORs) and hazard ratios (HRs) were calculated using univariate, multiple logistic and Cox proportional hazards regressions.

Main data analysis was performed using SAS v9·4 software; exploratory analyses were done using R 4·3·1.

Role of the funding source

AbbVie sponsored the study, contributed to the analysis and interpretation of the data, and AbbVie participated in the writing, review, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this manuscript. No honoraria or payments were made for authorship. Venetoclax is being developed in a collaboration between AbbVie and Genentech.

Results

Overall, 287 patients were screened and 258 patients with R/R CLL were enrolled (first patient first visit June 22, 2016; last patient last visit March 11, 2022)~~, of whom~~ 191 were BCRi-naïve and 67 were BCRi-experienced (full details in **Appendix page 6**). The most common reasons for venetoclax discontinuation were enrolment into the extension study (19%; n=48/258; whereby patients were recorded as having discontinued venetoclax treatment in VENICE-1 so they could receive venetoclax

in the subsequent study) and progressive disease (19%; n=48/258); this was followed by AE (15%; n=39/258; **Figure 1**). Median duration of treatment exposure was 108 weeks (inter-quartile range [IQR] 73·7–190·0) overall, 110 weeks (IQR 85·9–202·1) in the BCRi-naïve group, and 107 weeks (IQR 24·3–119·6) in the BCRi-experienced group. Median (IQR) follow-up in the overall cohort, and BCRi-naïve and -experienced groups was 49·5 (47·2, 54·1), 49·2 (47·2, 53·2), and 49·7 (47·4, 54·3) months, respectively. All ~~258~~ enrolled patients received ≥1 dose of venetoclax and were included in the efficacy and safety analyses.

Patients were predominantly male (70%; n=180/258), with a median age of 68 years (IQR 61–74; **Table 1**). Median number of prior CLL therapies was two overall, one in the BCRi-naïve group, and three in the BCRi-experienced group. Among 67 patients with prior BCRi experience, 50 received prior ibrutinib, 26 received prior idelalisib, and two patients received acalabrutinib; some patients received both ibrutinib and idelalisib. Eighty-two reasons were recorded for the discontinuation of the 78 BCRi treatments; 23 were progressive disease and 47 were toxicities. Median treatment duration of prior BCRi was 9·0 months (IQR 4·0–20·7; n=67). Centrally assessed *IGHV* mutation, del17p, and *TP53* mutations were reported for 27% (n=42/153), 20% (n=35/172), and 24% (n=42/173) of patients with mutation data in the overall population, respectively; 20% (n=35/172) of patients with data for GC had high GC (≥5 CAs). Concordance rates for centrally assessed and locally assessed genomic characteristics can be seen in **Appendix page 8**.

Overall, CR/CRi rate at Week 48 was 33% (95% CI 26·9–38·6; n=84/258; **Figure 2**). The CR/CRi rate in BCRi-naïve patients (primary endpoint) was 35% (95% CI 27·8−41·8; n=66/191) with a rate ratio of 1.29 (95% CI, 0.764, 2.166) CR/CRi rate was 27% (95% CI 16·8–39·1; n=18/67) in the BCRi-experienced group. CR/CRi rate was similar across subgroups based on sex, race, age group, Eastern Cooperative Oncology Group (ECOG) status, prior number of therapies, absolute lymphocyte count, and baseline node size (**Appendix page 17**). Overall CR/CRi rate was 28% (n=11/39) and 38% (n=35/93) in patients with and without a *TP53* mutation, and 27% (n=12/44) and 34% (n=59/172) in patients with and without del17p per investigator-assessed mutation status. CR/CRi rates were comparable regardless of number of prior therapies in the overall population (one therapy, 34% [n=36/106]; two therapies, 33% [n=21/64]; more than two therapies, 31% [n=27/88]). ORR was 80% (n=206/258) overall, 85% (n=163/191) in the BCRi-naïve group, and 64% (n=43/67) in the BCRi-experienced group (**Table 2**). Post hoc analyses of the effect of prognostic factors – *IGHV* and *TP53* mutation, del17p, and GC status – as centrally assessed at study entry on clinical outcomes are reported in the **Appendix** (**pages 9 and 10 and pages 19–21)**.

The overall median DoR for patients who achieved a response (n=205) was 25·1 months (95% CI 19·4–28·6). Median DoR was 24·4 months (95% CI 18·1–27·9) in the BCRi-naïve population (n=162) and 28·6 months (95% CI 16·8–45·3) in the BCRi-experienced population (n=43; **Appendix page 23**). The overall TTP (n=258) was 28·3 months (95% CI 23·4–32·6; **Appendix page 23**). Median TTP was 24·6 months (95% CI 21·9–30·6) for the BCRi-naïve population (n=191) and 33·8 months (95% CI 23·4–not estimable) for the BCRi-experienced population (n=67).

In the overall cohort, 92/258 (36%) patients had PFS events, with median PFS of 28·3 months (95% CI 22·2–30·5; **Figure 3A**). In the BCRi-naïve and BCRi-experienced groups, 63/191 (33%) and 29/67 (43%) had PFS events and median PFS was 28·8 months (95% CI 22·2–31·8) and 23·4 months (95% CI 16·8–33·8), respectively (**Figure 3B**). In the overall cohort and BCRi-naïve and -experienced groups, 70/258 (27%), 45/191 (24%), and 25/67 (37%) patients, respectively, died; median OS was not reached in the overall, BCRi-naïve or BCRi-experienced populations (**Figure 3C and 3D**). Five-year survival estimates were 71% (95% CI 65·0−76·5), 75% (95% CI 67·5−80·6), and 61% (95% CI 47·7−71·6) for the overall, BCRi-naïve, and BCRi-experienced patients, respectively.

For the overall cohort, patients showed a mean (standard deviation [SD]) improvement of 8·5 (14·4) points (95% CI 6·5–10·5; n=204) in the EQ-5D VAS score; this decreased to 7·1 (14·6) points (95% CI 4·8–9·4; n=156) by Week 108. In the BCRi-naïve and -experienced groups, mean (SD) improvements in EQ-5D VAS scores were 8·6 (14·53; n=164) and 8·0 (14·18; n=43), respectively at Week 48, and 7·3 (14·37; n=124) and 6·1 (15·75; n=32), respectively at Week 108. FACT-Leu leukaemia subscale scores also improved at Week 48 in the overall cohort, BCRi-naïve group and BCRi-experienced group (mean [SD] scores of 6·8 [7·99], n=202; 6·5 [8·19], n=161; and 7·8 [7·20], n=41, respectively) and at Week 108 (6·0 [9·08], n=153; 6·2 [8·77], n=122; and 5·2 [10·33], n=31, respectively); similarly, the FACT-Leu trial outcome index showed improvements at Week 48 in overall (9·8 [14·23]; n=201), BCRi-naïve (9·0 [14·52]; n=160), and BCRi-experienced (13·0 [12·71]; n=201) populations, and changes were maintained at Week 108. FACT-G Total Score improvements were seen at Week 48 in the overall cohort (5·5 [12·34], n=200) and in the BCRi-naïve and -experienced groups (4·8 [12·19; n=160] and 8·0 [12·74; n=40], respectively) and all were maintained at Week 108. At Week 48, patients showed a mean (SD) improvement of 4·9 (9·43) points (95% CI 3·6–6·2; n=205) from baseline in the FACIT-fatigue score, which decreased by Week 108 to 3·3 (9·96) points (95% CI 1·7–4·8; n=154).

A total of 198 patients had at least one on-therapy PB MRD assessment, with 60 patients missing ≥1 assessment. Overall, 104/258 patients (40% of intent-to-treat [ITT] population, 53% of patients with MRD assessments) and 99/206 responders (48% of ITT population, 50% of patients with MRD

assessments) had undetectable MRD (uMRD) by PB assessment. Of the 84 total patients with CR/CRi and known MRD levels, 46 (55%) had uMRD by PB assessment. A total of 76 patients had a BM MRD assessment, including 51/84 patients with CR/CRi. Among the 84 patients who had a CR/CRi, 23 (27%) were determined to be uMRD by BM; rates of uMRD were similar for the BCRi-naïve (26%; n=17) and BCRi-experienced (33%; n=6) groups.

A listing of all AEs of any grade (Grade 3–5 and grade 1 and 2 ≥10%) are included in **Table 3**. The majority of patients (98%; n=254/258) experienced a TEAE of any grade; most frequently reported were neutropenia (43%; n=112/258), diarrhoea (39%; n=100/258), and nausea (27%; n=69/258). Grade ≥3 TEAEs were reported in 79% (n=203/258) of patients, most common being neutropenia (37%; n=96/258), anaemia (13%; n=34/258), and thrombocytopenia (13%; n=33/258); and serious TEAEs were reported in 53% (n=136/258) of patients, most commonly being pneumonia (8%; n=21/258) and febrile neutropenia (6%; n=15/258). For the overall cohort (n=248) there were 70 (27%) deaths during the study, of which 21 (8%) occurred within 30 days of the last dose of venetoclax, and 13 (5%) were attributable to AEs (details in **Appendix page 11**); 33 (13%]) deaths were due to disease progression. A total of six symptomatic COVID-19 infections (2%), including two SAEs were reported among BCRi-naïve patients. No patients discontinued venetoclax or died due to COVID-19 infection.

Generally, patients in the BCRi-naïve group experienced lower rates of TEAEs than patients with previous BCRi exposure, especially for grade 4 TEAEs (30% vs 57%), SAEs (50% vs 60%), and deaths (24% vs 37%). However, grade 5 TEAEs and AEs leading to death were observed in 11 BCRi-naïve patients [6%] versus two BCRi-experienced [3%]. Both treatment groups experienced TEAEs leading to venetoclax dose interruption, reduction, or discontinuation at similar rates (**Table 3**). Full reasons for discontinuation are provided in **Appendix page 12.**

At study entry, most patients were categorised as at high risk of TLS and 98% (n=252/258) received prophylaxis for TLS, including hydration (98%; n=252/258), allopurinol (90%; n=231/258), and rasburicase (28%; n=71/258). Overall, 118 of 258 (46%) patients were hospitalised during ramp-up to receive TLS prophylaxis; 46% in both the BCRi-naïve (n=87/191) and BCRi-experienced (n=31/67) groups. No patients had clinical TLS, or grade 4 or 5 AEs of TLS. Thirteen (5%) patients met Howard criteria for laboratory TLS, of which TEAEs of TLS were reported for six (2%) patients (two patients with grade 1 events and four with grade 3 events). Two patients had serious TLS events, and venetoclax dose interruptions and reductions due to TLS occurred in three and one patients, respectively; no patients discontinued due to TLS.

Overall, 145 of 258 (56%) patients experienced neutropenia-related AEs of special interest. Granulocyte colony-stimulating factor was administered to 119 of 258 (46%) patients for blood count recovery. BCRi-naïve patients experienced lower rates of febrile neutropenia than BCRi-experienced patients (4% [n=8/191] vs 15% [n=10/67], respectively). Neutropenia AEs were most commonly managed using dose interruptions (n=36/258; 14%) and reductions (n=10/258; 4%). One patient discontinued venetoclax due to neutropenia. A total of 50 of 258 (19%) patients had serious infections, including opportunistic infections, and of these, 43 patients had grade ≥3 infections (grade 4, n=6; grade 5, n=2). The most common serious infections were pneumonia (8%; n=21/258), lower respiratory tract infection (2%; n=4/258), and influenza (1%; n=3/258). Overall, 50 of 258 patients (19%) developed neoplasms (benign, malignant, or unspecified); 20% (n=39/191) in the BCRi-naïve group and 16% (n=11/67) in the BCRi-experienced group.

A full listing of subsequent anticancer treatments is provided in **Appendix page 13**.

Discussion

Thi~~i~~s study ~~phase 3b, multicentre, international study~~ demonstrated a CR/CRi rate of 35% in R/R in BCRi-naïve CLL patients. ~~Approximately one-quarter (26%)~~Twenty-six percent of the study population were BCRi-experienced patients. CR/CRi rate and ORR of 27% and 64%, respectively, suggest encouraging efficacy of venetoclax monotherapy in this ~~patient~~ population. Venetoclax monotherapy ~~had~~ was previously ~~been~~ investigated in phase 2 trials with R/R BCRi-experienced CLL~~;~~, CR/CRi rates were lower than in the current study, although ORR and median PFS were not different.[3,13] The results of this study are consistent with a real-world retrospective analysis of heavily pretreated R/R BCRi-experienced CLL patients receiving venetoclax monotherapy, where 85% responded and 23% achieved CR/CRi.[19]

Prior exposure to BCRi and number of prior therapies have been associated with reduced response rates in previous clinical trials and real-world studies[14,15,19] and suggest that early use of venetoclax should be the preferred choice; however, the current BCRi-experienced cohort ORR was 64%, suggesting that patients still benefit following BCRi discontinuation.

Post hoc PFS analyses were performed to stratify patients' risk using *IGHV* status, del17p status, and GC.[20,21] Interestingly, patients with mutated *IGHV* ~~-~~had longer PFS than those with unmutated. Unlike BCRi-naïve patients, in BCRi-experienced patients, *IGHV* status, *TP53* status, and GC appeared not to associate with differential outcomes. Patients also achieved uMRD less frequently with mutated *IGHV* versus unmutated; these findings contrast with previously published studies of venetoclax in R/R CLL[22] and should be evaluated in larger cohorts and cautiously interpreted at present. In the BCRi-naïve group, there appeared to be differences in each stratified analysis, an observation that

does not hold true for BCRi-experienced patients. However, fewer lines of therapy and fewer negative prognostic factors present in the BCRi-naïve group may have contributed to this. These findings warrant additional analysis and will be explored in future publications.

The safety profile reported here was consistent with previously published venetoclax data in R/R CLL.[3,4,10,13] No clinical TLS AEs were observed, and no patients discontinued venetoclax due to TLS. Although common, neutropenia was managed with brief interruptions/reductions in venetoclax dosing.

Limitations of this study include the single-arm study design without comparator, and lack of statistical power for subgroup analyses~~, particularly within the BCRi-experienced population~~.

This phase 3b trial VENICE-I indicates venetoclax monotherapy can achieve deep and durable responses in patients with R/R CLL, including BCRi-experienced patients; high rates of CR/CRi were observed over long-term follow-up, with no new safety signals identified. This is the largest study of venetoclax monotherapy to be carried out in this setting and is consistent with the data previously reported, supporting early use of venetoclax within CLL.

Acknowledgements:

AbbVie sponsored the study, (NCT02756611); contributed to the analysis and interpretation of the data; and AbbVie participated in the writing, review, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this manuscript. No honoraria or payments were made for authorship. Medical writing support was provided by Hayley Ellis, PhD, of Fishawack Facilitate Ltd, part of Avalere Health, funded by AbbVie. The authors wish to thank the patients and their families, the study coordinators, and support staff. The authors would also like to acknowledge all investigators of the NCT02756611 study. The authors would also like to thank Adam Luo for contribution to statistical analyses.

Data sharing statement:

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select “Home.”

Authorship contributions: Study concept and Design: Arnon Kater, Brenda Chyla, Viktor Komlosi, German Pena, Francesco Forconi.

Clinical data collection: Arnon Kater, Onder Aslan, Fatih Demirkan, Yair Herishanu, Burhan Ferhanoglu, Marcos Gonzalez Diaz, Brian Leber, Marco Montillo, Panayiotis Panayiotidis, Davide Rossi, Alan Skarbnik, Adrian Tempescul, Mehemt Turgut and Francesco Forconi.

Exploratory data and PRO data collection, and statistical analyses: Clemens Mellink, Anne-Marie vander Kevie-Kersemaekers, Stuart Lanham, Ben Sale, Luis Del Rio, Relja Popovic, Brenda Chyla, Todd Busman, Xifeng Wang, Kavita Sail and Tamas Vizkelety.

All authors participated in the analysis and interpretation of results, and manuscript preparation. At least two authors (Brenda J. Chyla, Todd Busman, and Tamas Vizkelety) have accessed and verified the raw data.

Declaration of Interests:

Arnon P. Kater: AK performed advisory board function and received research funding from Astra Zeneca, Janssen, Roche/Genentech, AbbVie, BMS, LAVA.

Önder Arslan: AbbVie speaker and advisory board member.

Fatih Demirkan: Nothing to disclose.

Yair Herishanu: Honoraria; AbbVie, Janssen, Astra-Zeneca, Roche, Medison. Advisory Board; AbbVie, Jansen, Astra-Zeneca, Medison, Lilly. Research grant; Janssen.

Burhan Ferhanoglu: Advisory board: Takeda Pharmaceuticals, Janssen, and Pfizer. AbbVie speaker fee.

Marcos Gonzalez Diaz: AbbVie speaker.

Brian Leber: Speakers bureau/honoraria: AbbVie, Alexion, AMGEN, Astellas, Astex, BMS/Celgene, Jazz, Janssen Novartis, Otsuka, Paladin, Pfizer, Roche, Treadwell. Consulting fees : AbbVie, Novartis, Pfizer.

Marco Montillo: AbbVie speaker Bureau, Honoraria. Janssen Honoraria.

Panayiotis Panayiotidis: Research support grant: AbbVie; Honoraria/speaker's bureau: AbbVie, AstraZeneca, Roche.

Davide Rossi: Nothing to disclose.

Alan Skarbnik: Consultancy and/or Speaker fees from: Alexion, AbbVie, AstraZeneca, ADC Therapeutics, Beigene, Bristol-Myers Squibb, Celgene, Epizyme, Genentech, Janssen, Jazz Therapeutics, Kite Pharma, Lilly, MorphoSys, Novartis, Pharmacyclics, SeaGen, GenMab, TG Therapeutics. Payments for presentations, lectures etc: AstraZeneca, ADC Therapeutics, Abbvie, Beigene, Genentech, GenMab, Jazz Therapeutics, Janssen, Kite Pharma, Lilly, Pharmacyclics, SeaGen, TG Therapeutics. Data Safety Monitoring Board: Alexion.

Adrian Tempescul: Nothing to disclose.

Mehmet Turgut: Nothing to disclose.

Clemens Mellink: AbbVie Inc. funded microarray analysis.

Anne-Marie van der Kevie-Kersemaekers: AbbVie Inc. funded microarray analysis.

Stuart Lanham: Nothing to disclose.

Ben Sale: Nothing to disclose.

Luis Del Rio: Nothing to disclose.

Relja Popovic: AbbVie employee and may hold stock or options.

Brenda J. Chyla: AbbVie employee and may hold stock or options.

Todd Busman: AbbVie employee and may hold stock or options.

Viktor Komlosi: was an AbbVie employee at time of study and may hold stock or options.

Xifeng Wang: AbbVie employee and may hold stock or options.

Kavita Sail: AbbVie employee and may hold stock or options.

German E. Pena: AbbVie employee and may hold stock or options.

Tamas Vizkelety: AbbVie employee and may hold stock or options.

Francesco Forconi: Advisory board for BeiGene; Honoraria: Abbvie, Janssen-Cilag, Beigene, AstraZeneca; Speakers bureau: Abbvie, Janssen-Cilag, Astra-Zeneca; Travel and Accommodation: Abbvie, Janssen-Cilag, Beigene.

References

1. Byrd JC, Furman RR, Coutre SE, et al. Ibrutinib treatment for first-line and relapsed/refractory chronic lymphocytic leukemia: Final analysis of the pivotal phase Ib/II PCYC-1102 study. *Clin Cancer Res* 2020; **26**(15): 3918–27.

2. Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leukemia* 2019; **33**(4): 969–80.

3. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: An interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2018; **19**(1): 65–75.

4. Davids MS, Hallek M, Wierda W, et al. Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukemia. *Clin Cancer Res* 2018; **24**(18): 4371–9.

5. Perez-Carretero C, Gonzalez-Gascon YMI, Rodriguez-Vicente AE, et al. The evolving landscape of chronic lymphocytic leukemia on diagnosis, prognosis and treatment. *Diagnostics (Basel)* 2021; **11**(5).

6. Cimmino A, Calin GA, Fabbri M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci USA* 2005; **102**(39): 13944–9.

7. Calin GA, Dumitru CD, Shimizu M, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc Natl Acad Sci USA* 2002; **99**(24): 15524–9.

8. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2021; **32**(1): 23–33.

9. Del Gaizo Moore V, Brown JR, Certo M, Love TM, Novina CD, Letai A. Chronic lymphocytic leukemia requires BCL2 to sequester prodeath BIM, explaining sensitivity to BCL2 antagonist ABT-737. *J Clin Invest* 2007; **117**(1): 112–21.

10. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: Results from the full population of a phase ii pivotal trial. *J Clin Oncol* 2018; **36**(19): 1973–80.

11. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med* 2019; **380**(23): 2225–36.

12. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2016; **374**(4): 311–22.

13. Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood* 2018; **131**(15): 1704–11.

14. Roberts AW, Ma S, Kipps TJ, et al. Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables. *Blood* 2019; **134**(2): 111–22.

15. Innocenti I, Morelli F, Autore F, et al. Venetoclax in CLL patients who progress after B-cell Receptor inhibitor treatment: A retrospective multi-centre Italian experience. *Br J Haematol* 2019; **187**(1): e8–e11.

16. Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: Post-treatment follow-up of the MURANO phase III study. *J Clin Oncol* 2019; **37**(4): 269–77.

17. Al-Sawaf O, Zhang C, Lu T, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: Extended off-treatment follow-up from the randomized CLL14 study. *J Clin Oncol* 2021; **39**(36): 4049–60.

18. Kater Arnon P, Owen C, Moreno C, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *NEJM Evidence* 2022; **1**(7): EVIDoa2200006.

19. Eyre TA, Kirkwood AA, Gohill S, et al. Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis. *Br J Haematol* 2019; **185**(4): 656–69.

20. Ahn IE, Underbayev C, Albitar A, et al. Clonal evolution leading to ibrutinib resistance in chronic lymphocytic leukemia. *Blood* 2017; **129**(11): 1469–79.

21. Forconi F, Lanham SA, Chiodin G. Biological and clinical insight from analysis of the tumor B-cell receptor structure and function in chronic lymphocytic leukemia. *Cancers (Basel)* 2022; **14**(3).

22. Kater AP, Wu JQ, Kipps T, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. *J Clin Oncol* 2020; **38**(34): 4042–54.

Figure 1. CONSORT diagram
*Other includes receiving a medication/therapy not allowed by the protocol, receiving compassionate use venetoclax, death, stem cell transplant, thrombocytopenia, and withdrawal of consent.

Figure 2. Response rates (95% CI) for patients with R/R CLL treated with venetoclax monotherapy at Week 48
*PR needs to be confirmed later than 7 weeks or more for overall response.
BCRi, B-cell receptor pathway inhibitor; CR, complete remission; CRi, complete remission with incomplete blood recovery; nPR, nodular partial response; PR, partial response; R/R CLL, relapsed/refractory chronic lymphocytic leukaemia.

Figure 3. PFS and for the A) overall population and B) by prior BCRi exposure, and OS for the C) overall population and D) by prior BCRi exposure
BCRi, B-cell receptor pathway inhibitor; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Efficacy of venetoclax in patients with relapsed/refractory chronic lymphocytic leukaemia: analysis of the international single-arm phase 3b trial VENICE-1

Author list:

Arnon P. Kater, MD[1], Önder Arslan, MD[2], Fatih Demirkan, MD[3], Yair Herishanu, MD[4], Burhan Ferhanoglu, MD[5], Marcos Gonzalez Diaz, MD[6], Brian Leber, MD[7], Marco Montillo, MD[8], Panayiotis Panayiotidis, MD[9], Davide Rossi, PhD[10,11], Alan Skarbnik, MD[12,13], Adrian Tempescul, PhD[14], Mehmet Turgut, MD[15], Clemens H. Mellink, PhD[16], Anne-Marie F. van der Kevie-Kersemaekers, PhD[17], Stuart Lanham, PhD[18], Ben Sale, MSc[18], Luis Del Rio, MSc[18], Relja Popovic, MD [19], Brenda J. Chyla, PhD[19], Todd Busman, MS[19], Viktor Komlosi, PhD[19], Xifeng Wang, PhD[19], Kavita Sail, PhD[19], German E. Pena, MD [19], Tamas Vizkelety, MD[19], Francesco Forconi, MD[18,20]

Author affiliations:

[1]Department of Hematology, Cancer Center Amsterdam, Lymphoma and Myeloma Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands [AP Kater, MD].

[2]Department of Hematology, Ankara University, Faculty of Medicine, Ankara, Turkey [Ö Arslan, MD].

[3]Department of Hematology, Dokuz Eylül University, Faculty of Medicine, İzmir, Turkey [F Demirkan, MD].

[4]Department of Hematology, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel [Y Herishanu, MD].

[5]Department of Hematology, Koç University Medical Faculty, Istanbul, Turkey [B Ferhanoglu, MD].

[6]Department of Hematology, Center for Cancer Research-IBMCC (USAL-CSIC), PI of CIBERONC, IBSAL-University Hospital, Salamanca, Spain [M Gonzalez Diaz, MD].

[7]Division of Hematology and Thromboembolism, Department of Medicine, McMaster University, Hamilton, Canada [B Leber, MD].

[8]Department of Haematology, Niguarda Cancer Center, Niguarda Hospital, Milan, Italy [M Montillo, MD].

[9]First Department of Propedeutic Internal Medicine, National and Kapodistrian University of Athens, Laikon University Hospital, Athens, Greece [P Panayiotidis, MD].

[10]Institute of Oncology Research, Università della Svizzera Italiana, Bellinzona, Switzerland [D Rossi, PhD].

[11]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland [D Rossi, PhD].

[12]Lymphoproliferative Disorders Program, Novant Health Cancer Institute, Charlotte, NC, USA [A Skarbnik, MD].

[13]John Theurer Cancer Center, Hackensack, NJ, USA [A Skarbnik, MD].

[14]Department of Clinical Hematology, University Teaching Hospital Brest, Brest, France [A Tempescul, PhD].

[15]Department of Hematology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey [M Turgut, MD].

[16]Department of Human Genetics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands [C Mellink, PhD].

[17]Department of Genetics, UMC Utrecht, Utrecht, The Netherlands [AMF van der Kevie-Kersemaekers, PhD].

[18]Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK [S Lanham, PhD; B Sale, MSc; L Del Rio, MSc; F Forconi, MD].

[19]AbbVie Inc., North Chicago, IL, USA [R Popovic, MD; BJ Chyla, PhD; T Busman, MS; V Komlosi, PhD; X Wang, PhD; K Sail, PhD; GE Pena, MD; T Vizkelety, MD].

[20]Haematology Department, Cancer Care Directorate, University Hospital Southampton NHS Trust, Southampton, UK [F Forconi, MD].

Corresponding author:

Name of Author: Francesco Forconi

Address: Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

Tel.: +44-2381205780

Email: f.forconi@soton.ac.uk

Target journal: ***Lancet Oncology***

Word count: 3545/3500

Tables/figures: 3 tables, 3 figures

References: 24/30

Research in context

Evidence before this study: We searched PubMed using the search terms "chronic lymphocytic leukemia", "clinical trials", "relapsed chronic lymphocytic leukemia", "refractory chronic lymphocytic leukemia", and "CLL and BCL-2" for studies published between Jan 1, 2011, and Dec 31, 2015. At the time this study was initiated in 2016, venetoclax had received its first approval by the United States Food and Drug Administration (FDA) as monotherapy in patients with chronic lymphocytic leukaemia (CLL) with the 17p deletion (as detected by an FDA-approved test) who have received ≥1 prior therapy; venetoclax was also nearing approval for similar indications in the EU and Canada. The efficacy and safety data supporting approval of venetoclax monotherapy was derived from the following phase I–II studies in relapsed/refractory CLL (R/R CLL) patients: [1] the first-in-human (FIH) study (NCT01328626) that enrolled 116 patients with R/R CLL who received target dosages of 150–1200 mg/day, in which patients had an overall objective response rate (ORR) of 79% with 20% of patients achieving either complete response (CR) or complete response with incomplete count recovery (CRi); [2] a single arm phase II trial (NCT01889186; Clinicaltrials.gov) that enrolled 107 patients with R/R CLL, with 17p deletion, who received the eventual venetoclax label-dose of 400 mg/day, that resulted in an ORR of 79% and CR/CRi rate of 8%; [3] and a phase II trial (NCT02141282; Clinicaltrials.gov) that again evaluated 400 mg/day of venetoclax in patients with CLL that had relapsed or were refractory to the B-Cell receptor targeted agents ibrutinib (n=41) or idelalasib (n=13), that resulted in an ORR of 61% and 50% and CR rate of 8% and 0%, respective to each prior therapy. The findings were broadly similar regardless of patient characteristics, including those often associated with poor chemoimmunotherapy outcomes, such as the presence of the 17p deletion or fludarabine resistance; however, there was a slightly lower ORR among the patients with prior B-cell receptor-associated kinase inhibitors (BCRi) therapy. Since venetoclax therapy in R/R CLL was, at that time, being further developed as a combination regimen with CD20 antibodies, this study (VENICE-I) was intended to provide data across a large population of R/R CLL patients with diverse molecular features and prior treatment experience.

Added value of this study: This phase 3b trial of venetoclax monotherapy is the largest and has the longest follow-up for any trial evaluating venetoclax monotherapy and demonstrated deep and durable responses and prolonged overall survival, irrespective of prior BCRi. With dose modifications, the safety profile of venetoclax was manageable even given this extended period of follow-up, and many patients transitioned to an extension study to continue receiving venetoclax therapy.

Implications of all the available evidence: These data suggest that patients with R/R CLL, including those with prior BCRi experience, can derive significant clinical benefit from venetoclax monotherapy, even over extended periods of time.

Abstract (299/300 words)

Background: Most patients with chronic lymphocytic leukaemia (CLL) progress following (re)treatment with targeted- or chemoimmuno-therapy and have limited subsequent treatment options. Response levels to single-agent venetoclax in the relapsed setting were unknown. This study aimed to assess venetoclax efficacy in B-cell receptor-associated kinase inhibitors (BCRi)-naïve or prior BCRi-treated patients.

Methods: The phase 3b VENICE-I trial (NCT02756611) assessed efficacy and safety of venetoclax monotherapy in adults with relapsed/refractory (R/R) CLL, stratified by previous exposure to a BCRi. Eligible participants were aged ≥18 years with previously treated R/R CLL. Presence of del17p or *TP53* aberrations and prior BCRi treatment were permitted. Patients received 5-week ramp-up to 400 mg of oral venetoclax and were treated for ≤108 weeks with 2 years follow-up after discontinuation, or optional extended access. The primary efficacy endpoint was complete remission (CR) rate (CR + CR with incomplete marrow recovery [CRi]) in BCRi-naïve patients. Analyses used the intent-to-treat population.

Findings: This study enrolled 258 patients (first patient first visit June 22, 2016; last patient last visit March 11, 2022 [study completion]) with R/R CLL; 191 were BCRi-naïve and 67 were BCRi-experienced. Overall, 70% (180) of patients were male. Median (IQR) follow-up in the overall cohort, and BCRi-naïve and -experienced groups was 49·5 (47·2, 54·1), 49·2 (47·2, 53·2), and 49·7 (47·4, 54·3) months, respectively. Of 191 BCRi-naïve patients, 66 (35%) achieved CR + CRi; 18/67(27%) BCRi-experienced patients achieved CR + CRi. Grade ≥3 TEAEs and SAEs were reported in 79% (n=203/258) and 53% (n=136/258) of patients, respectively. The most common TEAE and SAE was neutropenia (37%; n=96/258). and pneumonia (8%; n=21/258), respectively. There were 13 (5%) deaths reported due to AEs. No new safety signals were identified.

Interpretation: These data demonstrate deep and durable responses with venetoclax monotherapy in patients with R/R CLL, including BCRi-experienced patients.

Funding: AbbVie-sponsored study.

Introduction

Treatment with targeted agents, including B-cell receptor-associated kinase inhibitors (BCRi) has improved survival outcomes of chronic lymphocytic leukaemia (CLL).[1-3] However, BCRi need to be taken until progression, and are associated with long-term toxicities.[4,5] B-cell lymphoma-2 (BCL-2) protein, another therapeutic target, is overexpressed in CLL.[6,7] Venetoclax,a first-in-class orally bioavailable BCL-2 inhibitor approved for the treatment of CLL,[8] acts by inducing rapid apoptosis in CLL cells.[6,9] It has demonstrated deep and durable responses in patients with relapsed/refractory (R/R) CLL, including those with poor prognostic features.[10-12] Single-agent venetoclax can induce overall response rates (ORR) ≥65% in these patients, with a manageable safety profile.[3,10,13] Although BCRi refractoriness can impact rate and duration of response (DoR) to venetoclax, data indicate venetoclax is efficacious even after BCRi failure.[3,13-15] The efficacy and safety of fixed-duration venetoclax combinations has been established in R/R and previously untreated CLL,[16-18] but long-term data on single-agent venetoclax treatment in R/R CLL, including BCRi R/R CLL, are sparse.

VENICE-I (NCT02756611) is the largest, multicentre, phase 3b trial designed to assess venetoclax monotherapy efficacy and safety in BCRi-naïve and BCRi-experienced patients with R/R CLL, irrespective of 17p deletion or *TP53* mutation status. Here, we report the VENICE-I primary efficacy analyses and minimal residual disease (MRD) responses.

Methods

Study design and participants

This open-label, single arm, phase 3b study (NCT02756611) was conducted at 59 sites across 21 countries in Europe and North America (**Appendix page 16**).

The starting dose for venetoclax was 20 mg orally once daily, increased weekly to 50 mg, 100 mg, 200 mg, up to the target of 400 mg once daily, which was the dose administered for up to 108 weeks, unless earlier discontinuation occurred due to unacceptable toxicity, disease progression, or lack of tolerability. Dose interruptions and/or dose reductions were applied for haematological and other toxicities related to venetoclax (details in the **Appendix page 5**). In countries where venetoclax was not commercially available, patients who continued to derive benefit after 2 years' treatment were able to extend treatment for ≤3 additional years in the extension phase of the trial. Patients were followed for disease progression and survival for 2 years after venetoclax discontinuation.

The review boards of participating institutions approved the study protocol, which was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Eligible participants were aged ≥18 years with previously treated R/R CLL (progression on prior treatment determined by investigator medical assessment), had a creatinine clearance rate of ≥50 mL/min, and required treatment according to International Workshop on Chronic Lymphocytic Leukaemia 2008 criteria. Presence of del17p or *TP53* aberrations and prior BCRi treatment were permitted. Patients who had developed Richter transformation or prolymphocytic leukaemia, and those who had received prior venetoclax were not eligible. Prior to the start of venetoclax, patients could not have received antineoplastic biologic agents ≤30 days; any anticancer therapy (except BCRi) or radiotherapy within five half-lives or 14 days; steroids or strong/moderate Cytochrome P450 3A (CYP3A) inducers ≤7 days; or strong/moderate CYP3A inhibitors or BCRi ≤3 days. Full inclusion and exclusion criteria are listed in **Appendix pages 2 and 3**. Disease response was assessed at screening, and Weeks 24, 36, and 48. Assessment was conducted by study investigator according to the 2008 modified iwCLL criteria. Laboratory tests were conducted at screening to assess eligibility and included full blood chemistry/haematology panel.

Procedures

Patient sex, race, and ethnicity were provided by the individual investigators.

The starting dose for venetoclax was 20 mg orally once daily (tablet form), increased weekly to 50 mg, 100 mg, 200 mg, then to the target dose of 400 mg once daily. Computed tomography imaging was performed on all patients at screening and also at Week 48, alongside BM biopsy and aspirate to confirm response in patients with CR/CRi.

Blood chemistry/haematology tests were also performed at 6–8 and 24 hours following the first dose increase in patients with low to high risk of TLS.

Each patient could withdraw from the study at any time. Investigators could also discontinue a patient from study drug treatment at any time if the investigator considered it necessary for any reason, including: unsatisfactory response to therapy requirement for other cancer treatment during the study period; unacceptable toxicity; the patient became pregnant while on study; drug protocol non-compliance, and determination that it is in the patient's best interest.

QoL was assessed using the EuroQol 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L), the Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) questionnaire, and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale (detailed in **Appendix page 4**).

Detailed methods for MRD and molecular assessments can be found in **Appendix page 3.** Array-based genomic complexity (GC) status was defined by numbers of copy number aberrations (CA): non-complex (0–2); low (3–4); or high (≥5) as has been previously defined.[17]

Adverse events (AEs) were monitored and recorded throughout the study. Recommended dose modifications are listed in **Appendix page 5**. Safety analyses were performed on patients who received ≥1 dose of venetoclax. Safety evaluations included drug exposure, AEs, serious AEs, deaths, and laboratory parameters. AE analyses only included treatment emergent AEs (TEAEs) with onset on or after first dose and ≤30 days after last dose. AE severity was rated according to NCI Common Terminology Criteria for Adverse Event (NCI CTCAE v4·03).

Outcomes

The primary efficacy endpoint was complete remission (CR) rate (defined as the proportion of patients achieving a CR or CR with incomplete marrow recovery [CRi] as their best response [per investigator assessment] based on iwCLL NCI-WG criteria) in BCRi-naïve patients.

Secondary efficacy endpoints included CR/CRi in BCRi-experienced patients, progression-free survival (PFS [days from first dose to earliest disease progression or death]), ORR (CR+CRi+nPR+PR rates), DoR (days from first response to earliest recurrence or progressive disease), time to progression (TTP; days from first dose to earliest disease progression), and overall survival (OS; days from first dose to death). Exploratory efficacy endpoints included assessment of MRD and rate of MRD negativity (defined as the proportion of patients with <1 CLL cell per 10,000 leukocytes ($<10^{-4}$) in peripheral blood (PB) and bone marrow (BM). Patient-reported quality of life (QoL), assessed through the FACT-Leu, FACIT-F, and EQ-5D-5L instruments, was an additional efficacy endpoint; scores for all QoL assessments were calculated according to their respective scoring manuals.

Statistical analysis

The study is registered with ClinicalTrials.gov (NCT02756611). At protocol initiation a sample size of 250 patients was calculated to provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favour of an alternative hypotheses that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate). Prior to readout, the primary hypothesis was revised and a sample size of 190 patients who had not previously received BCRi therapy was required to reject the null hypothesis of a CR/CRi rate ≤6% at approximately 80% power based on an exact test for single proportions using a two-sided alpha of 5%. As the study aimed to enrol approximately 250 patients, up to 60 patients with BCRi experience could be included allowing descriptive reporting of outcomes for this subgroup within the trial population.

Analyses were performed on the overall cohort and prespecified subgroups (BCRi-naïve and BCRi-experienced). Primary efficacy analysis was conducted once all patients had completed a Week 48 disease assessment. All patients who received ≥1 dose of venetoclax were included; patients who

had not achieved CR/CRi at Week 48 were considered nonresponders in the calculation of CR rate. CR/CRi rate and ORR and were evaluated using point estimates and corresponding 95% confidence intervals (CI) were calculated based on binomial distribution.

All time-to-event endpoints were analysed for the whole study period using Kaplan–Meier methodology; patients who did not experience an event (progressive disease or death, where appropriate) were censored at their last adequate disease assessment date (or last known alive date for OS). Descriptive statistics were calculated for baseline demographics and clinical characteristics, QoL, and safety events.

Additional post hoc efficacy analyses (univariate and multivariable) were conducted to assess prominent prognostic factors (*IGHV* status~~,~~ *TP53* status, del17p status, or GC), on outcomes. These were conducted in patients with available baseline molecular results (patients without a specimen or inconclusive results were excluded). Odds ratios (ORs) and hazard ratios (HRs) were calculated using univariate, multiple logistic and Cox proportional hazards regressions.

Main data analysis was performed using SAS v9·4 software; exploratory analyses were done using R 4·3·1.

Role of the funding source

AbbVie sponsored the study, contributed to the analysis and interpretation of the data, and AbbVie participated in the writing, review, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this manuscript. No honoraria or payments were made for authorship. Venetoclax is being developed in a collaboration between AbbVie and Genentech.

Results

Overall, 287 patients were screened and 258 patients with R/R CLL were enrolled (first patient first visit June 22, 2016; last patient last visit March 11, 2022); 191 were BCRi-naïve and 67 were BCRi-experienced (full details in **Appendix page 6**). The most common reasons for venetoclax discontinuation were enrolment into the extension study (19%; n=48/258; whereby patients were recorded as having discontinued venetoclax treatment in VENICE-1 so they could receive venetoclax in the subsequent study) and progressive disease (19%; n=48/258); this was followed by AE (15%; n=39/258; **Figure 1**). Median duration of treatment exposure was 108 weeks (inter-quartile range [IQR] 73·7–190·0) overall, 110 weeks (IQR 85·9–202·1) in the BCRi-naïve group, and 107 weeks (IQR 24·3–119·6) in the BCRi-experienced group. Median (IQR) follow-up in the overall cohort, and BCRi-naïve and -experienced groups was 49·5 (47·2, 54·1), 49·2 (47·2, 53·2), and 49·7 (47·4, 54·3) months,

respectively. All enrolled patients received ≥1 dose of venetoclax and were included in the efficacy and safety analyses.

Patients were predominantly male (70%; n=180/258), with a median age of 68 years (IQR 61–74; **Table 1**). Median number of prior CLL therapies was two overall, one in the BCRi-naïve group, and three in the BCRi-experienced group. Among 67 patients with prior BCRi experience, 50 received prior ibrutinib, 26 received prior idelalisib, and two patients received acalabrutinib; some patients received both ibrutinib and idelalisib. Eighty-two reasons were recorded for the discontinuation of the 78 BCRi treatments; 23 were progressive disease and 47 were toxicities. Median treatment duration of prior BCRi was 9·0 months (IQR 4·0–20·7; n=67). Centrally assessed *IGHV* mutation, del17p, and *TP53* mutations were reported for 27% (n=42/153), 20% (n=35/172), and 24% (n=42/173) of patients with mutation data in the overall population, respectively; 20% (n=35/172) of patients with data for GC had high GC (≥5 CAs). Concordance rates for centrally assessed and locally assessed genomic characteristics can be seen in **Appendix page 8**.

Overall, CR/CRi rate at Week 48 was 33% (95% CI 26·9–38·6; n=84/258; **Figure 2**). The CR/CRi rate in BCRi-naïve patients (primary endpoint) was 35% (95% CI 27·8−41·8; n=66/191) with a rate ratio of 1.29 (95% CI, 0.764, 2.166) CR/CRi rate was 27% (95% CI 16·8–39·1; n=18/67) in the BCRi-experienced group. CR/CRi rate was similar across subgroups based on sex, race, age group, Eastern Cooperative Oncology Group (ECOG) status, prior number of therapies, absolute lymphocyte count, and baseline node size (**Appendix page 17**). Overall CR/CRi rate was 28% (n=11/39) and 38% (n=35/93) in patients with and without a *TP53* mutation, and 27% (n=12/44) and 34% (n=59/172) in patients with and without del17p per investigator-assessed mutation status. CR/CRi rates were comparable regardless of number of prior therapies in the overall population (one therapy, 34% [n=36/106]; two therapies, 33% [n=21/64]; more than two therapies, 31% [n=27/88]). ORR was 80% (n=206/258) overall, 85% (n=163/191) in the BCRi-naïve group, and 64% (n=43/67) in the BCRi-experienced group (**Table 2**). Post hoc analyses of the effect of prognostic factors – *IGHV* and *TP53* mutation, del17p, and GC status – as centrally assessed at study entry on clinical outcomes are reported in the **Appendix** (**pages 9 and 10 and pages 19–21)**.

The overall median DoR for patients who achieved a response (n=205) was 25·1 months (95% CI 19·4–28·6). Median DoR was 24·4 months (95% CI 18·1−27·9) in the BCRi-naïve population (n=162) and 28·6 months (95% CI 16·8−45·3) in the BCRi-experienced population (n=43; **Appendix page 23**). The overall TTP (n=258) was 28·3 months (95% CI 23·4–32·6; **Appendix page 23**). Median TTP was 24·6 months (95% CI 21·9–30·6) for the BCRi-naïve population (n=191) and 33·8 months (95% CI 23·4–not estimable) for the BCRi-experienced population (n=67).

In the overall cohort, 92/258 (36%) patients had PFS events, with median PFS of 28·3 months (95% CI 22·2–30·5; **Figure 3A**). In the BCRi-naïve and BCRi-experienced groups, 63/191 (33%) and 29/67 (43%) had PFS events and median PFS was 28·8 months (95% CI 22·2–31·8) and 23·4 months (95% CI 16·8–33·8), respectively (**Figure 3B**). In the overall cohort and BCRi-naïve and -experienced groups, 70/258 (27%), 45/191 (24%), and 25/67 (37%) patients, respectively, died; median OS was not reached in the overall, BCRi-naïve or BCRi-experienced populations (**Figure 3C and 3D**). Five-year survival estimates were 71% (95% CI 65·0−76·5), 75% (95% CI 67·5−80·6), and 61% (95% CI 47·7−71·6) for the overall, BCRi-naïve, and BCRi-experienced patients, respectively.

For the overall cohort, patients showed a mean (standard deviation [SD]) improvement of 8·5 (14·4) points (95% CI 6·5–10·5; n=204) in the EQ-5D VAS score; this decreased to 7·1 (14·6) points (95% CI 4·8–9·4; n=156) by Week 108. In the BCRi-naïve and -experienced groups, mean (SD) improvements in EQ-5D VAS scores were 8·6 (14·53; n=164) and 8·0 (14·18; n=43), respectively at Week 48, and 7·3 (14·37; n=124) and 6·1 (15·75; n=32), respectively at Week 108. FACT-Leu leukaemia subscale scores also improved at Week 48 in the overall cohort, BCRi-naïve group and BCRi-experienced group (mean [SD] scores of 6·8 [7·99], n=202; 6·5 [8·19], n=161; and 7·8 [7·20], n=41, respectively) and at Week 108 (6·0 [9·08], n=153; 6·2 [8·77], n=122; and 5·2 [10·33], n=31, respectively); similarly, the FACT-Leu trial outcome index showed improvements at Week 48 in overall (9·8 [14·23]; n=201), BCRi-naïve (9·0 [14·52]; n=160), and BCRi-experienced (13·0 [12·71]; n=201) populations, and changes were maintained at Week 108. FACT-G Total Score improvements were seen at Week 48 in the overall cohort (5·5 [12·34], n=200) and in the BCRi-naïve and -experienced groups (4·8 [12·19; n=160] and 8·0 [12·74; n=40], respectively) and all were maintained at Week 108. At Week 48, patients showed a mean (SD) improvement of 4·9 (9·43) points (95% CI 3·6–6·2; n=205) from baseline in the FACIT-fatigue score, which decreased by Week 108 to 3·3 (9·96) points (95% CI 1·7–4·8; n=154).

A total of 198 patients had at least one on-therapy PB MRD assessment, with 60 patients missing ≥1 assessment. Overall, 104/258 patients (40% of intent-to-treat [ITT] population, 53% of patients with MRD assessments) and 99/206 responders (48% of ITT population, 50% of patients with MRD assessments) had undetectable MRD (uMRD) by PB assessment. Of the 84 total patients with CR/CRi and known MRD levels, 46 (55%) had uMRD by PB assessment. A total of 76 patients had a BM MRD assessment, including 51/84 patients with CR/CRi. Among the 84 patients who had a CR/CRi, 23 (27%) were determined to be uMRD by BM; rates of uMRD were similar for the BCRi-naïve (26%; n=17) and BCRi-experienced (33%; n=6) groups.

A listing of all AEs of any grade (Grade 3–5 and grade 1 and 2 ≥10%) are included in **Table 3**. The majority of patients (98%; n=254/258) experienced a TEAE of any grade; most frequently reported were neutropenia (43%; n=112/258), diarrhoea (39%; n=100/258), and nausea (27%; n=69/258). Grade ≥3 TEAEs were reported in 79% (n=203/258) of patients, most common being neutropenia (37%; n=96/258), anaemia (13%; n=34/258), and thrombocytopenia (13%; n=33/258); and serious TEAEs were reported in 53% (n=136/258) of patients, most commonly being pneumonia (8%; n=21/258) and febrile neutropenia (6%; n=15/258). For the overall cohort (n=248) there were 70 (27%) deaths during the study, of which 21 (8%) occurred within 30 days of the last dose of venetoclax, and 13 (5%) were attributable to AEs (details in **Appendix page 11**); 33 (13%]) deaths were due to disease progression. A total of six symptomatic COVID-19 infections (2%), including two SAEs were reported among BCRi-naïve patients. No patients discontinued venetoclax or died due to COVID-19 infection.

Generally, patients in the BCRi-naïve group experienced lower rates of TEAEs than patients with previous BCRi exposure, especially for grade 4 TEAEs (30% vs 57%), SAEs (50% vs 60%), and deaths (24% vs 37%). However, grade 5 TEAEs and AEs leading to death were observed in 11 BCRi-naïve patients [6%] versus two BCRi-experienced [3%]. Both treatment groups experienced TEAEs leading to venetoclax dose interruption, reduction, or discontinuation at similar rates (**Table 3**). Full reasons for discontinuation are provided in **Appendix page 12.**

At study entry, most patients were categorised as at high risk of TLS and 98% (n=252/258) received prophylaxis for TLS, including hydration (98%; n=252/258), allopurinol (90%; n=231/258), and rasburicase (28%; n=71/258). Overall, 118 of 258 (46%) patients were hospitalised during ramp-up to receive TLS prophylaxis; 46% in both the BCRi-naïve (n=87/191) and BCRi-experienced (n=31/67) groups. No patients had clinical TLS, or grade 4 or 5 AEs of TLS. Thirteen (5%) patients met Howard criteria for laboratory TLS, of which TEAEs of TLS were reported for six (2%) patients (two patients with grade 1 events and four with grade 3 events). Two patients had serious TLS events, and venetoclax dose interruptions and reductions due to TLS occurred in three and one patients, respectively; no patients discontinued due to TLS.

Overall, 145 of 258 (56%) patients experienced neutropenia-related AEs of special interest. Granulocyte colony-stimulating factor was administered to 119 of 258 (46%) patients for blood count recovery. BCRi-naïve patients experienced lower rates of febrile neutropenia than BCRi-experienced patients (4% [n=8/191] vs 15% [n=10/67], respectively). Neutropenia AEs were most commonly managed using dose interruptions (n=36/258; 14%) and reductions (n=10/258; 4%). One patient discontinued venetoclax due to neutropenia. A total of 50 of 258 (19%) patients had serious

infections, including opportunistic infections, and of these, 43 patients had grade ≥3 infections (grade 4, n=6; grade 5, n=2). The most common serious infections were pneumonia (8%; n=21/258), lower respiratory tract infection (2%; n=4/258), and influenza (1%; n=3/258). Overall, 50 of 258 patients (19%) developed neoplasms (benign, malignant, or unspecified); 20% (n=39/191) in the BCRi-naïve group and 16% (n=11/67) in the BCRi-experienced group.

A full listing of subsequent anticancer treatments is provided in **Appendix page 13**.

Discussion

This study demonstrated a CR/CRi rate of 35% in R/R in BCRi-naïve CLL patients. Twenty-six percent of the study population were BCRi-experienced patients. CR/CRi rate and ORR of 27% and 64%, respectively, suggest encouraging efficacy of venetoclax monotherapy in this population. Venetoclax monotherapy was previously investigated in phase 2 trials with R/R BCRi-experienced CLL; CR/CRi rates were lower than in the current study, although ORR and median PFS were not different.[3,13] The results of this study are consistent with a real-world retrospective analysis of heavily pretreated R/R BCRi-experienced CLL patients receiving venetoclax monotherapy, where 85% responded and 23% achieved CR/CRi.[19]

Prior exposure to BCRi and number of prior therapies have been associated with reduced response rates in previous clinical trials and real-world studies[14,15,19] and suggest that early use of venetoclax should be the preferred choice; however, the current BCRi-experienced cohort ORR was 64%, suggesting that patients still benefit following BCRi discontinuation.

Post hoc PFS analyses were performed to stratify patients' risk using *IGHV* status, del17p status, and GC.[20,21] Interestingly, patients with mutated *IGHV* had longer PFS than those with unmutated. Unlike BCRi-naïve patients, in BCRi-experienced patients, *IGHV* status, *TP53* status, and GC appeared not to associate with differential outcomes. Patients also achieved uMRD less frequently with mutated *IGHV* versus unmutated; these findings contrast with previously published studies of venetoclax in R/R CLL[22] and should be evaluated in larger cohorts and cautiously interpreted at present. In the BCRi-naïve group, there appeared to be differences in each stratified analysis, an observation that does not hold true for BCRi-experienced patients. However, fewer lines of therapy and fewer negative prognostic factors present in the BCRi-naïve group may have contributed to this. These findings warrant additional analysis and will be explored in future publications.

The safety profile reported here was consistent with previously published venetoclax data in R/R CLL.[3,4,10,13] No clinical TLS AEs were observed, and no patients discontinued venetoclax due to TLS. Although common, neutropenia was managed with brief interruptions/reductions in venetoclax dosing.

Limitations of this study include the single-arm study design without comparator, and lack of statistical power for subgroup analyses.

This phase 3b trial VENICE-I indicates venetoclax monotherapy can achieve deep and durable responses in patients with R/R CLL, including BCRi-experienced patients; high rates of CR/CRi were observed over long-term follow-up, with no new safety signals identified. This is the largest study of venetoclax monotherapy to be carried out in this setting and is consistent with the data previously reported, supporting early use of venetoclax within CLL.

Acknowledgements:

AbbVie sponsored the study, (NCT02756611); contributed to the analysis and interpretation of the data; and AbbVie participated in the writing, review, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this manuscript. No honoraria or payments were made for authorship. Medical writing support was provided by Hayley Ellis, PhD, of Fishawack Facilitate Ltd, part of Avalere Health, funded by AbbVie. The authors wish to thank the patients and their families, the study coordinators, and support staff. The authors would also like to acknowledge all investigators of the NCT02756611 study. The authors would also like to thank Adam Luo for contribution to statistical analyses.

Data sharing statement:

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select “Home.”

Authorship contributions: Study concept and Design: Arnon Kater, Brenda Chyla, Viktor Komlosi, German Pena, Francesco Forconi.

Clinical data collection: Arnon Kater, Onder Aslan, Fatih Demirkan, Yair Herishanu, Burhan Ferhanoglu, Marcos Gonzalez Diaz, Brian Leber, Marco Montillo, Panayiotis Panayiotidis, Davide Rossi, Alan Skarbnik, Adrian Tempescul, Mehemt Turgut and Francesco Forconi.

Exploratory data and PRO data collection, and statistical analyses: Clemens Mellink, Anne-Marie vander Kevie-Kersemaekers, Stuart Lanham, Ben Sale, Luis Del Rio, Relja Popovic, Brenda Chyla, Todd Busman, Xifeng Wang, Kavita Sail and Tamas Vizkelety.

All authors participated in the analysis and interpretation of results, and manuscript preparation. At least two authors (Brenda J. Chyla, Todd Busman, and Tamas Vizkelety) have accessed and verified the raw data.

Declaration of Interests:

Arnon P. Kater: AK performed advisory board function and received research funding from Astra Zeneca, Janssen, Roche/Genentech, AbbVie, BMS, LAVA.

Önder Arslan: AbbVie speaker and advisory board member.

Fatih Demirkan: Nothing to disclose.

Yair Herishanu: Honoraria; AbbVie, Janssen, Astra-Zeneca, Roche, Medison. Advisory Board; AbbVie, Jansen, Astra-Zeneca, Medison, Lilly. Research grant; Janssen.

Burhan Ferhanoglu: Advisory board: Takeda Pharmaceuticals, Janssen, and Pfizer. AbbVie speaker fee.

Marcos Gonzalez Diaz: AbbVie speaker.

Brian Leber: Speakers bureau/honoraria: AbbVie, Alexion, AMGEN, Astellas, Astex, BMS/Celgene, Jazz, Janssen Novartis, Otsuka, Paladin, Pfizer, Roche, Treadwell. Consulting fees : AbbVie, Novartis, Pfizer.

Marco Montillo: AbbVie speaker Bureau, Honoraria. Janssen Honoraria.

Panayiotis Panayiotidis: Research support grant: AbbVie; Honoraria/speaker's bureau: AbbVie, AstraZeneca, Roche.

Davide Rossi: Nothing to disclose.

Alan Skarbnik: Consultancy and/or Speaker fees from: Alexion, AbbVie, AstraZeneca, ADC Therapeutics, Beigene, Bristol-Myers Squibb, Celgene, Epizyme, Genentech, Janssen, Jazz Therapeutics, Kite Pharma, Lilly, MorphoSys, Novartis, Pharmacyclics, SeaGen, GenMab, TG Therapeutics. Payments for presentations, lectures etc: AstraZeneca, ADC Therapeutics, Abbvie, Beigene, Genentech, GenMab, Jazz Therapeutics, Janssen, Kite Pharma, Lilly, Pharmacyclics, SeaGen, TG Therapeutics. Data Safety Monitoring Board: Alexion.

Adrian Tempescul: Nothing to disclose.

Mehmet Turgut: Nothing to disclose.

Clemens Mellink: AbbVie Inc. funded microarray analysis.

Anne-Marie van der Kevie-Kersemaekers: AbbVie Inc. funded microarray analysis.

Stuart Lanham: Nothing to disclose.

Ben Sale: Nothing to disclose.

Luis Del Rio: Nothing to disclose.

Relja Popovic: AbbVie employee and may hold stock or options.

Brenda J. Chyla: AbbVie employee and may hold stock or options.

Todd Busman: AbbVie employee and may hold stock or options.

Viktor Komlosi: was an AbbVie employee at time of study and may hold stock or options.

Xifeng Wang: AbbVie employee and may hold stock or options.

Kavita Sail: AbbVie employee and may hold stock or options.

German E. Pena: AbbVie employee and may hold stock or options.

Tamas Vizkelety: AbbVie employee and may hold stock or options.

Francesco Forconi: Advisory board for BeiGene; Honoraria: Abbvie, Janssen-Cilag, Beigene, AstraZeneca; Speakers bureau: Abbvie, Janssen-Cilag, Astra-Zeneca; Travel and Accommodation: Abbvie, Janssen-Cilag, Beigene.

References

1. Byrd JC, Furman RR, Coutre SE, et al. Ibrutinib treatment for first-line and relapsed/refractory chronic lymphocytic leukemia: Final analysis of the pivotal phase Ib/II PCYC-1102 study. *Clin Cancer Res* 2020; **26**(15): 3918–27.

2. Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leukemia* 2019; **33**(4): 969–80.

3. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: An interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2018; **19**(1): 65–75.

4. Davids MS, Hallek M, Wierda W, et al. Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukemia. *Clin Cancer Res* 2018; **24**(18): 4371–9.

5. Perez-Carretero C, Gonzalez-Gascon YMI, Rodriguez-Vicente AE, et al. The evolving landscape of chronic lymphocytic leukemia on diagnosis, prognosis and treatment. *Diagnostics (Basel)* 2021; **11**(5).

6. Cimmino A, Calin GA, Fabbri M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci USA* 2005; **102**(39): 13944–9.

7. Calin GA, Dumitru CD, Shimizu M, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc Natl Acad Sci USA* 2002; **99**(24): 15524–9.

8. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2021; **32**(1): 23–33.

9. Del Gaizo Moore V, Brown JR, Certo M, Love TM, Novina CD, Letai A. Chronic lymphocytic leukemia requires BCL2 to sequester prodeath BIM, explaining sensitivity to BCL2 antagonist ABT-737. *J Clin Invest* 2007; **117**(1): 112–21.

10. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: Results from the full population of a phase ii pivotal trial. *J Clin Oncol* 2018; **36**(19): 1973–80.

11. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med* 2019; **380**(23): 2225–36.

12. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2016; **374**(4): 311–22.

13. Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood* 2018; **131**(15): 1704–11.

14. Roberts AW, Ma S, Kipps TJ, et al. Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables. *Blood* 2019; **134**(2): 111–22.

15. Innocenti I, Morelli F, Autore F, et al. Venetoclax in CLL patients who progress after B-cell Receptor inhibitor treatment: A retrospective multi-centre Italian experience. *Br J Haematol* 2019; **187**(1): e8–e11.

16. Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: Post-treatment follow-up of the MURANO phase III study. *J Clin Oncol* 2019; **37**(4): 269–77.

17. Al-Sawaf O, Zhang C, Lu T, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: Extended off-treatment follow-up from the randomized CLL14 study. *J Clin Oncol* 2021; **39**(36): 4049–60.

18. Kater Arnon P, Owen C, Moreno C, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *NEJM Evidence* 2022; **1**(7): EVIDoa2200006.

19. Eyre TA, Kirkwood AA, Gohill S, et al. Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis. *Br J Haematol* 2019; **185**(4): 656–69.

519 20. Ahn IE, Underbayev C, Albitar A, et al. Clonal evolution leading to ibrutinib resistance in
520 chronic lymphocytic leukemia. *Blood* 2017; **129**(11): 1469–79.
521 21. Forconi F, Lanham SA, Chiodin G. Biological and clinical insight from analysis of the tumor B-
522 cell receptor structure and function in chronic lymphocytic leukemia. *Cancers (Basel)* 2022; **14**(3).
523 22. Kater AP, Wu JQ, Kipps T, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic
524 leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from
525 the MURANO phase III study. *J Clin Oncol* 2020; **38**(34): 4042–54.

526

Figure 1. CONSORT diagram
*Other includes receiving a medication/therapy not allowed by the protocol, receiving compassionate use venetoclax, death, stem cell transplant, thrombocytopenia, and withdrawal of consent.

Figure 2. Response rates (95% CI) for patients with R/R CLL treated with venetoclax monotherapy at Week 48
*PR needs to be confirmed later than 7 weeks or more for overall response.
BCRi, B-cell receptor pathway inhibitor; CR, complete remission; CRi, complete remission with incomplete blood recovery; nPR, nodular partial response; PR, partial response; R/R CLL, relapsed/refractory chronic lymphocytic leukaemia.

Figure 3. PFS and for the A) overall population and B) by prior BCRi exposure, and OS for the C) overall population and D) by prior BCRi exposure
BCRi, B-cell receptor pathway inhibitor; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Table 1

Table 1. Demographic and disease characteristics

Characteristics	All patients N=258	BCRi-naïve n=191	BCRi-experienced n=67
Age			
Median age (IQR), years	68 (61–72)	68 (61–74)	69 (63–75)
≥65 years	164 (64)	118 (62)	46 (69)
Sex			
Male	180 (70)	136 (71)	44 (66)
Female	78 (30)	55 (29)	23 (34)
Race			
White	252 (98)	186 (97)	66 (99)
Black or African American	3 (1)	3 (2)	0
Asian	2 (1)	1 (1)	1 (1)
Other	0	0	0
Missing	1 (<1)	1 (1)	0
Ethnicity			
Not Hispanic or Latino	248 (96)	181 (95)	67 (100)
Hispanic or Latino	9 (3)	9 (5)	0
Missing	1 (<1)	1 (1)	0
ECOG PS			
0	142 (55)	110 (58)	32 (48)
1	95 (37)	67 (35)	28 (42)
2	21 (8)	14 (7)	7 (10)
Prior lines of CLL-directed treatments			
1	106 (41)	101 (53)	5 (7)
2	64 (25)	47 (25)	17 (25)
≥3	88 (34)	43 (23)	45 (67)
Number of prior lines anti-CLL, median (IQR)	2 (1–3)	1 (1–2)	3 (2–4)
Prior ibrutinib failure			
First line	3 (1)	NA	3 (4)
Second-line and beyond	47 (18)	NA	47 (70)
Not reported	208 (81)	191 (100)	17 (25)
Prior idelalisib failure			
First line	3 (1)	NA	3 (4)
Second-line and beyond	24 (9)	1 (1)*	23 (34)
Not reported	231 (90)	190 (99)	41 (61)
Fludarabine-experienced	157 (61)	112 (59)	45 (67)
Mutation presence (centrally assessed)†			
IGHV mutational status			
Mutated	42 (16)	30 (16)	12 (18)
Unmutated	111 (43)	86 (45)	25 (37)

Missing/indeterminate	105 (41)	75 (39)	30 (45)
17p deletion[‡]			
Present	35 (14)	20 (11)	15 (22)
Absent	137 (53)	107 (56)	30 (45)
Missing/indeterminate	86 (33)	64 (33)	22 (33)
TP53 mutation			
Present	42 (16)	28 (15)	14 (21)
Absent	131 (51)	100 (52)	31 (46)
Missing/indeterminate	85 (33)	63 (33)	22 (33)
Genomic complexity category			
High	35 (14)	21 (11)	14 (21)
Low	36 (14)	31 (16)	5 (8)
Non-complex	101 (39)	75 (39)	26 (39)
Missing	86 (33)	64 (34)	22 (33)
Absolute lymphocyte count			
$<25 \times 10^9$/L	122 (47)	86 (45)	36 (54)
$\geq 25 <100 \times 10^9$/L	92 (36)	71 (37)	21 (31)
$\geq 100 \times 10^9$/L	40 (16)	32 (17)	8 (12)
Not reported[§]	4 (2)	2 (1)	2 (3)
Largest lymph node diameter			
<5 cm	165 (64)	121 (63)	44 (66)
5–<10 cm	56 (22)	43 (23)	13 (19)
≥10 cm	31 (12)	23 (12)	8 (12)
Not reported[§]	6 (2)	4 (2)	2 (3)

Data are n (%) unless otherwise stated.

*Patient discontinued during ramp-up and prior to any post-baseline disease assessment.

[†]Mutation data were not mandatory for inclusion into the study.

[‡]Determined by array comparative genomic hybridisation.

[§]Values were not recorded ≤24 hours prior to venetoclax start.

BCRi, B-cell receptor pathway inhibitor; CLL, chronic lymphocytic leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; NA, not applicable.

Table 2

Table 2. Summary of response rates at Week 48 (all treated patients)

	All patients N=258	**BCRi-naïve n=191**	**BCRi-experienced n=67**
Best response			
CR	76 (29)	59 (31)	17 (25)
CRi	8 (3)	7 (4)	1 (1)
nPR	5 (2)	5 (3)	0
PR	117 (45)	92 (48)	25 (37)
SD	17 (7)	11 (6)	6 (9)
PD	9 (3)	3 (2)	6 (9)
No post-baseline disease assessment	26 (10)	14 (7)	12 (18)
Complete remission rate (CR/CRi), n (%) [95% CI]	84 (33) [26·9–38·6]	66 (35) [27·8–41·8]	18 (27) [16·8–39·1]
Partial remission rate (nPR + PR), n (%) [95% CI]	122 (47) [41·1–53·6]	97 (51) [43·5–58·1]	25 (37) [25·8–50·0]
Overall response rate (CR + CRi + nPR + PR)*, n (%) [95% CI]	206 (80) [74·4–84·6]	163 (85) [79·5–90·0]	43 (64) [51·5–75·5]

Data are n (%) unless otherwise stated.

*PR was confirmed later than 7 weeks or more for objective response.

BCRi, B-cell receptor inhibitor; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete marrow recovery; nPR, nodular partial remission; PR, partial remission; PD, progressive disease; SD, stable disease.

Table 3

Table 3. Summary of TEAEs (all treated patients)

	Grade 1 or 2 (≥10%)*			Grade 3			Grade 4			Grade 5		
	Total (N=258)	**BCRi-naïve (n=191)**	**BCRi-experienced (n=67)**	**Total (N=258)**	**BCRi-naïve (n=191)**	**BCRi-experienced (n=67)**	**Total (N=258)**	**BCRi-naïve (n=191)**	**BCRi-experienced (n=67)**	**Total (N=258)**	**BCRi-naïve (n=191)**	**BCRi-experienced (n=67)**
Any AE	245 (95)	178 (93)	67 (100)	105 (41)	89 (47)	16 (24)	85 (33)	49 (26)	36 (54)	13 (5)	11 (6)	2 (3)
Blood and lymphatic system disorders	72 (28)	54 (28)	18 (27)	71 (28)	62 (33)	9 (13)	55 (21)	33 (17)	22 (33)	1 (<1)	1 (1)	0
Anaemia	28 (11)	19 (10)	9 (13)	32 (12)	21 (11)	11 (16)	2 (1)	2 (1)	0	0	0	0
Aplasia pure red cell				1 (<1)	1 (1)	0	0	0	0	0	0	0
Autoimmune haemolytic anaemia				2 (1)	1 (1)	1 (2)	0	0	0	1 (<1)	1 (1)	0
Bone marrow failure				0	0	0	1 (<1)	1 (1)	0	0	0	0
Febrile neutropenia				11 (4)	4 (2)	7 (10)	6 (2)	3 (2)	3 (5)	0	0	0
Granulomatous lymphadenitis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Haemolysis				2 (1)	2 (1)	0	0	0	0	0	0	0
Haemolytic anaemia				1 (<1)	1 (1)	0	0	0	0	0	0	0
Immune thrombocytopenia				1 (<1)	1 (1)	0	1 (<1)	1 (1)	0	0	0	0
Intravascular haemolysis				0	0	0	0	0	0	1 (<1)	1 (1)	0
Leukocytosis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Leukopenia				0	0	0	1 (<1)	1 (1)	0	0	0	0
Lymphopenia				3 (1)	3 (2)	0	2 (1)	2 (1)	0	0	0	0
Neutropenia				57 (22)	49 (26)	8 (12)	39 (15)	22 (12)	17 (25)	0	0	0
Pancytopenia				1 (<1)	1 (1)	0	2 (1)	1 (1)	1 (2)	0	0	0
Thrombocytopenia				14 (5)	13 (7)	1 (2)	19 (7)	11 (6)	8 (12)	0	0	0
Cardiac disorders				9 (4)	6 (3)	3 (5)	2 (1)	2 (1)	0	3 (1)	3 (2)	0
Aortic valve disease				1 (<1)	0	1 (2)	0	0	0	0	0	0
Aortic valve stenosis				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Atrial fibrillation				1 (<1)	1 (1)	0	0	0	0	1 (<1)	1 (1)	0
Atrioventricular block				1 (<1)	1 (1)	0	0	0	0	0	0	0

Bifascicular block				1 (<1)	1 (1)	0	0	0	0	0	0	0
Bradycardia				0	0	0	1 (<1)	1 (1)	0	0	0	0
Cardiac arrest				0	0	0	1 (<1)	1 (1)	0	0	0	0
Cardiac failure				1 (<1)	1 (1)	0	0	0	0	0	0	0
Cardiac failure congestive				1 (<1)	0	1 (2)	0	0	0	0	0	0
Coronary artery disease				1 (<1)	1 (1)	0	0	0	0	1 (<1)	1 (1)	0
Myocardial infarction				0	0	0	0	0	0	1 (<1)	1 (1)	0
Ear and labyrinth disorders				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Deafness				1 (<1)	1 (1)	0	0	0	0	0	0	0
Vertigo				1 (<1)	0	1 (2)	0	0	0	0	0	0
Eye disorders	28 (11)	22 (12)	6 (9)	3 (1)	3 (2)	0	1 (<1)	0	1 (2)	0	0	0
Cataract				3 (1)	3 (2)	0	0	0	0	0	0	0
Eyelid function disorder				0	0	0	1 (<1)	0	1 (2)	0	0	0
Ocular hyperaemia				0	0	0	1 (<1)	0	1 (2)	0	0	0
Gastrointestinal disorders	158 (61)	112 (59)	46 (69)	22 (9)	17 (9)	5 (8)	1 (<1)	0	1 (2)	0	0	0
Abdominal pain				3 (1)	2 (1)	1 (2)	0	0	0	0	0	0
Constipation	33 (13)	18 (9)	15 (22)	1 (<1)	1 (1)	0	0	0	0	0	0	0
Dental caries				2 (1)	2 (1)	0	0	0	0	0	0	0
Diarrhoea	91 (35)	67 (35)	24 (36)	9 (4)	7 (4)	2 (3)	0	0	0	0	0	0
Inguinal hernia				3 (1)	2 (1)	1 (2)	0	0	0	0	0	0
Intestinal obstruction				1 (<1)	1 (1)	0	0	0	0	0	0	0
Nausea	67 (26)	46 (24)	21 (31)	2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Oral pain				1 (<1)	1 (1)	0	0	0	0	0	0	0
Rectal perforation				0	0	0	1 (<1)	0	1 (2)	0	0	0
Varices oesophageal				1 (<1)	1 (1)	0	0	0	0	0	0	0
Vomiting				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
General disorders and administration site conditions	118 (46)	80 (42)	38 (57)	14 (5)	7 (4)	7 (10)	1 (<1)	0	1 (2)	2 (1)	2 (1)	0
Asthenia	31 (12)	20 (11)	11 (16)	1 (<1)	0	1 (2)	0	0	0	0	0	0
Fatigue	40 (16)	24 (13)	16 (24)	6 (2)	3 (2)	3 (5)	0	0	0	0	0	0
General physical health deterioration				1 (<1)	0	1 (2)	0	0	0	0	0	0

Malaise				1 (<1)	1 (1)	0	0	0	0	0	0	0
Multiple organ dysfunction syndrome				0	0	0	0	0	0	2 (1)	2 (1)	0
Pain				1 (<1)	0	1 (2)	0	0	0	0	0	0
Pyrexia	49 (19)	33 (17)	16 (24)	4 (2)	3 (2)	1 (2)	1 (<1)	0	1 (2)	0	0	0
Hepatobiliary disorders				5 (2)	3 (2)	2 (3)	1 (<1)	0	1 (2)	0	0	0
Bile duct stone				1 (<1)	0	1 (2)	0	0	0	0	0	0
Biliary colic				1 (<1)	0	1 (2)	0	0	0	0	0	0
Cholangitis				1 (<1)	0	1 (2)	0	0	0	0	0	0
Cholelithiasis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Cholestasis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Gallbladder necrosis				0	0	0	1 (<1)	0	1 (2)	0	0	0
Hepatic cirrhosis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Liver disorder				1 (<1)	1 (1)	0	0	0	0	0	0	0
Immune system disorders				4 (2)	2 (1)	2 (3)	0	0	0	0	0	0
Drug hypersensitivity				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Hypersensitivity				1 (<1)	1 (1)	0	0	0	0	0	0	0
Hypogammaglobulinaemia				1 (<1)	0	1 (2)	0	0	0	0	0	0
Infections and infestations	163 (63)	120 (63)	43 (64)	45 (17)	29 (15)	16 (24)	6 (2)	6 (3)	0	2 (1)	2 (1)	0
Abscess limb				1 (<1)	0	1 (2)	0	0	0	0	0	0
Acute sinusitis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Arthritis bacterial				1 (<1)	0	1 (2)	0	0	0	0	0	0
Aspergillus infection				1 (<1)	1 (1)	0	0	0	0	0	0	0
Bronchiolitis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Bronchitis				1 (<1)	0	1 (2)	0	0	0	0	0	0
COVID-19				2 (1)	2 (1)	0	0	0	0	0	0	0
Cellulitis				3 (1)	2 (1)	1 (2)	0	0	0	0	0	0
Diverticulitis				1 (<1)	1 (1)	0	1 (<1)	1 (1)	0	0	0	0
Ear infection				1 (<1)	1 (1)	0	0	0	0	0	0	0
Endophthalmitis				0	0	0	1 (<1)	1 (1)	0	0	0	0
Epididymitis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Escherichia bacteraemia				1 (<1)	1 (1)	0	0	0	0	0	0	0

Escherichia infection				1 (<1)	1 (1)	0	0	0	0	0	0	0
Gastroenteritis				0	0	0	1 (<1)	1 (1)	0	0	0	0
Herpes zoster				2 (1)	2 (1)	0	0	0	0	0	0	0
Infection				1 (<1)	0	1 (2)	0	0	0	0	0	0
Influenza				1 (<1)	1 (1)	0	0	0	0	0	0	0
Localised infection				1 (<1)	1 (1)	0	0	0	0	0	0	0
Lower respiratory tract infection				3 (1)	3 (2)	1 (2)	0	0	0	0	0	0
Nasopharyngitis	38 (15)	30 (16)	8 (12)	1 (<1)	0	1 (2)	0	0	0	0	0	0
Neutropenic sepsis				0	0	0	1 (<1)	1 (1)	0	0	0	0
Osteomyelitis				1 (<1)	0	1 (2)	0	0	0	0	0	0
Pathogen resistance				1 (<1)	1 (1)	0	0	0	0	0	0	0
Pneumonia				18 (7)	10 (5)	8 (12)	2 (1)	2 (1)	0	0	0	0
Pneumonia pseudomonal				1 (<1)	0	1 (2)	0	0	0	0	0	0
Progressive multifocal leukoencephalopathy				1 (<1)	0	1 (2)	0	0	0	0	0	0
Pyelonephritis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Respiratory syncytial virus infection				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Respiratory tract infection				1 (<1)	0	1 (2)	0	0	0	0	0	0
Sepsis				1 (<1)	0	1 (2)	0	0	0	0	0	0
Septic shock				0	0	0	0	0	0	2 (1)	2 (1)	0
Sinusitis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Skin infection				1 (<1)	1 (1)	0	0	0	0	0	0	0
Staphylococcal infection				1 (<1)	1 (1)	0	0	0	0	0	0	0
Tonsillitis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Upper respiratory tract infection	47 (18)	36 (19)	11 (16)	2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Urinary tract infection				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Urosepsis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Injury, poisoning, and procedural complications	58 (23)	39 (20)	19 (28)	6 (2)	3 (2)	3 (5)	0	0	0	0	0	0
Contusion				1 (<1)	1 (1)	0	0	0	0	0	0	0
Fall				1 (<1)	1 (1)	0	0	0	0	0	0	0

Femoral neck fracture				1 (<1)	1 (1)	0	0	0	0	0	0	0
Hip fracture				2 (1)	0	2 (3)	0	0	0	0	0	0
Humerus fracture				1 (<1)	1 (1)	0	0	0	0	0	0	0
Infusion related reaction				1 (<1)	0	1 (2)	0	0	0	0	0	0
Limb injury				1 (<1)	0	1 (2)	0	0	0	0	0	0
Pelvic fracture				1 (<1)	1 (1)	0	0	0	0	0	0	0
Investigations	97 (38)	71 (37)	26 (39)	28 (11)	16 (8)	12 (18)	21 (8)	11 (6)	10 (15)	0	0	0
ALT increased				0	0	0	1 (<1)	0	1 (2)	0	0	0
AST increased				4 (2)	4 (2)	0	1 (<1)	0	1 (2)	0	0	0
Blood alkaline phosphatase increased				1 (<1)	0	1 (2)	0	0	0	0	0	0
Blood LDH increased				3 (1)	2 (1)	1 (2)	0	0	0	0	0	0
Blood phosphorus increased				1 (<1)	1 (1)	0	0	0	0	0	0	0
Blood uric acid increased				1 (<1)	1 (1)	0	0	0	0	0	0	0
Cardiac murmur				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Gamma-glutamyltransferase increased				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
General physical condition abnormal				0	0	0	1 (<1)	0	1 (2)	0	0	0
Haemoglobin decreased				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Hepatic enzyme increased				1 (<1)	1 (1)	0	0	0	0	0	0	0
Immunoglobulins decreased				1 (<1)	0	1 (2)	0	0	0	0	0	0
International normalised ratio increased				1 (<1)	0	1 (2)	0	0	0	0	0	0
Lipase increased				0	0	0	1 (<1)	0	1 (2)	0	0	0
Lymphocyte count decreased				5 (2)	4 (2)	1 (2)	3 (1)	3 (2)	0	0	0	0
Lymphocyte count increased				1 (<1)	0	1 (2)	0	0	0	0	0	0
Neutrophil count decreased				10 (4)	6 (3)	4 (6)	12 (5)	7 (4)	5 (8)	0	0	0
Platelet count decreased				6 (2)	4 (2)	2 (3)	4 (2)	1 (1)	3 (5)	0	0	0
Weight decreased				1 (<1)	0	1 (2)	0	0	0	0	0	0
Weight increased				1 (<1)	0	1 (2)	0	0	0	0	0	0

White blood cell count decreased				5 (2)	3 (2)	2 (3)	1 (<1)	1 (1)	0	0	0	0
Metabolism and nutrition disorders	101 (39)	73 (38)	28 (42)	24 (9)	16 (8)	8 (12)	7 (3)	3 (2)	4 (6)	0	0	0
Cachexia				1 (<1)	0	1 (2)	0	0	0	0	0	0
Decreased appetite				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Fluid retention				1 (<1)	0	1 (2)	0	0	0	0	0	0
Hypercalcaemia				0	0	0	1 (<1)	0	1 (2)	0	0	0
Hyperglycaemia				1 (<1)	0	1 (2)	1 (<1)	0	1 (2)	0	0	0
Hyperkalaemia				3 (1)	3 (2)	0	1 (<1)	0	1 (2)	0	0	0
Hyperphosphataemia				4 (2)	2 (1)	2 (3)	0	0	0	0	0	0
Hypertriglyceridaemia				0	0	0	1 (<1)	0	1 (2)	0	0	0
Hyperuricaemia				0	0	0	2 (1)	2 (1)	0	0	0	0
Hypoalbuminaemia				3 (1)	2 (1)	1 (2)	0	0	0	0	0	0
Hypocalcaemia				3 (1)	3 (2)	0	0	0	0	0	0	0
Hypoglycaemia				0	0	0	1 (<1)	0	1 (2)	0	0	0
Hypokalaemia				3 (1)	2 (1)	1 (2)	1 (<1)	1 (1)	0	0	0	0
Hypomagnesaemia				1 (<1)	1 (1)	0	0	0	0	0	0	0
Hyponatraemia				5 (2)	2 (1)	3 (5)	0	0	0	0	0	0
Hypophosphataemia				6 (2)	6 (3)	0	0	0	0	0	0	0
Tumour lysis syndrome				4 (2)	2 (1)	2 (3)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	87 (34)	62 (33)	25 (37)	9 (4)	6 (3)	3 (5)	0	0	0	0	0	0
Arthralgia	37 (14)	24 (13)	13 (19)	0	0	0	0	0	0	0	0	0
Back pain	33 (13)	20 (11)	13 (19)	2 (1)	2 (1)	0	0	0	0	0	0	0
Bone pain				1 (<1)	1 (1)	0	0	0	0	0	0	0
Haematoma muscle				1 (<1)	0	1 (2)	0	0	0	0	0	0
Osteoarthritis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Osteoporosis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Pain in extremity				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Spinal pain				1 (<1)	0	1 (2)	0	0	0	0	0	0
Tenosynovitis				1 (<1)	1 (1)	0	0	0	0	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38 (15)	28 (15)	10 (15)	16 (6)	14 (7)	2 (3)	7 (3)	4 (2)	3 (5)	1 (<1)	0	1 (2)
Adenocarcinoma				1 (<1)	1 (1)	0	0	0	0	0	0	0
Adenoma benign				1 (<1)	1 (1)	0	0	0	0	0	0	0
Bladder cancer				1 (<1)	1 (1)	0	0	0	0	0	0	0
Breast cancer				1 (<1)	1 (1)	0	0	0	0	0	0	0
CNS lymphoma				0	0	0	1 (<1)	0	1 (2)	0	0	0
CLL transformation				1 (<1)	1 (1)	0	0	0	0	0	0	0
CML				1 (<1)	1 (1)	0	0	0	0	0	0	0
Diffuse large B-cell lymphoma				1 (<1)	1 (1)	0	1 (<1)	1 (1)	0	0	0	0
Hepatocellular carcinoma				1 (<1)	1 (1)	0	0	0	0	0	0	0
Infected neoplasm				0	0	0	1 (<1)	0	1 (2)	0	0	0
Lung adenocarcinoma				1 (<1)	1 (1)	0	1 (<1)	1 (1)	0	0	0	0
Myelodysplastic syndrome				2 (1)	2 (1)	0	3 (1)	2 (1)	1 (2)	0	0	0
Prostate cancer				2 (1)	2 (1)	0	0	0	0	0	0	0
Prostate cancer metastatic				1 (<1)	0	1 (2)	0	0	0	0	0	0
Rectal adenocarcinoma				1 (<1)	0	1 (2)	0	0	0	0	0	0
Skin neoplasm bleeding				0	0	0	0	0	0	1 (<1)	0	1 (2)
SQ cell carcinoma				1 (<1)	1 (1)	0	0	0	0	0	0	0
SQ cell carcinoma of skin				1 (<1)	1 (1)	0	0	0	0	0	0	0
Nervous system disorders	63 (24)	41 (22)	22 (33)	9 (4)	7 (4)	2 (3)	3 (1)	1 (1)	2 (3)	2 (1)	1 (1)	1 (2)
Dizziness				3 (1)	2 (1)	1 (2)	0	0	0	0	0	0
Facial paralysis				0	0	0	1 (<1)	0	1 (2)	0	0	0
Haemorrhage intracranial				0	0	0	0	0	0	1 (<1)	0	1 (2)
Headache				2 (1)	0	2 (3)	0	0	0	0	0	0
Ischaemic stroke				0	0	0	1 (<1)	0	1 (2)	1 (<1)	1 (1)	0
Parkinson's disease				1 (<1)	1 (1)	0	0	0	0	0	0	0
Polyneuropathy				1 (<1)	1 (1)	0	0	0	0	0	0	0
Sciatica				1 (<1)	1 (1)	0	0	0	0	0	0	0
Seizure				1 (<1)	1 (1)	0	0	0	0	0	0	0
Somnolence				0	0	0	1 (<1)	1 (1)	0	0	0	0

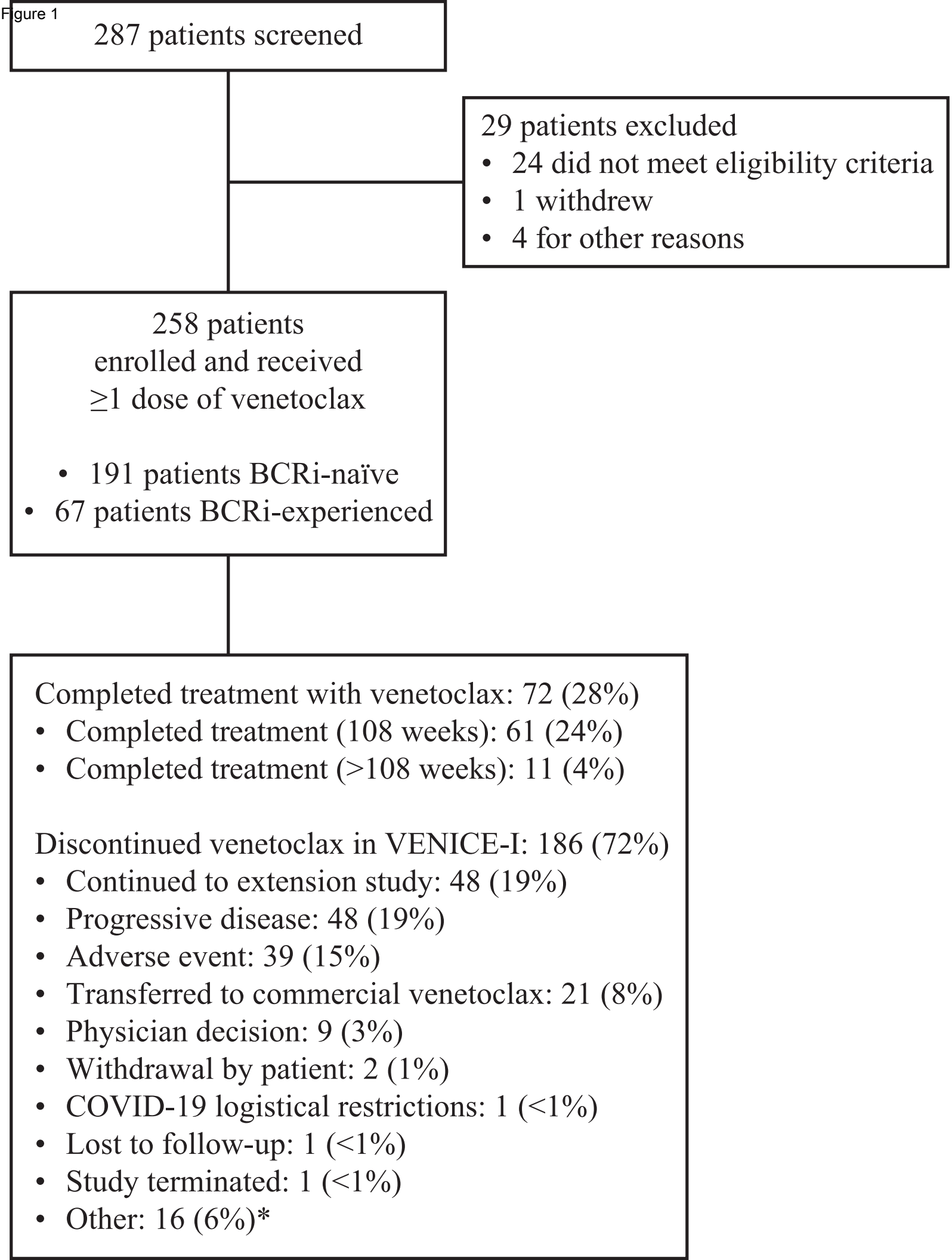
Syncope				3 (1)	3 (2)	0	0	0	0	0	0	0
Psychiatric disorders	34 (13)	19 (10)	15 (22)	4 (2)	1 (1)	3 (5)	0	0	0	0	0	0
Confusional state				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Depression				1 (<1)	0	1 (2)	0	0	0	0	0	0
Mental status changes				1 (<1)	0	1 (2)	0	0	0	0	0	0
Renal and urinary disorders	30 (12)	22 (12)	8 (12)	2 (1)	2 (1)	0	0	0	0	0	0	0
Chronic kidney disease				1 (<1)	1 (1)	0	0	0	0	0	0	0
Urinary retention				1 (<1)	1 (1)	0	0	0	0	0	0	0
Reproductive system and breast disorders				2 (1)	2 (1)	0	1 (<1)	1 (1)	0	0	0	0
Benign prostatic hyperplasia				2 (1)	2 (1)	0	1 (<1)	1 (1)	0	0	0	0
Prostatic pain				1 (<1)	1 (1)	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	111 (43)	78 (41)	33 (49)	20 (8)	12 (6)	8 (12)	4 (2)	2 (1)	2 (3)	2 (1)	2 (1)	0
Acute respiratory failure				0	0	0	2 (1)	1 (1)	1 (2)	0	0	0
Atelectasis				1 (<1)	0	1 (2)	0	0	0	0	0	0
Bronchiectasis				1 (<1)	1 (1)	0	0	0	0	0	0	0
COPD				1 (<1)	1 (1)	0	0	0	0	0	0	0
Cough	51 (20)	36 (19)	15 (22)	4 (2)	2 (1)	2 (3)	0	0	0	0	0	0
Dyspnoea				8 (3)	6 (3)	2 (3)	0	0	0	0	0	0
Dyspnoea exertional				1 (<1)	1 (1)	0	0	0	0	0	0	0
Epistaxis				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Lung disorder				1 (<1)	1 (1)	0	0	0	0	0	0	0
Oropharyngeal pain				1 (<1)	1 (1)	0	0	0	0	0	0	0
Pharyngeal disorder				0	0	0	1 (<1)	0	1 (2)	0	0	0
Pharyngeal swelling				1 (<1)	1 (1)	0	0	0	0	0	0	0
Pleural effusion				1 (<1)	0	1 (2)	0	0	0	1 (<1)	1 (1)	0
Pneumonitis				1 (<1)	0	1 (2)	0	0	0	0	0	0
Pulmonary embolism				0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (1)	0
Respiratory failure				1 (<1)	1 (1)	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	99 (38)	69 (36)	30 (45)	7 (3)	5 (3)	2 (3)	0	0	0	0	0	0
Erythema multiforme				1 (<1)	1 (1)	0	0	0	0	0	0	0

Rash				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Skin lesion				2 (1)	2 (1)	0	0	0	0	0	0	0
Skin ulcer				2 (1)	1 (1)	1 (2)	0	0	0	0	0	0
Vascular disorders	39 (15)	30 (16)	9 (13)	17 (7)	11 (6)	6 (9)	2 (1)	2 (1)	0	0	0	0
Aneurysm				1 (<1)	1 (1)	0	0	0	0	0	0	0
Aortic intramural haematoma				0	0	0	1 (<1)	1	0	0	0	0
Deep vein thrombosis				0	0	0	1 (<1)	1 (1)	0	0	0	0
Hypertension				14 (5)	8 (4)	6 (9)	0	0	0	0	0	0
Hypertensive crisis				1 (<1)	1 (1)	0	0	0	0	0	0	0
Hypotension				1 (<1)	1 (1)	0	0	0	0	0	0	0
Jugular vein thrombosis				1 (<1)	1 (1)	0	0	0	0	0	0	0

*Missing data for Grade 1 or 2 AEs were either not reported or occurred in <10% of the overall cohort.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; SQ, squamous.

Figure 1


287 patients screened
29 patients excluded
• 24 did not meet eligibility criteria
• 1 withdrew
• 4 for other reasons
258 patients
enrolled and received
≥1 dose of venetoclax
• 191 patients BCRi-naïve
• 67 patients BCRi-experienced
Completed treatment with venetoclax: 72 (28%)
• Completed treatment (108 weeks): 61 (24%)
• Completed treatment (>108 weeks): 11 (4%)
Discontinued venetoclax in VENICE-I: 186 (72%)
• Continued to extension study: 48 (19%)
• Progressive disease: 48 (19%)
• Adverse event: 39 (15%)
• Transferred to commercial venetoclax: 21 (8%)
• Physician decision: 9 (3%)
• Withdrawal by patient: 2 (1%)
• COVID-19 logistical restrictions: 1 (<1%)
• Lost to follow-up: 1 (<1%)
• Study terminated: 1 (<1%)
• Other: 16 (6%)*

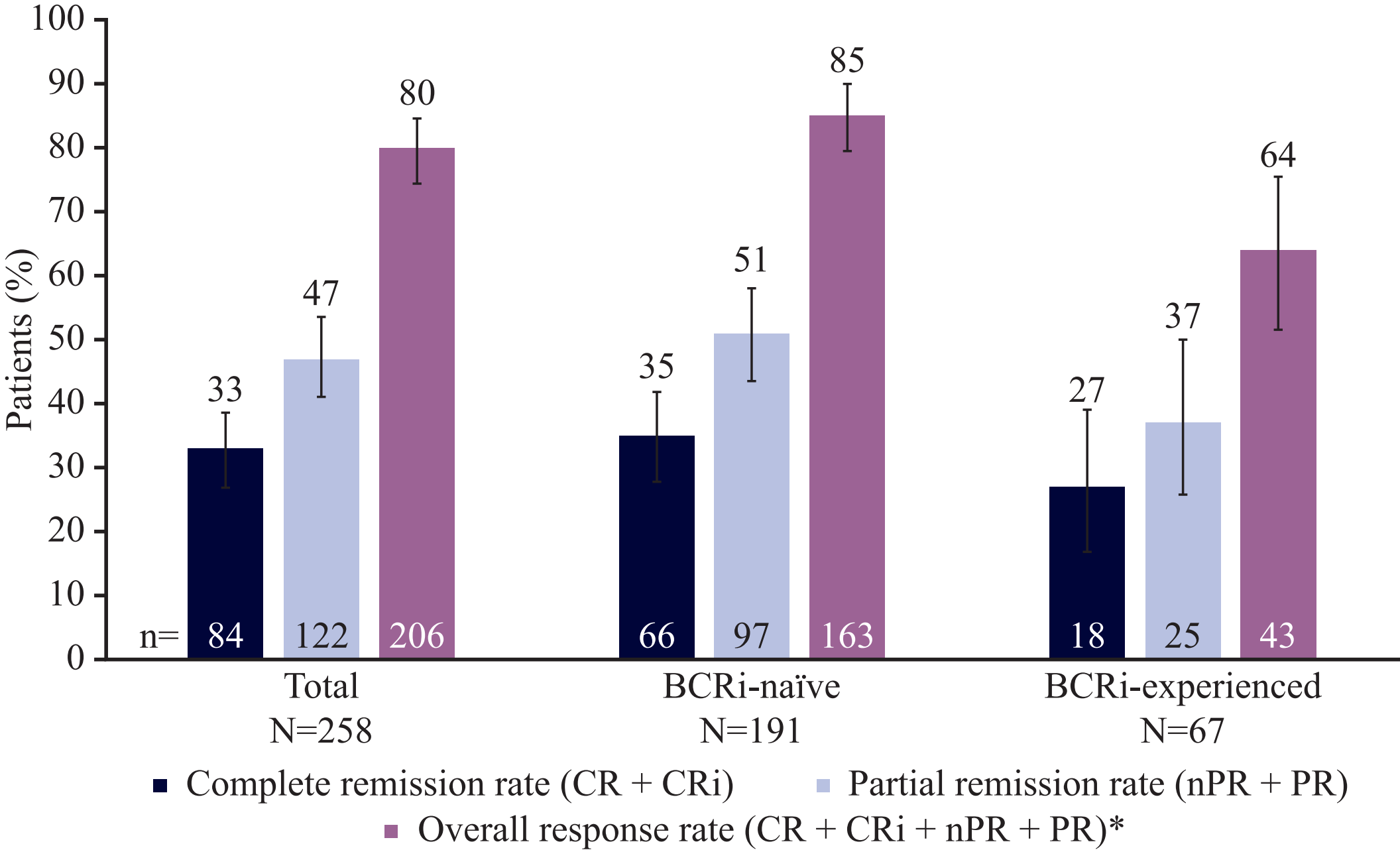
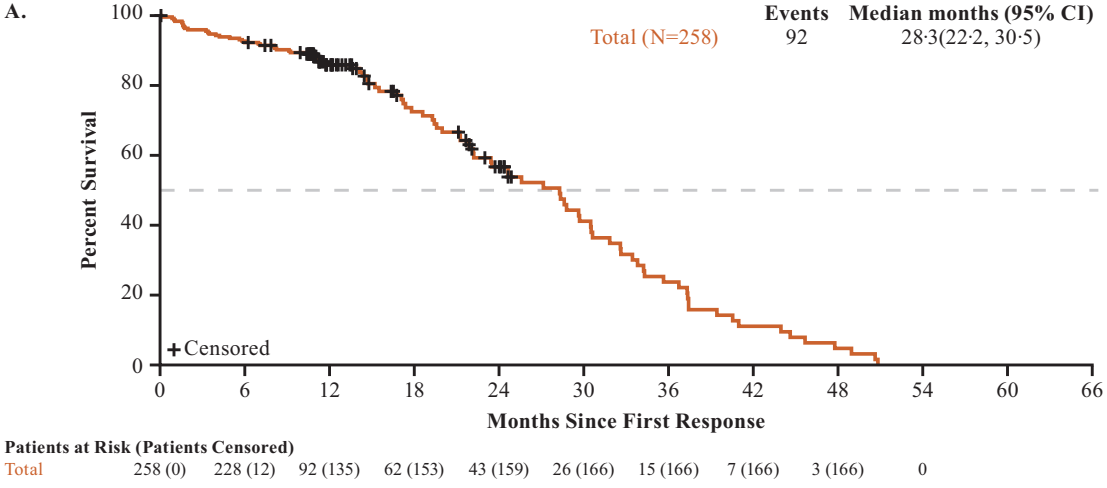
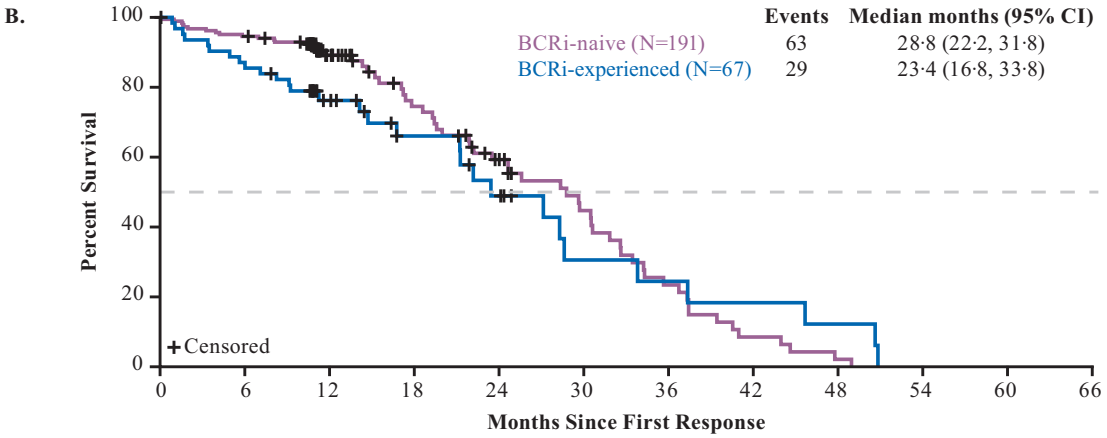

Patients (%)
100
90
80
70
60
50
40
30
20
10
0
n=
84
122
206
66
97
163
18
25
43
33
47
80
35
51
85
27
37
64
Total
N=258
BCRi-naïve
N=191
BCRi-experienced
N=67
Complete remission rate (CR + CRi)
Partial remission rate (nPR + PR)
Overall response rate (CR + CRi + nPR + PR)*

Figure 3



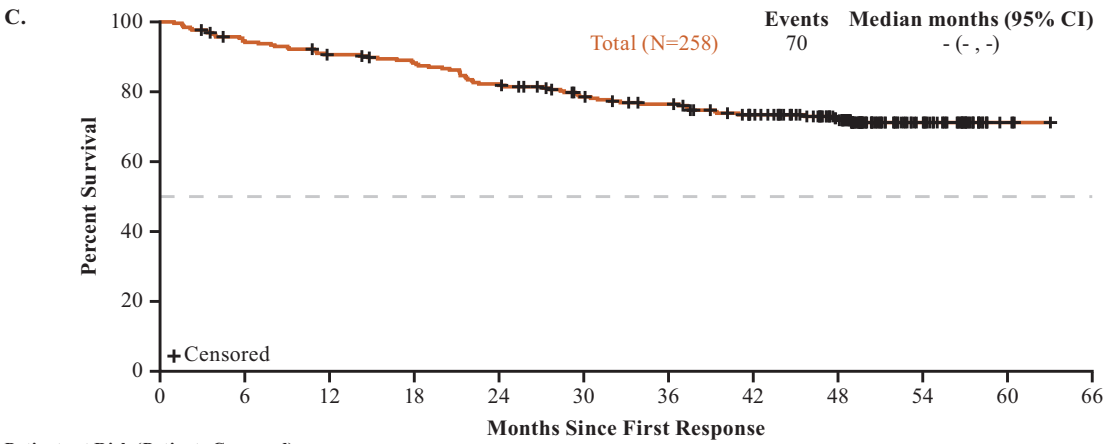
Patients at Risk (Patients Censored)

Total	258 (0)	228 (12)	92 (135)	62 (153)	43 (159)	26 (166)	15 (166)	7 (166)	3 (166)	0



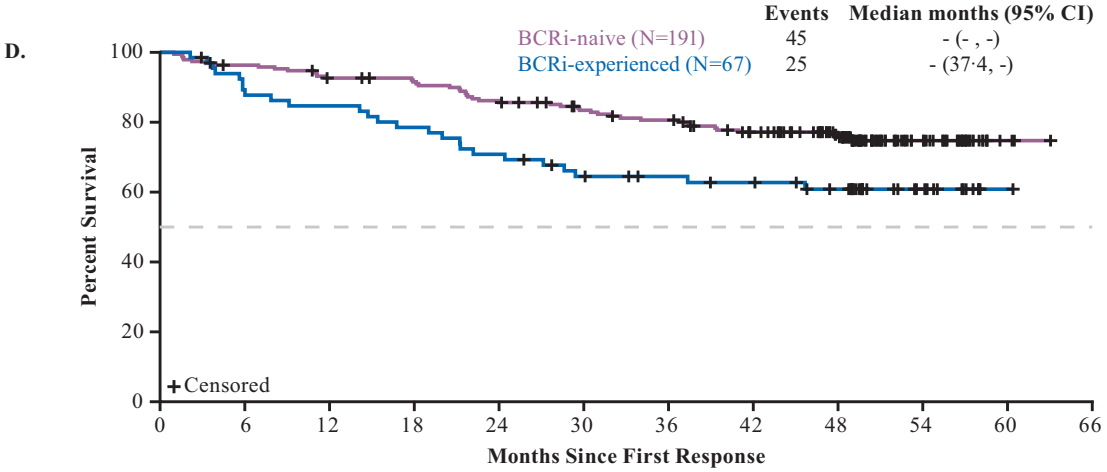
Patients at Risk (Patients Censored)

BCRi-naive	191 (0)	174 (7)	65 (109)	45 (120)	32 (124)	21 (128)	11 (128)	4 (128)	1 (128)	0
BCRi-experienced	67 (0)	54 (5)	27 (26)	17 (33)	11 (35)	5 (38)	4 (38)	3 (38)	2 (38)	0



Patients at Risk (Patients Censored)

Total	258 (0)	241 (3)	229 (5)	221 (7)	205 (7)	189 (15)	180 (19)	163 (29)	132 (57)	47 (141)	4 (184)	0



Patients at Risk (Patients Censored)

BCRi-naive	191 (0)	183 (1)	174 (3)	170 (5)	159 (5)	149 (11)	143 (12)	128 (21)	102 (45)	35 (111)	3 (143)	0
BCRi-experienced	67 (0)	58 (2)	55 (2)	51 (2)	46 (2)	40 (4)	37 (7)	35 (8)	30 (12)	12 (30)	1 (41)	0

1.0 Title Page

Clinical Study Protocol M15-550

Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)

Incorporating Administrative Change 1 (GLOBAL) and Amendments 0.01 (US Only), 0.01.01 (US Only) and 0.01.01.01 (US Only)

AbbVie Investigational Product:	Venetoclax (ABT-199, GDC-0199)
Date:	06 June 2018
Development Phase:	3b
Study Design:	Open-label, single arm, Phase IIIB, multi-center study
EudraCT Number:	2015-003667-11
Investigators:	Investigator Information on file at AbbVie
Sponsor:	AbbVie*
Sponsor/Emergency Contact:	[redacted] MD, PhD Medical Director, [redacted] Global Medical Affairs AbbVie Neuhofstrasse 23 CH-6341 Baar Switzerland Phone: Fax: Email: [redacted] AND [redacted] MD Medical Director AbbVie 26525 North Riverwoods Blvd. Mettawa, IL 60060 USA Phone: Email: [redacted]

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice, with the latest version of the Declaration of Helsinki and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	24 February 2016
Amendment 0.01	28 April 2016
Administrative Change 1 (GLOBAL)	30 June 2016
Amendment 0.01.01	03 August 2017

The purpose of this amendment is to:

- Revise the contact details on the front page of the protocol.

  Rationale: *To change the phone number to Sponsor/Emergency Contact* [redacted] *MD.*

- Revise Section 1.3 - List of Abbreviations and terms of definitions.

  Rationale: *To change 'absolute lymphocyte count' to 'Absolute Lymphocyte Count' with initial capital letters to be consistent with the other abbreviations.*

  Rationale: *To add the abbreviation for Bone Marrow (BM) to the list of abbreviations since this abbreviation was inadvertently excluded from the list of abbreviations in prior versions of the protocol.*

  Rationale: *To delete Serum Glutamic Pyruvic Transaminase from the list of abbreviations since this abbreviation is not mentioned in the protocol.*

- Revise Section 3.0 Introduction - Venetoclax Clinical Data

  Rationale: *To update the Venetoclax Clinical Data section to align with the most recent version of the Investigator's Brochure.*

- Revise Section 4.0 Study Objective and Section 5.3.3 - Efficacy variables and Synopsis Section - Objectives - Secondary Objectives and Exploratory Objectives- Additional Exploratory Analyses.

  Rationale: *To change the level of Minimal Residual Disease (MRD) and the rate of MRD negativity from secondary endpoints to exploratory endpoints because a non-alpha controlled secondary is essentially exploratory.*

Rationale: *To clarify in this section that Minimal Residual Disease (MRD) will be assessed in the peripheral blood and bone marrow (BM) by flow cytometry and PCR.*

- Update Section 5.1 - Overall Study Design and Plan: Description, third paragraph and Synopsis - Study Sites.

  Rationale: *To add 6 sites to the study.*

- Update Section 5.1, fourth paragraph.

  Rationale: *To add a ± 2 day visit window as of Week 8.*

- Update Section 5.1, sixth paragraph.

  Rationale: *To clarify that Bone Marrow samples will be collected for subjects with Complete Response to confirm response.*

- Update Section 5.1, twelfth paragraph.

  Rationale: *To add that in countries where venetoclax is commercially available extension of therapy may not be allowed.*

- Revise Section 5.3.1.1 - Study Procedures - Physical Examination (Disease Assessment).

  Rationale: *To remove the requirement to evaluate lymph nodes at physical examinations at other visits than at screening and Weeks 24, 36 and 48.*

- Revise Section 5.3.1.1 - Study Procedures - Table 4 Clinical Laboratory Tests.

  Rationale: *A footnote was added to explain that Urea may be reported instead if BUN. This footnote was inadvertently excluded from the previous version of the protocol.*

- Revise Section 5.3.1.1 - Study Procedures - Disease Assessments (2008 Modified IWCLL NCI-WG Criteria) - first paragraph.

  Rationale: *To clarify that Bone marrow examinations at screening are not required but results will be recorded if available.*

- Revise Section 5.3.1.1 - Study Procedures - Disease Assessments (2008 Modified IWCLL NCI-WG Criteria) - third paragraph and Section 5.3.3.1 Primary Variables.

Rationale: *To clarify that if the CT is negative a bone marrow biopsy will be obtained to confirm clinical response. If a CT scan is performed and does not confirm a clinical response, a bone marrow biopsy should not be obtained.*

- Revise Section 5.3.1.1 - Study Procedures - Disease Assessments (2008 Modified IWCLL NCI-WG Criteria) - last paragraph.

  Rationale: *To add that for patients with only Partial Remission at Week 48, an additional CT and a bone marrow examination can be done between Week 48 and Week 108 to confirm Complete Response if there is a possibility that a patient is in Complete Remission based on laboratory tests and a disease assessment physical examination.*

- Revise Section 5.3.1.1 - Study Procedures - 30 Day Safety Visit.

  Rationale: *To clarify that If a subject has an ongoing AE or an unresolved clinically significant laboratory result 30 days following last dose of study drug, the site will attempt to provide follow-up until the AE has resolved to a ≤ Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.*

- Revise Section 5.1 - Study procedures - Extended Access Phase- and Synopsis - Methodology - Duration of Treatment.

  Rationale: *To add a new paragraph on the Extended Access Phase to explain that in countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy. The specific study assessments to be performed during these visits are detailed in Appendix E.*

- Revise Section 5.4.1 - Discontinuation of individual subjects.

  Rationale: *Clarify that each subject has the right to withdraw from the study and/or study drug treatment at any time.*

  Rationale: *Update the pregnancy verbiage to be in line with AbbVie's latest standard pregnancy language.*

- Revise Section 5.4.1 - Post treatment follow up calls.

Rationale: *To clarify that subjects will be followed for survival information every 6 months even if subjects had an event of progression, they require alternate therapy, etc.*

- A window (± 7 days) was added to the post treatment calls.
- Revise Section 5.5.2 - Identity of study drug - Table 6.

  Rationale: *To change venetoxlax to Venetoclax with a capital V.*
- Revise Section 6.1.7 - Data Monitoring Committee and Synopsis - Methodology.

  Rationale: *To explain that the Data Monitoring Committee (DMC) will review the safety data intermittently according to the DMC charter. Details of the DMC review are presented in the DMC charter. The separate charter has been created to provide detailed descriptions of the schedule of analyses and the DMC meetings.*
- Revise Section 6.1.8.2 - Dose Modifications Based on Toxicities - Table 7.

  Rationale: *To revise the footnote a. for clinical TLS to explain that Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias and/or seizures or sudden death.*
- Revise Section 7.0 - Protocol Deviations.

  Rationale: *To change the contact details for the Primary Contact to Anna Brooks, Study Project Manager I and Alternate Contact Eva Hermansson, Study Management Associate III.*
- Revise Section 8.1.2.2 - Secondary Efficacy Endpoints.

  Rationale: *To remove MRD analyses from this section as MRD analyses are changed to exploratory endpoints.*
- Add a new Section 8.1.2.3 - Exploratory Efficacy Endpoints.

  Rationale: *To add language explaining that the rate of MRD negativity in subjects will be summarized. This rate will be defined as the proportion of subjects who had MRD negativity status. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided. In addition, the relationship between venetoclax PK and efficacy parameters including MRD level and CR will be evaluated.*

- Revise Section 10.1 - Source Documents.

  Rationale: *To remove the below language that was duplicate in the previous version of the protocol:*

- "The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF."

- Revise Section 15.0 - Reference list.

  Rationale: *To add a reference for Investigator's Brochure version 9 is and remove the reference for Investigator's Brochure version 8.*

- Update Appendix B - List of signatories.

  Rationale: *To add [redacted] as the Study Project Manager and remove the previous Study Project Manager [redacted]*

- Revise Appendix D study activities.

  Rationale: *To add that Adverse Event/Concomitant medication assessment is to be done also at the following visits: within 72 hours of W2 D1, W3 D1, W4 D1 and W5 D1.*

  Rationale: *To separate the study activities list for Extended Access Visits from the main study activities list Appendix D. Appendix E is created to capture the main study activities and appendix E is created to capture the Extended Access Study Activities.*

  Rationale: *To be consistent with the changes and updates throughout the protocol.*

- Incorporate additional administrative changes.

An itemized list of all changes made to this protocol amendment can be found in Appendix K.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-550
Name of Study Drug: Venetoclax (ABT-199, GDC-0199)	**Phase of Development:** 3b
Name of Active Ingredient: Venetoclax	**Date of Protocol Synopsis:** 06 June 2018
Protocol Title: Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)	
Objectives: **Primary Objective:** The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). The primary efficacy endpoint will be measured by complete remission rate (Complete Remission Rate [CR] and Complete Remission with Incomplete Marrow Recovery [CRi]; CR + CRi) as assessed by the investigator, of the subjects who have not been previously treated with B-cell receptor inhibitor (BCRi) therapy. **Secondary Objectives:** The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and the CR rate in BCRi treated subjects. In addition, quality of life will be assessed using the following patient reported outcome (PRO) questionnaires: the EuroQoL 5 Dimensions (EQ-5D-5L) questionnaire, a measure of general health status, the Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu), a leukemia-specific health related quality of life for acute and chronic disease, and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). The safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated. **Exploratory Objectives:** The exploratory objectives are to evaluate the level of Minimal Residual Disease (MRD) and the rate of MRD negativity in the peripheral blood.	
Investigators: Multi-center	
Study Sites: Approximately 7 sites in the United States, 1 site in Puerto Rico, and approximately 67 sites globally.	
Study Population: Subjects with relapsed/refractory (R/R) CLL with or without the 17p deletion or TP53 mutation, including subjects with an unknown status, as well as R/R CLL subjects who have been previously treated with B-cell receptor inhibitor (BCRi) therapy.	
Number of Subjects to be Enrolled: Approximately 250 subjects	

Methodology:

This is a Phase 3b, single arm, open-label, multi-center study evaluating the efficacy of venetoclax in subjects with R/R CLL. All screening procedures must be performed within 28 days prior to initial study drug administration. A contrast computed tomography (CT) scan (or magnetic resonance imaging [MRI] if a CT with contrast is medically contraindicated) will be accepted if previously performed within 35 days prior to study drug administration, otherwise a CT scan (or MRI) must be performed within the screening period of 28 days. The starting dose of venetoclax is 20 mg once daily. The dose must be gradually increased over a 5 week period up to the daily dose of 400 mg. For all subjects, study visits will be conducted within 72 hours of dosing, on the day of dosing and the day after dosing during the dose titration phase. Please refer to Appendix D. Study visits will be reduced to a monthly frequency at Week 8, and at Week 48, they will be reduced to every 3 months until the end of study treatment (Week 108). In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. A Disease Assessment for clinical response by physical exam and hematologic assessments will be performed at Screening, Week 24, Week 36 and Week 48. To confirm the response, a CT scan will be performed at Week 48 on all subjects. Biospecimens will be collected at designated time points throughout the study to conduct research to better characterize the disease. MRD assessments will be performed by using peripheral blood specimens at Week 1 Day 1 (baseline), Week 24 and Week 48. When confirming a CR or CRi status per 2008 Modified International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute Working Group (IWCLL NCI WG) criteria with a bone marrow (BM) biopsy and aspirate, MRD assessment of the BM aspirate should also be performed. After treatment discontinuation, a final visit will be performed. Subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment follow-up calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

The Data Monitoring Committee (DMC) will review safety data intermittently according to the DMC charter.

Subsequent reviews may be conducted based on recommendations from the DMC or requests from the Sponsor. Details of the DMC review will be presented in the DMC charter.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

A subject will be eligible for study participation if he/she meets all of the following criteria:

1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
3. Subject has relapsed/refractory disease (received at least one prior therapy).
4. Diagnosis of CLL that meets published 2008 Modified IWCLL NCI-WG Guidelines and:
   - has an indication for treatment according to the 2008 Modified IWCLL NCI-WG criteria
   - has clinically measurable disease (lymphocytosis > 5×10^9/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam)
   - subjects with or without the 17p deletion or TP53 mutation are eligible.
   - subjects who have received prior B-cell receptor inhibitor therapy are also eligible (up to 60 subjects total in the study will be enrolled).

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

5. Adequate bone marrow function as follows:
   - hemoglobin ≥ 8.0 g/dL
   - platelets ≥ 25,000/mm^3 without any of the following:
     - transfusion support within 14 days of Screening
     - evidence of mucosal bleeding
     - known history of major bleeding episode within 3 months of Screening

Main Exclusion:

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject has developed Richter's transformation or Prolymphocytic leukemia (PLL)
2. Subject has previously received venetoclax.
3. History of active malignancies other than CLL within the past 2 years prior to first dose of venetoclax, with the exception of:
   - adequately treated in situ carcinoma of the cervix uteri
   - adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin
   - previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
4. Active and uncontrolled autoimmune cytopenias (within 2 weeks prior to Screening), including autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), despite low dose corticosteroids.
5. Prior allogeneic stem cell transplant.

Investigational Product:	Venetoclax: 10 mg, 50 mg and 100 mg tablet
Doses:	Venetoclax will be administered orally once daily (QD), continuously. The starting dose of venetoclax is 20 mg QD. After 1 week of treatment at 20 mg QD, the dose will be escalated to 50 mg QD followed by subsequent increases, each after 1 week, to 100 mg QD, 200 mg QD and the target dose of 400 mg QD.
Mode of Administration:	Oral
Reference Therapy:	Not applicable.
Doses:	Not applicable.
Mode of Administration:	Not applicable.

Duration of Treatment: Subjects may continue receiving venetoclax for up to 2 years provided they continue to tolerate the drug, have no evidence of disease progression (based on investigator assessment), do not have unacceptable toxicity and do not meet any of the criteria for subject discontinuation. After treatment discontinuation, subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy.

Criteria for Evaluation:

Efficacy:

Disease response will be assessed by the investigator, based on laboratory results and physical examinations using the 2008 Modified IWCLL NCI-WG criteria for Tumor Response including CT imaging and bone marrow biopsy and aspirate for subject with CR to confirm the response (or MRI in the case CT is medically contraindicated).

All measurable disease must be documented at Screening by physical examination, laboratory testing, and CT scan (or MRI in the case CT is medically contraindicated). During the study, clinical disease assessments will take place at Week 24, Week 36, and Week 48. To confirm the response, a CT scan will be performed at Week 48.

Minimal Residual Disease (MRD):

A peripheral blood specimen will be collected from all subjects at Week 1 Day 1 (baseline), Week 24 and Week 48 to determine the level of minimal residual disease. When confirming a CR/CRi status per 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy and aspirate, MRD assessment of the BM aspirate should also be performed. The level of MRD and MRD negativity will be assessed. MRD negativity in the 2008 Modified IWCLLNCI-WG criteria is defined as the presence of less than one CLL cell per 10,000 leukocytes (or below 10^{-4}).

Pharmacokinetics:

A single pharmacokinetic (PK) blood sample will be collected from each subject and analyzed for plasma venetoclax concentration.

Safety:

Adverse event monitoring, vital signs, physical examination, and laboratory assessments will be evaluated.

Statistical Methods:

The study analyses will be descriptive. All subjects participating in the study who received at least one dose of venetoclax will be included in the analyses unless otherwise noted in the separate, statistical analysis plan (SAP).

Statistical Methods (Continued):

Efficacy:

The following efficacy endpoints will be analyzed: Complete Remission rate (CR + CRi), Overall Response Rate (ORR), Duration of Overall Response (DOR), Duration of Progression-Free Survival (PFS) and Overall Survival (OS):

Complete Remission Rate (CR) and Complete Remission with Incomplete Marrow Recovery (CRi)

Defined as the proportion of subjects who achieved a CR or CRi (all subjects and previously BCRi treated subjects).

Overall Response Rate (ORR)

Defined as the proportion of subjects with an overall response (complete remission plus partial remission).

Duration of Response (DOR)

Defined as the number of days from the date of first response (per the 2008 Modified IWCLL NCI-WG criteria) to the date of disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Time to Progression (TTP)

Defined as the number of days from the date of first dose of venetoclax to date of disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Duration of Progression-Free Survival (PFS)

Defined as the number of days from the date of first dose of venetoclax to the date of disease progression or death, whichever occurs first. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Overall Survival (OS)

Defined as number of days from the date of first dose of venetoclax to the date of death.

Additional Exploratory Analyses Include:

Minimal Residual Disease (MRD) Level and Negativity Status:

The level of MRD and the rate of MRD negativity will be assessed in the peripheral blood of all subjects at Week 1 Day 1 (baseline), Week 24 and Week 48. MRD negativity will be defined as less than one CLL cell per 10,000 leukocytes (or below 10^{-4}). Additionally, bone marrow samples collected from subjects achieving CR/CRi will also be assessed for both the level of MRD and the rate of MRD negativity. Rate of MRD status will be defined as the proportion of subjects who have MRD negativity status. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided. The relationship between venetoclax PK and efficacy parameters including MRD level and CR will be evaluated.

Pharmacokinetics:

An analysis of venetoclax plasma concentrations will be performed using a population PK modeling approach.

Statistical Methods (Continued):

Health Economic and Patient Reported Outcome (PRO) Measures:

Quality of life will be assessed by using the following PROs: the EQ-5D-5L, FACT-Leu, and the FACIT-F.

Quality of life endpoints will be summarized based on the scoring manuals for the instrument.

Sample Size Estimation:

Using the CR rate of 6% reported for current therapies* 250 subjects would provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate).

In order to provide approximately 80% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% CR rate in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate), the study will enroll 190 subjects who have not been previously treated with BCRi therapy. Since there are approximately a total of 250 subjects, up to 60 subjects previously treated with BCRi therapy can be enrolled.

Safety:

A safety analysis will be performed for all subjects participating in the study who took at least one dose of study drug. For the study as a whole, adverse events will be evaluated and summarized. Laboratory test results and vital signs will be explored for trends and summarized.

* Resonate Trial. ASH. 2014. Abstract 3331.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ABT-199	Study Drug Compound, "Venetoclax"
AE	Adverse Event
AIHA	Autoimmune Hemolytic Anemia
ALC	Absolute Lymphocyte Count
ALT	Alanine transaminase
AML	Acute Myeloid Leukemia
AST	Aspartate transaminase
aPTT	Activated Partial Thromboplastin Time
Bcl	B-Cell Lymphoma
BCR	B-Cell receptor
BCRi	B-Cell receptor inhibitor
BCR PI	B-cell receptor pathway inhibitor
BM	Bone Marrow
BUN	Blood Urea Nitrogen
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
CR	Complete Remission
CRi	Complete Remission with Incomplete Marrow Recovery
CT	Computed Tomography
CTLS	Clinical Tumor Lysis Syndrome
CYP3A	Cytochrome P450 3A
DNA	Deoxyribonucleic Acid
DMC	Data Monitoring Committee
DOR	Duration of Overall Response
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	EuroQoL 5 Dimension 5 Level Questionnaire
eCCr	Estimated creatinine clearance rate using Cockcroft-Gault Formula
eCRF	Electronic Case Report Form
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia Questionnaire
FL	Follicular Lymphoma

G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GDC-0199	Venetoclax (ABT-199)
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
Hr	Hour
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITP	Immune Thrombocytopenia
IV	Intravenous
IVIG	Intravenous immunoglobulins
IWCLL NCI WG	2008 Modified International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute Working Group
Kg	Kilogram
LDi	Longest Diameter
LDH	Lactate Dehydrogenase
LN	Lymph Node
LTLS	Laboratory Tumor Lysis Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MM	Multiple Myeloma
mm	Millimeter
µM	Micromolar
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's Lymphoma
nM	Nanomolar
nPR	Nodular Partial Remission

ORR	Overall Response Rate
OS	Overall Survival
PB	Peripheral Blood
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free Survival
PR	Partial Remission
PRO	Patient-reported Outcomes
PT	Prothrombin Time
QD	Once Daily
RBC	Red Blood Cell
RNA	Ribonucleic Acid
R/R	Relapsed/Refractory
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic-oxaloacetic Transaminase
SLL	Small Lymphocytic Lymphoma
SPD	Sum of the products of the greatest diameters
STAT	Immediately
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TLS	Tumor Lysis Syndrome
TTP	Time to progression
ULN	Upper Limit of Normal
US	Ultrasound
VAS	Visual Analog Scale
WBC	White Blood Cell
WOCP	Women of Childbearing Potential

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

Bcl-2 Family Proteins

The B-cell lymphoma–2 (Bcl-2) family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma (FL) where the t(14;18) chromosomal translocation results in significant over-expression of the protein in B-cells. The Bcl-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 Homology (BH) domains.[1-4] Bcl-2 overexpression is a major contributor to the pathogenesis of some types of lymphoid malignancies. Bcl-2 is also overexpressed in acute and chronic leukemias. Chronic lymphocytic leukemia (CLL) is a genetic disease where the microRNAs miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or down-regulated, resulting in uncontrolled expression of Bcl-2.[5,6]

Venetoclax (ABT-199)

Venetoclax, also known as ABT-199, is a novel, orally bioavailable, small molecule Bcl-2 family protein inhibitor that binds with high affinity (Ki < 0.010 nM) to antiapoptotic Bcl-2 and with lower affinity to other antiapoptotic Bcl-2 family proteins like B-cell lymphoma-extra large (Bcl-X_L) and B-cell lymphoma-Walter and Eliza Hall Institute (Bcl-w) (> 4,000-fold and > –2,000- to > 20,000-fold lower affinity than to Bcl-2, respectively).[8] Selective inhibition by venetoclax disrupts Bcl-2 signaling and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2-dependent human tumor cell lines.[8] Importantly, venetoclax inhibition of Bcl-2 is independent of p53 activity.

A detailed discussion of the non-clinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[8]

Venetoclax Clinical Data

In the Investigator's Brochure,[8] a total of 2495 subjects received at least 1 dose of venetoclax in company sponsored studies as of 28 November 2017. 2473 of these

subjects are included in overall pooled analyses for reporting Reference Safety Information. The 2473 subjects in the overall pooled analysis include 2224 oncology subjects (987 in monotherapy studies and 1237 in combination therapy studies), 153 healthy volunteers, 23 subjects with hepatic impairment and 73 subjects with SLE. Of the 2224 oncology subjects, 1132 subjects had CLL/small lymphocytic lymphoma (SLL), 569 subjects had Non-Hodgkin's Lymphoma (NHL), 172 subjects had multiple myeloma (MM) 340 had Acute Myeloid Leukemia (AML), and 11 subjects had myelodysplastic syndrome (MDS) 787 subjects with blinded data have been treated with either venetoclax combination therapy or a comparator treatment in company-sponsored venetoclax oncology studies. Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg.

The most common adverse events reported in venetoclax monotherapy studies were neutropenia (39.3%), nausea (31.4%) and diarrhea (24.9%). The most common adverse events that were grade 3 and above were neutropenia (34.9%), anemia (13.8%) and thrombocytopenia (12.8%). The most common serious adverse events were febrile neutropenia (6.1%), pneumonia (5.4%), and malignant neoplasm progression (3.4%) and pyrexia (3.3%).

Tumor lysis syndrome (TLS) is an important risk, particularly in subjects with R/R CLL. As a result of on-target effects, the potential for TLS with venetoclax was identified early in the program when the initial 3 subjects with CLL/SLL received starting doses of 100 mg or 200 mg and experienced TLS, which was reported as an adverse event for each. Subsequently, 2 fatal events in the setting of TLS and another event of clinical TLS in subjects with CLL/SLL occurred in December 2012. After comprehensive review of all safety data available from studies with venetoclax, a revised dosing regimen with a dose-titration phase of 5 weeks and enhanced TLS prophylaxis and monitoring measures were implemented in all CLL studies. A subsequent analysis of data from subjects with CLL/SLL following the implementation of prophylaxis measures, who completed monotherapy indicated a marked reduction in severity and frequency of TLS when compared to the previous analysis. None of the subjects experienced any serious

(including fatal) or nonserious event of clinical TLS (CTLS) or laboratory TLS (LTLS) or had study treatment discontinued because of TLS. Since May 2014, a more personalized approach for prophylaxis and monitoring measures, where subjects with lower tumor burden could receive venetoclax on an out-patient basis, has been evaluated with no cases of clinical TLS. Overall, the clinical data strongly support that the risk of TLS with venetoclax in CLL/SLL subjects is highest when initiating venetoclax dosing (5-week dose titration phase), as well as being greater in subjects with a large tumor burden.

The safety profile in combination studies is consistent with that observed in monotherapy studies and with known toxicity profile of combination agents. Preliminary efficacy data indicate that venetoclax, both as monotherapy and in combination with other therapeutic agents, continues to show promising efficacy in oncology subject populations. The overall response rate (ORR) in subjects with CLL/SLL was 75.0% to 81.7% (dose escalation and safety expansion cohorts, respectively), with a complete remission rate (CR + CRi) of 32.1% in dose escalation and 11.7% in the safety expansion cohort for venetoclax monotherapy (Study M12-175 as of 10 June 2016).[9]

Additional safety and efficacy data are described in detail in the Investigator Brochure.[8]

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia is a lymphoproliferative disorder, characterized by progressive accumulation of monoclonal, small, mature-appearing CD5+ B cells in peripheral blood, bone marrow, and secondary lymphoid organs. It is the most common form of leukemia in adults in the Western World, accounting for approximately 30% of all leukemias.[10] Chronic lymphocytic leukemia primarily affects elderly individuals; however, approximately one third of subjects are less than 60 years of age at diagnosis.[11] It is currently estimated that annually approximately 15,000 people will be diagnosed with CLL in the United States and that almost 4,500 individuals will die of the disease.[12] In Europe, CLL accounts for approximately 30% of all leukemias in adults with a reported age standardized incidence rate of 3.79 per 100,000 individuals (for CLL/SLL) in the years 2000 – 2002.[10,13] The approximate 5-year survival rate for subjects with CLL is

73%.[14] CLL presents with a variable clinical course. Approximately one-third of subjects have indolent disease with prolonged median survival that does not require treatment, and die of causes unrelated to disease. Another third have an initial indolent phase that is followed by rapid progression of the disease requiring therapy. The remaining third have aggressive disease and require treatment at the time of diagnosis. Chronic lymphocytic leukemia subjects will often have compromised bone marrow reserve due to their underlying disease. The principal complication of CLL is immunodeficiency related to myelosuppression and as a result, infection is the major cause of death in subjects with CLL.[15]

Standard chemotherapeutic options for CLL cause significant immune suppression and myelosuppression, are not well-tolerated by the elderly population and have not consistently offered survival advantage. Treatment decisions for subjects with CLL are made on the basis of considerations such as age, clinical stage, expected survival, and anticipated toxicities. With the notable exception of allogeneic stem cell transplantation, CLL is currently an incurable disease, despite good initial responses to chemo immunotherapy. Nonetheless, globally access to allogeneic stem cell transplant and/or clinical trials is limited, and treatment options for relapsed disease tend to have increased toxicity and reduced antitumor activity.

Chromosome 17p Deletions and TP53 Gene Mutations in Chronic Lymphocytic Leukemia

Chromosome 17p deletions and TP53 gene mutations are among a group of genetic defects that occur in subsets of subjects with CLL in addition to defects causing Bcl-2 dysregulation. The short arm of chromosome 17 contains the TP53 gene that encodes tumor protein p53, a tumor suppressor involved in deoxyribonucleic acid (DNA) repair activation, cell cycling regulation, and apoptosis signaling. Standard cytotoxic chemotherapies used in the treatment of CLL (i.e., fludarabine, cyclophosphamide, and bendamustine), act by inducing DNA damage and triggering apoptosis. The p53 tumor suppressor is essential for relaying the DNA damage signal to the apoptotic machinery. When p53 is functionally inactivated, either through mutation or deletion, these signals

are not effectively relayed and the efficacy of these agents is diminished. Chromosome 17p deletions and TP53 mutations occur over the course of the disease and expand under treatment selection pressure as a result of the resistance to chemotherapy and chemoimmunotherapy they confer.[16-18] Notably, over 80% of subjects with 17p deletions also carry a TP53 mutation.[17,19]

The decreased likelihood of subjects with 17p deletions and/or TP53 mutations responding to standard chemotherapy and chemoimmunotherapy regimens is accompanied by a greater risk of disease progression and a shorter overall survival (OS).[7,16-18,20] In a long-term follow up study of the effects of 17p deletions/TP53 mutations in CLL subjects treated according to standard practice outside of a clinical study, survival periods measured from date of study sampling were 7.6 months or less for subjects with 17p deletions and/or TP53 mutations compared to 69 months for subjects without TP53 loss or mutations.[21]

Poorer outcomes in subjects with these aberrations have also been demonstrated in large randomized clinical treatment trials. In the CLL8 trial (n = 817) comparing first-line chemoimmunotherapy (fludarabine/cyclophosphamide/rituximab) to chemotherapy alone (fludarabine/cyclophosphamide), multivariate analyses of prognostic indicators for survival at a median follow-up of 70 months found hazard ratios [HR] of 2.916 (confidence interval [CI]: 1.779 – 4.781) and 2.715 (CI: 1.602 – 4.602) for progression-free survival (PFS) and OS, respectively, for subjects with 17p deletions and 2.123 (CI: 1.400 – 3.218) and 3.014 (CI: 1.889 – 4.808), respectively, for subjects with TP53 mutations indicated.[18] Poorer response to first-line treatment and shorter survival in subjects with 17p deletions and/or TP53 mutations were also observed in the CLL4 trial of 777 subjects randomized to chlorambucil or fludarabine with or without cyclophosphamide and in subjects with 17p deletions treated in the E2997 trial (n = 278) of fludarabine with or without cyclophosphamide.[22,23]

Relatively improved treatment responses have been shown in 17p deletion/TP53 mutant first-line and relapsed patient populations with alemtuzumab, a monoclonal antibody specific for B-cell surface molecule CD52, in combination with steroids

(e.g., methylprednisolone, dexamethasone).[24,25] In a Phase 2 study (n = 39) the overall response rate, complete response (including with incomplete bone marrow recovery) rate (CR/CRi), median PFS, and median OS were 85%, 36%, 11.8 months, and 23.5 months, respectively, in the entire cohort and 88%, 65%, 18.3 months, and 38.9 months, respectively, in the 17 previously untreated subjects. Treatment-related death occurred in 5% of subjects, 67% of subjects experienced Grade 3/4 hematologic and glucocorticoid-associated toxicity, and 51% experienced Grade 3 infection.[24]

The tyrosine kinase inhibitors ibrutinib and idelalisib that act downstream of the B-cell receptor have also been shown to produce relatively improved responses compared to standard therapies and have been approved for use in some jurisdictions for the treatment of CLL subjects with 17p deletion (ibrutinib, idelalisib) or TP53 mutations (idelalisib only). Ibrutinib inhibits Bruton's tyrosine kinase, an enzyme involved in B-cell receptor signaling, homing, and adhesion. A Phase 3 relapsed or refractory CLL study comparing ofatumumab (an anti-CD20 monoclonal antibody) to ibrutinib included 127 subjects with the 17p deletion. In this cohort, the median duration of PFS was 5.8 months in the ofatumumab arm but was not reached in the ibrutinib arm (HR 0.25; 95% CI: 0.14, 0.45). The overall response rate was 47.6% with ibrutinib compared with 4.7% with ofatumumab. No complete responses were observed.[25] Overall, 57% of subjects in the ibrutinib arm had at least one ≥ Grade 3 adverse event (AE). The most frequent non-hematologic AEs (> 20% of subjects) with ibrutinib were diarrhea, fatigue, pyrexia, and nausea.[26] Grade 3/4 AEs reported in ≥ 5% of the 357 subjects with mantle cell lymphoma or CLL that received ibrutinib during clinical development were anemia, neutropenia, pneumonia and thrombocytopenia.[27]

Idelalisib targets the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ) involved in signal transduction via multiple receptors including the B-cell receptor and chemokine receptors CXCR4 and CXCR5. A Phase 3 study comparing combined idelalisib/rituximab treatment with rituximab/placebo in previously treated subjects reported improved PFS in the idelalisib arm among the 96 subjects enrolled with 17p deletion or TP53 mutation (HR 0.12; CI: 0.05, 0.32). The majority of AEs in the

study were Grade 2 and the most common in the idelalisib arm were pyrexia, fatigue, nausea, chills, and diarrhea.[28] The overall safety profile determined in Phase 1 to 3 studies of idelalisib in hematologic malignancies as monotherapy or in combination with an anti-CD20 monoclonal antibody is characterized by a very common frequency (≥ 1/10 subjects) of ≥ Grade 3 infections, neutropenia, diarrhea/colitis and increased transaminase.[29]

CLL Subjects Who Have Received Prior B-Cell Receptor Inhibitor (BCRi) Therapy

Ibrutinib and idelalisib cause rapid response with reduction in lymph node size and splenic mass accompanied by increased PB (peripheral blood) lymphocytosis likely reflecting that microenvironment modulation could prevent these cells from receiving the survival signals delivered by the microenvironment.[30] In early trials of Ibrutinib, approximately 10% of the subjects developed progressive disease (PD). Few of these subjects developed resistance after achieving partial response lasting ≥ 6 months. Distinct single nucleotide variations were noted in these subjects.[31]

In addition, toxicities such as diarrhea, fatigue and pyrexia are common and can affect the subjects who receive these drugs.[26,28]

However, the mechanism of action of venetoclax is independent of the B-cell receptor (BCR) pathway.[32] Briefly, venetoclax inhibits Bcl-2 allowing the release of BIM, which includes oligomerization of pro-apoptotic molecules such as BAK and BAX which triggers rapid apoptosis. The clinical data to date with venetoclax monotherapy shows strong activity in refractory CLL indicating that it might be beneficial in a population that is refractory to these newer therapeutic agents.

Despite some improvement in disease outcomes in relapsed/refractory CLL subjects, including those who have received novel agents, significant toxicities remain a concern, complete disease responses are uncommon, and relapse is virtually inevitable. Subjects carrying TP53 aberrations and those who have received prior BCRi therapy continue to represent a significant unmet medical need and current treatment recommendations

include participation in investigative clinical trials proceeding to allogeneic hematopoietic stem cell transplantation in responding subjects eligible for transplant (e.g., younger age with no co-morbidities and a suitable donor).[16,33]

Further details of disease activity observed in clinical studies with venetoclax are provided in the Venetoclax Investigator's Brochure.[8]

3.1 Differences Statement

This is the first Phase 3b study to assess the efficacy of venetoclax monotherapy in relapsed or refractory CLL. The R/R CLL patient population will be enriched to include subjects who have previously received BCRi therapy. This will allow for the assessment of deep responses in this high risk/unmet need patient population. In this study, subjects will be assessed for efficacy with standard criteria.

3.2 Benefits and Risks

There is data that shows substantial efficacy of venetoclax monotherapy in the treatment of relapsed/refractory CLL characterized by 17p deletions. Venetoclax is expected to be as active in subject selected for TP53 mutations as these subject populations overlap and the oncogenic effect of both genetic defects occurs via p53 abrogation. In addition, there is limited data in the BCRi failure CLL population for subjects that subsequently receive venetoclax and also in subjects without the 17p deletion. Current CLL therapies do not reliably produce complete responses and are not curative in subjects with p53 aberrations or those refractory to BCRi. Furthermore, drugs more recently approved for these subjects are limited by toxicity.

Clinical safety data indicate that the adverse effects of venetoclax administered with appropriate measures are manageable and as expected from a treatment targeting hematologic cells including in subjects with 17p, TP53 mutation or subjects who have previously received BCRi therapy.

Additional safety and efficacy data can be found in the current Investigator Brochure.[8]

4.0 Study Objective

The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). The primary efficacy endpoint will be measured by complete remission rate (CR + CRi) of the subjects who have not been previously treated with BCRi therapy, as assessed by the investigator.

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and the CR rate in previously BCRi treated subjects.

Additional secondary objectives will also be evaluated as well. Quality of life will be assessed using the following patient reported outcomes (PRO) questionnaires: the EuroQoL 5 Dimensions (EQ-5D-5L), a measure of general health status, the Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu), a leukemia-specific health related quality of life for acute and chronic disease, and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F).

The safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated.

Additional exploratory objectives will be evaluated. Minimal Residual Disease (MRD) will be assessed in the peripheral blood and bone marrow (BM) by flow cytometry and PCR.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is an open-label, single arm, Phase 3b, multi-center study evaluating the efficacy of venetoclax monotherapy in relapsed/refractory CLL.

This study is designed to enroll approximately 250 subjects to meet scientific objectives without enrolling an undue number of subjects in alignment with ethical considerations. All efforts will be made to adhere to these specific enrollment numbers; however, it would not be ethical to deny treatment to eligible subjects already in screening as they may have undergone study related procedures. Sites will be notified once we approach 60 BCRi treated subjects enrolled. Approval will then be required to enroll additional subjects previously treated with BCRi therapy.

Subjects in this study will be enrolled at 7 sites in the United States, 1 site in Puerto Rico, and approximately 67 sites globally.

Subjects will undergo screening procedures within 28 days prior to initial venetoclax administration. For all subjects, a contrast computed tomography (CT) scan (or medically indicated alternative such as magnetic resonance imaging [MRI]) will be accepted if previously performed within 35 days prior to venetoclax administration. Otherwise, a CT scan (or MRI) must be performed within the screening period of 28 days. Following the 4-week Screening period, for all subjects, study visits will be conducted within 72 hours of dosing, on the day of dosing and the day after dosing during the dose titration phase. Please refer to Appendix D. Study visits will be reduced to a monthly frequency at Week 8, and at Week 48, they will be reduced to every 3 months until the end of study treatment (Week 108). As of Week 8 the visit window for scheduled visits is ±2 days. A 30 day Safety Follow-Up Visit should be performed approximately 30 days (± 3 days) following the last dose of venetoclax (to allow for AE collection 30 days following last dose of study drug). If a subject is discontinued from the study with an ongoing AE or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until the AE has resolved to a ≤ Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.

Venetoclax will be administered orally once daily (QD), continuously. Venetoclax tablets should be taken with a meal and water in the morning at approximately the same time each day. To mitigate the risk for TLS, the first 5 weeks of treatment include a dose-titration phase where venetoclax will be dosed in increments, as outlined in Figure 1. The

starting dose of venetoclax is 20 mg once daily. The dose will be gradually increased over a period of 5 weeks up to the daily dose of 400 mg.

Figure 1. 5-Week Dose-Titration Schedule

Week	VENETOCLAX Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

Disease response will be assessed by the investigator based on laboratory results and physical examinations using the 2008 Modified International Workshop on CLL National Cancer Institute – Working Group (IWCLL NCI-WG) Guidelines for Tumor Response with the addition of CT imaging (or MRI). A Disease Assessment for clinical response by physical exam and hematologic assessments will be performed at Screening, Week 24, Week 36 and Week 48. To confirm the response, a CT scan will be performed at Week 48 on all subjects and BM samples will be collected for subjects with CR to confirm the response.

MRD assessments will be performed by using peripheral blood specimens at Week 1 Day 1 (baseline), Week 24 and Week 48. When confirming a CR status or complete remission with incomplete bone marrow recovery (CRi) status per IWCLL NCI-WG guidelines with a bone marrow aspirate and biopsy, MRD assessment of the bone marrow aspirate should also be performed.

Quality of life will be assessed by using the following patient reported outcome questionnaires: the EQ-5D-5L, the FACT-Leu, and the FACIT-F. Quality of life endpoints will be summarized based on the scoring manual for the instruments.

Subjects may continue to receive venetoclax for up to 2 years provided they continue to tolerate the drug, have no evidence of disease progression (based on investigator's assessment), do not have unacceptable toxicity, and do not meet any of the criteria for discontinuation (see Section 5.4.1). A final visit will be conducted upon treatment discontinuation.

After treatment discontinuation, subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression, etc.) will be collected. This period will continue for two years following discontinuation of venetoclax.

All study procedures will be performed as outlined in Section 5.3.1.1 and Appendix D and Appendix E.

For subjects who continue to derive benefit after 2 years of treatment, AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy. In countries where venetoclax is commercially available, extension of therapy may not be allowed.

A safety analysis will be performed for all subjects participating in the study who took at least one dose of study drug. For the study as a whole, serious adverse events and adverse events will be evaluated and summarized. Laboratory test results and vital signs will be explored for trends and summarized.

5.2 Selection of Study Population

Subjects will undergo screening procedures within 28 days prior to initial venetoclax administration, with the exception of the CT scan (or MRI). A CT scan will be accepted if previously performed within 35 days prior to venetoclax administration.

Adult male and female subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria:

1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
3. Subject has relapsed/refractory disease (received at least one line of prior therapy).
4. Diagnosis of CLL that meets published 2008 Modified IWCLL NCI-WG Guidelines and:
   - has an indication for treatment according to the 2008 Modified IWCLL NCI-WG criteria
   - has clinically measurable disease (lymphocytosis > 5×10^9/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam)
   - subjects with or without the 17p deletion or TP53 mutation are eligible.
   - subjects who have received prior B-cell receptor inhibitor therapy are also eligible (up to 60 subjects total will be enrolled in the study).
5. Adequate bone marrow function as follows:
   - hemoglobin ≥ 8.0 g/dL
   - platelets ≥ 25,000/mm^3, without any of the following:
     - transfusion support within 14 days of Screening
     - evidence of mucosal bleeding
     - known history of bleeding episode within three months of Screening
6. Adequate coagulation parameters per local laboratory reference range as follows:
   - activated partial thromboplastin time (aPTT) and prothrombin time (PT) and/or International Normalized Ratio (INR) not to exceed 1.5 × the upper limit of normal (ULN)

7. Adequate renal function per local laboratory reference range as follows:

   - calculated creatinine clearance ≥ 50 mL/min using 24-hour creatinine clearance or estimated creatinine clearance using the modified Cockcroft-Gault equation:

$$\text{Estimated creatinine clearance (eCCr)} = \frac{(140 - \text{age}) \bullet \text{Weight(kg)} \bullet [0.85 \text{ if female}]}{72 \bullet \text{serum creatinine (mg/dL)}}$$

   or, if serum creatinine is in µmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{Weight(kg)} \bullet [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine (µmol/L)}}$$

8. Adequate hepatic function per local laboratory reference range as follows:

   - aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 × ULN
   - bilirubin ≤ 1.5 × ULN. Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN per correspondence between the investigator and AbbVie Therapeutic Area Medical Director (TA MD).

9. If female, subject must be either postmenopausal defined as:

   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

     OR

   - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

     OR

   A Women of Childbearing Potential (WOCP) practicing at least one protocol specified method of birth control (Refer to Section 5.2.4), starting at Study Day 1 through at least 30 days after the last dose of study drug.

10. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as define above) at Screening do not require pregnancy testing.
11. Subject voluntarily signs and dates an informed consent form that has been approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) prior to the initiation of any screening or study-specific procedures.

Rationale for Inclusion Criteria

1 – 4	To select the subject population
5 – 8	For the safety of the subjects
9 – 10	The impact of venetoclax on pregnancy is unknown
11	In accordance with Harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Subject has developed Richter's transformation or Prolymphocytic leukemia.
3. Subject has previously received venetoclax.
4. History of active malignancies other than CLL within the past 2 years prior to first dose of venetoclax, with the exception of:
    - adequately treated in situ carcinoma of the cervix uteri
    - adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin

- previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.

5. Active and uncontrolled autoimmune cytopenias (within 2 weeks prior to Screening), including autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), despite low dose corticosteroids.
6. Prior allogeneic stem cell transplant.
7. Treatment with the following **within 30 days** prior to the first dose of venetoclax:
   - a biologic agent (i.e., monoclonal antibodies) with anti-neoplastic intent.
8. Treatment with any of the following **within five half-lives or 14 days** (if half-life unknown) as applicable prior to the first dose of venetoclax, or clinically significant adverse effect(s)/toxicity(s) of the previous therapy have not resolved to < National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 Grade 2:
   - any anti-cancer therapy including chemotherapy or radiotherapy, with the exception of b-cell receptor pathway inhibitors (i.e., ibrutinib, idelalisib)
   - investigational therapy, including targeted small molecule agents
9. Treatment with any of the following **within 7 days** prior to the first dose of venetoclax:
   - Steroid therapy for anti-neoplastic intent.
   - Moderate or strong Cytochrome P450 3A (CYP3A) inducers (See Appendix C for examples)
10. Treatment, administration or consumption of any of the following **within 3 days** prior to the first dose of venetoclax.
    - Strong CYP3A inhibitors. (See Appendix C for examples)
    - Moderate CYP3A inhibitors (See Appendix C for examples)
    - B-cell receptor pathway inhibitors (i.e., ibrutinib, idelalisib)
    - grapefruit or grapefruit products
    - Seville oranges (including marmalade containing Seville oranges)

- Star fruit.

11. Subject is known to be positive for Human Immunodeficiency Virus (HIV) (due to potential drug-drug interactions between anti-retroviral medications and venetoclax, as well as anticipated venetoclax mechanism based lymphopenia that may potentially increase the risk of opportunistic infections).
12. Known allergy to xanthine oxidase inhibitors and/or rasburicase for subjects at risk for TLS.
13. Cardiovascular disability status of New York Heart Association Class ≥ 2. Class 2 is defined as cardiac disease in which subjects are comfortable at rest but ordinary physical activity, results in fatigue, palpitations, dyspnea or anginal pain.
14. Evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    - uncontrolled and/or active systemic infection (viral, bacterial or fungal)
    - chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment.
    - febrile neutropenia.
15. Significant history of renal, pulmonary, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular or hepatic disease that in the opinion of the investigator would adversely affect the subject's participation in this study.
16. Malabsorption syndrome or other condition that precludes enteral route of administration.

Rationale for Exclusion Criteria

1	The impact of venetoclax on pregnancy is unknown
2 – 5, 7	To select the appropriate subject population
6, 8 – 16	For the safety of the subjects

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

Subjects should receive full supportive care during study participation, including hematopoietic growth factors, transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate. Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Steroid therapy for anti-neoplastic intent will not be allowed either during or within 7 days prior to the first dose of venetoclax.

Inhaled steroids for the treatment of asthma or COPD, topical steroids, replacement corticosteroid therapy for an inherited or acquired deficiency are allowed.

In addition, limited corticosteroid treatment is allowed while on study for significant active autoimmune cytopenias, e.g., autoimmune hemolytic anemia (AIHA) or immune thrombocytopenia (ITP). IVIG (intravenous immune globulin) is also allowable.

For additional guidance regarding medications for management of neutropenia, refer to Section 6.1.8.3.

The AbbVie TA MD identified in Section 6.1.4 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

General guidelines regarding excluded, cautionary and allowed medications are summarized in Table 1 and Table 2 below.

Subjects may not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first venetoclax administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

Table 1. Excluded and Cautionary Medications

Excluded
Anticancer therapies including chemotherapy, radiotherapy, or other investigational therapy, including targeted small molecule agents: Excluded 5 half-lives prior to first dose and throughout venetoclax administration **Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic effect:** Excluded 30 days prior to first dose and throughout venetoclax administration
Excluded during initiation and the dose-titration phase and Cautionary at 400 mg Steady Daily Dose:
Strong CYP3A inhibitors Exclude during initiation and the dose-titration phase. If subject requires use of these medications after the dose titration phase at steady daily 400 mg doses, use with caution and reduce the venetoclax dose by at least 75% during co-administration. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor
Cautionary
Moderate CYP3A inhibitors Avoid concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, reduce the initiation dose, titration doses and the 400 mg steady daily dose of venetoclax by at least 50%. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor. **Strong and Moderate CYP3A inducers** Avoid concomitant use of venetoclax with strong or moderate CYP3A inducers. Consider alternative treatments with less CYP3A induction. **Warfarin** **P-gp substrates** **BCRP substrates** **OATP1B1/1B3 substrates** **P-gp inhibitors** **BCRP inhibitors**

Note: See Appendix C for Examples.

Table 2. Sample of Permitted Medications

Drug or Therapy	Comments
Colony stimulating factors e.g., G-CSF, GM-CSF	**Permitted**; per ASCO guidelines.[32] Notify AbbVie TA MD if subject requires use of these medications or recombinant human erythropoietin.
Best supportive care and treatment e.g., antiemetics, antibiotics, transfusions, nutritional support, pain control, etc.	**Permitted**
Antiherpes and anti-pneumocystis prophylaxis	**Permitted**; if clinically indicated.
Autoimmune thrombocytopenia and hemolytic anemia medications	**Permitted**; if clinically indicated.

A sample list of excluded medications and cautionary medications that fall into these categories is provided in Appendix C. It is not possible to produce a complete list of medications that fall into these categories, so if in question, please refer to the appropriate product label.

If the investigator determines that such a medication is medically necessary, the investigator will notify the AbbVie TA MD and discuss the investigator's use of these medications and the investigator's plans to medically monitor the study subject.

5.2.4 Contraception Recommendations

While participating in this research study, female subjects should not become pregnant or breastfeed a baby.

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Women of Childbearing Potential, practicing at least one of the following highly effective methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1. In addition to combined hormonal contraception, a barrier method must be used during this study from

initial study drug administration to 30 days after the last dose of study drug as drug-drug interaction with venetoclax upon the hormonal contraception is unknown.

- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1. In addition to a progestogen-only hormonal contraception, a barrier method must be used during this study from initial study drug administration to 30 days after the last dose of study drug as drug-drug interaction with venetoclax upon the hormonal contraception is unknown.
- Bilateral tubal occlusion/ligation at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure at least 1 month before study participation.
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix D and Appendix E.

Unless otherwise stated, the baseline measurement for any given variable will be defined as the last value obtained for the variable prior to the first dose of venetoclax.

5.3.1.1 Study Procedures

All study procedures outlined in Appendix D and Appendix E are discussed in detail in this section, with the exception of adverse event (AE) information (discussed in Section 6.1). All study data will be recorded on electronic case report forms (eCRFs).

Informed Consent

Subjects must voluntarily sign and date an informed consent form approved by an IEC/IRB, prior to the initiation of any screening, study-specific procedures, or before any prohibited medications are withheld from the subject in order to participate in the study. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Screening

Procedures performed at Screening will serve as baseline, unless repeated on Week 1 Day 1 prior to dosing; in which case the latter will serve as baseline. Any abnormal laboratory or vital sign assessment between screening and prior to administration of study drug will be recorded in the subject's medical history and will also serve as the subject's baseline. The schedule of study visit procedures is based on subject study drug administration. Scheduled study visits and/or procedures will need to be altered if there is an interruption in study drug administration. If study drug administration is interrupted for more than 3 days (i.e., adverse event), the site will contact the AbbVie study team or AbbVie TA MD to adjust the subject's visit schedule, procedures and/or dosing on a case by case basis.

Subjects who signed informed consent, have had at least one study procedure conducted, and are determined to be a screen failure, will not proceed in study.

Re-Screening Procedures

Subjects that initially screen fail for the study may be permitted to re-screen following re-consent. All Screening procedures will need to be repeated. The subject must meet all

inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including the CT scan and the re-screen visit is more than 35 days since the initial screening assessment, a CT scan should be repeated. As appropriate, sites are encouraged to contact the AbbVie TA MD to confirm if subjects should or should not be re-screened.

Detection of 17p Deletion or TP53 Mutation

Subjects may have 17p deletion and/or TP53 mutation as assessed by local laboratory (in bone marrow or peripheral blood) to be considered as having this deletion/mutation. However, the 17p deletion or TP53 mutation is not a protocol required test for subjects to be enrolled in this study. If a subject does have the 17p deletion or TP53 mutation, a recent test is desirable but any previous positive test is acceptable.

Medical and Oncology History

A complete medical history, including history of tobacco, nicotine-containing products and alcohol use, will be taken from each subject during the Screening visit, including:

- documentation of any clinically significant medical condition
- a detailed oncology history including:
  - histology
  - cytogenetics
  - date of CLL diagnosis
  - stage
  - any surgical procedures
  - treatments administered (including dates, type of modality, response to treatment and reason for treatment discontinuation)

On Week 1 Day 1, any additional medical history observed after signing of the informed consent but prior to initial venetoclax administration and not considered related to study-required procedures will be recorded in the subject's medical history.

Pregnancy Testing

- WOCP must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.
- Screening – quantitative beta-human chorionic gonadotropin (β-hCG) serum pregnancy test.
- Week 1 Day 1: Urine test, if it has been > 7 days since obtaining the Screening serum pregnancy test results.
- During the study a urine pregnancy test can be performed at the discretion of the investigator or per local guidelines.
- Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Inclusion Criterion 9) at Screening do not require pregnancy testing.

Adverse Event and Concomitant Medication Assessment

On Week 1 Day 1, any protocol-related events observed from the time of signing of the informed consent but prior to initial venetoclax administration will be recorded as a serious or nonserious adverse event, if considered by the investigator to be causally related to the study-required procedures (See Figure 3).

At each visit, including the Final Visit and the Post-Treatment Follow-Up, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary beginning with Screening through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate eCRF.

Vital Signs

Vital signs include body temperature (oral or tympanic), weight, blood pressure and pulse. On days when venetoclax is administered in the clinic, blood pressure and pulse rate will be measured after the subject has been sitting for at least 5 minutes.

NOTE: Starting with visit Week 8/Day 1, vital signs may be performed within 72 hours before or after the scheduled visit.

Physical Examination

At Screening, the subject should have a **complete physical examination**, including height and weight (height only performed during Screening). A complete physical examination should include the evaluation of head, eyes, ears, nose and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems.

A **symptom directed physical examination** may be performed at all other visits (other than screening) and should be limited to systems of primary relevance: cardiovascular, respiratory, and those associated with symptoms.

Physical Examination (Disease Assessment)

Physical examinations performed as a part of Disease Assessments (Screening, Weeks 24, 36, 48) are to include the evaluation of the presence and degree of enlarged lymph nodes in two dimension (cervical, supraclavicular, axillary, inguinal and femoral nodes), hepatomegaly, and splenomegaly. These lymph node evaluations should be noted on all physical examinations irrespective of being present or absent. Refer to Disease Assessments (2008 Modified IWCLL NCI-WG Criteria) for additional information pertaining to methods of measurement.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

If signs or symptoms suggestive of Richter's Syndrome are observed during physical examination, further assessments (i.e., nodes, Positron Emission Tomography [PET] scan) should be considered to exclude or confirm the transformation.

Please refer to Appendix D and Appendix E for timing of all physical examinations.

NOTE: Starting with Week 8 Day 1, all Physical examinations may be performed within 72 hours before or after the scheduled visit.

Tumor Lysis Syndrome (TLS) Risk Assessment

At Screening, all study subjects will be assessed for risk of developing TLS. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. See Appendix H for tumor burden categories. Reduced renal function (estimated creatinine clearance [eCrCl] < 80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases with venetoclax treatment.

Tumor burden assessments, including radiographic evaluation (e.g., CT scans) as well as chemistry/hematology assessments (refer to Table 4, Clinical Laboratory Tests) will be performed in all subjects prior to initiating venetoclax treatment.

Appropriate venetoclax dosing and management of subjects throughout their study treatment is guided by their individual risk for developing TLS. Risk-based TLS prophylaxis and management measures are described in Section 6.1.8.1 and Appendix H.

Eastern Cooperative Oncology Group (ECOG) Performance Status

For all subjects, the ECOG performance status[47] will be performed as outlined in Appendix D and Appendix E.

It is recommended, where possible, that a subject's performance status will be assessed by the same person throughout the study. ECOG performance status will be assessed as follows:

Table 3. ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

NOTE: Starting at Week 24 Day 1, ECOG performance status may be performed within 72 hours before or after the scheduled visit.

Coagulation Panel

Prothrombin time (PT) and/or International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) will be collected and will be analyzed by the local laboratory during Screening only.

Hematology and Chemistry

Hematology and chemistry will be analyzed by the local laboratory. Required tests are listed in Table 4.

Table 4. Clinical Laboratory Tests

Hematology	Chemistry	Coagulation[a]
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Lymphocytes Platelet count (estimate not acceptable) Reticulocyte count	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid[b] Glucose Albumin Lactate dehydrogenase (LDH)	Prothrombin time (PT) AND/OR International Normalized Ratio (INR) Activated partial thromboplastin time (aPTT)

* Urea may be reported instead of BUN

a. Performed at Screening and as clinically indicated.

b. For samples from subjects treated with rasburicase: rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples left at room temperature, potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation. Uric acid must be analyzed in plasma. Blood must be collected into pre-chilled tubes containing heparin anticoagulant. **Immediately immerse plasma samples for uric acid measurement in an ice water bath.** Plasma samples must be prepared by centrifugation in a pre-cooled centrifuge (4°C). Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.

PRE-DOSE LABS

Prior to the Initial Dose of Venetoclax, for all Subjects:

- During the Screening Period: For all subjects, the chemistry/hematology panel (see Table 4, Clinical Laboratory Tests) is required.
  - Pre-existing abnormalities should be corrected.
- Within 72 hours of Week 1 Day 1: If the screening labs were done more than 72h before the planned first dose, the chemistry/hematology panel should be repeated. These results should be reviewed prior to dosing.
  - Labs should be assessed and pre-existing abnormalities should be corrected

- On the day of Week 1 Day 1: Before dosing, the chemistry/hematology panel should be drawn.

The results of the labs drawn on Week 1 Day 1 need to be reviewed prior to dosing **IF** an additional lab within 72 hours of the initial dose at Week 1 Day 1 was not drawn **AND** reviewed.

Prior to Each Subsequent Dose Increase, for all Subjects:

- Within 72 hours of each subsequent dose increase: The chemistry/hematology panel should be repeated. The results should be reviewed prior to dose increasing.
- Prior to dosing, on the day of each subsequent dose increase: Before dosing, the chemistry/hematology panel should be drawn. The results of the labs drawn on Day 1 of each dose increase need to be reviewed prior to dosing **IF** an additional lab draw within 72 hours of the dose increase was not drawn **AND** reviewed.

POST-DOSE LABS:

Post-Dose Labs for Subjects with LOW Risk for TLS:

- The chemistry/hematology panel should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax (20 mg) and after the first dose increase (50 mg).
- Electrolyte abnormalities should be corrected promptly. The next venetoclax doses (Day 2, 20 mg venetoclax dose and Day 2, 50 mg venetoclax dose) should not be administered until the 24 hour lab results have been evaluated.

Post-Dose Labs for Subjects with MEDIUM Risk for TLS:

- Consider hospitalization for subjects with CrCl < 80 ml/min at first dose of 20 mg and 50 mg
- Labs should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax (20 mg) and after the first dose increase (50 mg).

- Electrolyte abnormalities should be corrected promptly. The next venetoclax doses (Day 2, 20 mg venetoclax dose and Day 2, 50 mg venetoclax dose) should not be administered until the 24 hour lab results have been evaluated.

Post-Dose Labs for Subjects with HIGH Risk for TLS:

- Subjects should be hospitalized during the first dose of 20 mg and 50 mg. Labs should be monitored at 4, 8, 12, and at 24 hours after the first dose of venetoclax (20 mg) and after the first dose increase (50 mg).
- Subject can be Outpatient at subsequent dose increases and labs (refer to Table 4 Clinical Laboratory Tests) should be monitored at 6 to 8 hours and at 24 hours.

This monitoring is also recommended during the re-initiation of the therapy after a dose interruption.

Additional monitoring may be required based on the risk assessment by the investigator and as directed by the AbbVie TA MD.

Local laboratories will be utilized to process and provide results for clinical laboratory tests allowing for immediate subject medical management. The principal investigator or sub-investigator will review, initial, and date all laboratory results used for subject treatment management after receipt from the local laboratory. Local laboratory values will be entered by the site directly onto the appropriate eCRF and laboratory normal ranges for the laboratory that is used will be provided to the AbbVie Clinical Team.

A laboratory test value that requires a subject to be discontinued from the study, requires a subject to receive treatment, meets protocol specific criteria (see Section 6.1.8 regarding toxicity management), or if the Investigator considers clinically significant will be recorded as an adverse event.

NOTE: Starting with Week 8/Day 1, clinical laboratory tests may be collected within 72 hours prior to the scheduled visit.

Disease Assessments (2008 Modified IWCLL NCI-WG Criteria)

All measurable disease must be documented at Screening (baseline), prior to the first dose of venetoclax, for all subjects based on the analysis of clinical laboratory tests (hematology), disease assessment physical examination, contrast-enhanced CT scan of involved neck, chest, abdomen and pelvis (or MRI, if CT scan with contrast is medically contraindicated). Bone marrow examinations at screening are not required but results will be recorded if available.

For all subjects, clinical response will be assessed by the investigator at Week 24, Week 36 and Week 48. Disease response will be based on the analysis of clinical laboratory tests and a disease assessment physical examination. To confirm the response, a contrast-enhanced CT scan (or MRI, if CT scan with contrast is medically contraindicated) will be performed at Week 48 for all subjects. Subjects will be evaluated using the 2008 Modified IWCLL NCI-WG criteria for Tumor Response with the addition of CT imaging (or MRI).

For determination of complete remission (CR), the CT scan and bone marrow are required to be negative, per the IWCLL NCI-WG criteria. It is recommended that the CT scan is performed first; if it does confirm a clinical response, then a bone marrow biopsy will be obtained. If a CT scan is performed and does not confirm a clinical response, a bone marrow biopsy should not be obtained.

If a subject exhibits clinical signs of possible disease progression (i.e., increased or *de novo* enlargement of liver, spleen or lymph nodes on physical examination) without an increase in lymphocytes meeting the progression of disease criteria, then additional assessments including contrast-enhanced CT scan and/or bone marrow can be performed to confirm or rule out disease progression.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

For any subject who has not experienced progressive disease at the time of permanent discontinuation of venetoclax, follow-up phone calls will continue until death, discontinuation from the study or upon study completion.

Response criteria definitions are outlined in 2008 Modified IWCLL-WG Criteria for Tumor Response. See Table 5.

NOTE: Disease assessments may be performed approximately 7 days prior to the scheduled visit.

For patients with only Partial Remission at Week 48 an additional CT and a bone marrow examination can be done between Week 48 and Week 108 to confirm CR if there is a possibility that a patient is in Complete Remission based on laboratory tests and a disease assessment physical examination.

Computed Tomography Scans (or Magnetic Resonance Imaging)

A CT scan with contrast will be accepted if previously performed within 35 days prior to the first dose of venetoclax. Otherwise, a CT scan must be performed within the Screening window (28 days) for all subjects. A CT scan will be performed for all subjects at Week 48 to confirm disease response. Contrast-enhanced CT scans including neck, chest, abdomen, and pelvis will be performed to assess response to treatment. A contrast-enhanced MRI of the neck, chest, abdomen and pelvis with a non-contrast CT scan of the chest may be used for subjects in whom a contrast CT is medically contraindicated (i.e., subjects with a severe allergy to CT contrast agents or subjects with impaired renal clearance). Whichever method is used at Screening should be consistently used throughout the duration of the study.

Any CT scan (or MRI) performed as standard of care throughout the study should be captured on the eCRF.

NOTE: CT scans (or MRI) may be performed 7 days prior to the scheduled visit.

Bone Marrow Aspirate and Biopsy

At baseline, a bone marrow aspirate and biopsy are not required; however results should be recorded if available. If the subject achieves a CR by clinical criteria and confirmatory CT scan, a bone marrow aspirate and biopsy will be performed to confirm the CR. Whenever possible the bone marrow aspirate for biomarker MRD assessment should be split from this sample. If a CT scan is performed and does not confirm a CR, a bone marrow biopsy should not be obtained.

Bone marrow aspirates and biopsies performed as standard of care throughout the study should also be captured on an eCRF.

Subject Calendars/Diaries

For all subjects, subject calendars/diaries will be provided at the Week 20 visit. Subjects will be instructed to bring their calendars/diaries back to the site to be reviewed at the Week 24 visit.

Subjects will be instructed to record the date and time of each dose taken (indicating if any doses of study drug are missed) from Week 20 to Week 24, and whether or not the dose was taken with a meal. This information will be transcribed into the eCRF.

At the Week 24 visit, the calendars/diaries are to be returned to the site and appropriately filed with the subject's source documents for this study.

Health Economic and Patient Reported Outcome Measures

Quality of life will be assessed using the following questionnaires: the EQ-5D-5L the FACT-Leu and the FACIT-F.

Quality of life will be assessed at baseline (Week 1, Day 1 prior to the first dose), Week 4, Week 12, Week 24, and then every 3 months until the end of study treatment (Week 108). The Health Economic and Patient Reported Outcomes questionnaires should be administered and completed prior to any other study procedures being performed at these

visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

Final Visit

Upon treatment discontinuation (See Section 5.4.1), the reason(s) for discontinuation will be recorded in the eCRFs and a Final Visit will be performed. The Final Visit procedures as listed in Appendix D and Appendix E should be performed as soon as possible after study drug discontinuation.

At the Final Visit, all used/unused study drug and the subject's calendars/diaries, if applicable are to be returned to the site and drug accountability performed.

30-Day Safety Visit

A 30-Day Safety Follow-up Visit should be performed approximately 30 days (± 3 days) following the last dose of venetoclax (to allow for AE collection 30 days following last dose of study drug). Refer to Appendix D and Appendix E for procedures to be performed.

If a subject has an ongoing AE or an unresolved clinically significant laboratory result 30 days following last dose of study drug, the site will attempt to provide follow-up until the AE has resolved to a ≤ Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.

Additionally, CT or MRI scans are not required, however if collected by the site as standard of care, the data should be recorded in EDC.

Post-Treatment and Survival Assessments

After treatment discontinuation, subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.)

will be collected. This period will continue for 2 years following discontinuation of venetoclax.

Extended Access Phase

In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy. The Extended Access Visits will include:

- Collection of Survival information
- AE/SAE/Con Med assessment
- Study drug reconciliation and dispensing

All other procedures should be performed as standard of care. The specific study assessments to be performed during these visits are detailed in Appendix E Study Activities.

Assignment of Subject Numbers

Subjects will be assigned unique consecutive subject numbers at screening, as described in Section 5.5.3. The results of all screening evaluations must be within clinically acceptable limits, upon review by the investigator before a subject can be administered study drug. Subjects will not be enrolled in the study if laboratory or other screening results are unacceptable.

5.3.1.2 Collection and Handling of Biomarker Research Samples

Biospecimens may be utilized to evaluate known and/or novel disease-related or drug-related biomarkers. The biomarker rationale will be discussed in the Biomarker Research Variables Section (Section 5.3.6).

Biomarker Samples

Minimal Residual Disease (MRD) Assessment

Peripheral blood for MRD will be collected from all subjects as outlined in Appendix D and Appendix E.

When confirming a CR or CRi status per the 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy, whenever possible, a bone marrow aspirate should be collected for MRD assessment. The bone marrow aspirate should be split and a sample sent to the Central Laboratory.

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual.

AbbVie (or people or companies working with AbbVie) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on venetoclax, or drugs of this class, or this disease and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

5.3.2 Drug Concentration Methods

5.3.2.1 Collection of Samples for Analysis

Blood samples for venetoclax and possible metabolite(s) will be collected by venipuncture per Appendix D and Appendix E. The date and time (to the nearest minute) of the last dose and second to last dose of venetoclax will be recorded on the eCRF. The date and time (to the nearest minute) of each blood sample collection will be recorded on the sample requisition form.

Blood samples (3 mL) for venetoclax assay will be collected at the following time:

- Week 24 Day 1: 0 hour (pre-dose)

A total of 1 blood sample is planned to be collected per subject for venetoclax PK analysis. Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

5.3.2.2 Measurement Methods

Plasma concentrations of venetoclax will be determined by the Drug Analysis Department at AbbVie using validated methods. Plasma concentrations of other possible metabolites from venetoclax may be determined with validated or non-validated methods.

5.3.3 Efficacy Variables

The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). The primary efficacy endpoint will be measured by complete remission rate (CR + CRi) of the subjects who have not been previously treated with B-cell receptor inhibitor (BCRi) therapy, as assessed by the investigator.

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression, (TTP), progression-free survival (PFS), overall survival (OS), and the CR rate in BCRi treated subjects.

Additional secondary objectives will be evaluated. Health Economic and Patient-Reported Outcome Measures will include the EQ-5D-5L, the FACT-Leu and the FACIT-F. Minimal residual disease (MRD) and the rate of MRD negativity in the peripheral blood are assessed as exploratory objectives in the peripheral blood and bone marrow (BM) by flow cytometry, PCR and/or sequencing.

Analyses of these endpoints are described in Section 8.0.

5.3.3.1 Primary Variables

For disease assessments, response will be assessed by the investigator based on analysis of clinical laboratory tests (hematology laboratory values), disease assessment physical examination, CT scan including neck, chest, abdomen, and pelvis (or MRI if CT with contrast is medically contraindicated); bone marrow aspirate are not required but results will be recorded if available. Subjects will be evaluated against the 2008 Modified IWCLL NCI-WG Criteria for Tumor Response[46] with CT imaging (or MRI). BM sample assessment is required to confirm CR.

At screening (baseline), all measurable disease must be documented by laboratory testing (hematologic status), physical examination, and CT scan. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 4 weeks before the beginning of the treatment with the exception of the CT scan (or MRI) which will be accepted if previously performed within 35 days prior to study drug initiation. During the study, subjects will have a disease assessment at Week 24, Week 36 and Week 48. To confirm the response, a CT scan will be performed at Week 48 on all subjects. For subjects with CR as response at Week 48, a BM sample is required to confirm the response.

Methods of Measurement

Disease response and progression will be assessed by analysis of peripheral blood, clinical examination, radiographic scans and bone marrow aspirate and biopsy.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Details on the analysis of peripheral blood required to assess response are provided in Section 5.3.1.2.

A full disease assessment physical examination should be performed to assess the extent of disease involvement. Physical examinations should include the evaluation of the

presence and degree of enlarged lymph nodes in two dimension (cervical, supraclavicular, axillary, inguinal and femoral nodes), hepatomegaly, and splenomegaly. These should be noted on all examinations irrespective of being present or absent. All measurements should be taken and recorded in metric notation using a ruler or calipers. Clinical lesions will only be considered measurable when they are superficial (e.g., palpable lymph nodes). The diameter, in two planes, of the largest palpable nodes in each of the following sites should be measured: cervical, supraclavicular, axillary, inguinal, and femoral. The presence of hepatomegaly and splenomegaly should be performed.

The 12 largest bi-dimensional lesions should be recorded in the eCRF.

- Target Lesions: A maximum of 12 target lesions may be selected (up to 6 nodal and 6 extra nodal). Target nodal lesions must be abnormal (> 1.5 cm in LDi [Longest Diameter] at baseline), clearly measurable and suitable for consistent, reproducible measurement in at least two perpendicular dimensions. Target extra nodal lesions must be > 1 cm in two perpendicular diameters at baseline.
- Non-Target Lesions: Sites will be classified as non-target lesions where disease is present but not selected for target lesions. A maximum of 10 non-target lesions can be selected. Non-target nodal lesions must be abnormal (> 1.5 cm in LDi at baseline). Non-target extra nodal lesions must be > 1 cm in two perpendicular diameters. Nodal and extra nodal lesions that were not selected as target lesions at baseline can be followed as non-target lesions.

Computed tomography (CT) is the preferred method to measure lesions selected for response assessment. CT scans (with contrast) should include neck, chest, abdomen, and pelvis scans. CT scans for response assessment may be limited to areas of prior involvement only, if required by local regulatory authorities. A contrast-enhanced MRI of the neck, chest, abdomen and pelvis with a non-contrast CT scan of the chest may be used if CT with contrast is medically contraindicated (e.g., severe contrast allergy). If MRIs are used instead of CT scans, MRIs should be used consistently throughout the study. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice

thickness contiguously. Spiral CT should be performed by use of 5 mm contiguous reconstruction algorithm; this specification applies to the regions of the neck, chest, abdomen and pelvis at baseline and follow-ups. The 12 largest bi-dimensional lesions should be recorded in the eCRF (6 nodal and 6 extra nodal).

For accurate overall response evaluation, ultrasound (US) should not be used to measure tumor lesions.

Details on bone marrow biopsy and aspirate are provided in Section 5.3.1.1. Study Procedures.

Tumor Response Criteria

Complete Remission (CR)

CR requires all of the following criteria:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L (4000/μL)
- Absence of lymphadenopathy (nodes > 15 mm in longest diameter or any extra nodal disease) by physical examination and CT scan
- No hepatomegaly or splenomegaly by physical examination (as determined by measurement below the relevant costal margin)
- Absence of disease or constitutional symptoms (B symptoms: unexplained fevers > 38°C or 100.4°F, drenching night sweats, > 10% body mass weight loss in the preceding 6 months)
- Blood counts above the following laboratory values:
  - Neutrophils > 1.5×10^9/L [1500/μL] (without the need for exogenous growth factors)
  - Platelets > 100×10^9/L [100,000/μL] (without the need for platelet transfusion or exogenous growth factors)
  - Hemoglobin > 110 g/L [11 g/dL] (without the need for blood transfusions or exogenous erythropoietin)

- Bone marrow at least normocellular for age, < 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. Bone marrow aspirate and biopsy should be performed after CR/CRi has been achieved. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. A marrow biopsy should be compared to a pre-treatment marrow if available. Subjects who are otherwise in a complete remission, but bone marrow nodules can be identified histologically should be considered to be nodular PR (nPR). Immunohistochemistry (IHC) should be performed to define whether these nodules are composed of primarily T cells or lymphocytes other than CLL cells, or CLL cells.

Complete Remission with Incomplete Marrow Recovery (CRi)

Subjects who fulfill the criteria for CR (including bone marrow) but who have persistent cytopenia (anemia or thrombocytopenia or neutropenia) apparently unrelated to CLL but related to drug toxicity will be considered CRi. The marrow evaluation described above should be performed with scrutiny and not show any clonal infiltrate.

Partial Remission (PR)

To be considered a PR at least 2 of the following must be met:

- ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.
- ≥ 50% reduction in lymphadenopathy.
- ≥ 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy).

In addition at least **one** of the following criteria must be met:

- Neutrophils > 1,500/μL or ≥ 50% improvement over baseline.
- Platelets > 100,000/μL or ≥ 50% improvement over baseline.

- Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline without transfusions or exogenous growth factors.

Table 5. 2008 Modified IWCLL NCI-WG Criteria for Tumor Response

Parameter	Complete Remission (CR) All Criteria Must be Met[a]	Partial Remission (PR) at Least 2 Criteria from Group A AND at Least 1 Criterion from Group B Must be Met	Progressive Disease (PD) at Least 1 Criterion from Group A OR 1 Criterion from Group B Must be Met[b]	Stable Disease (SD) All Criteria Must be Met
Group A				
Lymphadenopathy	None > 1.5 cm	Decrease ≥ 50%[c]	Increase ≥ 50%[d] or any new LN > 1.5 cm	Change of –49% to +49%[e]
Blood Lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline (≥ 5000/µL)	Change of –49% to +49%
Hepatomegaly[f]	None	Decrease ≥ 50%	Increase ≥ 50%[g]	Change of –49% to +49%
Splenomegaly[f]	None	Decrease ≥ 50%	Increase ≥ 50%[g]	Change of –49% to +49%
Marrow	Normocellular, < 30% lymphocytes, no B lymphoid nodules; hypocellular marrow defines CRi	N/A	N/A	N/A
Group B				
Platelet Count	> 100,000/µL[h]	> 100,000/µL or increase ≥ 50% over baseline[h]	Decrease of ≥ 50% from baseline secondary to CLL	Change of –49% to +49%
Hemoglobin	> 11.0 g/dL[h]	> 11.0 g/dL or increase ≥ 50% over baseline[h]	Decrease of > 2 g/dL from baseline secondary to CLL	Increase to ≤ 11.0 g/dL over baseline, or decrease < 2 g/dL
Neutrophils	> 1500/µL[h]	> 1500/µL or increase ≥ 50% over baseline[h]	Decrease ≥ 50% from baseline secondary to CLL	N/A
New Lesions	None	None	Appearance of new palpable lymph nodes (> 1.5 cm in longest diameter) or any new extra nodal lesion (regardless of size) or transformation to a more aggressive histology, e.g., Richter Syndrome[d]	None

Table 5. 2008 Modified IWCLL NCI-WG Criteria for Tumor Response (Continued)

Parameter	Complete Remission (CR) All Criteria Must be Met[a]	Partial Remission (PR) at Least 2 Criteria from Group A AND at Least 1 Criterion from Group B Must be Met	Progressive Disease (PD) at Least 1 Criterion from Group A OR 1 Criterion from Group B Must be Met[b]	Stable Disease (SD) All Criteria Must be Met
Other Considerations				
Non-Target Lesions	Nodes must be normal size as visually estimated; extra nodal and other assessable disease should be absent	No change/decreased	Unequivocal progression	No change or decrease or non-substantial increase
Target Extra Nodal Disease	Absence of any extra nodal disease by physical examination (palpable, visualized extra nodal) and CT scan	≥ 50% decrease in SPD	≥ 50% increase in the longest diameter of any extra nodal lesion	Not CR, CRi, PR, or PD

CLL = chronic lymphocytic leukemia; LN = lymph nodes; N/A = Not applicable; SPD = sum of the products of diameters; CRi = complete remission with incomplete marrow recovery

a. CR also requires the lack of disease-related constitutional symptoms.

b. Transformation to a more aggressive histology (e.g., Richter Syndrome) would also qualify as a PD.

c. Sum of the products of multiple LNs (as evaluated by CT scans). Note in eCRF if by physical examination only.

d. Increase in SPD of multiple nodes, or in greatest diameter of any previous site, or appearance of any new lymphadenopathy or organomegaly. Degree of change in LN or lymphocyte counts should be measured from nadir (lowest post-treatment) values.

e. Sum products of up to 6 LNs or LN masses (target lesions), with no increase in an LN or new enlarged LN. Increase of < 25% in small LNs (< 2 cm) not significant. Decreases should be measured compared to baseline (pre-treatment) values.

f. If enlarged before therapy.

g. An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.

h. Without the need for exogenous growth factors or transfusions.

5.3.3.2 Definition of Disease Progression

Disease progression according to 2008 Modified IWCLL NCI-WG Criteria for Tumor Response is characterized by at least one of the following:

- Appearance of any new lesion, such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. An increase by 50% or more in greatest determined diameter of any previous site.
- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per microliter. The increase should be assessed against the best response while on study.
- Transformation to a more aggressive histology (e.g., Richter's Syndrome). Whenever possible, this diagnosis should be confirmed by lymph node biopsy. For subjects experiencing disease progression due to Richter's Syndrome while on study, supplemental data may be collected.
- Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL.

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: serious adverse event and adverse event monitoring including AEs of special interest (Section 6.1.1.4), vital signs, physical examination, and laboratory assessments. Certain types of events require immediate reporting to the Sponsor, as outlined in Section 6.1.5. Safety will be monitored on an ongoing basis and summarize periodically in aggregate safety reports and end of study.

5.3.5 Pharmacokinetic Variables

Values for the PK parameters of venetoclax, including the apparent clearance (CL/F), will be determined using a population PK modeling approach. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.6 Biomarker Variables

Biomarker Research Variables

Peripheral blood and/or bone marrow biospecimens will be collected to conduct exploratory analyses to investigate biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. Cells isolated from the peripheral blood/bone marrow may be analyzed to assess specific genetic mutations within the tumor cells, or to track the tumor cells to determine the presence of minimal residual disease. Additionally, the expression levels (RNA or protein) of molecules involved in controlling the apoptosis machinery, including but not limited to BCL-2 family members, may also be correlated with efficacy.

Evaluations may include analyzing biomarkers related to the pathway(s) targeted by the study drug or those believed to be related to the disease or to drug response. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to CLL, and/or in the development of new therapies and diagnostic tests. The results of biomarker testing may not be included with the study summary.

5.3.7 Health Economic and Patient-Reported Outcome Measures

5.3.7.1 Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) Questionnaire

The FACT-Leu is a 44-item, leukemia-specific questionnaire designed to assess subject health-related quality of life (HRQoL) and leukemia-specific symptoms using a 'core' set of questions (Functional Assessment of Cancer Therapy-General; FACT-G), as well as a cancer site-specific leukemia subscale.[34] The FACT-G is a 27-item compilation of general questions scored on a 5-point scale ranging from 0 = "not at all" to 4 = "very much."[35] The items are divided into 4 primary HRQOL domains: Physical Well-being (7 items; score range, 0 – 28), Social/Family Well-being (7 items; score range, 0 – 28), Emotional Well-being (6 items; score range, 0 – 24), Functional Well-being (7 items; score range, 0 – 28).[36]

The leukemia-specific subscale consists of 17 items (score range, 0 – 68) that assess subject concerns relating to leukemia. Three summary scales: FACT-Trial Outcome Index (score range, 0 – 124) a summary scale composed of the Physical Well-being, Functional Well-being, and leukemia-specific subscales; FACT-G (score range, 0 – 108) and the FACT-Leukemia Total (score range, 0 – 176) can also be calculated. Higher scores are reflective of better HRQOL. Minimally important differences (MIDs) have been identified for the different FACT-Leu scales: Physical Well-being, 2 – 3 points; Social/Family Well-being, not available; Emotional Well-being, 2 points; Functional Well-being, 2 – 3 points; FACT-G, 3 – 7 points; Leukemia-specific subscale, 4 – 7 points; FACT-Trial Outcome Index, 5 – 6 points; and FACT-Leukemia Total, 6 – 12 points.

Scores will be summarized descriptively at each assessment. The impact of treatment on quality of life over time will be assessed by calculating the change in scores from baseline at each assessment time point. Scores will be calculated according to the FACT-Leu scoring manual.

5.3.7.2 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Scale

The FACIT-F measures fatigue and its effect on functioning and daily activities.[37] The FACIT-F has 13 items answered on a 5-point rating scale based on a 7-day recall period. Scores range from 0 to 52, with lower scores reflecting greater fatigue. The instrument has shown good reliability and validity based on analyses of the general population in the United States, subjects with cancer, and subjects with rheumatoid arthritis.[37-39] The MID of the FACIT-F scale has been determined to be 3 points.[40]

Scores will be summarized descriptively at each assessment. The impact of treatment on fatigue over time will be assessed by calculating the change in score from baseline at each assessment time point. Scores will be calculated according to the FACIT-F scoring manual.

5.3.7.3 EuroQol 5 Dimensions (EQ-5D-5L)

The EuroQol 5 Dimensions (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations.[41,42] The EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The scores for the 5 dimensions are used to compute a single utility index score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health. The MID for the EQ-5D utility index score in cancer subjects is 0.08, and the MID for EQ-5D VAS is 7.[43,44]

Each of the five dimensions of the EQ-5D-5L, the VAS and overall utility score will be calculated using the EuroQol scoring manual, and summarized (mean, std. dev., median) at each assessment. The impact of treatment over time will be assessed by calculating the change in score from baseline at each assessment time point.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study and/or study drug treatment at any time. In addition, the investigator may discontinue a subject from study drug treatment at any time if the investigator considers it necessary for any reason including:

- The investigator believes it is in the best interest of the subject
- Subject's response to therapy is unsatisfactory, as evidenced by progression of disease while on study drug
- The subject requires other cancer treatment (e.g., radiotherapy, cancer-related surgery as a result of tumor progression, alternate anti-neoplastic agents) during the study period
- unacceptable toxicity
- The subject becomes pregnant while on study

- drug protocol non-compliance

The investigator will inform AbbVie prior to discontinuing a subject from the study by contacting the Clinical Team Leader as identified in Section 7.0. All subjects will be included for analysis of safety data. Subjects who withdraw from the study will not be replaced unless they are not evaluable.

Subjects will continue to be followed for unresolved AEs and survival information for any subject who has not experienced PD at the time of venetoclax discontinuation.

Final Visit

Upon study drug discontinuation and/or upon discontinuation from the study, the reason(s) for discontinuation will be recorded in electronic case report forms (eCRFs) and a final visit will be performed. The final visit procedures as listed in Appendix D should be performed as soon as possible after discontinuation from study drug.

30-Day Safety Follow-Up Visit

A 30-Day Safety Follow-up Visit should be performed approximately 30 days (± 3 days) following the last dose of venetoclax. The 30 day safety follow up procedures listed in Appendix D should be performed.

Post Treatment and Survival Follow-Up Calls

For subjects who discontinue venetoclax therapy, but do not discontinue the study post treatment follow-up calls will be performed every 6 months (± 7 days) for survival information (i.e., disease progression, the date and cause of death, post-treatment cancer therapies, etc.) and will be collected via telephone calls for a period of 2 years and recorded in the eCRFs.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended

termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Venetoclax tablets should be taken orally once daily with a meal and water in the morning at approximately the same time each day. Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

If the subject misses a dose of venetoclax within 8 hours of the time it is taken, the subject should take the missed dose as soon as possible on the same day and resume the normal daily dosing schedule the following day. If a subject misses a dose by more than 8 hours, the subject should not take the missed dose and resume the normal daily dosing schedule the following day.

In cases of vomiting after taking venetoclax, no additional dose (tablets) should be taken that day. The next dose should be taken at the usual time the following day.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 6.

Table 6. Identity of Investigational Product

Study Drug	Trademark	Formulation	Route of Administration	Manufacturer
Venetoclax	N/A	10 mg Tablet Film coated	Oral	AbbVie
Venetoclax	N/A	50 mg Tablet Film coated	Oral	AbbVie
Venetoclax	N/A	100 mg Tablet Film coated	Oral	AbbVie

Each site will be responsible for tracking the lot numbers and expiration dates for all non-investigational medicinal products (e.g., generic name and generic name) that are dispensed.

5.5.2.1 Packaging and Labeling

The venetoclax tablets will be packaged in blister packs during the dose-titration phase and in high density polyethylene (HDPE) plastic bottles thereafter to accommodate the study design. Each container will be labeled as required per country requirements. Labels must remain affixed to the container.

5.5.2.2 Storage and Disposition of Study Drug

The venetoclax supplied in this study is for investigational use only, and must only be used within this study. All study drug must be maintained under adequate security and stored under conditions specified on the label until dispensed for subject use or returned to AbbVie or representative.

The tablets must be stored at a controlled room temperature of 15° to 25°C (59° to 77°F).

5.5.3 Method of Assigning Subjects to Treatment Groups

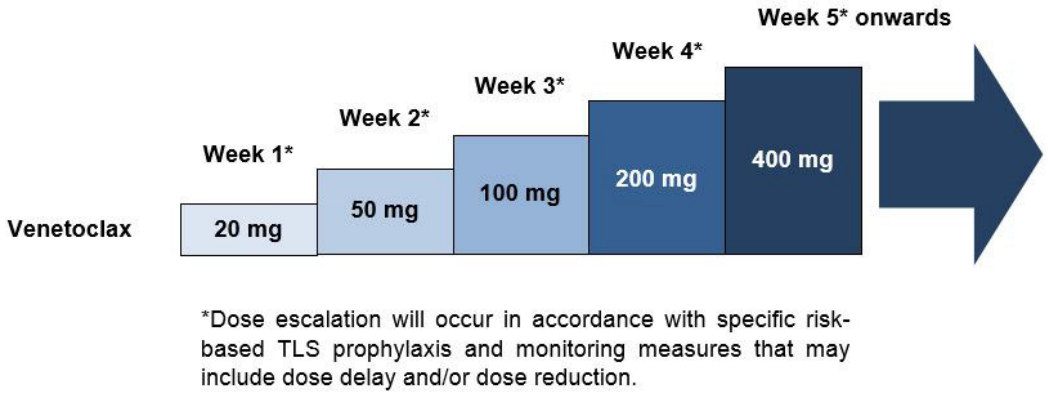
All subjects are assigned to the same treatment group in this single arm study. Subjects will be allocated a unique consecutive subject number at Screening. Subject numbers will consist of 5 digits (XXX01), with the first three digits denoting site number and the last

2 digits as the subject number, beginning with 01. All subjects will be enrolled using an (Interactive Response Technology) IRT. Before the study is initiated, each site will be provided with the IRT user instructions, which provides direction on how to use the IRT via the Web or the telephone. Since this is an open-label study, subjects will maintain the same subject number, regardless of the number of re-screens and through the duration of the study. The site, in conjunction with the Sponsor, will be responsible for assignment of all unique subject numbers at Screening and dose assignments if the subject is not a screening failure.

5.5.4 Selection and Timing of Dose for Each Subject

Venetoclax will be administered orally once daily (QD) beginning with a dose-titration phase. As shown in Figure 2, the initial venetoclax dose is 20 mg QD. After 1 week of treatment at 20 mg QD, the dose will be escalated to 50 mg QD followed by subsequent increases, each after 1 week, to 100 mg QD, 200 mg QD and the maximum dose of 400 mg QD. The maximum dose of venetoclax for this protocol will not exceed 400 mg per day. The 5-week dose-titration phase is designed to gradually reduce tumor burden (debulk) and decrease the risk of tumor lysis syndrome. All study subjects will be categorized at Screening according to their risk for developing TLS. Their dose management, including during the dose-titration phase, will be conducted in accordance with their risk for developing TLS (see Section 6.1.8.1) and may include dose delay and/or dose reduction as required for prophylaxis and management of TLS.

Figure 2. 5-Week Dose-Titration Schematic



5.5.5 Blinding

This is an open-label, single arm study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

To document compliance with the treatment regimen, subjects will be instructed to return all unused tablets and/or containers, even if empty and any other study related items as necessary, to the study coordinator at scheduled study visits. Compliance will be monitored and documented by the study coordinator on the appropriate form. The study coordinator will question the subject regarding adherence to the dosing regimen, record the number of tablets and/or containers returned, the date returned and determine treatment compliance before dispensing new venetoclax to the subject. Compliance below 80% will require counseling of the subject by study site personnel.

5.5.7 Drug Accountability

Investigator or representative will verify that study drug supplies are received intact and in the correct amounts. Documentation of the receipt of supplies will be supported by a signed and dated Proof of Receipt or similar shipping document in IRT. A current (running) and accurate inventory of venetoclax will be kept by the site and will include lot number, Proof of Receipt number(s), container numbers, blister pack numbers, subject initials, initials of person who dispensed the drug and the date study drug was administered for each subject. An overall accountability of study drug will be performed and verified by AbbVie monitor(s) throughout the study and at the study site closeout visit. All study drug unit doses must be inventoried, accounted for, and returned to AbbVie or destroyed per instructions from AbbVie and according to local regulations. All original containers (containing partially used or unused study drug) will be returned to AbbVie according to instructions from AbbVie or the designated monitor(s). If pre-arranged between AbbVie and the site, destruction of used and unused study drug containers will be performed at the site. Empty containers will be destroyed at the site. Labels must remain attached to the containers.

The investigator and/or named sub-investigators agree not to supply study medication to any persons not enrolled in the study.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Study M15-550 is being conducted primarily to assess the efficacy of venetoclax monotherapy. This study is a single-arm trial; therefore, there is no control group or treatment blinding. The study will be conducted at multiple study centers globally to ensure a broad representation of the patient population and clinical care settings.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study.

5.6.3 Suitability of Subject Population

Venetoclax monotherapy has shown favorable activity in relapsed/refractory CLL subjects including subjects with 17p deletions. Venetoclax is expected to be as active in subjects selected for TP53 mutations as these patient populations overlap and the oncogenic effect of both genetic defects occurs via p53 abrogation. In addition, venetoclax has shown activity in subjects with relapsed or refractory CLL who have been previously treated with a B-cell receptor inhibitor. These subjects can participate in this study and may have relapsed or be refractory to ibrutinib or idelalisib containing regimen.

All subjects enrolled in the study will have adequate performance status and hematologic, renal and hepatic function to undergo venetoclax treatment.

5.6.4 Selection of Doses in the Study

Venetoclax dosing will be introduced at an initial dose of 20 mg QD and escalated to a final dose of 400 mg QD. The maximum dose of venetoclax for this protocol will not exceed 400 mg per day. The daily dose will be titrated in the following weekly increments, as tolerated: 20 mg, 50 mg, 100 mg, 200 mg, and 400 mg. The 400 mg final dose was selected for the ongoing, Phase 2 study of venetoclax monotherapy in relapsed/refractory CLL subjects with 17p deletion (Study M13-982) based on time-to-response and logistic regression modelling of data from CLL/SLL subjects enrolled in the Phase 1 Study M12-175.

The initial 20 mg venetoclax dose and weekly incremental increases in the dose-titration phase were implemented for Study M13-982 to reduce the risk of TLS. Preliminary safety data from that study indicate the initial dose, the dose-titration phase and the final maximum dose are tolerable.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability,

reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1.1 through 6.1.5. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.1.8 Toxicity Management) or if the investigator considers them to be adverse events.

For this protocol, disease progression is an efficacy endpoint. These data will be captured as efficacy assessment data only. Thus, events that are clearly consistent with the expected pattern of progression of the underlying disease (such as transformation to more aggressive histology) will result in discontinuation from the study and should not be recorded as adverse events but reported on the Study Completion eCRF. However, if a subject experiences an adverse event (e.g., pneumonia, pyrexia, fatigue, etc.) and is also found to have disease progression, report the adverse event. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done, will be considered an adverse event.

A treatment-emergent AE is defined as any AE reported by a subject with onset or worsening from the time that the first dose of venetoclax is administered until 30 days have elapsed following discontinuation of venetoclax administration.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) **within 24 hours** of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form. Deaths related to disease progression will not be recorded as serious adverse events (see Section 6.1.2.1.1).

Hospitalization of a subject to allow observation and management (e.g., for IV hydration) for the purpose of TLS prophylaxis will not be captured as an SAE, unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization (e.g., abnormal post-dose TLS laboratories that necessitate therapeutic medical intervention, etc.).

Hospitalization of a subject following the 30-Day Safety Follow-Up visit due to a subsequent line of therapy will not be captured as a SAE.

6.1.1.3 Adverse Events Commonly Associated with CLL Study Population and/or Progression of CLL

Certain AEs are anticipated to occur in the study population at some frequency independent of drug exposure. Such events include known consequences of CLL (e.g., symptoms, disease progression) and events unlikely to be related to the underlying

disease under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population).

These events are listed in Appendix J.

These AEs may occur alone or in various combinations and are considered expected for reporting purposes for this protocol.

Cytopenias (anemia, neutropenia, or thrombocytopenia) are part of the natural history of CLL. Persistent cytopenias at the same CTCAE grade as reported at baseline are not to be captured as adverse events, unless they fulfill a seriousness criteria, result in permanent discontinuation of a study drug, or the investigator had an identifiable cause other than the underlying disease. However, all laboratory data should be entered regardless of whether an adverse event is reported.

Although exempted from expedited reporting to certain Health Authorities and ECs/IRBs as individual cases, if an event commonly associated with CLL or progression of CLL meets seriousness criteria, it must be reported to AbbVie within 24 hours of the site being made aware of the SAE (as defined in Section 6.1.4). However, if the event was unequivocally due to disease progression, it should not be reported as an adverse event even if serious or fatal. For deaths related to disease progression, the date and cause of death will be recorded on the appropriate case report form, but the death will not be expedited as an individual case safety report (ICSR) to regulatory authorities.

6.1.1.4 Adverse Events of Special Interest

TLS and neutropenia are identified risks. Serious Infection is a potential risk.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each AE according to the NCI CTCAE v4.03. If a reported AE increases in severity, the initial AE should be given an outcome date and a new AE must be reported on a different onset date than the end date of the previous adverse event to reflect the change in severity. The dates on the AEs cannot overlap. For

all reported SAEs that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity.

For AEs not captured by the NCI CTCAE, the following should be used:

Grade 1	The adverse event is transient and easily tolerated by the subject (mild).
Grade 2	The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe).
Grade 4	The adverse event is life-threatening requiring urgent intervention (severe).
Grade 5	The adverse event resulted in death of the subject (severe).

6.1.2.1 Adverse Events Expected Due to Study-Related Endpoints

6.1.2.1.1 Deaths

For this protocol, overall survival is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 6.1.4) that are attributed by the investigator solely to progression of CLL should be recorded ONLY on the Study Completion eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 6.1.4 and Section 6.1.5). Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event

eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. During survival follow-up, deaths attributed to progression of CLL should be recorded only on the Survival eCRF.

6.1.2.1.2 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be subject to expedited reporting.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other Cause" of event must be provided by the investigator for the SAE.

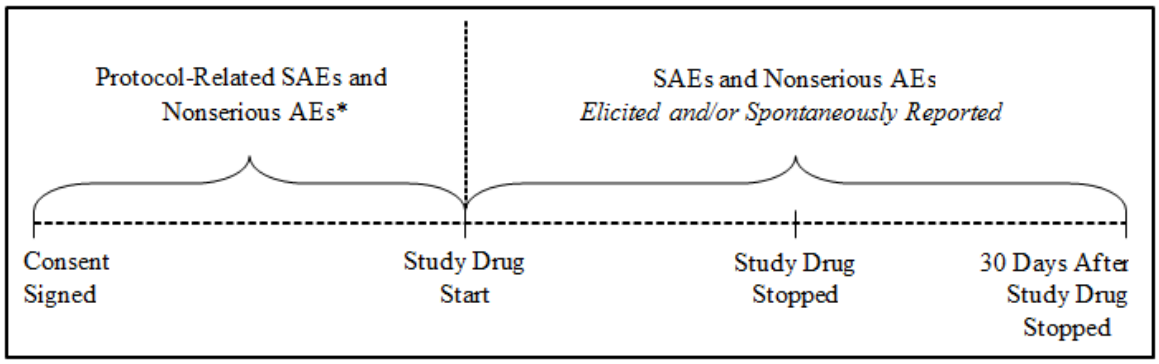
6.1.4 Adverse Event Collection Period

All adverse events reported from the time of venetoclax administration until 30 days, following discontinuation of venetoclax administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol related serious adverse events and nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

All AEs should be followed until resolution, return to baseline or determined to be stable per the investigator.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



* Only if considered by the investigator to be causally related to study-required procedures.

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical

Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Oncology Safety Team at:

[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Safety Phone: (847) 935-2609
Safety Email: SafetyManagement_Oncology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

[redacted] MD PhD
Medical Director
Oncology Global Medical Affairs
AbbVie
Neuhofstrasse 23
CH-6341 Baar
Switzerland

Office/Cell: [redacted]
Fax:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

All subjects should be informed that contraceptive measures should be taken throughout the study and for 30 days after the last dose of venetoclax. Male subjects should be informed that contraceptive measures should be taken by their female partners.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of a pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. The medical outcome of either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Data Monitoring Committee

The Data Monitoring Committee (DMC) will review safety data intermittently according to the DMC charter. Details of the DMC review are presented in the DMC charter. The separate charter has been created to provide detailed descriptions of the schedule of

analyses and the DMC meetings. DMC membership, responsibilities and the description of the data coordinating center are documented in the charter.

6.1.8 Toxicity Management

6.1.8.1 Prophylaxis and Management of Tumor Lysis Syndrome

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 – 8 hours following the first dose of venetoclax and at each dose increase.

Risk Assessment for tumor lysis syndrome: The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Refer to Appendix H for disease burden categories. Reduced renal function (creatinine clearance [CrCl] < 80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases with venetoclax treatment.

Additional comorbidities may further increase the risk for TLS.

Prior to initiating venetoclax, tumor burden assessment, including radiographic evaluation (refer to Section 5.3.1.1 Study Procedures – CT scans) must be performed for all subjects during Screening. The full blood chemistry/hematology panel (refer to Table 4 Clinical Laboratory Tests) should be performed in all subjects during the Screening period in order to assess eligibility and to correct pre-existing abnormalities.

If the chemistry/hematology panel was assessed more than 72 hours prior to the 1st dose of venetoclax, an additional full lab panel should be performed and reviewed within 72 hours prior to dosing in order to make a treatment decision. Please refer to Section 5.3.1.1 Study Procedures – Hematology and Chemistry and Appendix H for blood chemistry monitoring and frequency for subjects whether treated in the outpatient setting or in the hospital, during the 5-week titration period.

Prophylaxis for tumor lysis syndrome: The prophylaxis measures listed below should be followed. More intensive measures, including hospitalization, should be employed as overall risk increases. Interrupt dosing if needed. Please refer to Appendix H:

Hydration: Subjects should be adequately hydrated prior to starting treatment with venetoclax and during the dose-titration phase. The recommended volume is 1.5 to 2.0 L (approximately 6 to 8 glasses) of water each day. Subjects should be instructed to drink water starting 2 days before and on the day of the first dose, and every time the dose is increased. Intravenous (IV) fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration. For subjects for whom volume overload is considered a significant risk, hospitalization should be considered.

Anti-hyperuricemic agents: Anti-hyperuricemic agents should be administered 2 to 3 days prior to starting treatment with venetoclax and may be continued through the titration phase. Rasburicase should be considered if the subject's baseline uric acid is elevated.

Laboratory Assessments:

Please refer to Section 5.3.1.1 – Study Procedures – Hematology and Chemistry and Appendix H.

Hospitalization: High disease burden subjects can be hospitalized on the day of the first dose of 20 mg and 50 mg of venetoclax for more intensive prophylaxis and monitoring through the first 24 hours. Additional laboratory time points can be performed (4, 8, 12 and 24 hours post dose). Refer to Appendix H for additional details on patient prophylaxis and blood chemistry monitoring. Hospitalization should be considered for subsequent dose increases based on reassessment of risk.

6.1.8.2 Dose Modifications Based on Toxicities

Dosing interruption and/or dose reduction may be required. See Table 7 for dose modifications for hematologic and other toxicities related to venetoclax. For subjects who have had a dosing interruption greater than 1 week during the first 5 weeks of dose titration or greater than 2 weeks when at the daily dose of 400 mg, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose titration).

Tumor Lysis Syndrome

If a subject experiences blood chemistry changes suggestive of TLS, the following day's venetoclax dose should be withheld. If resolved within 24 to 48 hours of last dose, treatment with venetoclax can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see Table 7 and Table 8). When resuming treatment with venetoclax after interruption due to TLS, the instructions for Prophylaxis for tumor lysis syndrome should be followed.

Other Toxicities

Treatment with venetoclax should be withheld for any grade 3 or 4 non-haematological, grade 3 or 4 neutropenia with infection or fever, or grade 4 haematological toxicities, except lymphopenia. To reduce the risk of infection associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to grade 1 or baseline level (recovery), therapy with venetoclax may be restarted at the same dose. If the toxicity recurs, and for any subsequent occurrences, the dose reduction guidelines in Table 7 and Table 8 should be followed when resuming treatment with venetoclax following resolution. A larger dose reduction may occur at the discretion of the investigator. For subjects who require dose reductions to less than 100 mg for more than 2 weeks due to adverse events, discontinuation of venetoclax should be considered.

Table 7. Recommended Dose Modifications for Toxicities

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 – 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 8).
		For any events of clinical TLS[a], resume at a reduced dose following resolution (see Table 8).
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in Table 8 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the investigator.
Hematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 8 when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the physician.
Consider discontinuing venetoclax for patients who require dose reductions to less than 100 mg for more than 2 weeks.		

a. Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias and/or seizures or sudden death.

Note: Adverse reactions were graded using NCI CTCAE version 4.03.

Table 8. Dose Modification for Toxicity During Venetoclax Treatment

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10

a. During the dose titration phase, continue the reduced dose for 1 week before increasing the dose.

Dose Modifications for Use with CYP3A Inhibitors

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase. Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated.

Concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation and titration doses of venetoclax should be reduced by at least 50%. Subjects should be monitored more closely for signs of toxicities.

For subjects who have completed the dose-titration phase and are on a steady daily dose of venetoclax, the venetoclax dose should be reduced by at least 50% when used concomitantly with moderate CYP3A inhibitors and by at least 75% when used concomitantly with strong CYP3A inhibitors. Subjects should be monitored more closely for signs of toxicities. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the CYP3A inhibitor.

Missed Dose

If a subject misses a dose of venetoclax within 8 hours of the time it is usually taken, the subject should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a subject misses a dose by more than 8 hours, the subject should not take the missed dose and should resume the usual dosing schedule the following day.

If a subject vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.

6.1.8.3 Management of Neutropenia

Nonclinical and clinical experience indicates that venetoclax may cause neutropenia. Subjects with a history of neutropenia who have received multiple prior therapies and/or have significant bone marrow involvement may be at a particularly high risk.

Grade 3 or 4 neutropenia has been reported in subjects treated with venetoclax. Complete blood counts should be monitored throughout the treatment period. Dose interruptions or dose reductions are recommended for subjects with severe neutropenia. Supportive measures including antimicrobials for any signs of infection and prophylactic use of growth factors (e.g., G-CSF) should be considered.

6.1.8.4 Immunization

Live attenuated vaccines should not be administered prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied. Patients should be advised that vaccinations may be less effective.

6.1.8.5 Management of Hematologic Toxicities Other Than Neutropenia or Lymphopenia

Venetoclax treatment should be withheld for any Grade 4 hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in Table 8 should be

followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

6.1.8.6 Management of Non-Hematologic Toxicity

Venetoclax treatment should be withheld for any clinically relevant ≥ Grade 3 non-hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in Table 8 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event by entering the product complaint in RAVE, the EDC system. If the EDC system is not operable, the Product Complaint Form should be used and emailed to: RD_PQC_QA@abbvie.com **within 24 hours** of the study site's knowledge of the event. Product Complaints occurring during

the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and their assigned AbbVie Clinical Monitor(s). In addition, the following AbbVie representatives should be contacted:

Primary Contact:

[redacted]
Study Project Manager I
AbbVie Oncology
Clinical Program Development
1 N. Waukegan Rd.
North Chicago, IL 60064
USA

Office: [redacted]
Email:

Alternate Contact:

[redacted]
Study Management Associate III
AbbVie AB
Hemvärnsgatan 9 (visitor address)
Box 1523
SE-171 29 Solna
Sweden

Office: [redacted]
Email:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Efficacy analyses will be performed on all subjects enrolled into the study, unless otherwise specified. The date of enrollment is defined as the date that the Interactive Response Technology (IRT) provided a subject number.

Safety analyses will be performed on all subjects who receive at least one dose of venetoclax.

Detailed analysis descriptions will be provided in a separate statistical analysis plan.

8.1.1 Baseline Characteristics

All baseline summary statistics will be based on characteristics prior to the initiation of study drug. Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to the first dose of study drug.

8.1.1.1 Demographics

Descriptive statistics will be provided for baseline demographic variables. Age, height and weight will be summarized with means, medians, standard deviations and ranges. Frequencies and percentages will be provided for gender and race.

8.1.1.2 Medical Histories

Frequencies and percentages will be summarized for each medical history parameter.

8.1.2 Efficacy Endpoints

8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint will be complete remission rate (CR + CRi) of the subjects who have not been previously treated with BCRi therapy defined as the proportion of subjects achieving a CR or CRi as their best response (per the investigator assessment) based on IWCLL NCI-WG criteria.

In addition, the ninety-five percent (95%) confidence interval based on binomial distribution will be constructed for the calculated CR rate.

The assessment of response will be performed when all subjects enrolled have completed their Week 48 disease assessment, or after all enrolled subjects have discontinued venetoclax, whichever is earlier. Subjects who have not achieved complete remission (CR + CRi) prior to this time will be considered to be non-responders in the calculation of CR rate.

8.1.2.2 Secondary Efficacy Endpoints

Key secondary efficacy endpoints will include overall response rate, duration of response, time to progression, progression-free survival, overall survival, and the CR rate in previously BCRi treated subjects.

ORR will be assessed as the proportion of subjects with an overall response (CR + CRi + nPR + PR) based on the IWCLL NCI-WG criteria. The ninety-five percent (95%) confidence interval based on binomial distribution will be constructed for the calculated CR rate.

Duration of response will be defined as the number of days from the date of first response (CR, CRi, nPR, or PR) to the earliest recurrence or PD. If a subject is still responding, then the subject's data will be censored at the date of the subject's last available disease assessment. For subjects who never experience response, the subject's data will be censored on the date of enrollment. Duration of response will be analyzed by Kaplan-Meier methodology using data for all enrolled subjects. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

Time to progression (TTP) will be defined as the number of days from the date of first dose or enrollment if not dosed to the date of earliest disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject does not experience disease progression, then the data will be censored at the date of last available disease assessment. Data for patients who receive non-protocol, CLL therapy prior to disease progression will be censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the baseline visit will be censored at the time of enrollment plus 1 day. TTP will be analyzed by Kaplan-Meier methodology using data for all subjects enrolled. Median time TTP will be calculated and 95% confidence interval for median time TTP will be presented.

Progression-free survival (PFS) will be defined as the number of days from the date of first dose to the date of earliest disease progression or death. All disease progression will be included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject does not experience disease progression or death, then the data will be censored at the date of last disease

assessment. Data for subjects who receive non-protocol CLL therapy prior to disease progression will be censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the baseline visit will be censored at the time of enrollment plus 1 day. PFS will be analyzed by Kaplan-Meier methodology using data for all subjects enrolled. Median time PFS will be calculated and 95% confidence interval for median time PFS will be presented.

Overall survival (OS) will be defined as number of days from the date of first dose to the date of death for all dosed subjects. For subjects who did not die, their data will be censored at the date of last study visit or the last known date to be alive, whichever is later. OS will be analyzed by Kaplan-Meier methodology using data from all enrolled subjects. Median time survival will be estimated and 95% confidence interval for the median time survival will be presented.

The CR rate (CR + CRi) in previously treated BCRi subjects will be assessed based on the 2008 Modified IWCLL NCI-WG criteria. The ninety-five percent (95%) confidence interval based on binomial distribution will be constructed for the calculated CR rate.

8.1.2.3 Exploratory Efficacy Endpoints

The rate of MRD negativity in subjects will be summarized. This rate will be defined as the proportion of subjects who had MRD negativity status. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided. In addition, the relationship between venetoclax PK and efficacy parameters including MRD level and CR will be evaluated.

8.1.3 Timing of Efficacy Endpoints and Safety Evaluations

The date the last enrolled subjects has completed their Week 48 disease assessment, or after all enrolled subjects have discontinued venetoclax, whichever is earlier, will be defined as the data "cutoff" date for the efficacy analyses. Efficacy and safety data up to and including this date will be collected. Exact data cutoff date for the efficacy analysis will be detailed in a SAP which will be signed off prior to the data cut-off date. During

this data collection period, active subjects will continue to receive venetoclax, as applicable. When data collection is complete and all data management quality assurance (QA) and quality control (QC) procedures are performed, the clinical database data will be extracted for documentation and statistical analyses. Any active subjects will continue to receive venetoclax until they discontinue or for up to 2 years. Once the last enrolled subject discontinues/completes the study, the study will be considered complete and all remaining data will be collected and entered into the clinical database.

8.1.4 Additional Efficacy Analyses

Health Economic and Patient Reported Outcome measures will include the FACT-Leu, the FACIT-F, and the EQ-5D-5L.

For the FACT-Leu, scores will be summarized descriptively at each assessment. The impact of treatment on quality of life over time will be assessed by calculating the change in scores from baseline at each assessment time point. Scores will be calculated according to the FACT-Leu scoring manual.

For the FACIT-F, scores will be summarized descriptively at each assessment. The impact of treatment on fatigue over time will be assessed by calculating the change in score from baseline at each assessment time point. Scores will be calculated according to the FACIT-F scoring manual.

Each of the five dimensions of the EQ-5D-5L, the Visual Analog Scale (VAS) and overall utility score will be calculated using the EuroQol scoring manual, and summarized (mean, std. dev., median) at each assessment. The impact of treatment over time will be assessed by calculating the change in score from baseline to each assessment time point.

Alternative statistical analyses may be performed if deemed necessary and helpful in understanding the drug effect.

8.1.5 Safety

The safety of venetoclax will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, and laboratory parameters.

Safety analyses will be performed for all subjects who take at least one dose of venetoclax.

8.1.5.1 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of venetoclax.

Analyses will not include those that have an onset greater than 30 days after the last dose of venetoclax.

Treatment-emergent adverse events will be summarized by preferred terms within a System and Organ Class according to the most current MedDRA. In addition, the percentage of subjects experiencing an adverse event at a NCI CTCAE toxicity grade, and relationship to study drug will be provided.

8.1.5.2 Serious Adverse Events

Serious adverse events will be summarized using the same methods as Adverse Events described above.

8.1.5.3 Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of the last dose of study drug, and (2) for deaths occurring more than 30 days of the last dose of study drug.

8.1.5.4 Analyses of Laboratory Data

Where applicable, blood chemistry and hematology determinations will be categorized according to NCI CTCAE version 4.03 grades, and shifts from baseline NCI CTCAE grades to maximum and final post-baseline grades will be assessed.

The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the last post-baseline measurement collected no more than 30 days after the last dose of study drug. The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post-baseline grades of 3 to 4 will be summarized. Detailed listings of data for subjects experiencing NCI CTCAE Grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

8.1.6 Pharmacokinetics

Plasma concentrations of venetoclax will be tabulated for each subject.

An analysis of venetoclax plasma concentrations will be performed using a nonlinear mixed-effect population PK modeling approach. The relationship between venetoclax PK and efficacy, including MRD level and CR, will also be evaluated. The results from the population PK analysis and evaluation of efficacy may not be reported within the clinical study report. Additional analyses may be performed if useful in the interpretation of the data.

8.2 Determination of Sample Size

Using the CR rate of 6% reported for current therapies[45] 250 subjects would provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate).

In order to provide approximately 80% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% CR rate in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate), the study will enroll 190 subjects who have not been previously treated with BCRi therapy. Since there are approximately a total of 250 subjects, up to 60 subjects previously treated with BCRi therapy can be enrolled.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval and approval by Regulatory Authority(ies), if required by local regulations, prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP and all other applicable regulatory requirements.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that

affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

In the event a subject withdraws consent to participate from the study, stored biomarker samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The following patient reported outcomes (PRO) assessments will be completed by the subject and will be considered source documentation:

- EQ-5D-5L
- FACT-Leu
- FACIT-F

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available

through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

PRO data is collected directly onto paper source by the subjects. The completion of these forms is verified by the site staff. The forms are entered into the clinical database and then can be viewed within the EDC system by the site staff.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigative sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

To ensure data integrity and subject safety, a study monitor will continuously, throughout the study, verify that all subjects sign the informed consent prior to any study specific

procedures being conducted, that the protocol procedures are being followed appropriately, and that the information provided in the eCRF is complete, accurate, and supported by information in source documents. Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any research that may be done using research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Data from research may be provided to investigators and used in scientific publications or presented at medical conventions. Research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit or date of the last follow-up contact, whichever is later.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for venetoclax.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)
Protocol Date:	06 June 2018

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

1. Willis S, Day CL, Hinds MG, et al. The Bcl-2-regulated apoptotic pathway. J Cell Sci. 2003;116 (Pt 20):4053-6.
2. Cory S, Adams JM. The Bcl-2 family: regulators of the cellular life-or-death switch. Nature Reviews. Cancer. 2002;2(9):647-56.
3. Borner C. The Bcl-2 protein family: sensors and checkpoints for life-or-death decisions. Molecular Immunology. 2003;39(11):615-47.
4. Cory S, Huang DCS, Adam JM. The Bcl-2 family: roles in cell survival and oncogenesis. Oncogene. 2003;22(53):8590-607.
5. Cimmino A, Calin GA, Fabbri M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci USA. 2005;102(39):13944-9.
6. Calin GA, Cimmino A, Fabbri M, et al. MiR-15a and miR-16-1 cluster functions in human leukemia. Proc Natl Acad Sci. 2008;105(13):5166-71.
7. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 2013;19(2):202-208.
8. AbbVie. Venetoclax Investigator's Brochure Edition 9. 08 Mar 2018.
9. Roberts A, Davids M, Pagel J, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374(4):311-22.
10. Jaglowski S, Jones JA. Choosing first-line therapy for chronic lymphocytic leukemia. Expert Rev Anticancer Ther. 2011;11(9):1379-90.
11. Zwiebel JA, Cheson BD. Chronic lymphocytic leukemia: staging and prognostic factors. Semin Oncol. 1998;25(1):42-59.
12. American Cancer Society: Cancer Facts and Figures 2013. Atlanta, GA: American Cancer Society, 2013.
13. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19);3724-34. Erratum in: Blood. 2011;117(12):3477.

14. Jemal A, Clegg LX, Ward E, et al. Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival. Cancer. 2004;101(1):3-27.

15. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-6.

16. Hallek M, Cheson BD, Catovsky D et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.

17. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:481-8.

18. Zent CS, Burack WR. Mutations in chronic lymphocytic leukemia and how they affect therapy choice: focus on NOTCH1, SF3B1, and TP53. Hematology Am Soc Hematol Educ Program. 2014;2014(1):119-24.

19. Stilgenbauer S, Schnaiter A, Paschka P et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014;123(21):3247-54.

20. Tam CS, Stilgenbauer S. How best to manage patients with chronic lymphocytic leukemia with 17p deletion and/or TP53 mutation? Leuk Lymphoma. 2015:1-7.

21. Zenz T, Kröber A, Scherer K et al. Monoallelic TP53 inactivation is associated with poor prognosis in chronic lymphocytic leukemia: results from a detailed genetic characterization with long-term follow-up. Blood. 2008;112(8):3322-9.

22. Gonzalez D, Martinez P, Wade R et al. Mutational status of the TP53 gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. J Clin Oncol. 2011;29(16):2223-9.

23. Lucas DM, Ruppert AS, Lozanski G, et al. Cytogenetic prioritization with inclusion of molecular markers predicts outcome in previously untreated patients with chronic lymphocytic leukemia treated with fludarabine or fludarabine plus cyclophosphamide: a long-term follow-up study of the US intergroup phase III trial E2997. Leuk Lymphoma. 2015:1-7.

24. Pettitt AR, Jackson R, Carruthers S, et al. Alemtuzumab in combination with methylprednisolone is a highly effective induction regimen for patients with chronic lymphocytic leukemia and deletion of TP53: final results of the National Cancer Research Institute CLL206 trial. J Clin Oncol. 2012;30(14):1647-55.

25. Stilgenbauer S, Cymbalista F, Leblond V et al. Alemtuzumab combined with dexamethasone, followed by alemtuzumab maintenance or Allo-SCT in "ultra high-risk" CLL: final results from the CLL2O phase II study. ASH 2014, San Francisco, abstract no. 1991. 2014a.

26. Byrd JC, Brown JR, O'Brien S et al. Ibrutinib versus of atumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213-23.

27. Ibrutinib [Summary of Product Characteristics]. 2014. Available from: http://www.ema.europa.eu/ema.

28. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370(11):997-1007.

29. Idelalisib [Summary of Product Characteristics]. 2014. Available from: http://www.ema.europa.eu/ema.

30. Oppezzo P, Dighiero G. "Role of the B-cell receptor and the microenvironment in chronic lymphocytic leukemia." Blood Cancer J. 2013;3:e149.

31. Chang BY, Furman RR, Zapatka M, et al. Use of tumor genomic profiling to reveal mechanisms of resistance to the BTK inhibitor ibrutinib in chronic lymphocytic leukemia (CLL). J Clin Oncol. 2013;31 (15 Suppl):7014.

32. Herishanu Y, Katz B-Z, Lipsky A, et al. Biology of chronic lymphocytic leukemia in different microenvironments: clinical and therapeutic implications. Hematol Oncol Clin North Am. 2013;27(2):173-206.

33. Eichorst B, Dreyling M, Robak T, et al. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22 (Suppl 6):vi504.

34. Cella D, Jensen SE, Webster K, et al. Measuring health-related quality of life in leukemia: the Functional Assessment of Cancer Therapy - Leukemia (FACT-Leu) Questionnaire. Value Health. 2012;15:1051-8.

35. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy (FACT) scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-9.

36. Cella D. The manual of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system. Center on outcomes, research and education. Evanston Northwestern Healthcare and Northwestern University. 1997.

37. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage. 1997;13:63-74.

38. Cella D, Yount S, Sorensen M, et al. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005;32:811-9.

39. Cella D, Lai JS, Chang CH, et al. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002;94:528-38.

40. Cella DF, Eton DT, Lai JS, et al. Combining anchor and distribution-based methods to derive minimal clinically important differences on the functional assessment of cancer therapy (FACT) anaemia and fatigue scales. J Pain Symptom Manage. 2002;24:547-61.

41. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

42. Oppe M, Devlin NJ, van Hout B, et al. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. Value Health. 2014;17:445-53.

43. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70-8.

44. Cella D, Pickard AS, Duh MS, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomized phase III trial. Eur J Cancer. 2012;48:311-23.

45. Resonate Trial. ASH. 2014. Abstract 3331.

46. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56. Erratum in: Blood. 2008;112:5259.

47. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Assistant Director	Statistics
	Medical Director	Medical Affairs
	Medical Director	Safety
	Group Project Director	Clinical
	Study Project Manager I	Clinical
	Associate Director	Clinical Pharmacology

Appendix C. Sample List of Excluded and Cautionary Medications

Excluded during initiation and the dose-titration phase and Cautionary at 400 mg Steady Daily Dose:
Strong CYP3A inhibitors Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib*, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, paritaprevir/ritonavir combinations, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole
Cautionary
Moderate CYP3A inhibitors Amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib*, cyclosporine*, darunavir/ritonavir, diltiazem[1], erythromycin, fluconazole, fosamprenavir, imatinib*, isavuconazole, tofisopam, verapamil **Strong CYP3A inducers** Avasimibe, carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. john's wort **Moderate CYP3A inducers** Bosentan, efavirenz, etravirine, modafinil, nafcillin **Warfarin**** **P-gp substrates** Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan* **BCRP substrates** Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan **P-gp inhibitors** Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, quinidine, ronalzine, ticagrelor **BCRP inhibitors** Geftinib*

* These are anticancer agents; consult contact AbbVie TA MD before use.

** Closely monitor the international normalized ratio (INR)

1 Moderate CYP3A inhibitor per venetoclax FDA USPI

Notes: that this is not an exhaustive list. For an updated list, see the following link:
http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm
In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruits.

Appendix D. Study Activities

Screening Through Week 5 Day 2

Activity	Scr[a]	Within 72 Hours of W1 D1	W1 D1	W1 D2	Within 72 Hours of W2 D1	W2 D1	W2 D2	Within 72 Hours of W3 D1	W3 D1	W3 D2	Within 72 Hours of W4 D1	W4 D1	W4 D2	Within 72 Hours of W5 D1	W5 D1	W5 D2
Informed Consent	X															
17p Deletion or TP53 Mutation	X[b]															
Medical History/Oncology History Assessment	X		X													
Pregnancy Test[c]	X		X													
Adverse Event/Concomitant Medication Assessment	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[e]	X		X			X			X			X			X	
TLS Risk Assessment[f]	X															
ECOG Performance Status	X		X													
Coagulation Panel	X															
Hematology/Chemistry[g]	X	X[h]	X[i]	X[j]	X[k]	X[l]	X[j]	X[k]	X[l]	X[j]	X[k]	X[l]	X[j]	X[k]	X[l]	X[j]
Disease Assessments[m]	X															
Contrasted CT or MRI Scan[n]	X															
Bone Marrow Aspirate and Biopsy[o]																
MRD Assessment in Peripheral Blood[p]			X													

Activity	Scr[a]	Within 72 Hours of W1 D1	W1 D1	W1 D2	Within 72 Hours of W2 D1	W2 D1	W2 D2	Within 72 Hours of W3 D1	W3 D1	W3 D2	Within 72 Hours of W4 D1	W4 D1	W4 D2	Within 72 Hours of W5 D1	W5 D1	W5 D2
Venetoclax dispensation and accountability[q]			X	X		X	X		X	X		X	X		X	X
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[r]			X									X				

Week 8 Through Post-Treatment Follow-Up

Activity	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1	W28 D1	W32 D1	W36 D1	W40 D1	W44 D1	W48 D1	Every 12 Weeks Starting at W48	Week 108/Final Visit	30 Day Safety Visit[s]	Post-Treatment Follow-Up[t]
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[e]*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status[u]					X						X	X	X	X	
Hematology/Chemistry**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Disease Assessment[m]*					X			X			X				
Contrasted CT or MRI Scan[n]											X				
Bone Marrow Aspirate and Biopsy[o]											X[o]				
MRD Assessment in Peripheral Blood[p]					X						X				
PK sample[v]					X										
Venetoclax dispensation and accountability***	X	X	X	X	X	X	X	X	X	X	X	X	X[x]		
Dispense/Collect Subject Calendars/Diaries				X	X										

Activity	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1	W28 D1	W32 D1	W36 D1	W40 D1	W44 D1	W48 D1	Every 12 Weeks Starting at W48	Week 108/Final Visit	30 Day Safety Visit[s]	Post-Treatment Follow-Up[t]
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[r]		X			X			X			X	X	X		
Collection of Survival information[w]														X	X

Scr = Screening; W = Wk = Week; D = Day; Post-Treat = Post-Treatment; FV = Final Visit

Study Windows:

* Within 72 hours before or after scheduled visit starting with Week 8 Day 1.

** Within 72 hours prior to scheduled visit starting with Week 8 Day 1.

*** As of Week 8 the visit window for scheduled visits is ± 2 days.

a. Subjects will undergo screening procedures within 28 days prior to the first study drug administration, except where otherwise indicated.

b. Subjects who have 17p deletion or TP53 mutation as assessed by local laboratory (in bone marrow or peripheral blood) may be considered for enrollment. A recent test is desirable but any previous positive test is acceptable. Subjects that do not have the 17p deletion or TP53 mutation or have an unknown status are also eligible.

c. For females of childbearing potential, as defined in the protocol, a urine pregnancy test must be obtained and processed locally at Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening. During the study, a urine pregnancy test can be performed at the discretion of the investigator or per local guidelines.

d. All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study-specific informed consent until study drug administration.

e. A complete physical examination will be performed at Screening. A symptom directed physical examination may be performed as needed. Refer to Section 5.3.1.1 Physical Examination, for more details.

f. For subjects who have a dose interruption lasting more than 1 week during the first 5 weeks of dose-titration or more than 2 weeks when at the daily dose of 400 mg, the TLS risk should be reassessed to determine if restarting at a reduced dose is necessary.

g. All clinical laboratory tests will be analyzed by the local laboratory. Required tests are listed in Table 4 Clinical Laboratory Tests, refer to Section 5.3.1.1 Study Procedures, sub header Hematology and Chemistry as well as Section 6.1.8 Toxicity Management, for more details.

h. For all subjects, if the screening labs were done more than 72 hours before the planned first dose, the chemistry/hematology panel should be repeated and results reviewed prior to the initial dose in order to make a treatment decision. Labs should be assessed and pre-existing abnormalities should be corrected.

i. For all subjects, on the day of Week 1 Day 1, before dosing, the chemistry/hematology panel should be collected. The results of the labs drawn on Week 1 Day 1 need to be reviewed prior to dosing **IF** an additional lab within 72 hours of the initial dose at Week 1 Day 1 was not drawn **AND** reviewed.

j. The Day 2 venetoclax doses should not be administered until the Day 1 24 hour post-dose lab results have been evaluated. Electrolyte abnormalities should be corrected promptly. There is recommended TLS prophylaxis based on subject tumor burden. Please refer to Section 5.3.1.1 Study Procedures – Hematology and Chemistry and Appendix H. Note: There is a ± 2 hour window around the 24 hour lab draw.

k. For all subjects, within 72 hours of each subsequent dose increase, the chemistry/hematology panel should be repeated. The results should be reviewed prior to dose increasing.

l. Prior to dosing, on the day of each subsequent dose increase, the chemistry/hematology panel is required. The results of the labs drawn on Day 1 of each dose increase need to be reviewed prior to dosing **IF** additional labs within 72 hours of the dose increase were not drawn **AND** reviewed.

m. All measurable disease must be documented at Screening by laboratory testing, physical examination and CT scans (or MRI if CT is medically contraindicated); bone marrow examinations are not required at screening but results will be recorded if available. All baseline evaluations should be performed as closely as possible to the beginning of treatment. For all subsequent disease assessments, disease response will be assessed by the investigator based on the analysis of clinical laboratory tests (hematology) and a complete physical examination at Week 24, Week 36 and Week 48.

n. CT scans with contrast (or MRI if CT is medically contraindicated) should include neck, chest, abdomen and pelvic sequences can be accepted if previously performed within 35 days prior to the initial venetoclax dose. Otherwise, CT scans (or MRI) must be performed within the 28 day screening period. To confirm response, a CT scan (or MRI) must be performed at Week 48 for all subjects. CT scans (or MRI) may be performed 7 days prior to the scheduled Week 48 visit. If a subject exhibits clinical signs of possible disease progression (i.e., increased or de novo enlargement of liver, spleen or lymph nodes on physical examination) without an increase in lymphocytes meeting the progression of disease criteria, then additional assessments including contrast-enhanced CT scan and/or bone marrow can be performed to confirm or rule out disease progression. Refer to Section 5.3.1.1 Computed Tomography Scans and Disease Assessments, for more details. For patients with only Partial Remission at Week 48 an additional CT and a bone marrow examination can be done between Week 48 and Week 108 to confirm CR if there is a possibility that a patient is in Complete Remission based on laboratory tests and a disease assessment physical examination.

o. For determination of complete remission (CR), the CT scan and bone marrow are required to be negative, per the IWCLL NCI-WG guidelines. If the subject achieves a CR by clinical criteria and confirmatory CT scan, a bone marrow aspirate and biopsy will be performed to confirm the CR. Whenever possible the bone marrow aspirate for biomarker MRD assessment should be split from this sample. Refer to Section 5.3.1.1 Disease Assessments and Bone Marrow Aspirate and Biopsy, for more details.

p. MRD will be assessed by using peripheral blood at Week 1 Day 1 (baseline), Week 24 and Week 48. Refer to Section 5.3.1.1 and Section 5.3.1.2 for more details. When confirming a complete remission (CR + CRi) status per 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy and aspirate. The aspirate should be split and a sample sent to the central laboratory for MRD analysis.

q. Venetoclax tablets should be taken orally once daily with a meal and water in the morning at approximately the same time each day. Dosing may occur at study visits on Week 1 Days 1 & 2 through Week 5 Days 1 and 2.

r. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

s. 30-Day Safety Follow-up visit should occur approximately 30 days (± 3 days) after the last dose of venetoclax.

t. Upon discontinuation of study drug treatment, survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 6 months (± 7 days) for a period of 2 years.

u. ECOG performance status may be performed within 72 hours before or after the scheduled visit starting with Week 24.

v. Collect (immediately) prior to venetoclax dosing (0 hour) on Week 24 Day 1. The date and time (to the nearest minute) the venetoclax doses were taken, and whether or not the venetoclax doses were taken with a meal, will be recorded on the eCRF for the Week 24 Day 1 venetoclax PK day and for the 2 days prior to the Week 24 Day 1.

w. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.

x. In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy. Subjects who participate in the 2 year Extended Access phase will have study drug assigned at Week 108. For patients that are not participating in the 2 year Extended Access phase the Week 108 visit is the Final visit. The specific study assessments to be performed at the Extended Access visits are detailed in Appendix E, Study Activities.

Appendix E. Schedule of Extended Access Phase*

Procedure	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	Week 180	Week 192	Week 204	Week 216/ Final Visit	30 Day Safety Visit[d]	Post Treatment Follow up[e]
Vital signs**	X									X	X	
Physical Examination[a]**	X									X	X	
ECOG Performance Status**	X									X	X	
Hematology/Chemistry***	X									X	X	
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Venetoclax dispensation and accountability****	X	X	X	X	X	X	X	X	X			
Collection of Survival Information[b]	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[c]	X											

* In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy.

** Within 72 hours before or after scheduled visit.

*** Within 72 hours prior to scheduled visit.

****The visit window for scheduled visits is ± 2 days.

a. Refer to Section 5.3.1.1 Physical Examination, for more details.

b. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.

c. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

d. 30-Day Safety Follow-up visit should occur approximately 30 days (± 3 days) after the last dose of venetoclax.

e. Upon discontinuation of study drug treatment, survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 6 months (± 7 days) for a period of 2 years.

Appendix F. Schedule of Biomarker Collection

Sample Collections (Sample Type)	Week 1 Day 1	Week 24 Day 1	Week 48 Day 1	Confirmation of CR/CRi	Comments
MRD Assessment					
Peripheral Blood	X	X	X	X	12 mL, EDTA Tube, Ship DOC
Bone Marrow Aspirate[a]				X	2 – 3 mL, EDTA Tube, Ship DOC

a. Whenever possible the bone marrow aspirate should be split and a sample sent to the central laboratory for biomarker MRD analysis.

Appendix G. Definitions of Laboratory and Clinical Tumor Lysis Syndrome

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperruricemia	Uric acid > 8.0 mg/dL (475.8 µmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/liter) in adults or > 6.5 mg/dL (2.1 mmol/liter) in children	
Hyperkalemia	Potassium > 6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/liter) or ionized calcium < 1.12 (0.3 mmol/liter)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury‡	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) (or a single value > 1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output < 0.5 mL/kg/hr for 6 hrs

† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4-albumin in grams per deciliter).

‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome. Data about acute kidney injury from Levin et al.

Note: In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

Appendix H. TLS Prophylaxis Based on Tumor Burden From Clinical Trial Data (Consider All Subject Co-Morbidities Before Final Determination of Prophylaxis and Monitoring Schedule)

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN < 5 cm AND ALC < 25×10^9/L	Oral (1.5 – 2 L)	Allopurinol[b]	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses
Medium	Any LN 5 cm to < 10 cm OR ALC ≥ 25×10^9/L	Oral (1.5 – 2 L) and consider additional intravenous	Allopurinol	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses • Consider hospitalization for subjects with CrCl < 80 ml/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥ 10 cm OR ALC ≥ 25×10^9/L AND any LN ≥ 5 cm	Oral (1.5 – 2 L) and intravenous (150 – 200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of 20 mg and 50 mg • Pre-dose, 4, 8,12 and 24 hours Outpatient at subsequent ramp-up doses • Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; LN = lymph node

a. Administer intravenous hydration for any subject who cannot tolerate oral hydration.

b. Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.

c. Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

d. For subjects at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

Appendix I. Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS)

Section 1: First Dose of Venetoclax or Dose Escalation

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the subject should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. Rapidly rising serum potassium is a medical emergency.
- Nephrology (or other acute dialysis service) should be contacted/consulted (per institutional standards to ensure emergency dialysis is available) on admission for any subject hospitalized prophylactically or in response to laboratory changes.
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

In addition to the recommendations in the table below, for subjects receiving the first dose of venetoclax.

- For potassium increase ≥ 0.5 mmol/L from baseline, or any value > 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT and follow first guideline.
- For phosphorus increase of > 0.5 mg/dL AND > 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.

Abnormality	**Management Recommendations**
Hyperkalemia (Including Rapidly Rising Potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At the discretion of the investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. o If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hrs., if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. o If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase* (dose based on local guidelines and/or institutional standards). o If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase* (dose based on local guidelines and/or institutional standards). o When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. o If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hrs., later, if no other evidence of tumor lysis.
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Subject symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT. o If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hrs., later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.

Abnormality	Management Recommendations
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT. ○ If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hrs., later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

* Check rasburicase label for contraindications.

Section 2: Ongoing Dosing of Venetoclax

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose escalation (e.g., 48 or 72 hours) are as below.

Note: If the subject is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit subject for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
  - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see prior table).
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see prior table).

Appendix J. Adverse Events Commonly Associated with CLL Study Population and/or Progression of CLL

Disease-Related Events – CLL

Lymphadenopathy

Splenomegaly

Hepatomegaly

Leukemia cutis (macules, papules, plaques, nodules, ulcers, or blisters) Lymphocytosis

Cytopenias (neutropenia, anemia and thrombocytopenia)

Febrile neutropenia

Autoimmune hemolytic anemia

Autoimmune thrombocytopenia

Hypogammaglobulinemia

Infections (bacterial, viral, and fungal)

Second primary cancers, all types Fatigue

Unexplained weight loss

Pyrexia

Bruising

Minor hemorrhages

Pain, all types

Malignant neoplasm progression, including death

Population-Related Comorbidities

Hypertension

Rheumatoid arthritis/osteoarthritis

Hyperlipidemia

Peptic ulcer

Inflammatory bowel disease

Coronary artery disease

Peripheral vascular disease

Cardiomyopathy

Valvular disease

Atrial fibrillation

Diabetes mellitus

Chronic obstructive pulmonary disease

Cerebrovascular accident

Transient ischemia attack

Appendix K. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Global Protocol Changes

"Appendix D" has been changed to read "Appendix D and Appendix E"

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:"
[redacted] "Phone:" previously read:

Sponsor/Emergency Contact:	[redacted] MD [redacted] Medical Director AbbVie 26525 North Riverwoods Blvd. Mettawa, IL 60060 USA	Phone: [redacted] Email: VenPh3bStudy@abbvie.com

Has been changed to read:

Sponsor/Emergency Contact:	[redacted] MD [redacted] Medical Director AbbVie 26525 North Riverwoods Blvd. Mettawa, IL 60060 USA	Phone: Email: [redacted]

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M15-550
Name of Study Drug: Venetoclax (ABT-199, GDC-0199)	**Phase of Development:** 3b
Name of Active Ingredient: Venetoclax	**Date of Protocol Synopsis:** 03 August 2017
Protocol Title: Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)	

Objectives: **Primary Objective:** The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). The primary efficacy endpoint will be measured by complete remission rate (Complete Remission Rate [CR] and Complete Remission with Incomplete Marrow Recovery [CRi]; CR + CRi) as assessed by the investigator, of the subjects who have not been previously treated with B-cell receptor inhibitor (BCRi) therapy. **Secondary Objectives:** The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), CR rate in BCRi treated subjects, the level of Minimal Residual Disease (MRD) and the rate of MRD negativity in the peripheral blood. In addition, quality of life will be assessed using the following patient reported outcome (PRO) questionnaires: the EuroQoL 5 Dimensions (EQ-5D-5L) questionnaire, a measure of general health status, the Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu), a leukemia-specific health related quality of life for acute and chronic disease, and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). The safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated.
Investigators: Multi-center
Study Sites: Approximately 7 sites in the United States, 1 site in Puerto Rico, and approximately 61 sites globally.
Study Population: Subjects with relapsed/refractory (R/R) CLL with or without the 17p deletion or TP53 mutation, including subjects with an unknown status, as well as R/R CLL subjects who have been previously treated with B-cell receptor inhibitor (BCRi) therapy.
Number of Subjects to be Enrolled: Approximately 250 subjects

Methodology:

This is a Phase 3b, single arm, open-label, multi-center study evaluating the efficacy of venetoclax in subjects with R/R CLL. All screening procedures must be performed within 28 days prior to initial study drug administration. A contrast computed tomography (CT) scan (or magnetic resonance imaging [MRI] if a CT with contrast is medically contraindicated) will be accepted if previously performed within 35 days prior to study drug administration, otherwise a CT scan (or MRI) must be performed within the screening period of 28 days. The starting dose of venetoclax is 20 mg once daily. The dose must be gradually increased over a 5 week period up to the daily dose of 400 mg. For all subjects, study visits will be conducted within 72 hours of dosing, on the day of dosing and the day after dosing during the dose titration phase. Please refer to Appendix D. Study visits will be reduced to a monthly frequency at Week 8, and at Week 48, they will be reduced to every 3 months until the end of study treatment (Week 108). A Disease Assessment for clinical response by physical exam and hematologic assessments will be performed at Screening, Week 24, Week 36 and Week 48. To confirm the response, a CT scan will be performed at Week 48 on all subjects. Biospecimens will be collected at designated time points throughout the study to conduct research to better characterize the disease. MRD assessments will be performed by using peripheral blood specimens at Week 1 Day 1 (baseline), Week 24 and Week 48. When confirming a CR or CRi status per 2008 Modified International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute Working Group (IWCLL NCI WG) criteria with a bone marrow (BM) biopsy and aspirate, MRD assessment of the BM aspirate should also be performed. After treatment discontinuation, a final visit will be performed. Subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment follow-up calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

To ensure subject safety, a Data Monitoring Committee (DMC) will review safety data when approximately 20 subjects have completed a minimum 12 weeks of treatment.

Subsequent reviews may be conducted based on recommendations from the DMC or requests from the Sponsor. Details of the DMC review will be presented in the DMC charter.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

A subject will be eligible for study participation if he/she meets all of the following criteria:

1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
3. Subject has relapsed/refractory disease (received at least one prior therapy).
4. Diagnosis of CLL that meets published 2008 Modified IWCLL NCI-WG Guidelines and:
   - has an indication for treatment according to the 2008 Modified IWCLL NCI-WG criteria
   - has clinically measurable disease (lymphocytosis > 5×10^9/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam)
   - subjects with or without the 17p deletion or TP53 mutation are eligible.
   - subjects who have received prior B-cell receptor inhibitor therapy are also eligible (up to 60 subjects total in the study will be enrolled).

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

5. Adequate bone marrow function as follows:
   - hemoglobin ≥ 8.0 g/dL
   - platelets ≥ 25,000/mm^3 without any of the following:
     - transfusion support within 14 days of Screening
     - evidence of mucosal bleeding
     - known history of major bleeding episode within 3 months of Screening

Main Exclusion:

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject has developed Richter's transformation or Prolymphocytic leukemia (PLL)
2. Subject has previously received venetoclax.
3. History of active malignancies other than CLL within the past 2 years prior to first dose of venetoclax, with the exception of:
   - adequately treated in situ carcinoma of the cervix uteri
   - adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin
   - previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
4. Active and uncontrolled autoimmune cytopenias (within 2 weeks prior to Screening), including autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), despite low dose corticosteroids.
5. Prior allogeneic stem cell transplant.

Investigational Product:	Venetoclax: 10 mg, 50 mg and 100 mg tablet
Doses:	Venetoclax will be administered orally once daily (QD), continuously. The starting dose of venetoclax is 20 mg QD. After 1 week of treatment at 20 mg QD, the dose will be escalated to 50 mg QD followed by subsequent increases, each after 1 week, to 100 mg QD, 200 mg QD and the target dose of 400 mg QD.
Mode of Administration:	Oral
Reference Therapy:	Not applicable.
Doses:	Not applicable.
Mode of Administration:	Not applicable.

Duration of Treatment: Subjects may continue receiving venetoclax for up to 2 years provided they continue to tolerate the drug, have no evidence of disease progression (based on investigator assessment), do not have unacceptable toxicity and do not meet any of the criteria for subject discontinuation. After treatment discontinuation, subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

For subjects who continue to derive benefit after 2 years of treatment, AbbVie will work with the investigator to consider the potential continuation of venetoclax therapy.

Criteria for Evaluation:

Efficacy:

Disease response will be assessed by the investigator, based on laboratory results and physical examinations using the 2008 Modified IWCLL NCI-WG criteria for Tumor Response with the addition of CT imaging (or MRI in the case CT is medically contraindicated) when available.

All measurable disease must be documented at Screening by physical examination, laboratory testing, and CT scan (or MRI in the case CT is medically contraindicated). During the study, clinical disease assessments will take place at Week 24, Week 36, and Week 48. To confirm the response, a CT scan will be performed at Week 48.

Minimal Residual Disease (MRD):

A peripheral blood specimen will be collected from all subjects at Week 1 Day 1 (baseline), Week 24 and Week 48 to determine the level of minimal residual disease. When confirming a CR/CRi status per 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy and aspirate, MRD assessment of the BM aspirate should also be performed. The level of MRD and MRD negativity will be assessed. MRD negativity in the 2008 Modified IWCLLNCI-WG criteria is defined as the presence of less than one CLL cell per 10,000 leukocytes (or below 10^{-4}).

Pharmacokinetics:

A single pharmacokinetic (PK) blood sample will be collected from each subject and analyzed for plasma venetoclax concentration.

Safety:

Adverse event monitoring, vital signs, physical examination, and laboratory assessments will be evaluated.

Statistical Methods:

The study analyses will be descriptive. All subjects participating in the study who received at least one dose of venetoclax will be included in the analyses unless otherwise noted in the separate, statistical analysis plan (SAP).

Statistical Methods (Continued):

Efficacy:

The following efficacy endpoints will be analyzed: Complete Remission rate (CR + CRi), Overall Response Rate (ORR), Duration of Overall Response (DOR), Duration of Progression-Free Survival (PFS) and Overall Survival (OS):

Complete Remission Rate (CR) and Complete Remission with Incomplete Marrow Recovery (CRi)

Defined as the proportion of subjects who achieved a CR or CRi (all subjects and previously BCRi treated subjects).

Overall Response Rate (ORR)

Defined as the proportion of subjects with an overall response (complete remission plus partial remission).

Duration of Response (DOR)

Defined as the number of days from the date of first response (per the 2008 Modified IWCLL NCI-WG criteria) to the date of disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Time to Progression (TTP)

Defined as the number of days from the date of first dose of venetoclax to date of disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Duration of Progression-Free Survival (PFS)

Defined as the number of days from the date of first dose of venetoclax to the date of disease progression or death, whichever occurs first. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Overall Survival (OS)

Defined as number of days from the date of first dose of venetoclax to the date of death.

Additional Efficacy Analyses Include:

Minimal Residual Disease (MRD) Level and Negativity Status:

The level of MRD and the rate of MRD negativity will be assessed in the peripheral blood of all subjects at Week 1 Day 1 (baseline), Week 24 and Week 48. MRD negativity will be defined as less than one CLL cell per 10,000 leukocytes (or below 10^{-4}). Additionally, bone marrow samples collected from subjects achieving CR/CRi will also be assessed for both the level of MRD and the rate of MRD negativity. Rate of MRD status will be defined as the proportion of subjects who have MRD negativity status. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided. The relationship between venetoclax PK and efficacy parameters including MRD level and CR will be evaluated.

Pharmacokinetics:

An analysis of venetoclax plasma concentrations will be performed using a population PK modeling approach.

Statistical Methods (Continued):

Health Economic and Patient Reported Outcome (PRO) Measures:

Quality of life will be assessed by using the following PROs: the EQ-5D-5L, FACT-Leu, and the FACIT-F.

Quality of life endpoints will be summarized based on the scoring manuals for the instrument.

Sample Size Estimation:

Using the CR rate of 6% reported for current therapies* 250 subjects would provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate).

In order to provide approximately 80% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% CR rate in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate), the study will enroll 190 subjects who have not been previously treated with BCRi therapy. Since there are approximately a total of 250 subjects, up to 60 subjects previously treated with BCRi therapy can be enrolled.

Safety:

A safety analysis will be performed for all subjects participating in the study who took at least one dose of study drug. For the study as a whole, adverse events will be evaluated and summarized. Laboratory test results and vital signs will be explored for trends and summarized.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M15-550
Name of Study Drug: Venetoclax (ABT-199, GDC-0199)	**Phase of Development:** 3b
Name of Active Ingredient: Venetoclax	**Date of Protocol Synopsis:** 06 June 2018
Protocol Title: Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)	
Objectives: **Primary Objective:** The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). The primary efficacy endpoint will be measured by complete remission rate (Complete Remission Rate [CR] and Complete Remission with Incomplete Marrow Recovery [CRi]; CR + CRi) as assessed by the investigator, of the subjects who have not been previously treated with B-cell receptor inhibitor (BCRi) therapy. **Secondary Objectives:** The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and the CR rate in BCRi treated subjects. In addition, quality of life will be assessed using the following patient reported outcome (PRO) questionnaires: the EuroQoL 5 Dimensions (EQ-5D-5L) questionnaire, a measure of general health status, the Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu), a leukemia-specific health related quality of life for acute and chronic disease, and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). The safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated. **Exploratory Objectives:** The exploratory objectives are to evaluate the level of Minimal Residual Disease (MRD) and the rate of MRD negativity in the peripheral blood.	
Investigators: Multi-center	
Study Sites: Approximately 7 sites in the United States, 1 site in Puerto Rico, and approximately 67 sites globally.	
Study Population: Subjects with relapsed/refractory (R/R) CLL with or without the 17p deletion or TP53 mutation, including subjects with an unknown status, as well as R/R CLL subjects who have been previously treated with B-cell receptor inhibitor (BCRi) therapy.	
Number of Subjects to be Enrolled: Approximately 250 subjects	

Methodology:

This is a Phase 3b, single arm, open-label, multi-center study evaluating the efficacy of venetoclax in subjects with R/R CLL. All screening procedures must be performed within 28 days prior to initial study drug administration. A contrast computed tomography (CT) scan (or magnetic resonance imaging [MRI] if a CT with contrast is medically contraindicated) will be accepted if previously performed within 35 days prior to study drug administration, otherwise a CT scan (or MRI) must be performed within the screening period of 28 days. The starting dose of venetoclax is 20 mg once daily. The dose must be gradually increased over a 5 week period up to the daily dose of 400 mg. For all subjects, study visits will be conducted within 72 hours of dosing, on the day of dosing and the day after dosing during the dose titration phase. Please refer to Appendix D. Study visits will be reduced to a monthly frequency at Week 8, and at Week 48, they will be reduced to every 3 months until the end of study treatment (Week 108). In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. A Disease Assessment for clinical response by physical exam and hematologic assessments will be performed at Screening, Week 24, Week 36 and Week 48. To confirm the response, a CT scan will be performed at Week 48 on all subjects. Biospecimens will be collected at designated time points throughout the study to conduct research to better characterize the disease. MRD assessments will be performed by using peripheral blood specimens at Week 1 Day 1 (baseline), Week 24 and Week 48. When confirming a CR or CRi status per 2008 Modified International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute Working Group (IWCLL NCI WG) criteria with a bone marrow (BM) biopsy and aspirate, MRD assessment of the BM aspirate should also be performed. After treatment discontinuation, a final visit will be performed. Subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment follow-up calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

The Data Monitoring Committee (DMC) will review safety data intermittently according to the DMC charter.

Subsequent reviews may be conducted based on recommendations from the DMC or requests from the Sponsor. Details of the DMC review will be presented in the DMC charter.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

A subject will be eligible for study participation if he/she meets all of the following criteria:

1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
3. Subject has relapsed/refractory disease (received at least one prior therapy).
4. Diagnosis of CLL that meets published 2008 Modified IWCLL NCI-WG Guidelines and:
   - has an indication for treatment according to the 2008 Modified IWCLL NCI-WG criteria
   - has clinically measurable disease (lymphocytosis > 5×10^9/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam)
   - subjects with or without the 17p deletion or TP53 mutation are eligible.
   - subjects who have received prior B-cell receptor inhibitor therapy are also eligible (up to 60 subjects total in the study will be enrolled).

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

5. Adequate bone marrow function as follows:
   - hemoglobin ≥ 8.0 g/dL
   - platelets ≥ 25,000/mm^3 without any of the following:
     - transfusion support within 14 days of Screening
     - evidence of mucosal bleeding
     - known history of major bleeding episode within 3 months of Screening

Main Exclusion:

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject has developed Richter's transformation or Prolymphocytic leukemia (PLL)
2. Subject has previously received venetoclax.
3. History of active malignancies other than CLL within the past 2 years prior to first dose of venetoclax, with the exception of:
   - adequately treated in situ carcinoma of the cervix uteri
   - adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin
   - previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
4. Active and uncontrolled autoimmune cytopenias (within 2 weeks prior to Screening), including autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), despite low dose corticosteroids.
5. Prior allogeneic stem cell transplant.

Investigational Product:	Venetoclax: 10 mg, 50 mg and 100 mg tablet
Doses:	Venetoclax will be administered orally once daily (QD), continuously. The starting dose of venetoclax is 20 mg QD. After 1 week of treatment at 20 mg QD, the dose will be escalated to 50 mg QD followed by subsequent increases, each after 1 week, to 100 mg QD, 200 mg QD and the target dose of 400 mg QD.
Mode of Administration:	Oral
Reference Therapy:	Not applicable.
Doses:	Not applicable.
Mode of Administration:	Not applicable.

Duration of Treatment: Subjects may continue receiving venetoclax for up to 2 years provided they continue to tolerate the drug, have no evidence of disease progression (based on investigator assessment), do not have unacceptable toxicity and do not meet any of the criteria for subject discontinuation. After treatment discontinuation, subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy.

Criteria for Evaluation:

Efficacy:

Disease response will be assessed by the investigator, based on laboratory results and physical examinations using the 2008 Modified IWCLL NCI-WG criteria for Tumor Response including CT imaging and bone marrow biopsy and aspirate for subject with CR to confirm the response (or MRI in the case CT is medically contraindicated).

All measurable disease must be documented at Screening by physical examination, laboratory testing, and CT scan (or MRI in the case CT is medically contraindicated). During the study, clinical disease assessments will take place at Week 24, Week 36, and Week 48. To confirm the response, a CT scan will be performed at Week 48.

Minimal Residual Disease (MRD):

A peripheral blood specimen will be collected from all subjects at Week 1 Day 1 (baseline), Week 24 and Week 48 to determine the level of minimal residual disease. When confirming a CR/CRi status per 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy and aspirate, MRD assessment of the BM aspirate should also be performed. The level of MRD and MRD negativity will be assessed. MRD negativity in the 2008 Modified IWCLLNCI-WG criteria is defined as the presence of less than one CLL cell per 10,000 leukocytes (or below 10^{-4}).

Pharmacokinetics:

A single pharmacokinetic (PK) blood sample will be collected from each subject and analyzed for plasma venetoclax concentration.

Safety:

Adverse event monitoring, vital signs, physical examination, and laboratory assessments will be evaluated.

Statistical Methods:

The study analyses will be descriptive. All subjects participating in the study who received at least one dose of venetoclax will be included in the analyses unless otherwise noted in the separate, statistical analysis plan (SAP).

Statistical Methods (Continued):

Efficacy:

The following efficacy endpoints will be analyzed: Complete Remission rate (CR + CRi), Overall Response Rate (ORR), Duration of Overall Response (DOR), Duration of Progression-Free Survival (PFS) and Overall Survival (OS):

Complete Remission Rate (CR) and Complete Remission with Incomplete Marrow Recovery (CRi)

Defined as the proportion of subjects who achieved a CR or CRi (all subjects and previously BCRi treated subjects).

Overall Response Rate (ORR)

Defined as the proportion of subjects with an overall response (complete remission plus partial remission).

Duration of Response (DOR)

Defined as the number of days from the date of first response (per the 2008 Modified IWCLL NCI-WG criteria) to the date of disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Time to Progression (TTP)

Defined as the number of days from the date of first dose of venetoclax to date of disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Duration of Progression-Free Survival (PFS)

Defined as the number of days from the date of first dose of venetoclax to the date of disease progression or death, whichever occurs first. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Overall Survival (OS)

Defined as number of days from the date of first dose of venetoclax to the date of death.

Additional Exploratory Analyses Include:

Minimal Residual Disease (MRD) Level and Negativity Status:

The level of MRD and the rate of MRD negativity will be assessed in the peripheral blood of all subjects at Week 1 Day 1 (baseline), Week 24 and Week 48. MRD negativity will be defined as less than one CLL cell per 10,000 leukocytes (or below 10^{-4}). Additionally, bone marrow samples collected from subjects achieving CR/CRi will also be assessed for both the level of MRD and the rate of MRD negativity. Rate of MRD status will be defined as the proportion of subjects who have MRD negativity status. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided. The relationship between venetoclax PK and efficacy parameters including MRD level and CR will be evaluated.

Pharmacokinetics:

An analysis of venetoclax plasma concentrations will be performed using a population PK modeling approach.

Statistical Methods (Continued):

Health Economic and Patient Reported Outcome (PRO) Measures:

Quality of life will be assessed by using the following PROs: the EQ-5D-5L, FACT-Leu, and the FACIT-F.

Quality of life endpoints will be summarized based on the scoring manuals for the instrument.

Sample Size Estimation:

Using the CR rate of 6% reported for current therapies* 250 subjects would provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate).

In order to provide approximately 80% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% CR rate in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate), the study will enroll 190 subjects who have not been previously treated with BCRi therapy. Since there are approximately a total of 250 subjects, up to 60 subjects previously treated with BCRi therapy can be enrolled.

Safety:

A safety analysis will be performed for all subjects participating in the study who took at least one dose of study drug. For the study as a whole, adverse events will be evaluated and summarized. Laboratory test results and vital signs will be explored for trends and summarized.

* Resonate Trial. ASH. 2014. Abstract 3331.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection <u>Abbreviations</u>
Add:

BM Bone Marrow

Section 1.3 List of Abbreviations and Definition of Terms
Subsection <u>Abbreviations</u>
Delete:

SGPT Serum Glutamic-pyruvic Transaminase

Section 3.0 Introduction
Subsection <u>Venetoclax Clinical Data</u>
Previously read:

In the Investigator's Brochure,[8] a total of 2573 oncology subjects received at least 1 dose of venetoclax in AbbVie and Genentech/Roche studies and had data available as of 28 November 2016. Of these 2573 subjects, 1429 subjects had CLL/small lymphocytic

lymphoma (SLL), 637 subjects had Non-Hodgkin's Lymphoma (NHL), 180 subjects had multiple myeloma (MM), 327 had Acute Myeloid Leukemia (AML), and 114 were healthy volunteers. A total of 749 received the drug as monotherapy and 1922 received the drug in combination with other therapies. Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg.

The most common adverse events reported for all subjects in monotherapy studies were nausea (40.2%), diarrhea (42.2%), and neutropenia (41.0%). The most common adverse events that were grade 3 and above were neutropenia (36.8%), anemia (15.6%) and thrombocytopenia (13.4%). The most common serious adverse events were pneumonia (6.8%), febrile neutropenia (5.4%) and malignant neoplasm progression (5.9%).

Tumor lysis syndrome (TLS) is an important risk, particularly in subjects with R/R CLL. As a result of on-target effects, the potential for TLS with venetoclax was identified early in the program when the initial 3 subjects with CLL/SLL received starting doses of 100 mg or 200 mg and experienced TLS, which was reported as an adverse event for each. Subsequently, 2 fatal events in the setting of TLS and another event of clinical TLS in subjects with CLL/SLL occurred in December 2012. After comprehensive review of all safety data available from studies with venetoclax, a revised dosing regimen with a dose-titration phase of 5 weeks and enhanced TLS prophylaxis and monitoring measures were implemented in all CLL studies. A subsequent analysis of data from subjects with CLL/SLL following the implementation of prophylaxis measures, who completed monotherapy indicated a marked reduction in severity and frequency of TLS when compared to the previous analysis. None of the subjects experienced any serious (including fatal) or nonserious event of clinical TLS (CTLS) or laboratory TLS (LTLS) or had study treatment discontinued because of TLS. Since May 2014, a more personalized approach for prophylaxis and monitoring measures, where subjects with lower tumor burden could receive venetoclax on an out-patient basis, has been evaluated with no cases of clinical TLS. Overall, the clinical data strongly support that the risk of TLS with venetoclax in CLL/SLL subjects is highest when initiating venetoclax dosing (5-week dose titration phase), as well as being greater in subjects with a large tumor burden.

The safety profile in combination studies is consistent with that observed in monotherapy studies and with known toxicity profile of combination agents. Preliminary efficacy data indicate that venetoclax, both as monotherapy and in combination with other therapeutic agents, continues to show promising efficacy in oncology subject populations. The overall response rate (ORR) in subjects with CLL/SLL was 77% to 82% (dose escalation and safety expansion cohorts, respectively), with a complete remission rate (CR + CRi) of 30% in dose escalation and 10% in the safety expansion cohort for venetoclax monotherapy (Study M12-175).[9]

Additional safety and efficacy data are described in detail in the Investigator Brochure.[8]

Has been changed to read:

In the Investigator's Brochure,[8] a total of 2495 subjects received at least 1 dose of venetoclax in company sponsored studies as of 28 November 2017. 2473 of these subjects are included in overall pooled analyses for reporting Reference Safety Information. The 2473 subjects in the overall pooled analysis include 2224 oncology subjects (987 in monotherapy studies and 1237 in combination therapy studies), 153 healthy volunteers, 23 subjects with hepatic impairment and 73 subjects with SLE. Of the 2224 oncology subjects, 1132 subjects had CLL/small lymphocytic lymphoma (SLL), 569 subjects had Non-Hodgkin's Lymphoma (NHL), 172 subjects had multiple myeloma (MM) 340 had Acute Myeloid Leukemia (AML), and 11 subjects had myelodysplastic syndrome (MDS) 787 subjects with blinded data have been treated with either venetoclax combination therapy or a comparator treatment in company-sponsored venetoclax oncology studies. Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg.

The most common adverse events reported in venetoclax monotherapy studies were neutropenia (39.3%), nausea (31.4%) and diarrhea (24.9%). The most common adverse events that were grade 3 and above were neutropenia (34.9%), anemia (13.8%) and thrombocytopenia (12.8%). The most common serious adverse events were febrile

neutropenia (6.1%), pneumonia (5.4%), and malignant neoplasm progression (3.4%) and pyrexia (3.3%).

Tumor lysis syndrome (TLS) is an important risk, particularly in subjects with R/R CLL. As a result of on-target effects, the potential for TLS with venetoclax was identified early in the program when the initial 3 subjects with CLL/SLL received starting doses of 100 mg or 200 mg and experienced TLS, which was reported as an adverse event for each. Subsequently, 2 fatal events in the setting of TLS and another event of clinical TLS in subjects with CLL/SLL occurred in December 2012. After comprehensive review of all safety data available from studies with venetoclax, a revised dosing regimen with a dose-titration phase of 5 weeks and enhanced TLS prophylaxis and monitoring measures were implemented in all CLL studies. A subsequent analysis of data from subjects with CLL/SLL following the implementation of prophylaxis measures, who completed monotherapy indicated a marked reduction in severity and frequency of TLS when compared to the previous analysis. None of the subjects experienced any serious (including fatal) or nonserious event of clinical TLS (CTLS) or laboratory TLS (LTLS) or had study treatment discontinued because of TLS. Since May 2014, a more personalized approach for prophylaxis and monitoring measures, where subjects with lower tumor burden could receive venetoclax on an out-patient basis, has been evaluated with no cases of clinical TLS. Overall, the clinical data strongly support that the risk of TLS with venetoclax in CLL/SLL subjects is highest when initiating venetoclax dosing (5-week dose titration phase), as well as being greater in subjects with a large tumor burden.

The safety profile in combination studies is consistent with that observed in monotherapy studies and with known toxicity profile of combination agents. Preliminary efficacy data indicate that venetoclax, both as monotherapy and in combination with other therapeutic agents, continues to show promising efficacy in oncology subject populations. The overall response rate (ORR) in subjects with CLL/SLL was 75.0% to 81.7% (dose escalation and safety expansion cohorts, respectively), with a complete remission rate (CR + CRi) of 32.1% in dose escalation and 11.7% in the safety expansion cohort for venetoclax monotherapy (Study M12-175 as of 10 June 2016).[9]

Additional safety and efficacy data are described in detail in the Investigator Brochure.[8]

Section 4.0 Study Objective
Second paragraph previously read:

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), CR rate in BCRi treated subjects and both the level of Minimal Residual Disease (MRD) and the rate of MRD negativity.

Has been changed to read:

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and the CR rate in previously BCRi treated subjects.

Section 4.0 Study Objective
Third paragraph, first sentence previously read:

Additional secondary objectives will also be evaluated.

Has been changed to read:

Additional secondary objectives will also be evaluated as well.

Section 4.0 Study Objective
Add: new fifth paragraph

Additional exploratory objectives will be evaluated. Minimal Residual Disease (MRD) will be assessed in the peripheral blood and bone marrow (BM) by flow cytometry and PCR.

Section 5.1 Overall Study Design and Plan: Description
Third paragraph previously read:

Subjects in this study will be enrolled at 7 sites in the United States, 1 site in Puerto Rico, and approximately 61 sites globally.

Has been changed to read:

Subjects in this study will be enrolled at 7 sites in the United States, 1 site in Puerto Rico, and approximately 67 sites globally.

Section 5.1 Overall Study Design and Plan: Description
Fourth paragraph
Fifth sentence previously read:

Please refer to Appendix G.

Has been changed to read:

Please refer to Appendix D.

Section 5.1 Overall Study Design and Plan: Description
Fourth paragraph
Add: new seventh sentence

As of Week 8 the visit window for scheduled visits is ±2 days.

Section 5.1 Overall Study Design and Plan: Description
Sixth paragraph, first sentence previously read:

Disease response will be assessed by the investigator based on laboratory results and physical examinations using the 2008 Modified International Workshop on CLL National Cancer Institute – Working Group (IWCLL NCI-WG) Guidelines for Tumor Response with the addition of CT imaging (or MRI) when available.

Has been changed to read:

Disease response will be assessed by the investigator based on laboratory results and physical examinations using the 2008 Modified International Workshop on CLL National Cancer Institute – Working Group (IWCLL NCI-WG) Guidelines for Tumor Response with the addition of CT imaging (or MRI).

Section 5.1 Overall Study Design and Plan: Description
Sixth paragraph, last sentence previously read:

To confirm the response, a CT scan will be performed at Week 48 on all subjects.

Has been changed to read:

To confirm the response, a CT scan will be performed at Week 48 on all subjects and BM samples will be collected for subjects with CR to confirm the response.

Section 5.1 Overall Study Design and Plan: Description
Twelfth paragraph
Add: new last sentence

In countries where venetoclax is commercially available, extension of therapy may not be allowed.

Section 5.3.1.1 Study Procedures
Subsection <u>Physical Examination (Disease Assessment)</u>
First paragraph, first sentence previously read:

All physical examinations (complete or symptom-directed) should also include the evaluation of the presence and degree of enlarged lymph nodes in two dimension (cervical, supraclavicular, axillary, inguinal and femoral nodes), hepatomegaly, and splenomegaly.

Has been changed to read:

Physical examinations performed as a part of Disease Assessments (Screening, Weeks 24, 36, 48) are to include the evaluation of the presence and degree of enlarged lymph nodes

in two dimension (cervical, supraclavicular, axillary, inguinal and femoral nodes), hepatomegaly, and splenomegaly.

Section 5.3.1.1 Study Procedures
Subsection Disease Assessments (2008 Modified IWCLL NCI-WG Criteria)
First paragraph, last sentence previously read:

Bone marrow examinations are not required but results will be recorded if available.

Has been changed to read:

Bone marrow examinations at screening are not required but results will be recorded if available.

Section 5.3.1.1 Study Procedures
Subsection Disease Assessments (2008 Modified IWCLL NCI-WG Criteria)
Third paragraph, second sentence previously read:

It is recommended that the CT scan is performed first; if it does confirm a clinical response, then a bone marrow biopsy can be obtained.

Has been changed to read:

It is recommended that the CT scan is performed first; if it does confirm a clinical response, then a bone marrow biopsy will be obtained.

Section 5.3.1.1 Study Procedures
Subsection Disease Assessments (2008 Modified IWCLL NCI-WG Criteria)
Add: new last paragraph

For patients with only Partial Remission at Week 48 an additional CT and a bone marrow examination can be done between Week 48 and Week 108 to confirm CR if there is a possibility that a patient is in Complete Remission based on laboratory tests and a disease assessment physical examination.

Section 5.3.1.1 Study Procedures
Subsection Bone Marrow Aspirate and Biopsy
First paragraph, second sentence previously read:

If the subject achieves a CR by clinical criteria and confirmatory CT scan, a bone marrow aspirate and biopsy may be performed to confirm the CR.

Has been changed to read:

If the subject achieves a CR by clinical criteria and confirmatory CT scan, a bone marrow aspirate and biopsy will be performed to confirm the CR.

Section 5.3.1.1 Study Procedures
Subsection 30-Day Safety Visit
Second paragraph previously read:

If a subject is discontinued from the study with an ongoing AE or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until the AE has resolved to a ≤ Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.

Has been changed to read:

If a subject has an ongoing AE or an unresolved clinically significant laboratory result 30 days following last dose of study drug, the site will attempt to provide follow-up until the AE has resolved to a ≤ Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.

Section 5.3.1.1 Study Procedures
Subsection Extended Access Phase
Add: new subsection title and text

Extended Access Phase

In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2

additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy. The Extended Access Visits will include:

- Collection of Survival information
- AE/SAE/Con Med assessment
- Study drug reconciliation and dispensing

All other procedures should be performed as standard of care. The specific study assessments to be performed during these visits are detailed in Appendix E Study Activities.

Section 5.3.3 Efficacy Variables
Second paragraph previously read:

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression, (TTP), progression-free survival (PFS), overall survival (OS), CR rate in BCRi treated subjects, the level of MRD and the rate of MRD negativity in the peripheral blood.

Has been changed to read:

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression, (TTP), progression-free survival (PFS), overall survival (OS), and the CR rate in BCRi treated subjects.

Section 5.3.3 Efficacy Variables
Third paragraph
Add: new last sentence

Minimal residual disease (MRD) and the rate of MRD negativity in the peripheral blood are assessed as exploratory objectives in the peripheral blood and bone marrow (BM) by flow cytometry, PCR and/or sequencing.

Section 5.3.3.1 Primary Variables
First paragraph, last sentence previously read:

Subjects will be evaluated against the 2008 Modified IWCLL NCI WG Criteria for Tumor Response[46] with the addition of CT imaging (or MRI).

Has been changed to read:

Subjects will be evaluated against the 2008 Modified IWCLL NCI-WG Criteria for Tumor Response[46] with CT imaging (or MRI). BM sample assessment is required to confirm CR.

Section 5.3.3.1 Primary Variables
Second paragraph
Add: new last sentence

For subjects with CR as response at Week 48, a BM sample is required to confirm the response.

Section 5.4.1 Discontinuation of Individual Subjects
First paragraph previously read:

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason including:

Has been changed to read:

Each subject has the right to withdraw from the study and/or study drug treatment at any time. In addition, the investigator may discontinue a subject from study drug treatment at any time if the investigator considers it necessary for any reason including:

Section 5.4.1 Discontinuation of Individual Subjects
Fifth and sixth bullet previously read:

- pregnancy
- protocol non-compliance

Has been changed to read:

- The subject becomes pregnant while on study
- drug protocol non-compliance

Section 5.4.1 Discontinuation of Individual Subjects
Subsection Post Treatment and Survival Follow-Up Calls
Previously read:

For subjects who discontinue venetoclax therapy, but do not discontinue the study (i.e., have not had an event of progression, do not require alternate therapy, etc.), post treatment follow-up calls will be performed every 6 months for survival information (i.e., disease progression, the date and cause of death, post-treatment cancer therapies, etc.) and will be collected via telephone calls for a period of 2 years and recorded in the eCRFs.

Has been changed to read:

For subjects who discontinue venetoclax therapy, but do not discontinue the study post treatment follow-up calls will be performed every 6 months (± 7 days) for survival information (i.e., disease progression, the date and cause of death, post-treatment cancer therapies, etc.) and will be collected via telephone calls for a period of 2 years and recorded in the eCRFs.

Section 6.1.7 Data Monitoring Committee
Previously read:

A Data Monitoring Committee (DMC) will review the safety data when approximately 20 subjects have completed a minimum of 12 weeks of treatment.

A separate charter will be created to provide detailed descriptions of the schedule of analyses and the DMC meetings. DMC membership, responsibilities and the description of the data coordinating center are documented in the charter.

Subsequent reviews may be conducted based on recommendations from the DMC or requests from the Sponsor. Details of the DMC review will be presented in the DMC charter.

Has been changed to read:

The Data Monitoring Committee (DMC) will review safety data intermittently according to the DMC charter. Details of the DMC review are presented in the DMC charter. The separate charter has been created to provide detailed descriptions of the schedule of analyses and the DMC meetings. DMC membership, responsibilities and the description of the data coordinating center are documented in the charter.

Table 7. Recommended Dose Modifications for Toxicities
Footnote "a." previously read:

Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden and/or seizures.

Has been changed to read:

Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias and/or seizures or sudden death.

Section 7.0 Protocol Deviations
"Primary Contact:" and "Alternate Contact:" previously read:

Primary Contact:

[redacted]
Study Project Manager II
AbbVie Oncology
Clinical Program Development
1 N. Waukegan Rd.
North Chicago, IL 60064
USA

Office: [redacted]
Email:

Alternate Contact:

[redacted]
Study Management Associate III
AbbVie Oncology
Clinical Program Development
1 N. Waukegan Rd.
North Chicago, IL 60064
USA

Office: [redacted]
Fax:
Email:

Has been changed to read:

Primary Contact:

[redacted]
Study Project Manager I
AbbVie Oncology
Clinical Program Development
1 N. Waukegan Rd.
North Chicago, IL 60064
USA

Office: [redacted]
Email:

Alternate Contact:

[redacted]
Study Management Associate III
AbbVie AB
Hemvärnsgatan 9 (visitor address)
Box 1523
SE-171 29 Solna
Sweden

Office: [redacted]
Email:

Section 8.1.2.2 Secondary Efficacy Endpoints
First paragraph previously read:

Key secondary efficacy endpoints will include overall response rate, duration of response, time to progression, progression-free survival, overall survival, CR rate in previously BCRi treated subjects, and the level of MRD and the rate of MRD negativity. MRD

negativity will be based on the IWCLL NCI-WG criteria as less than 1 CLL cell in 10,000 cells.

Has been changed to read:

Key secondary efficacy endpoints will include overall response rate, duration of response, time to progression, progression-free survival, overall survival, and the CR rate in previously BCRi treated subjects.

Section 8.1.2.3 Secondary Efficacy Endpoints
Last paragraph
Add: new section title

8.1.2.3 Exploratory Efficacy Endpoints

Section 10.1 Source Documents
First paragraph
Delete: sixth and seventh sentence

The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

Section 15.0 Reference List
Reference 8 previously read:

AbbVie. Venetoclax Investigator's Brochure Edition 8.1. 03 May 2017.

Has been changed to read:

AbbVie. Venetoclax Investigator's Brochure Edition 9. 08 Mar 2018.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	Assistant Director	Statistics
	Medical Director	Medical Affairs
	Medical Director	Safety
	Group Project Director	Clinical
	Study Project Manager II	Clinical
	Associate Director	Clinical Pharmacology

Has been changed to read:

Name	Title	Functional Area
[redacted]	Assistant Director	Statistics
	Medical Director	Medical Affairs
	Medical Director	Safety
	Group Project Director	Clinical
	Study Project Manager I	Clinical
	Associate Director	Clinical Pharmacology

Appendix D. Study Activities
Subsection Screening Through Week 5 Day 2
"Adverse Event/Concomitant Medication Assessment" and "Dispense Venetoclax[q]" previously read:

Activity	Scr[a]	Within 72 Hours of W1 D1	W1 D1	W1 D2	Within 72 Hours of W2 D1	W2 D1	W2 D2	Within 72 Hours of W3 D1	W3 D1	W3 D2	Within 72 Hours of W4 D1	W4 D1	W4 D2	Within 72 Hours of W5 D1	W5 D1	W5 D2
Adverse Event/Concomitant Medication Assessment	X[d]	X	X	X		X	X		X	X		X	X		X	X
Dispense Venetoclax[q]			X	X		X	X		X	X		X	X		X	X

Has been changed to read:

Activity	Scr[a]	Within 72 Hours of W1 D1	W1 D1	W1 D2	Within 72 Hours of W2 D1	W2 D1	W2 D2	Within 72 Hours of W3 D1	W3 D1	W3 D2	Within 72 Hours of W4 D1	W4 D1	W4 D2	Within 72 Hours of W5 D1	W5 D1	W5 D2
Adverse Event/Concomitant Medication Assessment	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Venetoclax dispensation and accountability[q]			X	X		X	X		X	X		X	X		X	X

Appendix D. Study Activities
Subsection Week 8 Through Post-Treatment Follow-Up
Table previously read:

Activity	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1	W28 D1	W32 D1	W36 D1	W40 D1	W44 D1	W48 D1	Every 12 Weeks Starting at W48	W108 Final Visit	30 Day Safety Visit[s]	Post-Treatment Follow-Up[t]
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[e]*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status[u]					X						X	X	X	X	
Hematology/Chemistry**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Disease Assessment[m]*					X			X			X				
Contrasted CT or MRI Scan[n]											X				
Bone Marrow Aspirate and Biopsy[o]															
MRD Assessment in Peripheral Blood[p]					X						X				
PK sample[v]					X										
Dispense Venetoclax	X	X	X	X	X	X	X	X	X	X	X	X			
Dispense/Collect Subject Calendars/Diaries				X	X										
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[r]		X			X			X			X	X	X		

Scr = Screening; W = Wk = Week; D = Day; Post-Treat = Post-Treatment; FV = Final Visit

Study Windows:

* within 72 hours before or after scheduled visit starting with Week 8 Day 1.

** within 72 hours prior to scheduled visit starting with Week 8 Day 1.

a. Subjects will undergo screening procedures within 28 days prior to the first study drug administration, except where otherwise indicated.

b. Subjects who have 17p deletion or TP53 mutation as assessed by local laboratory (in bone marrow or peripheral blood) may be considered for enrollment. A recent test is desirable but any previous positive test is acceptable. Subjects that do not have the 17p deletion or TP53 mutation or have an unknown status are also eligible.

c. For females of childbearing potential, as defined in the protocol, a urine pregnancy test must be obtained and processed locally at Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening. During the study, a urine pregnancy test can be performed at the discretion of the investigator or per local guidelines.

d. All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study-specific informed consent until study drug administration.

e. A complete physical examination will be performed at Screening. A symptom directed physical examination may be performed as needed. Refer to Section 5.3.1.1 Physical Examination, for more details.

f. For subjects who have a dose interruption lasting more than 1 week during the first 5 weeks of dose-titration or more than 2 weeks when at the daily dose of 400 mg, the TLS risk should be reassessed to determine if restarting at a reduced dose is necessary.

g. All clinical laboratory tests will be analyzed by the local laboratory. Required tests are listed in Table 4 Clinical Laboratory Tests, refer to Section 5.3.1.1 Study Procedures, sub header Hematology and Chemistry as well as Section 6.1.8 Toxicity Management, for more details.

h. For all subjects, if the screening labs were done more than 72 hours before the planned first dose, the chemistry/hematology panel should be repeated and results reviewed prior to the initial dose in order to make a treatment decision. Labs should be assessed and pre-existing abnormalities should be corrected.

i. For all subjects, on the day of Week 1 Day 1, before dosing, the chemistry/hematology panel should be collected. The results of the labs drawn on Week 1 Day 1 need to be reviewed prior to dosing **IF** an additional lab within 72 hours of the initial dose at Week 1 Day 1 was not drawn **AND** reviewed.

j. The Day 2 venetoclax doses should not be administered until the Day 1 24 hour post-dose lab results have been evaluated. Electrolyte abnormalities should be corrected promptly. There is recommended TLS prophylaxis based on subject tumor burden. Please refer to Section 5.3.1.1 Study Procedures – Hematology and Chemistry and Appendix G. Note: There is a ± 2 hour window around the 24 hour lab draw.

k. For all subjects, within 72 hours of each subsequent dose increase, the chemistry/hematology panel should be repeated. The results should be reviewed prior to dose increasing.

l. Prior to dosing, on the day of each subsequent dose increase, the chemistry/hematology panel is required. The results of the labs drawn on Day 1 of each dose increase need to be reviewed prior to dosing **IF** additional labs within 72 hours of the dose increase were not drawn **AND** reviewed.

m. All measurable disease must be documented at Screening by laboratory testing, physical examination and CT scans (or MRI if CT is medically contraindicated); bone marrow examinations are not required but results will be recorded if available. All baseline evaluations should be performed as closely as possible to the beginning of treatment. For all subsequent disease assessments, disease response will be assessed by the investigator based on the analysis of clinical laboratory tests (hematology) and a complete physical examination at Week 24, Week 36 and Week 48.

n. CT scans with contrast (or MRI if CT is medically contraindicated) should include neck, chest, abdomen and pelvic sequences can be accepted if previously performed within 35 days prior to the initial venetoclax dose. Otherwise, CT scans (or MRI) must be performed within the 28 day screening period. To confirm response, a CT scan (or MRI) must be performed at Week 48 for all subjects. If a subject exhibits clinical signs of possible disease progression (i.e., increased or de novo enlargement of liver, spleen or lymph nodes on physical examination) without an increase in lymphocytes meeting the progression of disease criteria, then additional assessments including contrast-enhanced CT scan and/or bone marrow can be performed to confirm or rule out disease progression. Refer to Section 5.3.1.1 Computed Tomography Scans and Disease Assessments, for more details.

o. Bone marrow examinations are not required but results will be recorded if available. For determination of complete remission (CR), the CT scan and bone marrow are required to be negative, per the IWCLL NCI-WG guidelines. If the subject achieves a CR by clinical criteria and confirmatory CT scan, a bone marrow aspirate and biopsy may be performed to confirm the CR. Whenever possible the bone marrow aspirate for biomarker MRD assessment should be split from this sample. Refer to Section 5.3.1.1 Disease Assessments and Bone Marrow Aspirate and Biopsy, for more details.

p. MRD will be assessed by using peripheral blood at Week 1 Day 1 (baseline), Week 24 and Week 48. Refer to Section 5.3.1.1 and Section 5.3.1.2 for more details. When confirming a complete remission (CR + CRi) status per 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy and aspirate. The aspirate should be split and a sample sent to the central laboratory for MRD analysis.

q. Venetoclax tablets should be taken orally once daily with a meal and water in the morning at approximately the same time each day. Dosing may occur at study visits on Week 1 Days 1 & 2 through Week 5 Days 1 and 2.

r. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

s. 30-Day Safety Follow-up visit should occur approximately 30 days (± 3 days) after the last dose of venetoclax.

t. Upon discontinuation of study drug treatment, survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 6 months for a period of 2 years.

u. ECOG performance status may be performed within 72 hours before or after the scheduled visit starting with Week 24.

v. Collect (immediately) prior to venetoclax dosing (0 hour) on Week 24 Day 1. The date and time (to the nearest minute) the venetoclax doses were taken, and whether or not the venetoclax doses were taken with a meal, will be recorded on the eCRF for the Week 24 Day 1 venetoclax PK day and for the 2 days prior to the Week 24 Day 1.

Has been changed to read:

Activity	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1	W28 D1	W32 D1	W36 D1	W40 D1	W44 D1	W48 D1	Every 12 Weeks Starting at W48	Week 108/Final Visit	30 Day Safety Visit[s]	Post-Treatment Follow-Up[t]
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[e]*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status[u]					X						X	X	X	X	
Hematology/Chemistry**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Disease Assessment[m]*					X			X			X				
Contrasted CT or MRI Scan[n]											X				
Bone Marrow Aspirate and Biopsy[o]											X[o]				
MRD Assessment in Peripheral Blood[p]					X						X				
PK sample[v]					X										
Venetoclax dispensation and accountability***	X	X	X	X	X	X	X	X	X	X	X	X	X[x]		
Dispense/Collect Subject Calendars/Diaries				X	X										

Activity	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1	W28 D1	W32 D1	W36 D1	W40 D1	W44 D1	W48 D1	Every 12 Weeks Starting at W48	Week 108/Final Visit	30 Day Safety Visit[s]	Post-Treatment Follow-Up[t]
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[r]		X			X			X			X	X	X		
Collection of Survival information[w]														X	X

Scr = Screening; W = Wk = Week; D = Day; Post-Treat = Post-Treatment; FV = Final Visit

Study Windows:

* Within 72 hours before or after scheduled visit starting with Week 8 Day 1.

** Within 72 hours prior to scheduled visit starting with Week 8 Day 1.

*** As of Week 8 the visit window for scheduled visits is ± 2 days.

a. Subjects will undergo screening procedures within 28 days prior to the first study drug administration, except where otherwise indicated.

b. Subjects who have 17p deletion or TP53 mutation as assessed by local laboratory (in bone marrow or peripheral blood) may be considered for enrollment. A recent test is desirable but any previous positive test is acceptable. Subjects that do not have the 17p deletion or TP53 mutation or have an unknown status are also eligible.

c. For females of childbearing potential, as defined in the protocol, a urine pregnancy test must be obtained and processed locally at Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening. During the study, a urine pregnancy test can be performed at the discretion of the investigator or per local guidelines.

d. All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study-specific informed consent until study drug administration.

e. A complete physical examination will be performed at Screening. A symptom directed physical examination may be performed as needed. Refer to Section 5.3.1.1 Physical Examination, for more details.

f. For subjects who have a dose interruption lasting more than 1 week during the first 5 weeks of dose-titration or more than 2 weeks when at the daily dose of 400 mg, the TLS risk should be reassessed to determine if restarting at a reduced dose is necessary.

g. All clinical laboratory tests will be analyzed by the local laboratory. Required tests are listed in Table 4 Clinical Laboratory Tests, refer to Section 5.3.1.1 Study Procedures, sub header Hematology and Chemistry as well as Section 6.1.8 Toxicity Management, for more details.

h. For all subjects, if the screening labs were done more than 72 hours before the planned first dose, the chemistry/hematology panel should be repeated and results reviewed prior to the initial dose in order to make a treatment decision. Labs should be assessed and pre-existing abnormalities should be corrected.

i. For all subjects, on the day of Week 1 Day 1, before dosing, the chemistry/hematology panel should be collected. The results of the labs drawn on Week 1 Day 1 need to be reviewed prior to dosing **IF** an additional lab within 72 hours of the initial dose at Week 1 Day 1 was not drawn **AND** reviewed.

j. The Day 2 venetoclax doses should not be administered until the Day 1 24 hour post-dose lab results have been evaluated. Electrolyte abnormalities should be corrected promptly. There is recommended TLS prophylaxis based on subject tumor burden. Please refer to Section 5.3.1.1 Study Procedures – Hematology and Chemistry and Appendix H. Note: There is a ± 2 hour window around the 24 hour lab draw.

k. For all subjects, within 72 hours of each subsequent dose increase, the chemistry/hematology panel should be repeated. The results should be reviewed prior to dose increasing.

l. Prior to dosing, on the day of each subsequent dose increase, the chemistry/hematology panel is required. The results of the labs drawn on Day 1 of each dose increase need to be reviewed prior to dosing **IF** additional labs within 72 hours of the dose increase were not drawn **AND** reviewed.

m. All measurable disease must be documented at Screening by laboratory testing, physical examination and CT scans (or MRI if CT is medically contraindicated); bone marrow examinations are not required at screening but results will be recorded if available. All baseline evaluations should be performed as closely as possible to the beginning of treatment. For all subsequent disease assessments, disease response will be assessed by the investigator based on the analysis of clinical laboratory tests (hematology) and a complete physical examination at Week 24, Week 36 and Week 48.

n. CT scans with contrast (or MRI if CT is medically contraindicated) should include neck, chest, abdomen and pelvic sequences can be accepted if previously performed within 35 days prior to the initial venetoclax dose. Otherwise, CT scans (or MRI) must be performed within the 28 day screening period. To confirm response, a CT scan (or MRI) must be performed at Week 48 for all subjects. CT scans (or MRI) may be performed 7 days prior to the scheduled Week 48 visit. If a subject exhibits clinical signs of possible disease progression (i.e., increased or de novo enlargement of liver, spleen or lymph nodes on physical examination) without an increase in lymphocytes meeting the progression of disease criteria, then additional assessments including contrast-enhanced CT scan and/or bone marrow can be performed to confirm or rule out disease progression. Refer to Section 5.3.1.1 Computed Tomography Scans and Disease Assessments, for more details. For patients with only Partial Remission at Week 48 an additional CT and a bone marrow examination can be done between Week 48 and Week 108 to confirm CR if there is a possibility that a patient is in Complete Remission based on laboratory tests and a disease assessment physical examination.

o. For determination of complete remission (CR), the CT scan and bone marrow are required to be negative, per the IWCLL NCI-WG guidelines. If the subject achieves a CR by clinical criteria and confirmatory CT scan, a bone marrow aspirate and biopsy will be performed to confirm the CR. Whenever possible the bone marrow aspirate for biomarker MRD assessment should be split from this sample. Refer to Section 5.3.1.1 Disease Assessments and Bone Marrow Aspirate and Biopsy, for more details.

p. MRD will be assessed by using peripheral blood at Week 1 Day 1 (baseline), Week 24 and Week 48. Refer to Section 5.3.1.1 and Section 5.3.1.2 for more details. When confirming a complete remission (CR + CRi) status per 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy and aspirate. The aspirate should be split and a sample sent to the central laboratory for MRD analysis.

q. Venetoclax tablets should be taken orally once daily with a meal and water in the morning at approximately the same time each day. Dosing may occur at study visits on Week 1 Days 1 & 2 through Week 5 Days 1 and 2.

r. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

s. 30-Day Safety Follow-up visit should occur approximately 30 days (± 3 days) after the last dose of venetoclax.

t. Upon discontinuation of study drug treatment, survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 6 months (± 7 days) for a period of 2 years.

u. ECOG performance status may be performed within 72 hours before or after the scheduled visit starting with Week 24.

v. Collect (immediately) prior to venetoclax dosing (0 hour) on Week 24 Day 1. The date and time (to the nearest minute) the venetoclax doses were taken, and whether or not the venetoclax doses were taken with a meal, will be recorded on the eCRF for the Week 24 Day 1 venetoclax PK day and for the 2 days prior to the Week 24 Day 1.

w. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.

x. In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy. Subjects who participate in the 2 year Extended Access phase will have study drug assigned at Week 108. For patients that are not participating in the 2 year Extended Access phase the Week 108 visit is the Final visit. The specific study assessments to be performed at the Extended Access visits are detailed in Appendix E, Study Activities.

Appendix E. Schedule of Extended Access Phase*
Add: new appendix title and text

Appendix E. Schedule of Extended Access Phase*

Procedure	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	Week 180	Week 192	Week 204	Week 216/ Final Visit	30 Day Safety Visit[d]	Post Treatment Follow up[e]
Vital signs**	X									X	X	
Physical Examination[a]**	X									X	X	
ECOG Performance Status**	X									X	X	
Hematology/Chemistry***	X									X	X	
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Venetoclax dispensation and accountability****	X	X	X	X	X	X	X	X	X			
Collection of Survival Information[b]	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[c]	X											

* In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy.

** Within 72 hours before or after scheduled visit.

*** Within 72 hours prior to scheduled visit.

****The visit window for scheduled visits is ± 2 days.

a. Refer to Section 5.3.1.1 Physical Examination, for more details.

b. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.

c. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

d. 30-Day Safety Follow-up visit should occur approximately 30 days (± 3 days) after the last dose of venetoclax.

e. Upon discontinuation of study drug treatment, survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 6 months (± 7 days) for a period of 2 years.

Appendix H. Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS)
Subsection Section 1: First Dose of Venetoclax or Dose Escalation
First paragraph
In-text table
Abnormality "Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)"
Column "Management Recommendation"
Sixth bullet previously read:

Administer sodium bicarbonate 1 to 2 mEq IV push.

Has been changed to read:

Administer sodium bicarbonate 1 to 2 mEq/kg IV push.

1.0 Title Page

Statistical Analysis Plan

Study M15-550

Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)

Date: 20 Dec 2018

Version 2.0

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be performed for Study M15-550. Study M15-550 evaluates the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL).

This statistical analysis plan (SAP) provides details to elaborate the statistical methods outlined in Clinical Study Protocol M15-550 Amendments 0.01 (US Only), 0.01.01 (US Only), and 0.0.1.01.01 (US Only) and Amendments 0.02 (ROW), 0.02.01 (ROW), and 0.02.01.01 (ROW). It will provide details of statistical methods and describe analysis conventions to guide the statistical programming work.

Unless noted otherwise, all analyses will be performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory CLL. Efficacy will be measured by complete remission rate (complete remission, CR, and complete remission with incomplete bone marrow recovery, CRi) of the subjects who have not been previously treated with BCRi therapy, as assessed by the investigator.

Secondary Objectives

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DOR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and complete remission rate in BCRi treated subjects.

Additional secondary objectives are to evaluate the quality of life measures using the following patient reported outcomes (PRO) questionnaires: the EuroQoL 5 Dimensions (EQ-5D-5L), the Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu), and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). Safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated.

Exploratory Objective

The exploratory objective is to evaluate the level of Minimal Residual Disease (MRD) and the rate of MRD negativity in the peripheral blood.

4.2 Study Design and Plan

This is a Phase 3b, open-label, single arm, and multicenter study evaluating the efficacy of venetoclax monotherapy in subjects with relapsed/refractory CLL.

This study is designed to enroll approximately 250 subjects to meet scientific objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Subjects meeting the eligibility criteria will be treated with venetoclax once daily (QD), continuously up to two years.

Dosing Schedule Overview

Venetoclax is administered orally once daily (QD), continuously. To mitigate the risk for tumor lysis syndrome (TLS), a lead-in period (up to 5 weeks) is employed to evaluate a step wise dose-titration as specified in the protocol, and Figure 1.

Figure 1. 5-Week Dose-Titration/Dose Ramp-up Schedule

Week	VENETOCLAX Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

4.3 Sample Size

Using the CR rate of 6% reported for current therapies,[1] 250 subjects would provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate).

In order to provide approximately 80% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% CR rate in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate), the study will enroll 190 subjects who have not been previously treated with BCRi therapy. Since there are approximately a total of 250 subjects, up to 60 subjects previously treated with BCRi therapy can be enrolled.

The power calculation was performed in nQuery Version 7.

4.4 Interim Analysis

Data Monitoring Committee (DMC)

An Independent Data Monitoring Committee (DMC) will review the safety data when approximately 20 subjects have completed a minimum of 12 weeks of treatment. Subsequent reviews may be conducted based on recommendations from the DMC or

requests from the Sponsor. Details of the DMC review will be presented in the DMC charter.

4.5 Timing of Efficacy Analyses and Safety Evaluations

Table 1. Summary of Analyses with Cutoff Dates and Data Included

	Analysis Number/Database Version	Cutoff Date	Efficacy/PRO Data Included	Safety Data Included
DMC	C	24 Apr 2017	Not included	All safety data[a]
DMC	I	03 Nov 2017	Not included	All safety data[a]
DMC	J	30 Apr 2018	Included	All safety data[a]

a. Safety population is defined in Section 5.1.2.

Efficacy and safety data up to and including the cutoff date specified in Table 1 will be analyzed. During this data collection period, active subjects will continue to receive venetoclax, as applicable. When data collection is complete and all data management quality assurance (QA) and quality control (QC) procedures are performed, the clinical database data will be extracted for documentation and statistical analyses. Any active subjects will continue to receive venetoclax until they discontinue or for up to 2 years. Subjects that continue to derive clinical benefit after 2 years of treatment and where venetoclax is not commercially available may continue with treatment with venetoclax for up to 2 additional years. AbbVie will work with investigator on case by case basis to consider the potential continuation of the treatment. Once the last enrolled subject discontinues/completes the study, the study will be considered complete and all remaining data will be collected and entered into the clinical database.

All analyses will be conducted at AbbVie (or their designees) according to the methodologies specified in this SAP.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

5.1.1 Efficacy Populations

5.1.1.1 Intent-to-Treat (ITT) Population

All enrolled subjects treated with at least one dose of venetoclax will be included in the ITT population. Efficacy analyses will be performed on the ITT population, unless otherwise specified.

5.1.1.2 ITT BCRi-Naive (ITT-BN) Population

ITT-BN population includes subjects who have not been previously treated with BCRi therapy in the ITT population.

5.1.1.3 ITT BCRi-Experienced (ITT-BE) Population

ITT-BE population includes subjects who were previously treated with BCRi therapy in the ITT population.

5.1.2 Safety Population

All ITT subjects will be included in the safety population.

5.2 Variables Used for Stratification of Randomization

No stratification is used for this open-label single-arm study.

6.0 Analysis Conventions

6.1 Baseline

Definition of Baseline

The baseline value (except for laboratory variables) is defined as the last non-missing measurement collected before the first dose of venetoclax. The baseline value for laboratory variables will be defined as:

- For subject with IV hydration for TLS prophylaxis, the baseline value will be the non-missing lab value taken before the subject receiving IV hydration prior to the first dose of venetoclax.
- For subject without IV hydration for TLS prophylaxis, the baseline value will be the non-missing lab value taken before the first dose of venetoclax.

6.2 Treatment Days

Definition of Treatment Days (Days Relative to the First Dose of Venetoclax)

Treatment (Rx) days are calculated for each time point relative to the first dose date of venetoclax. They are defined as the number of days between the day of the first dose of venetoclax and the specific time point. Rx days are negative values when the time point of interest is prior to the first venetoclax dose day. Rx days are positive values when the time point of interest is after the first venetoclax dose day. The day of the first dose of venetoclax is defined as Rx Day 1, while the day prior to the first venetoclax dose is defined as Rx Day –1 (there is no Rx Day 0).

Definition of Final Observation

The final observation (Final Visit) is defined as the last non-missing observation collected within 30 days following the last dose of venetoclax, unless otherwise specified.

6.3 Definition of Analysis Windows

For visit wise analyses including quality of life (Qol), the time windows specified in Table 2 describe how the data are assigned to protocol specified visits. Analysis time windows are constructed using the following algorithm:

- Determine the nominal study Rx day for each scheduled visit.
- Determine the window around a specific nominal study Rx day as in Table 2.
- If more than one assessment is included in a time window the most conservative value (i.e., the smallest score) should be used for the analysis of quality of life measures. A sensitivity analysis should be performed based on considering the most favorable (i.e., the largest value) assessment of the quality of life measures. Except the quality of life measures, if there are two observations with equal distance to the nominal day, the latest one will be used in analyses.

Table 2. Time Windows for Quality of Life

Scheduled Visit	Nominal Day	Time Window (Study Day Range)
Week 1 Day 1/Baseline	≤ 1	See the baseline definition (Section 6.0)
Week 4 Day 1	22	2 to 56
Week 12 Day 1	78	57 to 153
Week 24 Day 1	162	154 to 237
Week 36 Day 1	246	238 to 321
Week 48 Day 1	330	322 to 405
Week 60 Day 1	414	406 to 489
Week 72 Day 1	498	490 to 573
Week 84 Day 1	582	574 to 657
Week 96 Day 1	666	658 to 743
Week 108 Day 1	750	744 to 835
Final Observation	Last non-missing value within 30 days of last dose of Venetoclax	

6.4 Missing Data Imputation

If a respondent answers at least 50% of the items in FACIT-F, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. Similarly, the missing items of the FACIT-Leu questionnaire will be imputed with the average score of the answered items in the same scale as long as more than 50% of the items in the scale are answered. For EQ-5D-5L index, no imputation will be performed for missing items.

Subjects with missing disease progression date, missing death date, or missing last known alive date will be considered as censored subjects for time to progression, progression free survival analysis, and survival analysis. And the subject will be censored at the interim data cutoff date.

7.0 Subject Disposition

The number and percentage of subjects will be summarized for each of the following categories, for overall and by country:

- Subjects enrolled into the study.
- Subjects who discontinued venetoclax – overall and for each reported primary reason.
- Subjects who discontinued the study – overall and for each reported primary reason.

The number and percentage of subjects who discontinued venetoclax will be summarized by reason (all reasons) and by primary reason (per eCRF). Similar summaries will be provided for discontinuations from the study.

The number and percentage of subjects with reported study drug interruptions will be summarized. Reasons for study drug interruptions will be presented in the CSR listings.

8.0 Demographics, Baseline Characteristics, Medical History, and Previous Concomitant Medications

8.1 General Consideration

The ITT population, ITT-BE, and ITT-BN population will be used to summarize demographics and baseline characteristics. The safety population will be used to summarize medical history and previous, concomitant, and post-treatment medications.

8.2 Demographic and Baseline Characteristics

Categorical baseline variables will be summarized with the number and percentage of subjects in each category. Continuous baseline variables will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, maximum and minimum).

Categorical baseline variables include:

- Sex (male, female)
- Race (White, Black or African American, Asian, and Other)
- Geographic region (US, EUROPE)
- Ethnicity (Not Hispanic or Latino, and Hispanic or Latino)
- Age (< 65, ≥ 65, < 75, and ≥ 75)
- Tobacco use (current, former, never, and unknown)
- Alcohol use (current, former, never, and unknown)
- ECOG performance status (grade: 0, 1, 2)
- LDH ($\leq$ ULN, > ULN)
- Prior number of oncology therapies (1, 2, ≥ 3)
- Previous line of Ibrutinib failure (1, > 1)
- Previous line of Idelalisib failure (1, > 1)
- 17p deletion status (deleted, not deleted, indeterminate)
- Rai stage (0, 1, 2, 3, 4)
- Binet stage (A, B, C)

- IgVH status (mutated, unmutated)
- ZAP-70 (positive, negative, indeterminate)
- CD-38 (positive, negative, indeterminate)
- Beta 2-microglobulin (< 3 mg/L, ≥ 3 mg/L)
- TP53 mutation (yes, no, unknown)
- 11q (deleted, not deleted, indeterminate)
- 13q (deleted, not deleted, indeterminate)
- 12q trisomy (present, not present, indeterminate)
- Absolute lymphocyte count (ALC) (< 25×10^9/L, ≥ 25×10^9/L; < 100×10^9/L, ≥ 100×10^9/L)
- Bulky disease nodes (< 5 cm, 5 cm To 10 cm, ≥ 10 cm)
- Prior BCRi treated (yes, no)
- TLS risk category-US (low, medium, high)
- TLS risk category-ROW (yes, no)
- Hospitalized for TLS prophylaxis before venetoclax (yes, no)

Continuous baseline variables include:

- Age (year)
- Weight (kg) by male and female
- Height (cm)
- Number of prior oncology therapy
- Beta-2 microglobulin (MG/L)
- Lactate dehydrogenase (LDH)
- Absolute lymphocytes count (10^9/L)
- Bulky disease nodes (cm)
- Duration of BCRI therapy before venetoclax (month)

8.3 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the CRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

8.4 Previous Treatment and Concomitant Medications

A prior medication is defined as any medication taken prior to the first dose of venetoclax. A concomitant medication is defined as any medication that started prior to the first dose of venetoclax and continued to be taken after the first dose of venetoclax or any medication that started after the first dose of venetoclax, but not after the last dose of venetoclax. The number and percentage of subjects who have taken medications will be summarized by generic drug name for prior medications, concomitant medication, and prior oncology therapies. In addition, the number and percentage of subjects who have taken zero, one, two, three, four, and five or more drugs will be summarized for prior medications, concomitant medications, and prior oncology therapies.

For summaries of concomitant medications, if an incomplete start date was collected for a medication, the medication will be assumed to be a concomitant medication unless there is evidence that confirms that the medication was not a concomitant medication (e.g., the medication end date was prior to the first dose of venetoclax).

A subject who reports the use of two or more medications will be counted only once in the summary of "Any Concomitant Medication." A subject who reports two or more uses of the same medication will be counted only once in the total for the associated generic drug name. Similar rules apply to prior medications as well.

9.0 Venetoclax Exposure and Compliance

The duration of exposure to Venetoclax will be summarized. Duration of exposure is defined for each subject as (last dose date – first dose date) + 1. Duration of exposure will be summarized using the following statistics: sample size (N), mean, standard deviation, median, and range. In addition, the number and percentage of subjects exposed to Venetoclax will be summarized for the following categories of exposure duration: 0 to 5 weeks, > 5 weeks to 8 weeks, > 8 weeks to 12 weeks, > 12 weeks to 16 weeks, > 16 weeks to 20 weeks, > 20 weeks to 24 weeks, > 24 weeks to 28 weeks, > 28 weeks to 32 weeks, > 32 weeks to 36 weeks, > 36 weeks to 48 weeks, > 48 weeks to 60 weeks, and > 60 weeks.

The compliance based on investigator opinion for each subject will be provided in the listing.

10.0 Efficacy Analysis

10.1 General Considerations

No statistical testing will be performed for the efficacy endpoints. Further details on the analysis sets used will be specified in efficacy analyses described below. All efficacy responses were assessed per investigator review.

10.1.1 Definitions for Efficacy Endpoints

Complete Remission Rate (CR + CRi)

Complete response rate, complete remission (CR) or complete remission with incomplete marrow recovery (CRi), will be defined as the proportion of subjects per the 2008 Modified IWCLL NCI-WG criteria as assessed by investigator using the best response at any time during the study. In addition, the 95% confidence interval for complete response rate (CR) rate based on the binomial distribution (Clopper-Pearson exact method) will be provided. Subjects who do not achieve a CR or CRi will be considered to be non-responders in the calculation of complete response rate.

Overall Response Rate (ORR)

ORR (CR + CRi + nPR + PR) will be defined as the proportion of subjects who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), nodular partial remission (nPR), or confirmed partial remission (PR) based on the 2008 Modified IWCLL NCI-WG criteria as assessed by investigator using the best response at any time during the study. Confirmatory PR response will be determined by not less than 49 days from the first PR was observed. The corresponding exact 95% confidence interval for the proportion (Clopper-Pearson exact method) will be constructed. Subjects who do not respond will be considered non-responders.

Duration or Response (DOR)

The DOR for a given subject will be defined as the number of days from the day the criteria are met for CR, CRi, nPR, or confirmed PR (whichever is recorded first) to the earliest date that progressive disease (PD) is objectively documented (radiographic or clinical) or death (i.e., DOR = PD/death/censoring date – earliest CR/CRi/nPR/PR date + 1 day). For subjects who have a PR before CR, CRi, or nPR in subsequent visits, the DOR is computed from the earliest PR. If a subject is still responding then the subject's data will be censored at the date of the last available disease assessment prior to the data cutoff date. Only subjects with the iWCLL response criteria will be included in the analysis of DOR. The distribution of the duration of overall response will be estimated using the Kaplan-Meier methodology. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

Time to Progression (TTP)

Time to progression for a given subject will be defined as the number of days from the date the subject started venetoclax to the date of earliest PD (radiographic or clinical) (i.e., TTP = PD/censoring date – first dose date + 1 day). If the subject does not experience disease progression then the subject's data will be censored at the date of the last available disease assessment prior to the data cutoff date. If a subject does not have

any post baseline disease assessments, the data will be censored at the first dose date plus 1 day. The distribution of the time to progression will be estimated using Kaplan-Meier methodology. Median time to progression and the corresponding 95% confidence interval will be estimated.

Progression Free Survival (PFS)

Progression-free survival (PFS) will be defined as the number of days from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical) or death (i.e., PFS = PD/death/censoring date – first dose date + 1 day). If the subject does not experience disease progression or death then the subject's data will be censored at the date of the last available disease assessment prior to the data cutoff date. If a subject does not have any post baseline tumor assessment or clinical assessment for progression, the data will be censored at the date of first dose plus 1 day. Progression-free survival will be analyzed by Kaplan-Meier methodology. Median duration of PFS will be calculated and 95% confidence interval for median duration of PFS will be presented.

Overall Survival (OS)

Overall survival (time to death) for a given subject will be defined as the number of days from the first dose date of venetoclax to the date of the subject's death (i.e., OS = death/censoring date – first dose date + 1 day). All events of death will be included, regardless of whether the event occurred while the subject was still taking any study drug, or after the subject discontinued any study drug. If a subject has not died, then the data will be censored at the date when the subject was last known to be alive prior to the cutoff date. The date of the last known to be alive will be determined by selecting the last available date of the following study procedures for a subject: study visit/contact date, tumor assessment, clinical disease progression, physical examination, vital signs assessment, clinical laboratory collection, study drug, adverse event assessment, concomitant medication assessment, drug or study completion, survival visit, and post treatment therapy assessment. The distribution of the time to death will be estimated

using Kaplan-Meier methodology. Median survival time and the corresponding 95% confidence interval will be estimated.

Minimal Residual Disease (MRD) Response Rate

The rate of MRD response in CLL subjects will be defined as the proportion of CLL subjects who achieved MRD negative status with less than one CLL cell per 10,000 leukocytes (or below 10^{-4}). All subjects with an MRD assessment will be included in the denominator for the calculation of MRD response rate. Minimal residual disease response will be summarized by categories: MRD negative, MRD positive, or MRD unknown/missing. The 95% confidence intervals based on the binomial distribution (Clopper-Pearson exact method) will be provided.

10.2 Efficacy Analyses

Data collected at any point prior to the specified cutoff date during the study will be used in efficacy analyses, unless otherwise specified.

10.2.1 Primary Efficacy Analysis

The primary efficacy endpoint will be complete remission rate (CR + CRi) of the subjects in ITT-BN population defined in Section 5.1.1.

In addition, the ninety-five percent (95%) confidence interval based on the Clopper-Pearson exact method for binomial distribution will be constructed for the calculated CR rate.

10.2.2 Secondary Efficacy Analyses

ORR will be assessed as the proportion of subjects with an overall response (CR + CRi + nPR + PR) based on the IWCLL NCI-WG criteria. The ninety-five percent (95%) confidence interval based on the Clopper-Pearson exact method for binomial distribution will be constructed for the calculated ORR rate.

DOR, TTP, PFS, and OS will be analyzed by Kaplan-Meier methodology using data for all subjects defined in Section 5.1.1. Median time of each endpoint will be calculated and 95% confidence interval for median time of each endpoint will be presented.

The analyses of ORR, DOR, TTP, PFS, and OS will be performed on ITT, ITT-BN, and ITT-BE population.

The complete remission (CR + CRi) rate in will be assessed based on the 2008 Modified IWCLL NCI-WG criteria for ITT and ITT-BE population. The ninety-five percent (95%) confidence interval based on binomial distribution will be constructed for the calculated complete remission rate.

10.2.3 Exploratory Efficacy Analysis

The rate of MRD negativity in subjects will be summarized. This rate will be defined as the proportion of subjects who had MRD negativity status in peripheral blood. Ninety-five percent (95%) confidence intervals based on the Clopper-Pearson exact method for binomial distribution will be provided.

10.3 Additional Secondary Efficacy Analyses

Additional efficacy endpoints to be analyzed for the ITT, ITT-BN, and ITT-BE populations are Health Economic and Patient Reported Outcome measures, which include the FACT-Leu, FACIT-F, and the EQ-5D-5L (measure of general health status) and EQ-5D-VAS (Visual Analog Scale).

For the FACT-Leu, scores will be summarized descriptively at each assessment. The impact of treatment on quality of life over time will be assessed by calculating the change in scores from baseline at each assessment time point. Scores will be calculated according to the FACT-Leu scoring manual. The scores will also be summarized (mean, standard deviation, median) at each assessment. In addition mean change in scores (each assessment versus baseline) will be estimated. The 95% confidence interval of the mean change will be constructed based on (a) paired t-test and (b) with model assumption. A

linear mixed effect model will be used for the analysis of repeated measures where the covariance pattern will be assumed as compound symmetry (CS).

For the FACIT-F, scores will be summarized descriptively at each assessment. The impact of treatment on fatigue over time will be assessed by calculating the change in score from baseline at each assessment time point. Scores will be calculated according to the FACIT-F scoring manual. The scores will also be summarized (mean, standard deviation, median) at each assessment. In addition mean change in scores (each assessment versus baseline) will be estimated. The 95% confidence interval of the mean change will be constructed based on (a) paired t-test and (b) with model assumption. A linear mixed effect model will be used for the analysis of repeated measures where the covariance pattern will be assumed as compound symmetry (CS).

The EQ-5D-5L is a generic preference instrument that has been validated in numerous populations. The EQ-5D-5L has five dimensions: mobility, self care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health.

For each of the five dimensions of the EQ-5D-5L, the number and percentage of subjects at each level will be summarized at each assessment. The VAS values and the score of the EQ-5D-5L will also be summarized (mean, standard deviation, median) at each assessment; in addition mean change in VAS values and the score of the EQ-5D-5L (each assessment versus baseline) will be estimated. The 95% confidence interval of the mean change will be constructed based on (a) paired t-test and (b) with model assumption. A linear mixed effect model will be used for the analysis of repeated measures where the covariance pattern will be assumed as compound symmetry (CS).

10.4 Subgroup Analyses of Efficacy and Quality of Life

To evaluate the impact of baseline conditions on efficacy, subgroup analyses will be performed for complete remission (CR + CRi) in the ITT, ITT-BN, and ITT-BE population.

The following subgroups below will be used for efficacy analyses:

- Sex (male, female)
- Race (White, Non-White)
- Age (< 65, ≥ 65; < 75, ≥ 75)
- ECOG status (0, 1, 2)
- 17p deletion status (deleted, not-deleted)
- TP53 mutation status (yes, no)
- Prior number of oncology therapies (1, 2, ≥ 3)
- Baseline ALC ($< 25 \times 10^9$/L, $\geq 25 \times 10^9$/L; $< 100 \times 10^9$/L, $\geq 100 \times 10^9$/L)
- Baseline node size (< 5 cm, 5 cm To 10 cm, ≥ 10 cm)

ORR and CR and their 95% CIs will be reported for each level of subgroups in a forest plot. KM plot for DOR, and PFS will be also be provided for 17p deleted versus non-17p del., TP53 mutation versus TP53 non-mutation, and prior BCRi treated versus prior BCRi naïve. MRD response rate will be additionally summarized by overall response category (CR/PR/non-responders) and the BCRi failure status (yes, no).

The following subgroups below will be used for quality of life analyses:

- 17p deletion status (deleted, not deleted)
- TP53 mutation (yes, no)
- Prior BCRi treated (yes, no)
- Prior number of oncology therapies (1, 2, ≥ 3)
- Baseline ALC ($< 25 \times 10^9$/L, $\geq 25 \times 10^9$/L; $< 100 \times 10^9$/L, $\geq 100 \times 10^9$/L)
- Baseline node size (< 5 cm, 5 cm to 10 cm, ≥ 10 cm)

- Hospitalized for TLS prophylaxis before venetoclax (yes, no)

10.5 Handling of Multiplicity

There will be no multiplicity adjustments performed.

11.0 Safety Analysis

11.1 General Considerations

Safety data will be summarized for the ITT population.

11.2 Analysis of Treatment-Emergent Adverse Events

All summaries/analyses involving AEs will include treatment-emergent adverse events (TEAE) only, unless otherwise specified. TEAE are defined as any event with onset after the first dose of venetoclax and no more than 30 days after the last dose of venetoclax. Events where the onset date is the same as the venetoclax start date are assumed to be treatment-emergent, unless the venetoclax start time and the AE start time are collected and the AE start time is prior to the venetoclax start time. If an incomplete onset date was collected for an AE, the AE will be assumed to be treatment-emergent unless there is evidence that confirms that the AE was not treatment-emergent (e.g., the AE end date was prior to the date of the first dose of venetoclax).

Treatment-emergent adverse events will be summarized by maximum severity grade level of each preferred term. Each adverse event will be assigned a grade level (grade 1, 2, 3, 4, or 5) by the investigator. If a subject has an AE with unknown severity, then the subject will be counted in the severity grade level category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same AE with the highest grade level (grade 5). In this case, the subject will be counted under the "Grade 5" category.

Treatment-emergent adverse events will be summarized by relationship of each preferred term to venetoclax, as assessed by the investigator. If a subject has an adverse event with

unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the clinical study report.

Adverse event data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) according to the MedDRA coding dictionary version 20.1 or higher.

Adverse Event

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent adverse event;
- Any treatment-emergent adverse event with reasonable possibility related to venetoclax by the investigator;
- Any treatment-emergent NCI toxicity (CTCAE V4.03) grade 3, 4, or 5 adverse events;
- Any treatment-emergent NCI toxicity (CTCAE V4.03) grade 3 or 4 adverse event;
- Adverse events broken down by NCI toxicity grade (Severity);
- Any treatment-emergent serious adverse event;
- Any treatment-emergent adverse event leading to discontinuation of venetoclax;
- Any treatment-emergent adverse event leading to venetoclax interruption
- Any treatment-emergent adverse event leading to venetoclax reduction

- Any treatment-emergent adverse event leading to death;

For summary tables of AE by PT, subjects reporting more than one AE for a given PT will be counted only once for that term (most severe/highest grade incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one AE within an SOC will be counted only once for that SOC. Subjects reporting more than one AE will be counted only once in the overall total.

Adverse Events of Special Interest

Adverse events of special interest will be summarized. The list of adverse events of special interest is shown in Table 3.

For each of the adverse event of interest, the number and percentage of subjects experiencing at least one treatment-emergent adverse event will be presented overall and by SOC and PT. In addition, a listing of treatment-emergent adverse events for subjects meeting each of the search criterions will be provided.

Table 3. Adverse Events of Special Interest

Risk	Search Criteria
Tumor Lysis Syndrome (three searches)	1) SMQ – "Tumour lysis syndrome" (Narrow-scope) 2) SMQ – "Tumuor lysis syndrome" (Narrow) plus PT terms of "Hyperkalaemia," "Hyperuricaemia," "Hyperphosphataemia," "Hypocalaemia," "Blood potassium increased," "Blood uric acid increased," "Blood phosphorus increased," "Blood calcium decreased" 3) SMQ – "Tumuor lysis syndrome" (Narrow) plus broad-scope terms with algorithm applied (i.e., two events from category B and one event from category C required for a subject to be counted as having a TLS event)
Neutropenia	PT terms – "Neutropenia," "Neutrophil count decreased," "Febrile neutropenia," "Agranulocytosis," "Neutropenic infection," and "Neutropenic sepsis"
Serious Infection, Including Opportunistic Infections	SAEs in the SOC of "Infections and Infestations"
Second Primary Malignancy	SMQ – "Malignant tumours" (Narrow) and "Myelodysplastic syndromes" (Narrow)
Lymphopenia	PT terms – "Lymphopenia" and "Lymphocyte count decreased"
Anemia	PT terms – "Anaemia" and "Haemoglobin decreased"
Thrombocytopenia	PT terms – "Thrombocytopenia" and "Platelet count decreased"
Drug Induced Liver Injury (DILI)	SMQ – "Drug related hepatic disorders – comprehensive search"
Medication Error	SMQ – "Medication error" (broad)

SMQ = Standardised MedDRA Query

11.3 Deaths

The number of deaths will be summarized (1) for death occurring during the first day of venetoclax and within 30 days after the last dose of venetoclax, (2) for death occurring > 30 days after the last dose of venetoclax, (3) for all deaths in this study, i.e., 1) and 2).

11.4 Analysis of Laboratory and Vital Signs Data

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses.

The value for baseline used in laboratory and vital sign analyses is defined in Section 6.0.

Hematology variables include: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, lymphocytes, platelet count, and reticulocyte count.

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, uric acid, glucose, albumin, LDH.

11.4.1 Analyses of Shift from Baseline in Clinical Laboratory Data

For shifts relative to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE version 4.03), baseline and post-baseline laboratory observations (maximum and final) will be categorized as grade 0, grade 1, grade 2, grade 3, or grade 4 according to NCI CTCAE grade version 4.03.

For laboratory tests for which a normal range limit is one end of the grade 1 range, then values that are either within the normal range or outside of it in direction opposite, the test will be classified as grade 0 values. For other tests, values outside of the grade 1 range in the direction opposite of that the test will be classified as grade 0.

The baseline and final grades will be defined respectively as defined in Section 6.1.

The maximum NCI toxicity grade value is the value with highest NCI toxicity grade collected after the first dose of venetoclax and within 30 days following the last dose of venetoclax. In cases where multiple values are collected on the same day, the maximum grade value will be selected as the value for that day.

For each variable, shift tables will be generated that cross tabulate the number of subjects with baseline values of grade 0, grade 1, grade 2, grade 3, or grade 4 versus maximum or final observations of grade 0, grade 1, grade 2, grade 3, or grade 4.

Detailed listings of data for subjects experiencing NCI CTCAE grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of venetoclax, will be included in these listings.

Potential Drug-Induced Liver Injury (DILI)

Potential DILI will be determined by searching post-dose laboratory ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN that occur within 72 hours of each other.

11.4.2 Assessment of Potentially Clinically Significant Vital Signs Values

Vital sign variables are systolic blood pressure, diastolic blood pressure, heart rate, and body temperature.

Pre-defined criteria for potentially clinically significant vital signs values are given in Table 4 below:

Table 4. Criteria for Potentially Clinically Significant Laboratory Values – Vital Signs Variables

Vital Signs Variables	Criterion	Definition of Potentially Clinically Significant
Systolic blood pressure	High	Value ≥ 160 mmHg
Diastolic blood pressure	High	Value ≥ 100 mmHg
Heart rate	Low	Value < 50 bpm
	High	Value ≥ 120 bpm
Temperature	Low	Value < 36°C
	High	Value ≥ 38.5°C

The number and percentage of subjects who have at least one post-baseline observation meeting the pre-defined criteria for potentially clinically significant values will be provided for each vital sign. A listing of all observations collected will be generated for subjects that had at least one post-baseline observation meeting pre-defined criteria for potentially clinically significant values.

11.4.3 ECG/2D Echocardiogram

For ECG testing, subjects were only required to have a screening and a final visit assessment. If an ECG was clinically indicated, additional measurement could have been performed. Only ECG results that were abnormal were collected in the database.

For 2D echocardiogram testing, subjects had a screening assessment if clinically indicated. If an echocardiogram was clinically indicated, additional measurement could have been performed.

Data from ECG or 2D Echocardiogram that were collected will be provided in data listings.

No analyses are planned given the limited collection of data.

12.0 Pharmacokinetic Analyses

Plasma concentrations of venetoclax and possible metabolites(s) will be listed for each subject by scheduled visit. Summary statistics will also be computed for each scheduled visit. Samples not taken pre-dose will be excluded from summary statistics calculation.

13.0 Summary of Changes

- Updated secondary endpoints and added exploratory endpoint
- Updated censoring rules for the analysis of time to event
- Updated the safety data analysis

14.0 References

1. Resonate Trial. ASH. 2014. Abstract 3331.

Appendix A. List of Abbreviations

AE	Adverse Event
BM	Bone Marrow
CLL	Chronic Lymphocytic Leukemia
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-Induced Liver Injury
DOR	Duration of Overall Response
ECOG	Eastern Cooperative Oncology Group
G-CSF	Granulocyte-colony stimulating factor
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
NCI	National Cancer Institute
NCI-WG	National Cancer Institute-Working Group
NPT	Non-protocol Anti-leukemia Therapy
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
QA	Quality Assurance
QC	Quality Control
QD	Once Daily
SAP	Statistical Analysis Plan
SMQ	Standard MedDRA Query
TEAE	Treatment-emergent Adverse Event
TLS	Tumor Lysis Syndrome
TTNT	Time to next anti-CLL treatment
TTP	Time to Progression
ULN	Upper Limit of Normal

Document Approval

Study M15550 - Statistical Analysis Plan Version 2 - 20Dec2018 (E3 16.1.9)

Version: 1.0 **Date:** 21-Dec-2018 05:44:14 PM **Company ID:** 12212018-00F9F68401B790-00001-en

Signed by:	Date:	Meaning Of Signature:
Busman_Todd_A	20-Dec-2018 01:59:55 PM	Approver
Qian_Jiang_X	20-Dec-2018 03:03:44 PM	Approver
Fort_Stan	20-Dec-2018 04:28:06 PM	Approver
Brooks_Anna_X	20-Dec-2018 05:51:20 PM	Approver
Masud_Abdullah	21-Dec-2018 05:44:14 PM	Author