CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s013

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	208573 S-13
Priority or Standard	Priority
Submit Date(s)	06 February 2019; 06 March 2019
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Division/Office	Division of Hematology Products
Review Completion Date	13 May 2019
Established Name	Venetoclax
Trade Name	Venclexta
Pharmacologic Class	BCL-2 inhibitor
Applicant	AbbVie Inc.
Formulation(s)	Tablet, for oral use
Dosing Regimen	400mg once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma

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OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
OIR= Office of *In Vitro* Diagnostics and Radiological Health
DMPP= Division of Medical Policy Programs
CDRH= Center for Devices and Radiological Health

Glossary

ADR	adverse drug reaction
AE	adverse event
AEGT	AE group term
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
AUC_{ss}	area under curve at steady state
BR	bendamustine+rituximab
BTD	Breakthrough Designation
CCOD	clinical cutoff date
CFR	Code of Federal Regulations
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
COA	Clinical outcome assessment
CR	complete response
CrCl	creatinine clearance
CRi	complete response with incomplete bone marrow recovery
CRF	case report form
CRT	clinical review template
CSR	clinical study report
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Co-operative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
E-R	exposure-response
FCR	fludarabine+cyclophosphamide+rituximab
GClb	obinutuzumab + chlorambucil
GCP	good clinical practice
GCSF	granulocyte colony stimulating factor
GCLLSG	German CLL Study Group
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
IRB	institutional review board
IRC	Independent Review Committee
IRR	infusion-related reaction

ITT	intent to treat
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
KM	Kaplan-Meier
MDASI	M.D. Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NGS	next generation sequencing
NLT	new leukemia treatment
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OCE	Oncology Center of Excellence
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
ORR	overall response rate
PBRER	Periodic Benefit-Risk Evaluation Report
PD	progressive disease
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetic/pharmacokinetics
PT	preferred term
PMR	postmarketing requirement
PR	partial remission
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QD	once a day
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEER	Surveillance, Epidemiology, and End Results
SLL	small lymphocytic leukemia
SMQ	standard MedDRA query
SOC	system organ class
TEAE	treatment emergent adverse event
TLS	tumor lysis syndrome
USPI	U.S Package Insert
VEN+G	venetoclax + obinutuzumab

1. Executive Summary

1.1 Product Introduction

Venclexta (venetoclax) is a small-molecule inhibitor of BCL-2, an anti-apoptotic protein.

Venclexta received initial US approval in 2016. The current approved indications for Venclexta are:

- For the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.
- In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The efficacy results from a single multicenter, randomized, open-label, actively controlled trial (BO25323/CLL14, NCT02242942) provide for substantial evidence of efficacy for the following recommended indication: Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

The BO25323 trial demonstrated clinically meaningful and statistically significant improvement in the primary efficacy endpoint, progression-free survival [hazard ratio 0.33 (95% CI 0.22, 0.51), P-value <0.0001], and key secondary endpoints of overall response rate (85% vs 71%, P-value 0.0007), complete remission (CR) and complete remission with incomplete marrow recovery rate (50% vs 23%, P-value <0.0001), and minimal residual disease negative rates at the end of treatment (ITT population: bone marrow 57% vs 17%, P-value <0.0001, peripheral blood 76% vs 35%, P-value <0.0001; Patients with CR: bone marrow 69% vs 45%, P-value 0.0048, peripheral blood 87% vs 62%, P-value 0.0005). Progression-free survival and overall response rate endpoints are standard efficacy endpoints for hematology-oncology clinical trials and have been used in other FDA approvals. The use of a single randomized trial to support approval is acceptable due to the disease setting, consistent demonstration of superiority across multiple efficacy endpoints, and robust efficacy results on statistical evaluation.

1.3 Benefit-Risk Assessment

In adult patients with previously untreated chronic lymphocytic leukemia (CLL), a multicenter, randomized, open-label, actively controlled trial (BO25323/CLL14, NCT02242942) demonstrated superiority of venetoclax plus obinutuzumab (VEN+G) compared to chlorambucil plus obinutuzumab (GClb). Clinically meaningful and statistically significant improvement in progression-free survival [hazard ratio 0.33 (95% CI 0.22, 0.51), P-value <0.0001], overall response rate (85% vs 71%, P-value 0.0007), complete remission (CR) and complete remission with incomplete marrow recovery rate (50% vs 23%, P-value <0.0001), and minimal residual disease negative rates at the end of treatment (ITT population: bone marrow 57% vs 17%, P-value <0.0001, peripheral blood 76% vs 35%, P-value <0.0001; Patients with CR: bone marrow 69% vs 45%, P-value 0.0048, peripheral blood 87% vs 62%, P-value 0.0005) provide substantial evidence of efficacy for the recommended indication. The recommended dosing regimen for venetoclax in combination with obinutuzumab is obinutuzumab administration at 100 mg on Cycle 1 Day 1, followed by 900 mg on Cycle 1 Day 2, followed by 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle, for a total of 6 cycles. On Cycle 1 Day 22, start venetoclax according to the 5-week ramp-up schedule starting at 20mg. After completing the ramp-up schedule on Cycle 2 Day 28, patients should continue venetoclax 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12.

In the BO25323 safety population (212 patients on VEN+G, 214 patients on GClb), the arms had similar incidences of treatment emergent fatal toxicities (2% per arm, most often from infection), serious adverse events (VEN+G 49%, GClb 42%, difference mostly due to infection), grade 3 or 4 adverse events (VEN+G 79%, GClb 76%), grade ≥3 neutropenia (VEN+G 56%, GClb 52%), and tumor lysis syndrome (≤ 2% in each arm). The safety profile of venetoclax in the BO25323 trial was consistent with the known safety profile of venetoclax across multiple clinical trials in patients with CLL or small lymphocytic leukemia. The most common adverse reactions (≥ 20%) for venetoclax in combination with obinutuzumab or rituximab or as monotherapy were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CLL represent approximately 30% of all adult leukemias and is an incurable malignancy, with relapse nearly universal.	CLL is a serious and life-threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Treatment options for patients with untreated CLL include multiagent chemoimmunotherapy. However, the majority of patients will experience disease relapse. • A large percentage of patients with CLL cannot tolerate multiagent chemoimmunotherapy due to age and comorbidities.	There is a need for more effective and tolerable first-line regimens for patients with CLL.
Benefit	• The BO25323 trial demonstrated clinically meaningful and statistically significant improvement in progression-free survival [hazard ratio 0.33 (95% CI 0.22, 0.51), P-value <0.0001], overall response rate (85% vs 71%, P-value 0.0007), complete remission (CR) and complete remission with incomplete marrow recovery rate (50% vs 23%, P-value <0.0001), and minimal residual disease negative rates at the end of treatment (ITT population: bone marrow 57% vs 17%, P-value <0.0001, peripheral blood 76% vs 35%, P-value <0.0001; Patients with CR: $_b$ one marrow 69% vs 45%, P-value 0.0048, peripheral blood 87% vs 62%, P-value 0.0005).	Substantial evidence of efficacy was demonstrated for venetoclax in combination with obinutuzumab (VEN+G) over chlorambucil plus obinutuzumab (GClb).
Risk and Risk Management	• In the BO25323 safety population (212 patients on VEN+G, 214 patients on GClb), the arms had similar incidences of treatment emergent fatal toxicities (2% per arm, most often from infection), serious adverse events (VEN+G 49%, GClb 42%, difference mostly due to infection), grade 3 or 4 adverse events (VEN+G 79%, GClb 76%), grade ≥3 neutropenia (VEN+G 56%, GClb 52%), and tumor lysis syndrome (≤ 2% in each arm). Rates of treatment modifications were also similar • The most common adverse events (≥ 10%) occurring ≥ 2% more with VEN+G were diarrhea, pyrexia, thrombocytopenia, cough, constipation, and vomiting.	• The safety profile of VEN+G is acceptable in the intended population and consistent with current labeling with VENCLEXTA. • To further mitigate infection risk, the prescribing information should include a Warning and Precaution for infection.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Serious infections occurred in 19% with VEN+G and 14% with GClb. Fatal cases of sepsis were reported in 3% with VEN+G and 1% with GClb.	

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Section 7.2.6
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X X

Nicholas Richardson, DO, MPH
Primary Clinical Reviewer

R. Angelo de Claro, MD
Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:
Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries, representing approximately 30% of all adult leukemias. The incidence of CLL varies by race and geographic location, with a lower incidence in Asia (<5% of leukemias) compared with Western countries. The incidence is higher in males than females, and increases with age (NIH SEER 2018).

CLL is a clonal disease of unknown etiology, characterized by the accumulation of mature B cells in blood, lymph nodes, spleen, liver, and bone marrow. The clonality of the disease is confirmed by the presence of a single immunoglobulin light chain.

CLL generally follows an indolent course. Treatment is usually associated with a high rate of initial responses followed inevitably by relapse. Subsequent treatments can induce remissions, but at a progressively lower rate with responses of shorter duration. Although the median survival of patients with CLL is around 10 years, the disease has an extremely variable clinical course, and the prognosis depends on disease stage and a range of prognostic biomarkers.
In the US, a recent Surveillance, Epidemiology, and End Results (SEER) report estimated an overall age-adjusted mortality rate for CLL of 1.3 per 100,000 persons per year with the median age at diagnosis of 70 years, the median age at death of 80 years, and approximately 5-year survival rate of 84.2% for the period of 2008–2014 (NIH SEER 2018). As incidence increases with age, the prevalence and mortality of CLL are likely to increase in the coming decades because of increasing life expectancy and changing demographics, particular in Western countries (Eichhorst et al. 2018).

Despite significant improvements in the treatment of first-line CLL over the last 20 years, CLL remains incurable. There remains an unmet need for the development of new chemotherapy-free, fixed-duration first-line treatments in CLL that are more tolerable, and produce deeper, more durable responses, with greater minimal residual disease (MRD) negativity rates, to ultimately improve clinical outcomes.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

2.2 Analysis of Current Treatment Options

The Applicant's Position:
Available and potential treatment options for patients with first-line CLL (ESMO 2017; NCCN 2019) are summarized below. Summary of efficacy and safety data from the main clinical studies that support currently available/potential future treatments for first-line CLL are provided in Section 1.3.1 of the Clinical Overview.

Available Therapies in the Chemo-Immunotherapy Setting:

- Fludarabine+cyclophosphamide+rituximab (FCR) is the standard treatment modality as first-line therapy for younger fit patients who do not have del(17p) CLL and is the most efficacious approved treatment to date. Approximately half of the patients treated with FCR have been shown to achieve complete response (CR)/CR with incomplete bone marrow recovery (CRi) (40%) and/or MRD negativity (48.5%) (Eichhorst et al. 2016). However, the majority of patients with first-line CLL cannot be treated with this regimen, due to significant toxicity including myelosuppression or neutropenic fever. In addition, patients with unmutated IGHV gene, and/or del(11q) and/or del(17p) treated with FCR have poor clinical outcomes (Lin et al. 2009; Fink et al. 2013; Stilgenbauer et al. 2014).
- Bendamustine+rituximab (BR) is an alternative treatment option, especially for fit elderly patients, based on the results of the CLL10 study (Eichhorst et al. 2016); however, BR has also shown poor efficacy results in high-risk patients with CLL, especially those with del(17p (Fischer et al. 2012), and BR treatment is associated with significant toxicities. Additionally, BR does not induce high CR/CRi and/or MRD negativity rates in patients.
- Chlorambucil+anti-CD20 monoclonal antibodies (such as obinutuzumab, ofatumumab, or rituximab) are used in the first-line CLL setting for frail patients with significant comorbid conditions (NCCN 2019). Patients with del(17p)/*TP53* mutation have limited response to chlorambucil in combination with anti-CD20 antibody treatment (Arpita 2015). These chemo-immunotherapy combinations produce low CR and MRD negativity rates (Hillmen et al. 2015).

Available Therapies in the Novel Targeted Agents Setting:

- Ibrutinib was approved for first-line use for all patients with CLL on the basis of data from the RESONATE-2 study (Burger et al. 2015) and is the preferred treatment option for first-line therapy for patients with del(17p) and/or *TP53* mutations (ESMO 2017; NCCN 2019). Although high clinical activity and improvement in progression-free survival (PFS) has been observed in patients with first-line CLL (Farooqui et al. 2015), relatively few patients in these studies achieved CR and/or MRD negativity, so the kinase inhibitor therapy must be continued and given daily until disease progression in order to control the disease. In addition, outcomes of patients relapsing after ibrutinib are extremely poor; approximately half of these patients relapse with Richter's transformation and die quickly, while those who relapse with CLL have short overall

survival (OS) durations (Jain et al. 2015; Maddocks et al. 2015). Recent data indicate that many patients (up to 42%) discontinue treatment with ibrutinib after a median of 7 months of treatment; of these, approximately 60% discontinue due to toxicity (Mato et al. 2016, Winqvist et al. 2016, Mato et al. 2018a).

- The iLLUMINATE study (Moreno et al. 2018) investigated the combination of ibrutinib (continuous, daily treatment until disease progression) and obinutuzumab versus obinutuzumab+chlorambucil (GClb) in patients with CLL/small lymphocytic leukemia (SLL) >65 years old or with comorbidities, and the combination was approved on 28 January 2019. Estimated 30-month PFS with ibrutinib plus obinutuzumab was 79%, and CR/CRi was achieved by 41% of patients, although only 35% achieved MRD negativity in bone marrow or peripheral blood.

Recent Phase III Data and Potential Future Therapies:

- Although not currently approved, Phase III data have recently become available from 2 studies exploring ibrutinib-based combinations, given until disease progression, as first-line treatment for patients with CLL. In the Alliance North America Intergroup study A041202 in patients >65 years old with CLL and no significant life-limiting inter-current illnesses or need for warfarin, treatment with ibrutinib alone or in combination with rituximab was compared with BR (Woyach et al. 2018). At the time of data cutoff, the median follow-up was 38 months. The 2-year PFS estimate and OS estimate for ibrutinib monotherapy and the combination of ibrutinib and rituximab were not significantly different. The CR rate and MRD negativity achieved were low, 12% and 4%, respectively.
- The Eastern Co-operative Oncology Group (ECOG)-ACRIN Cancer Research Group showed that for fitter patients with CLL aged ≤70 years, the combination of ibrutinib and rituximab demonstrated improved PFS compared with FCR, although this benefit was not observed IGVH-mutated patients (Shanafelt et al. 2018).

There is an unmet need for new chemotherapy-free, fixed-duration, first-line treatments in CLL with an acceptable and manageable safety profile for all patients, including the majority of patients who are older and/or have comorbidities. Additionally, these new regimens should produce deeper and more durable responses, with greater MRD negativity rates, to ultimately produce longer PFS and improve survival outcomes. The Applicant proposes that the combination of venetoclax and obinutuzumab (VEN+G) given for a fixed duration of 12 cycles has the potential to fulfill this need.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:
In the United States, the original NDA (208573) for VENCLEXTA® (venetoclax tablets), designated as breakthrough therapy on 27 April 2015, was granted accelerated approval on 11 April 2016 for the treatment of patients with CLL with del(17p), as detected by an FDA-approved test, who had received at least 1 prior therapy. In addition, the Sponsors submitted three supplemental NDAs; one for a labeling update for drug-drug interactions (NDA 208573/S-003; Reference ID: 4198479), which was approved on 20 December 2017, and two for the additional indication in R/R CLL (NDA 208573/S-004 and NDA 208573/S-005), both of which were approved on 8 June 2018 (Reference ID: 4275193). S-004 contributed to the full approval of venetoclax for the treatment of patients with CLL or SLL, with or without del(17p), who received at least 1 prior therapy. Furthermore, on 7 September 2018, the FDA approved the inclusion of MRD data from the pivotal Phase 3 Study GO28667/MURANO in the clinical section of the U.S Package Insert (USPI) under the labeling supplement NDA 208573/S-007 (Reference ID: 4316460).

The FDA's Assessment:
The FDA agrees with the Applicant's position.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
Orphan Drug Designation
Venetoclax was granted orphan drug status for the treatment of CLL by FDA on 20 September 2012.

Breakthrough Therapy Designation
Venetoclax was granted Breakthrough Therapy Designation (BTD) on 15 February 2019 for VEN+G for the treatment of adult patients with previously untreated CLL.

Other Regulatory Interactions Relevant to the Proposed Application
Key US regulatory interactions for first-line CLL are summarized in Appendix 1 of the Clinical Overview, and complete minutes of all interactions are provided in Module 1.

In a Type C written response, FDA agreed with the proposed modification to the timing of the interim analysis to take place at the earliest of 128 Independent Review Committee (IRC)-assessed PFS events, or February 28, 2018, providing that at least 110 IRC-assessed PFS events had been observed by February 28, 2018.

A pre-submission meeting to discuss the filing of an sNDA based on the results of Study BO25323 was held on 18 January 2019 with FDA. At this meeting, FDA confirmed the

use of the Real-Time Oncology Review (RTOR) and Assessment Aid pilot programs for the proposed sNDA based upon the results of the BO25323/CLL14 (herein referred to as Study BO25323) and GP28331 trials. The Sponsors formally submitted the Early Package Submission on 06 February 2019, comprised of sNDA elements agreed upon at the pre-submission meeting. A draft label (revised with Agency comments) was resubmitted on 22 February 2019.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations was not consulted for this submission. Previous inspections of clinical site by the FDA as part of the review of prior supplemental new drug applications for venetoclax revealed no concerns regarding clinical trial data.

4.2 Product Quality

There are no product quality issues with the supplement.

4.3 Devices and Companion Diagnostic Issues

In the BO25323 trial, minimal residual disease (MRD) was measured by allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The Center for Devices and Radiological Health (CDRH) has previously reviewed the analytical validity of the ASO-PCR test and found it acceptable (NDA 208573 Supplement 7). The analytical studies were based on MRD samples with Albumin control levels within 75% to 125% of the target Albumin level of 90,000 (67,500 to 111,250).

In the BO25323 trial, there were 6 total MRD results that could be impacted by allowing a MRD negative result at the completion of treatment on samples with Albumin control levels < 67,500. Five of the sample results have Albumin control levels > 40,000 and based on provided data, a MRD negative result is acceptable. Further, the 5 samples were also MRD negative by NGS assay. One patient may not have a reliable MRD negative result at the end of treatment due to an Albumin control level of only 16,600. The one patient was randomized to the GClb arm and overall the inclusion of this MRD negative result does not have a major impact on the efficacy analysis for BO25323.

5. Clinical Pharmacology

5.1 Executive Summary

The FDA's Assessment:

The recommended dose for the new combination therapy and schedule for venetoclax and obinutuzumab (CD20 antibody) fixed duration combination dosing regimen is as follows: Venetoclax should be given in combination with obinutuzumab for 6 cycles, followed by 6 cycles of venetoclax as a single agent;

- On Cycle 1 Day 1, start obinutuzumab administration at (b) (4) 100 mg and 900 mg on Days 1 and 2). Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of five subsequent cycles (total of 6 cycles, 28 days each).
- On Cycle 1 Day 22, start venetoclax according to the 5-week ramp-up schedule, continuing through Cycle 2 Day 28. After completing the ramp-up schedule, patients should continue venetoclax 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12.

Justification of venetoclax dose and regimen (400 mg QD) when administered as part of the combination treatment period or as part of the venetoclax single agent treatment period in patients with 1L (untreated) and R/R CLL is based upon efficacy, safety, tolerability, pharmacokinetics, and E-R (efficacy/safety/tolerability) analyses using data from supportive pharmacokinetics from the Phase Ib Study GP28331and the Pivotal Phase III Study BO25323. Exposure data for venetoclax and obinutuzumab in these studies were comparable to that observed in previous reported monotherapy and combination studies for either drug. Therefore, the proposed dosing is acceptable.

5.2 Summary of Clinical Pharmacology Assessment

5.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

- The clinical pharmacokinetic (PK) findings from Studies BO25323 and GP28331 for VEN+G were consistent with those previously submitted in the original NDA 208573.
- The co-administration of 400 mg once a day (QD) venetoclax with obinutuzumab resulted in no considerable changes in the PK of either drug.
- The exposure-response (E-R) analyses of venetoclax efficacy and safety parameters showed no statistically significant and clinically meaningful relationships with venetoclax exposures from the Study BO25323.
- Collectively, the PK and E-R analyses support the selected venetoclax dose and regimen (400 mg QD) when administered as part of the VEN+G treatment period or as part of the venetoclax single-agent treatment period in patients with first-line CLL and support a positive benefit-risk profile.

Please see Section 5.3.1 for more details.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

5.2.2 General Dosing and Therapeutic Individualization

5.2.2.1 General Dosing

The Applicant's Position:
The recommended venetoclax dose and schedule for the first-line CLL patients is 400 mg QD when administered in combination with obinutuzumab, which is the same dose and schedule as approved for venetoclax monotherapy and for venetoclax in combination with rituximab for patients with relapsed/refractory CLL.

The PK for venetoclax in Studies BO25323 and GP28331 in combination with obinutuzumab were comparable to those seen in the previous monotherapy studies and in combination with rituximab. No additional covariates (intrinsic/extrinsic) were identified affecting venetoclax PK in the two studies. There was no statistically significant relationship between venetoclax exposure and the primary efficacy endpoints (investigator- or IRC-assessed PFS) and the key treatment-emergent adverse events (TEAEs) of interest (Grade ≥3 neutropenia, Grade ≥3 thrombocytopenia, Grade ≥3 infection and serious adverse events [SAEs]) for patients with first-line CLL from Study BO25323.

Please see Section 5.3.2.2 for more details.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

5.2.2.2 Therapeutic Individualization

The Applicant's Position:
Venetoclax exposure can be impacted by food and by interaction with co-administered strong or moderate CYP3A inhibitors or P-gp inhibitors. These factors have been evaluated in the previously submitted clinical pharmacology studies, and appropriate dosing recommendations have been previously provided in the original label and label updates. A dedicated study was conducted to evaluate the safety and PK of venetoclax in patients with hepatic impairment (Study M15-342) to fulfil a post-marketing requirement (PMR No. 3068-2) in the United States.

The FDA's Assessment:
FDA agrees with the Applicant's position.

5.2.2.3 Outstanding Issues

The Applicant's Position:
None.

The FDA's Assessment:

There are no outstanding issues.

5.3 Comprehensive Clinical Pharmacology Review

5.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
The information from clinical studies contributing to the clinical pharmacology evaluation of venetoclax was included in the previously submitted reports (Summary of Clinical Pharmacology for the original submission, CSR M13-365, CSR GO28667 and PMR No. 3068-2 for Study M15-342).

The new clinical pharmacology information includes an evaluation of venetoclax PK and E-R (efficacy/safety/tolerability) relationship using data from patients with first-line CLL treated with VEN + G in the Pivotal Phase III Study BO25323 and pharmacokinetics from the first-line and R/R patients in the Supportive Phase Ib Study GP28331. The summary of the clinical pharmacology findings in Studies BO25323 and GP28331 are as follows:

- The co-administration of 400 mg QD venetoclax with obinutuzumab resulted in no considerable changes in the PK of either drug:
    - Venetoclax plasma concentrations in combination with obinutuzumab were comparable to previous monotherapy and rituximab combination studies.
    - The steady-state means of pre-dose obinutuzumab serum concentrations in the two studies were comparable to those previously reported in the BO21004/CLL11 study of obinutuzumab combined with chlorambucil (GClb).
    - A PopPK analysis of the venetoclax PK data using a Bayesian approach resulted in similar venetoclax PK parameters and the same covariates as those determined using the legacy PopPK model (Research Report 1092220).

The E-R analyses of venetoclax efficacy, safety and tolerability parameters in patients with first-line CLL treated with VEN+G in the Pivotal Phase III Study BO25323 are discussed in Section 5.3.2.2.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

5.3.2 Clinical Pharmacology Questions

5.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:
Evidence of positive benefit-risk is based on the efficacy, safety, and tolerability findings from the randomized portion of the Pivotal Phase III Study BO25323. While clinical pharmacology evaluation does not include a direct assessment of benefit-risk, consistent PK with prior venetoclax studies and a lack of significant E-R (efficacy/safety/tolerability) relationships

support the 400 mg QD venetoclax dose in combination with obinutuzumab as evaluated in Study BO25323, and is recommended for the proposed treatment of first-line CLL. Support for the venetoclax dose and schedule is provided in Section 5.3.2.2.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

5.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:
The recommended venetoclax dose and schedule for patients with first-line CLL is 400 mg QD when administered in combination with obinutuzumab, which is the same dose and regimen as that approved for venetoclax as monotherapy or in combination with rituximab for patients with R/R CLL.

In the pivotal Study BO25323 and supportive Study GP28331, following a 400 mg dose of venetoclax, the steady-state mean venetoclax plasma pre-dose concentrations in combination with obinutuzumab ranged between 0.58 – 0.83 µg/mL. These data were comparable to those reported in the previous monotherapy studies (Studies M12-175, M13-982 and M14-032) and in combination with rituximab (Studies M13-365 and GO28667), which were in the range of 0.63 – 0.81 µg/mL. In addition, the steady-state means of pre-dose obinutuzumab concentrations in Study BO25323 and Study GP28331 were comparable to the previously reported mean (254 ± 155 µg/mL) of trough concentrations at steady-state for subjects in the BO21004/CLL11 study, where obinutuzumab was co-administered with chlorambucil in first-line CLL patients (Gazyva PopPK report [Research Report 1058165]). Taken together, these findings suggest that the co-administration of 400 mg QD venetoclax with obinutuzumab resulted in no considerable changes in the PK of either drug.

The PopPK analysis of the venetoclax PK data from the two studies (BO25323 and GP28331) using a Bayesian approach resulted in similar PK parameters for venetoclax compared to those of the legacy PopPK model (R&D/15/0256). Co-administration of obinutuzumab resulted in no appreciable effect on venetoclax PK. No additional covariates (intrinsic/extrinsic) were identified affecting venetoclax PK in Study BO25323 or Study GP28331.

The E-R analyses of venetoclax efficacy and safety parameters showed no statistically significant or clinically meaningful relationships with venetoclax exposures in the first-line CLL patients (Research Report 1093000):

- No statistically significant relationship between venetoclax exposure and the primary efficacy endpoints (investigator- and IRC- assessed PFS)
- No statistically significant relationship between venetoclax exposure and key TEAEs of interest (Grade ≥ 3 neutropenia, Grade ≥ 3 thrombocytopenia or Grade ≥ 3 infection, and SAEs)

- No apparent relationships were observed between venetoclax exposure and obinutuzumab dose intensity, suggesting that venetoclax co-administration did not impact the delivery of obinutuzumab. Some trends were observed for lower dose intensities of venetoclax with increased venetoclax exposures; however, this was not considered clinically relevant given the lack of apparent E-R relationships with the primary efficacy endpoints and the key TEAEs of interest.

Collectively, the efficacy, safety, tolerability, PK, and E-R analyses support the selected 400 mg QD venetoclax dose regimen in combination with obinutuzumab in patients with first-line CLL as an appropriate dosage regimen, with highly favorable efficacy achieved with a manageable safety profile and supportive of a positive benefit-risk profile.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

5.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:
Based on the PopPK evaluation using the legacy PopPK model structure with the legacy parameters implemented as Bayesian priors, the PK data from Studies BO25323 and GP28331 were in agreement with the previously developed PopPK model in R/R CLL, non-Hodgkin's lymphoma, and healthy subjects.

Sex (decrease in V2/F by 29.7% for females compared to males) and subject population (V2/F in patients was 73.3% higher compared to healthy volunteers) impacted apparent central volume of distribution. However, the covariate effects on volume did not considerably impact venetoclax steady-state exposures, and hence, dose adjustments are not necessary for sex and subject population.

Furthermore, no new covariates (intrinsic/extrinsic) were identified affecting venetoclax PK in the Studies BO25323 and GP28331 that warrant dose adjustment of venetoclax.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

5.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:
Venetoclax exposure can be impacted by food and drug interactions which have been evaluated in the previously submitted clinical pharmacology studies, and appropriate dosing recommendations have been previously provided in the original label and label updates. No adjustments to the current dosage modifications or revised management strategies are warranted at this time. No apparent drug-drug interaction was observed between venetoclax

and obinutuzumab in Study BO25323 and Study GP28331.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

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Primary Reviewer
Christy S. John, Ph.D.

Team Leader
Olanrewaju Okusanya, Pharm.D., MS

6. Sources of Clinical Data

6.1 Table of Clinical Studies

The Applicant's Position:

Table 1: Listing of Clinical Trials Relevant to this sNDA

Protocol Number; NCT Number	Trial Design	Regimen/Schedule/Route	Objective(s) of the Study	Duration of Follow Up	Number of Patients Enrolled	Study Population	No. of Centers/ Investigators and Countries
Controlled Studies to Support Efficacy and Safety							
BO25323 (CLL14) Phase III; NCT02242942	Open-label, multicenter, randomized study, with non-randomized safety run-in	**Venetoclax**: 400 mg for 12 cycles (28-day cycle) / Ramp-up period, first dose 20 mg starting Day 22 of Cycle 1 and reaching 400 mg daily on Day 22 of Cycle 2, 400 mg daily thereafter / oral tablet *OR* **Chlorambucil:** 0.5 mg/kg for 12 cycles / Day 1 and Day 15 of cycle / oral tablet *AND* **Obinutuzumab**: 1000 mg for 6 cycles / Cycle 1, 1000 on Day 1 (or split over Day 1 and Day 2) and 1000 mg on Day 8 and Day 15; 1000 mg on Day 1 of cycle thereafter / IV infusion	Primary: PFS by investigator assessment (PFS assessed by IRC for U.S. regulatory decision making) Secondary: PFS assessed by IRC, ORR, CRR, MRD-negativity rate, OS Other: PRO, PK, PD, safety	Follow-up until 5 years from last patient enrolled	n 445 (13 in Safety Run-In; 432 in main phase of study)	Previously untreated patients with CLL and coexisting medical conditions	130 investigators in 21 countries
Supportive Study							
GP28331 Phase Ib; NCT01685892	Multicenter dose-finding, safety study	**Venetoclax**: As above **Obinutuzumab**: As above **Schedule A:** VEN introduced before G (G initiated following VEN ramp-up) **Schedule B:** VEN introduced after G (VEN initiated on Day 22 following G loading-dose period)	Primary: MTD, safety and tolerability of VEN+G Secondary: PK/PD, ORR, DOR, CR, PFS, OS Exploratory: MRD negativity rate	Follow-up until 2 years from last patient enrolled	32 patients with first-line CLL 50 patients with R/R CLL	Patients with R/R or first-line CLL	11 centers in United Kingdom and United States

Clb chlorambucil; CLL chronic lymphocytic leukemia; CSR clinical study report; CR complete response; CRR complete response rate; DOR duration of response; G obinutuzumab; IRC Independent Review Committee; IV intravenous; MRD minimal residual disease; MTD maximum tolerated dose; ORR overall response rate (CR+PR); N/A not applicable; QD once daily; PD pharmacodynamics; PFS progression-free survival; PK pharmacokinetic(s); PR partial response; PRO patient-reported outcomes; R/R relapsed or refractory; VEN venetoclax.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

7. Statistical and Clinical Evaluation

7.1 Review of Relevant Individual Trials Used to Support Efficacy

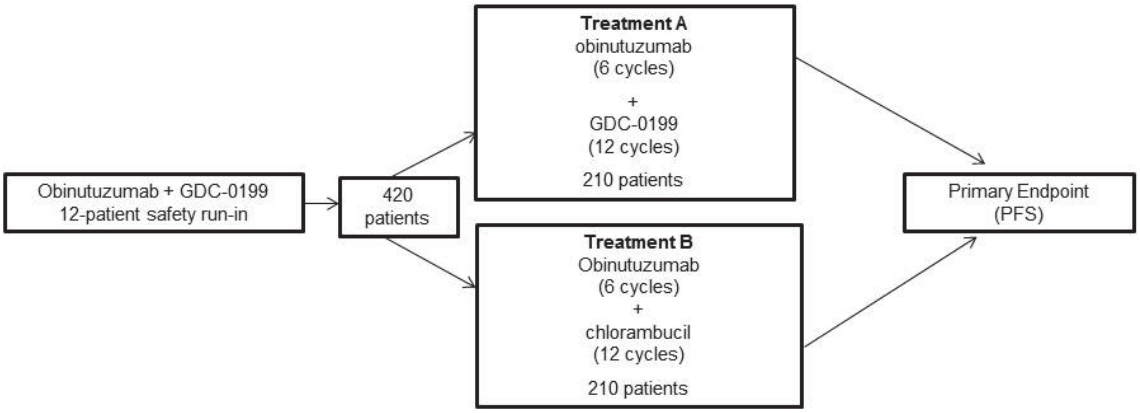
7.1.1 Study BO25323/CLL14

The Applicant's Position:

Trial Design

Study BO25323/CLL14 is an ongoing, open-label, multi-center, international, randomized Phase III study investigating the efficacy and safety of VEN+G compared with GClb in patients with first-line CLL who have coexisting medical conditions (see Figure 1 for safety-run and main phase of study).

Figure 1: Study BO25323: Study Design Schema and Treatment Plan



GDC-0199 venetoclax; PFS progression-free survival.

Note: 420 patients were planned to be randomized; 432 patients were actually randomized.

The duration of treatment was fixed at a maximum 12 months (12 cycles) in both arms (Table 1).

Trial Location

Australia/New Zealand, Central and Eastern Europe, Latin America, US/Canada/Central America, Western Europe.

Choice of Control Group

The Phase III CLL11 study confirmed obinutuzumab is superior to rituximab and in combination with chlorambucil as a standard-of-care in the elderly unfit patient population with coexisting medical conditions (Goede et al., 2014; NCCN 2019; ESMO 2017). The combination of

obinutuzumab and chlorambucil, therefore, was an appropriate control therapy for Study BO25323.

Diagnostic Criteria
The study enrolled patients with previously untreated CLL and coexisting medical conditions.

Key inclusion criteria included:

- Previously untreated CLL requiring treatment according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for CLL (Hallek et al. 2008)
- A total Cumulative Illness Rating Scale (CIRS) score > 6 or reduced renal function as measured by creatinine clearance (CrCl) < 70 mL/min
- Adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening, unless cytopenia due to marrow involvement of CLL
- Adequate liver function, unless directly attributable to the patient's CLL

Key exclusion criteria included:

- Transformation of CLL to aggressive non-Hodgkin's lymphoma (Richter's transformation or pro-lymphocytic leukemia)
- Known central nervous system involvement
- Any individual organ/system impairment score of 4 as assessed by the CIRS definition limiting the ability to receive the treatment regimen of the trial with the exception of the eye, ears, nose, throat organ system
- Patients with uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Inadequate renal function: CrCl <30 mL/min

Dose Selection
Venetoclax
Venetoclax dosing in Study BO25323 was based on experience from the Phase I dose-escalation Study M12-175, which examined single-agent venetoclax in patients with R/R CLL/SLL, and utilized a 5 week ramp-up to 400 mg, resulting in safe administration of venetoclax (Roberts et al. 2016). This dosing regimen has reduced the risk for tumor lysis syndrome (TLS) by gradually reducing the leukemia cell burden prior to administration of the full target dose, with no loss of effect. Furthermore, in Study M12-175, responses to single-agent venetoclax improved over time at the 36–50 week time-point as treatment continued; therefore, the treatment duration was set to 1 year.

The venetoclax dose to be used in combination with obinutuzumab has been determined to be 400 mg in patients with R/R or previously untreated CLL. Interim data from Study M12-175 showed that the 400 mg venetoclax dose as a single agent resulted in exposure that caused > 80% reduction in lymphocyte counts, tumor size, and bone marrow infiltrates in most patients. The relationship between venetoclax exposures and efficacy/safety in R/R CLL/SLL patients was characterized (R&D/15/0255) in support of 400 mg venetoclax dose as

monotherapy for R/R CLL patients with 17p deletion. In Study BO25323, venetoclax dosing was initiated with the first dose of the 5 week ramp-up on Day 22 of Cycle 1 with obinutuzumab first administered on Day 1 of Cycle 1 (see below and Table 1 for further details).

Obinutuzumab
The approved (in both EU and US) dosing regimen of obinutuzumab in combination with chlorambucil for first-line CLL with coexisting medical conditions was used in Study BO25323: 1000 mg Days 1 (or split dose Day 1 and Day 2), 8, and 15 in Cycle 1 followed by 1000 mg on Day 1 at Cycles 2–6 at intervals of 28 days.

Chlorambucil
The rationale for the chlorambucil dose and schedule (0.5 mg/kg on Day 1 and Day 15 of each 28-day cycle for 12 cycles) is based on the findings from Study CLL5 which demonstrated that chlorambucil was equally effective as fludarabine monotherapy in elderly (and in the subgroup of medically unfit) patients with CLL and was used in combination with obinutuzumab in Study CLL11 for 6 cycles, which formed the basis for approval of this chlorambucil dosing regimen in combination with obinutuzumab in patients with first-line CLL and comorbidities. To ensure clinical equipoise in the duration of therapy received in both treatment arms in Study BO25323, a total of 12 cycles of chlorambucil therapy was used in the control arm as well.

Assignment to Treatment
Patients in the main phase of the study were randomized in a 1:1 ratio to one of the two treatment arms through a block stratified randomization procedure by an IxRS. Randomization was stratified by the following:

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

Blinding
This is an open-label study. However, the Sponsors were blinded to treatment allocation during IVRS randomization and remained blinded until the Independent Data Monitoring Committee (iDMC) confirmed that the study had met its primary endpoint by crossing the pre-specified boundary and recommended that the study team be unblinded. Assessments by the IRC were blinded with respect to treatment arm and investigator assessment of response.

Dose Modification/Dose Discontinuation
Guidelines for dose delay or dose modification and treatment discontinuation in response to specific adverse events are detailed in Table 5 of the BO25323 CSR and Section 5.1.3 of the Protocol. In summary:

- Dose modification was recommended in the protocol following occurrence of certain Grade 3-4 AEs. Initial dose interruption of venetoclax, chlorambucil, and obinutuzumab was recommended, and upon treatment re-initiation, dose reductions were required for venetoclax for certain hematologic toxicities. Dose reductions for venetoclax and

chlorambucil were required for certain non-hematologic Grade 3-4 AEs upon re-initiating treatment. Dose reduction of obinutuzumab was not permitted.

- After resolution of AEs leading to dose reduction, gradual dose increase of venetoclax or chlorambucil was considered, if the patient had been stable for 2 weeks on the lower dose. In the event of recurrence of the AE, the patient could continue treatment on the lower dose.
- Patients, who interrupted all study treatments for longer than 28 days after treatment-related AEs, were to discontinue all study drugs (patients continued in survival follow-up). Patients who discontinued venetoclax or chlorambucil for toxicity also discontinued obinutuzumab.

Administrative Structure

This trial is being conducted globally under a collaboration agreement between F. Hoffmann-La Roche, Ltd., Genentech Inc. (Roche/GNE), AbbVie, Inc (AbbVie) and the German CLL Study Group (GCLLSG). This is described in detail in Section 3.3 of CSR BO25323. The study utilized both an iDMC and an IRC.

The iDMC initially reviewed safety data from the safety run-in phase of the study; after the first safety analysis during the main phase, subsequent iDMC reviews took place approximately twice per year and the iDMC reviewed all safety data collected during the study as well as assessing efficacy in addition to safety as part of the interim analyses. An independent Data Coordinator Center (iDCC) performed unblinded analyses to support the periodic iDMC review of safety data and the interim analysis.

PFS on the basis of an IRC assessment was considered the primary efficacy endpoint for U.S. Regulatory purposes. Results of the IRC review of individual patient data, including blinded review of clinical and laboratory findings and blinded radiology review of imaging assessments, were not communicated to investigators. IRC review was not performed in real-time and did not influence investigator assessment or treatment decisions. No attempt was made to reconcile the IRC and investigator assessments.

Procedures and Schedule

Screening tests were performed within 28 days prior to enrollment. During the treatment period, scheduled study visits were based on a 28-day (4 week) cycle, with Cycle 1 beginning at Day 1, and all patients were assessed for disease progression at the beginning of Cycles 4, 7, 9 and 12. Subsequently, patients were also assessed for disease progression at a treatment completion/early termination visit 28 days after the last study treatment administration (regardless of whether the patient completed or prematurely discontinued study therapy); 3 months after end of treatment and every 3 months thereafter until 24 months after end of treatment when assessments were scheduled every 6 months until 5 years from last patient enrolled. Following detection of disease progression, patients entered the survival period of the study where they were followed yearly until 5 years from last patient enrolled (Appendices 1, 2 and 3 of the Study BO25323 Protocol).

Concurrent Medications
Medications that were prohibited in the venetoclax ramp-up period and during venetoclax treatment, as well as medications whose use was to be considered cautionary are summarized in Table 7 and Table 9 of CSR BO25323.

Treatment Compliance
Accountability and study treatment compliance, as required per protocol, were assessed by review of the pharmacy drug dispensing records and administration logs.

Subjection Completion, Discontinuation, or Withdrawal
Patients were considered to have completed the study when the study concluded (i.e., 5 years from the last patient enrolled). Patients could voluntarily discontinue study drug or withdraw from the study at any time for any reason. The investigator also had the right to discontinue a patient from study drug or withdraw a patient from the study at any time. For efficacy analyses, patients who withdrew from the study prior to an event were censored at the date that they were last known to be event-free.

Study Endpoints
Key US regulatory discussions about study endpoints for Study BO25323 are provided in Appendix 1 of the Clinical Overview. In summary, the FDA agreed to using MRD as a secondary endpoint, which should be assessed at completion of therapy in peripheral blood and confirmed with bone marrow (FDA Reference 3560683). Additionally, the Sponsors made changes to the hierarchical testing for the secondary endpoints, incorporating some of FDA's recommendations (FDA Reference 4292329). Primary, key secondary, and exploratory endpoints are presented below.

Primary Endpoint
As per protocol, the primary efficacy endpoint was investigator-assessed PFS in the intent to treat (ITT) population, defined as the time from randomization to the first occurrence of progression or relapse (determined using standard iwCLL guidelines [2008]) or death from any cause, whichever occurred first. PFS on the basis of an IRC assessment was considered the primary endpoint for US regulatory purposes.

Key Secondary Endpoints
Key secondary endpoints which were tested for statistical significance on the basis of a hierarchical testing procedure were as follows:

- IRC-assessed PFS (primary outcome for US regulatory purposes)
- MRD response rate (measured by allele-specific oligonucleotide polymerase chain reaction [ASO-PCR]) in bone marrow at end of treatment (EOT) assessment
- Investigator-assessed CR at EOT assessment
- MRD response rate (measured by ASO-PCR) in peripheral blood at EOT assessment
- MRD response rate (measured by ASO-PCR) in patients with investigator-assessed CR in both bone marrow and peripheral blood at EOT assessment

- Investigator-assessed ORR at EOT assessment
- OS

Exploratory endpoints considered important to characterize overall efficacy
Exploratory analyses were performed, including graphical analyses, of the relationship between MRD (on the basis of peripheral blood results by ASO-PCR) and PFS.

Also, exploratory analyses of MRD negativity by time point were performed using new technologies, including next-generation sequencing (NGS) with MRD-negativity defined using a cutoff of 10^{-4} (less than 1 CLL cell in 10,000 leukocytes) for comparison with ASO-PCR, and by different cut-offs (10^{-5} or 10^{-6}) for NGS.

Statistical Analysis Plan and Amendments
The study was designed to enroll 420 patients into the randomized part of the study. A total of 170 efficacy events were required for the final analysis of PFS, giving 80% power to detect hazard ratio (HR) = 0.65 for the comparison of VEN+G experimental arm versus GClb, with median PFS for VEN+G increased from 27 months to 41.5 months.

Protocol Version 7 allowed that up to two formal interim efficacy analyses may be performed. The first potential interim efficacy analysis, occurring at 85 PFS events (50% of total planned PFS events), was not performed. The other interim analysis, corresponding to the analysis presented in the BO25323 CSR, was planned to be conducted after 110 PFS events. An OS final analysis will be conducted at the end of the study.

With the potential for several timepoints for decision-making (i.e., interim analysis, PFS final analysis, and OS final analysis), α-spent for each endpoint would be distributed over these timepoints. For the primary and first secondary endpoints (i.e., investigator-assessed PFS and IRC-assessed PFS) gamma-family α-spending method with gamma parameter γ = -9.21 was used. Assuming there were 110 Investigator-assessed PFS events at the time of the interim analysis, α boundary of 0.0019 will allow the study to stop for efficacy if a treatment effect HR of 0.55 or better in investigator-assessed PFS was observed.

A Fallback Procedure was used for the subsequent alpha-controlled secondary endpoints. This is a type of group-sequential procedure with the flexibility to be able to test hypotheses further in the sequence if a previous hypothesis is not rejected. Overall α is split for endpoints in a pre-specified order, thereby controlling multiplicity.

For OS, an α-spending function using gamma family with parameter γ = -4 was used. This ensured control of overall type-1 error and reserved most of the α for the final OS analysis.

There have been two versions of the statistical analysis plan (SAP). The first version was finalized on 26 Sep 2018, prior to unblinding the study. The Safety population definition was updated in the SAP v2 post-unblinding, dated 08 Nov 2018, and submitted to the Agency. The

definition was changed so that patients randomized to the VEN+G arm who received only obinutuzumab treatment were analyzed under the VEN+G arm rather than the GClb arm.

Analysis Populations

Three analysis populations were defined in the SAP:

- The ITT (all randomized) population included all patients who were randomized to the study, regardless of whether they received any study treatment, and formed the basis of all efficacy analyses.
- The PRO-evaluable population included all randomized patients who had a baseline and at least 1 post-baseline assessment of PRO scales.
- The Safety-evaluable population included all randomized patients who received any dose of study medication, and was the basis for all safety analyses.

Methods for Handling Missing Data

For the analyses of PFS, data for patients who did not experience an event were censored at the date they were last known to be alive and event-free. For the analysis of OS, data for patients who were alive at the time of the data cutoff were censored at the last date they were known to be alive. Data for patients who were randomized without any post-baseline information were censored at the date of randomization plus 1 day.

Statistical Methodology for Multiplicity

A testing hierarchy was used to control the overall Type I error rate at 5%, using the Fallback Procedure (described in SAP and Amendments section above). Overall α is split for endpoints in a pre-specified order thereby controlling multiplicity. See also interim analysis information below.

Interim Analysis

Protocol Version 7 included the possibility of up to 2 formal interim efficacy analyses (described in SAP and Amendments section above). The second interim analysis, corresponding to the analysis presented in the BO25323 CSR, was planned to be conducted after 110 PFS events. The current interim analysis crossed the pre-specified boundary for the primary endpoint of α = 0.0019 and so is considered the primary analysis. This analysis will be the only PFS analysis to be performed.

Planned Subgroup Analyses

Subgroup analyses of investigator-assessed PFS, IRC-assessed PFS, MRD, ORR, CR and OS were performed to assess internal consistency using the ITT population, with the results displayed in forest plots. Subgroups investigated included baseline characteristics and stratification factors (Binet stage and region).

Protocol Amendments

The initial BO25323 Study Protocol, dated 23 July 2014, was amended 6 times, twice prior to first patient enrolled and 4 times subsequently (see Table 9 of CSR BO25323). These changes did not impact the integrity of the trial or the interpretation of the results.

Changes were made to the planned analyses as a result of health authority feedback are summarized below:

- In addition to the planned analysis of MRD negativity rate defined in terms of MRD negativity alone, analyses were included where MRD negativity rate was determined as the proportion of patients with MRD-negativity and CR.
- Protocol (Version 7) Section 6.5 - Safety Analysis stated that the safety analyses were to include all 'randomized' patients who received at least one dose of any study treatment. However, to be consistent with normal analysis and reporting conventions, the analysis of safety was performed on all treated patients regardless of whether randomized or not, with the exception of safety run-in patients who were reported separately.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

7.1.2 Study Results

The Applicant's Position

Compliance with Good Clinical Practices

This study is being conducted in full conformance with the International Conference on Harmonization (ICH) E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki as described in the following sections of Protocol Version 7:

- Compliance with laws and regulations: Protocol Section 8.1.
  Informed Consent procedures: Protocol Section 8.2.
  Institutional Review Boards (IRBs) and/or Ethics Committee (ECs) approval: Protocol Section 8.3.
- Data Quality Assurance and Data Collection and Management: Protocol Section 7.
- Audits and GCP compliance: See statement of GCP compliance above. An audit certificate is provided in the CSR.
- Treatment Accountability and Compliance: Protocol Section 4.3.3

The Roche Clinical Quality Assurance group or designee conducted audits at 4 investigator sites. No critical audit findings were observed. For all audit findings, appropriate corrective and preventive actions were undertaken.

Financial Disclosures

During the study site initiation process, Roche/Genentech or their designee provided study-specific financial disclosure forms to all principal investigators and sub-investigators for use in disclosing financial interest in or receipt of significant payments from Roche/Genentech or AbbVie. Roche/Genentech and AbbVie Inc. were listed as Co-Development Partners in the financial disclosure forms that were distributed. During the course of the study, new or revised financial disclosure forms and other essential documents were collected.

Methods Used to Minimize Bias by the Sponsor for Study BO25323 and Study GP28331

- Study BO25323 is a multicenter, randomized trial and patients were enrolled at 134 sites across 21 countries, including the United States. Although this is an open-label study, assessments by the IRC were blinded to the treatment arm.
- Supportive Study GP28331 is a multi-center study and patients were enrolled at 11 sites across 2 countries.
- All investigator-positive disclosures were reviewed by Genentech and assessed whether their financial interest in Genentech, Roche, and/or AbbVie was significant per the Agency's guidance for industry – Financial Disclosure by Clinical Investigators. To ensure potential bias has not affected study integrity, the number of patients enrolled by these positive disclosed investigators was also evaluated.

Summary of Findings

For pivotal Study BO25323, 1207 out of 1215 (99.3%) principal investigators and sub-investigators provided financial disclosure information. Of the investigators who responded, positive disclosable financial interests were recorded by 5 out of 1215 (<1%) investigators. Despite due diligence on the part of the Applicant to obtain the information, a signed financial disclosure was not obtained for 8 sub-investigators.

Notes to File stating the reason the information could not be collected, and providing the Applicants' Due Diligence in attempting to obtain updated information, is provided in the sNDA Section 1.3.4.5.

Patient Disposition

A total of 514 patients were screened for the main phase of the study, of which 432 patients were randomized from 130 centers across 21 countries, including the United States (9 centers enrolling 28 patients).

- The ITT population was comprised of all 432 randomized patients, 216 in each treatment arm.
- The safety-evaluable population was comprised of 426 patients: 214 in the GClb arm and 212 in the VEN+G arm, excluding 6 patients who were randomized but did not receive any study treatment:
  - 2 in the GClb arm (1 patient died and 1 patient withdrew from the study prior to dosing)
  - 4 in the VEN+G arm (withdrawal by the subject prior to dosing).

At clinical cut-off (17 August 2018), all patients who received study treatment had either completed study treatment (n=166 and 160 for VEN+G and GClb, respectively) or withdrawn from study treatment (n=46 and 54 for VEN+G and GClb, respectively). The majority of patients were alive and ongoing in the study; 190 patients in the GClb arm and 186 in the VEN+G arm were in follow-up. The median duration of follow-up was similar between the two arms (median 29.2 months in the GClb arm and 28.8 months in the VEN+G arm). The median duration of follow-up from last treatment until discontinuation or clinical cut-off was 18.8 months in the GClb arm and 18.1 months in the VEN+G arm.

There were 306 major protocol deviations in 124 patients (57.4%) in the GClb arm and 296 in 122 patients (56.5%) in the VEN+G arm (see Section 4.4 of CSR BO25323). Few of the protocol deviations classified as major in the study database would have impacted the data integrity, patient safety, or study results or conclusions.

Table of Demographic Characteristics

The demographic characteristics of the patients were balanced across treatment arms (Table 2). The patients were elderly (median age, 72.0 years; range: 41 to 89 years; 34.7% were aged over 75 years) and principally white (89.4%). Approximately two-thirds of patients (66.9%) were male. The majority of patients were enrolled in Europe (301/432 [69.7%]). Imbalances in geographic region were not observed. Geographic region as recorded by IVRS was a stratification factor.

Table 2: Demographic Characteristics of the Primary Efficacy Analysis

	GClb (N=216)	VEN+G (N=216)	All Patients (N=432)
Age (years)			
n	216	216	432
Mean (SD)	71.1 (8.0)	71.1 (8.2)	71.1 (8.1)
Median	71.0	72.0	72.0
Min - Max	41 - 89	43 - 89	41 - 89
Age category			
n	216	216	432
40-59	16 (7.4%)	18 (8.3%)	34 (7.9%)
60-69	73 (33.8%)	64 (29.6%)	137 (31.7%)
>=70	127 (58.8%)	134 (62.0%)	261 (60.4%)
Sex			
n	216	216	432
Male	143 (66.2%)	146 (67.6%)	289 (66.9%)
Female	73 (33.8%)	70 (32.4%)	143 (33.1%)
Race			
n	216	216	432
White	194 (89.8%)	192 (88.9%)	386 (89.4%)
Native Hawaiian or other Pacific Islander	0	3 (1.4%)	3 (0.7%)
American Indian or Alaska Native	1 (0.5%)	0	1 (0.2%)
Black or African American	3 (1.4%)	1 (0.5%)	4 (0.9%)
Unknown	18 (8.3%)	20 (9.3%)	38 (8.8%)
Geographic Region-IVRS			
n	216	216	432
US/Canada/Central America	21 (9.7%)	20 (9.3%)	41 (9.5%)
Australia/New Zealand/Asia	32 (14.8%)	32 (14.8%)	64 (14.8%)
Western Europe	85 (39.4%)	85 (39.4%)	170 (39.4%)
Central and Eastern Europe	66 (30.6%)	65 (30.1%)	131 (30.3%)
Latin America	12 (5.6%)	14 (6.5%)	26 (6.0%)

Extracted from t_dm_NSFRFL_323_IT.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The treatment arms were balanced overall with respect to baseline disease characteristics and prognostic factors/cytogenetics (see Table 3).

Table 3: Summary of Baseline Disease Characteristics (ITT Population)

	GClb (N=216)	VEN+G (N=216)	All Patients (N=432)
Binet Stage at Screening			
n	216	216	432
STAGE A	44 (20.4%)	46 (21.3%)	90 (20.8%)
STAGE B	80 (37.0%)	77 (35.6%)	157 (36.3%)
STAGE C	92 (42.6%)	93 (43.1%)	185 (42.8%)
TP53 Mutation Status			
n	216	216	432
Mutated	13 (6.0%)	19 (8.8%)	32 (7.4%)
Unmutated	144 (66.7%)	152 (70.4%)	296 (68.5%)
Unknown	59 (27.3%)	45 (20.8%)	104 (24.1%)
TP53 Mutated and/or 17p Deletion			
n	161	172	333
Yes	22 (13.7%)	24 (14.0%)	46 (13.8%)
No	139 (86.3%)	148 (86.0%)	287 (86.2%)
IGVH Mutational Status			
n	216	216	432
Mutated	83 (38.4%)	76 (35.2%)	159 (36.8%)
Unmutated	123 (56.9%)	121 (56.0%)	244 (56.5%)
Not Evaluable	2 (0.9%)	3 (1.4%)	5 (1.2%)
Missing Sample	8 (3.7%)	16 (7.4%)	24 (5.6%)
Creatinine Clearance based on Cockcroft Gault Formula			
n	213	215	428
< 70 mL/min	118 (55.4%)	128 (59.5%)	246 (57.5%)
>= 70 mL/min	95 (44.6%)	87 (40.5%)	182 (42.5%)
Cytogenetic Abnormalities (Hierarchical Order)			
n	193	200	393
Del (17p)	14 (7.3%)	17 (8.5%)	31 (7.9%)
Del (11q)	38 (19.7%)	36 (18.0%)	74 (18.8%)
Trisomy 12	40 (20.7%)	36 (18.0%)	76 (19.3%)
Not Del(17p)/Del(11q)/Trisomy 12/Del(13q)	42 (21.8%)	50 (25.0%)	92 (23.4%)
Del (13q)	59 (30.6%)	61 (30.5%)	120 (30.5%)
Cumulative Illness Rating Scale			
n	216	216	432
Mean (SD)	8.83 (4.11)	9.35 (3.73)	9.09 (3.93)
Median	8.00	9.00	8.00
Min - Max	1.0 - 28.0	0.0 - 23.0	0.0 - 28.0

Extracted from t_dm_basc_san_NSFRFL_323_IT.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

In the VEN+G arm, 13 patients discontinued venetoclax during the combination treatment period, 5 for safety reasons (AE in 4 patients and death in 1 patient) and 8 for non-safety reasons (including 4 patients who never received venetoclax).

As of the clinical cut-off date (CCOD), 83.3% of patients received >7 months and up to 12 months of venetoclax treatment in the VEN+G arm. The median duration of exposure to venetoclax, from first venetoclax dose, was 315.0 days (10.5 months; range: 1–406 days [13.5 months]). Despite the high number of AEs leading to dose reduction or dose interruption in the VEN+G arm, it is of note that these had limited impact on dose intensity. Indeed, the median dose intensity, after reaching the target dose, was 97.5% in the VEN+G arm, suggesting that toxicities, such as neutropenia, were readily managed with standard of care in a population that had substantial burden of comorbidities.

The median dose intensity for chlorambucil in the GClb arm was 95.4% (range: 4%–111%). Patients received a median of 12.0 cycles of chlorambucil (range: 1.0–12.0).

The median dose intensity, cycles, and cumulative dose of obinutuzumab were the same in both arms: median dose intensity was 100% (range: 0%–111%) and patients received a median of 6.00 cycles (range: 1.0–6.0), and the median total cumulative dose was 8000.0 mg.

Concomitant Medications

The therapeutic classes of concomitant medications used by more than 50% of all patients in the safety population were analgesics (386 patients [90.6%]), antihistamines (385 patients [90.4%]), and steroids (398 patients [93.4%]). These medications were included, per protocol, as prophylaxis for infusion-related reactions at the first administration of obinutuzumab.

The following classes had a difference of > 5% between arms: antidiarrheals (10 patients [4.7%] in the GClb arm compared with 27 [12.7%] in the VEN + G arm); blood, blood components, and substitutes (44 [20.6%] compared with 32 [15.1%], respectively); general anesthetics (3 [1.4%] compared with 14 [6.6%], respectively); and laxatives and stool softeners (24 [11.2%] compared with 35 [16.5%], respectively).

A similar percentage of patients received granulocyte colony stimulating factor (GCSF) as prophylaxis during the study between the two arms. A similar proportion of patients received treatment for the indication of neutropenia (84 [38.9%] in the GClb arm and 81 [37.5%] in the VEN+G arm). By treatment period, use of GCSF was greatest during the combination treatment period, followed by the single agent treatment period, and very limited use during the post-treatment period. Few patients discontinued treatment for neutropenia (5 patients [2.4%] in the VEN+G arm and 5 [2.3%] in the GClb arm), respectively.

No differences in concomitant medication use were deemed large enough to impact any efficacy or safety outcomes in the study.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The study met its primary endpoint, demonstrating a clinically meaningful and statistically significant improvement in investigator-assessed PFS in patients with first-line CLL treated in the VEN+G arm compared with the GClb arm (see Table 4).

All key secondary hierarchically tested efficacy endpoints, apart from OS, which was expected as the data were considered immature to be evaluable for OS at the time of the CCOD, showed consistent, statistically significant improvement (see Table 5).

Primary Endpoint

Study BO25323 met its primary endpoint, demonstrating that the combination of VEN+G followed by venetoclax single-agent treatment was associated with a statistically significant and clinically meaningful prolongation of PFS compared with GClb treatment.

The results of the investigator-assessed PFS showed that the risk of a PFS event (disease progression or death) was significantly reduced by 65% for patients in the VEN+G arm

compared with patients in the GClb arm (HR 0.35 [95% CI: 0.23, 0.53], $p < 0.0001$, stratified log-rank test). As of the CCOD, the median PFS was not reached in either arm. At 2 years, the Kaplan-Meier (K-M) estimates of the PFS event-free rates were 88.15% in the VEN+G arm and 64.10% in the GClb arm (Table 4). The K-M plot of investigator-assessed PFS showed separation of the curves in favor of the VEN+G arm after 6 months, and the separation was maintained over time (Figure 2).

All pre-specified sensitivity analyses (censoring for More Than One Missed Response Assessment, censoring for new anti-CLL Treatment) were supportive of the results of the primary analysis of PFS (see Table 23 of CSR BO25323).

The IRC-assessed PFS was consistent with the investigator-assessed PFS, showing reduced risk of having a PFS event (defined as disease progression or death) for patients in the VEN+G arm, as presented in Table 4 and Figure 3.

Table 4: Summary of Investigator- and IRC- Assessed Progression-Free Survival (ITT Population)

Parameter [a]	GClb (N 216)	VEN+G (N 216)
Progression-Free Survival (Investigator Assessment)		
Patients with event	77 (35.6%)	30 (13.9%)
Time to event (months)		
Median [95% CI]	NE [31.1, NE]	NE [NE]
P-value (log-rank test, stratified)	p<0.0001	
Hazard ratio (stratified), [95% CI]	0.35 [0.23, 0.53]	
Estimate of 1-year PFS rate % (95% CI)	92.11 (88.40, 95.82)	94.62 (91.53, 97.71)
Estimate of 2-year PFS rate % (95% CI)	64.10 (57.39, 70.81)	88.15 (83.69, 92.60)
Progression-Free Survival (IRC Assessment)		
Patients with event	79 (36.6%)	29 (13.4%)
Time to event (months)		
Median [95% CI]	NE [31.1, NE]	NE [NE]
P-value (log-rank test, stratified)	p<0.0001	
Hazard ratio (stratified), [95% CI]	0.33 [0.22, 0.51]	
Estimate of 1-year PFS rate % (95% CI)	91.16 (87.27, 95.06)	94.60 (91.50, 97.71)
Estimate of 2-year PFS rate % (95% CI)	63.70 (56.99, 70.42)	88.59 (84.20, 92.98)

Extracted from t_ef_tte_PFSINV_NSFRFL_323_IT and t_ef_tte_PFSRAD1_NSFRFL_323_IT.

Figure 2: Kaplan-Meier Plot of Investigator-Assessed Progression-Free Survival (ITT Population)

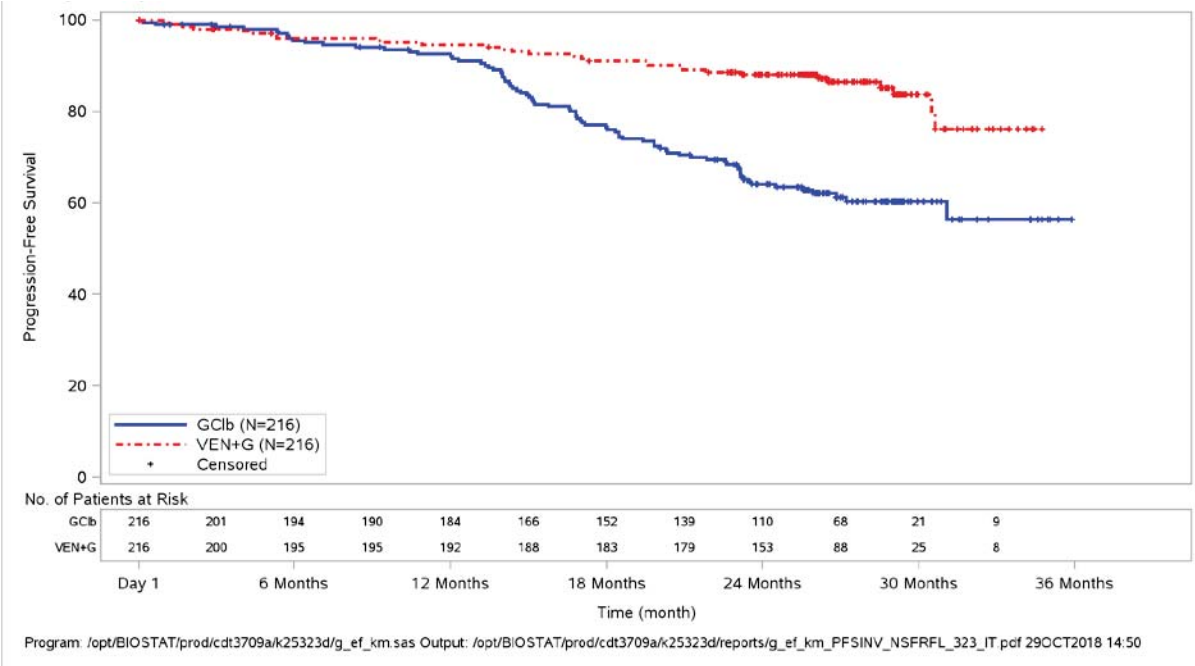
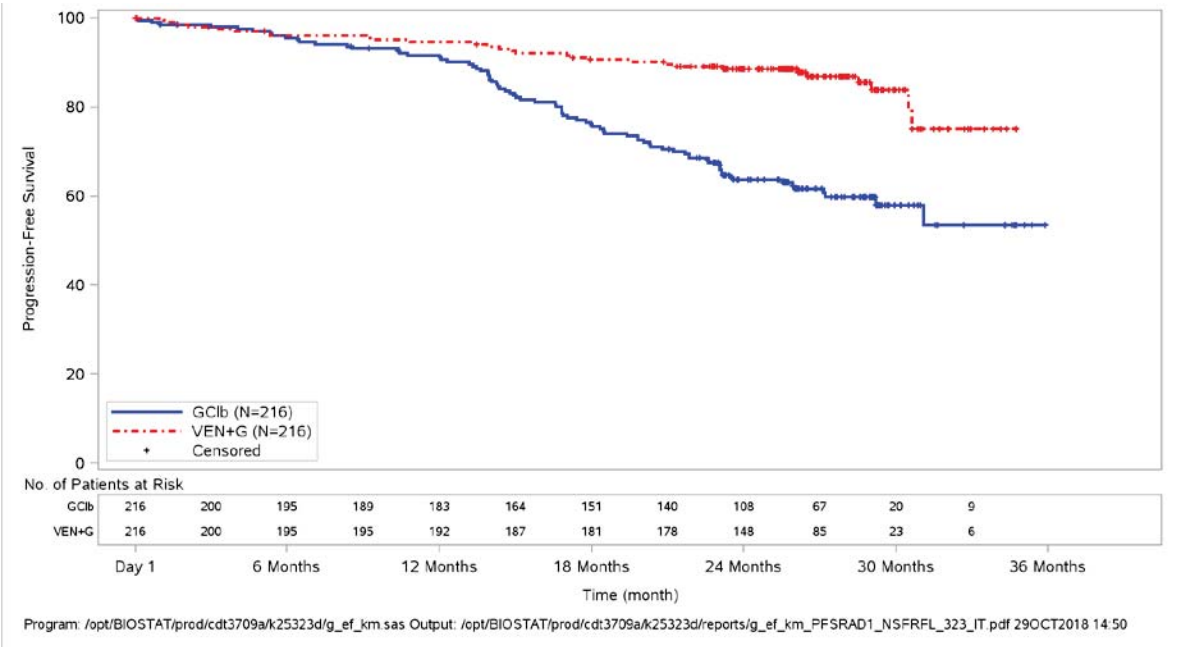


Figure 3: Kaplan-Meier Plot of IRC-Assessed Progression-Free Survival (ITT Population)



Subgroup Analyses

Subgroup analyses of PFS, as assessed by the investigator or by IRC, were performed to evaluate consistency of the primary efficacy analysis (see Section 5.4.3 of CSR BO25323).

Overall, the data provided evidence of consistent improvements in both investigator-assessed PFS and IRC-assessed PFS in patients treated with VEN+G in all subgroups including high-risk and low-risk as well as young and older patients (see Section 5.4 of CSR BO25323). Some of the analyzed subgroups showed wide confidence intervals and/or low number of events and thus interpretation is subject to uncertainty.

Data Quality and Integrity

Information requested by the Office of Scientific Investigations (OSI) for Study BO25323 and Study GP28331 is provided in Module 5.3.5.4 as part of the submission to the sNDA on 6 March 2019.

Efficacy Results – Secondary and other relevant endpoints

All the key secondary hierarchically tested efficacy endpoints as listed above showed consistent, statistically significant benefit apart from OS, which was not unexpected as the data are considered too immature to be meaningful at the time of CCOD with less than 10% of patients with events (Table 5). Additionally, pre-specified subgroups for secondary endpoints (ORR, CR, MRD in peripheral blood and bone marrow), including high-risk and low-risk as well as young and older patients, showed a treatment benefit consistent with the primary analysis in the VEN+G arm (see Sections 5.4.2 and 5.4.3 of CSR BO25323).

In addition to Table 5, the analyses are presented in further detail below:

Investigator-Assessed ORR at EOT Assessment

At EOT assessment, there was a statistically significant difference (p 0.0007, CMH test) in the proportion of patients with an overall response of CR, CRi, or PR per investigator assessment in favor of the VEN+G arm (84.7%) compared to the GClb arm (71.3%), indicating that patients treated with VEN+G achieved a higher ORR in comparison to the GClb arm.

Investigator-Assessed CR Rate at EOT Assessment

All response assessments of CR/CRi required confirmation by CT scans and bone marrow biopsy as per iWCLL criteria. At EOT assessment, there was a statistically significant difference ($p<0.0001$, CMH test) in the proportion of patients with a CR or CRi per investigator assessment in favor of the VEN+G arm (49.5%) compared to the GClb arm (23.1%). Thus, patients treated with VEN+G achieved a higher rate of CR/CRi in comparison to the GClb arm at end of treatment.

Table 5: Summary of Key Secondary Efficacy Parameters

Parameter [a]	GClb (N 216)	VEN+G (N 216)
Overall Response Rate (Investigator Assessment) at EOT Assessment		
Responders	154 (71.3%)	183 (84.7%)
95% CI	[64.77, 77.23]	[79.22, 89.24]
Difference in response rates [95% CI]	13.43 [5.47, 21.38]	
P-value (CMH test)	p 0.0007	
Complete Response Rate (Investigator Assessment) at EOT Assessment		
Responders	50 (23.1%)	107 (49.5%)
95% CI	[17.70, 29.35]	[42.68, 56.40]
Difference in response rates [95% CI]	26.39 [17.41, 35.36]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate[b]–Peripheral Blood at EOT Assessment		
MRD negative (at 10^{-4})	76 (35.2%)	163 (75.5%)
95% CI	[28.83, 41.95]	[69.17, 81.05]
Difference in MRD negative rates [95% CI]	40.28 [31.45, 49.10]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate[b]–Bone Marrow at EOT Assessment		
MRD negative (at 10^{-4})	37 (17.1%)	123 (56.9%)
95% CI	[12.36, 22.83]	[50.05, 63.64]
Difference in MRD negative rates [95% CI]	39.81 [31.27, 48.36]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate[b] in CR Patients–Peripheral Blood (Investigator Assessment) at EOT Assessment		
Responders	31 (14.4%)	91 (42.1%)
95% CI	[9.96, 19.75]	[35.46, 49.02]
Difference in MRD responder rates [95% CI]	27.78 [19.45, 36.10]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate[b] in CR Patients–Bone Marrow (Investigator Assessment) at EOT Assessment		
Responders	23 (10.6%)	73 (33.8%)
95% CI	[6.87, 15.55]	[27.52, 40.53]
Difference in MRD responder rates [95% CI]	23.15 [15.37, 30.93]	
P-value (CMH test)	p<0.0001	
Overall Survival[c]		
Patients with event	17 (7.9%)	20 (9.3%)
Time to event (months)		
Median [95% CI]	NE [NE]	NE [NE]
P-value (log-rank, stratified)	p 0.5216	
Hazard ratio (stratified), [95% CI]	1.24 [0.64, 2.40]	
Estimate of 1-year OS rate % (95% CI)	96.22 (93.66, 98.79)	95.67 (92.90, 98.44)
Estimate of 2-year OS rate % (95% CI)	93.34 (89.97, 96.71)	91.79 (88.05, 95.53)

CMH Cochran-Mantel-Haenszel; CR complete response; EOT end of treatment (i.e., 3 months after treatment completion/early termination); GClb obinutuzumab+chlorambucil; IRC Independent Review Committee; MRD minimum residual disease; NE not evaluable; OS overall survival; VEN+G venetoclax+obinutuzumab.

[a] The overall type-1 error rate at a pre-specified 2-sided level alpha=0.05 was controlled for all endpoints in this table.

[b] By ASO-PCR.

[c] As of the CCOD, the OS data were immature (<10% of randomized patients had died) to be meaningful.

MRD in Peripheral Blood at EOT Assessment

At EOT assessment, MRD-negativity rate ($<10^{-4}$ as determined by ASO-PCR) in peripheral blood in the ITT population was higher in the VEN+G arm than in the GClb arm, and the difference

was statistically significant ($p<0.0001$, CMH test). Of the patients in the GClb arm, 35.2% achieved MRD-negativity in peripheral blood compared with 75.5% of patients in the VEN+G arm. The difference in MRD-negative rates was 40.28% (95% CI: 31.45, 49.10). Of note, the missing rates were low and comparable between the two arms (10.2% in GClb arm and 8.8% in VEN+G arm).

MRD in Bone Marrow at EOT Assessment

At EOT assessment, MRD-negativity rate ($<10^{-4}$ as determined by ASO-PCR) in bone marrow in the ITT population was higher in the VEN+G arm than in the GClb arm and the difference was statistically significant ($p<0.0001$, CMH test). Of the patients in the GClb arm, 17.1% achieved MRD-negativity in bone marrow compared with 56.9% of patients in the VEN+G arm. The difference in MRD-negative rates was 39.81% (95% CI: 31.27, 48.36). Of note, the missing rates which included those patients who were non-responders (and therefore did not undergo bone marrow biopsy as per protocol) were comparable between the two arms (23.6% in GClb arm and 23.1% in VEN+G arm).

MRD in Patients with Investigator-Assessed CR in Bone Marrow/Peripheral Blood at EOT Assessment

At EOT assessment, investigator-assessed complete responders (ITT population) treated with VEN+G achieved higher bone marrow MRD-negativity rates ($<10^{-4}$ as determined by ASO-PCR) than patients treated with GClb (33.8% vs. 10.6%, respectively), and the difference was statistically significant ($p<0.0001$, CMH test).

At EOT assessment, investigator-assessed complete responders (ITT population) treated with VEN+G achieved higher peripheral blood MRD-negativity rates ($<10^{-4}$ as determined by ASO-PCR) than patients treated with GClb (42.1% vs. 14.4%, respectively), and the difference was statistically significant ($p<0.0001$, CMH test).

Overall Survival

As of the CCOD, the OS data were immature (<10% of patients had died; 20 patients (9.3%) in the VEN+G arm and 17 patients (7.9%) in the GClb arm). The median OS was not reached in either arm, and there was no evidence of difference in OS between the two arms (p 0.5216, HR 1.24 [95% CI: 0.64, 2.40]).

Dose/Dose Response

The recommended dose and regimen for venetoclax (400 mg QD) in combination with obinutuzumab in the first-line CLL patients was supported by the exposure-efficacy and exposure-safety analyses of venetoclax, and no statistically significant or clinically meaningful relationships with venetoclax exposures were observed (Research Report 1093000).

This 400 mg QD dose was consistent with both the approved venetoclax monotherapy dose and regimen for the treatment of patients with R/R CLL (see Section 5.2.2) and with the approved

venetoclax dose and schedule in combination with rituximab for the treatment of patients with R/R CLL.

Durability of Response
The duration of response was calculated only for the patients who responded per definition, 197/216 in GClb arm and 200/216 in VEN+G arm.

Duration of response was prolonged in the VEN+G arm compared with the GClb arm (stratified: HR 0.31, 95% CI [0.20, 0.50], p-value [stratified log-rank] < 0.0001 and unstratified: HR 0.30, 95% CI [0.19, 0.48], p-value [unstratified log-rank] < 0.0001). The event-free rates (where event referred to disease progression as assessed by the investigator or death) at 24 months were 89.27% in VEN+G arm and 64.14% in GClb arm. However, the median duration of response was not reached in either treatment arm.

Persistence of Effect
There is no evidence to date to suggest any effect of long-term venetoclax use on the loss of therapeutic effect over time. The efficacy results were consistent over time in the VEN+G arm.

With median follow-up of 28.79 months, and median follow-up after last dose of study drug of 18.49 months, the risk of a PFS event (defined as disease progression or death) was significantly reduced by 65% as assessed by investigator (stratified HR 0.35 [95% CI: 0.23 to 0.53]) for patients in the VEN+ G arm compared with patients in the GClb arm. The total number of patients with progressive disease (PD) on or after treatment in the ITT population was low in the VEN+G arm (14 patients, 6.48%) compared with the GCIb arm (69 patients, 31.9%).

At 24-months, the progression-free estimates were 88.15% and 64.10% in the VEN+G and GClb arms, respectively. A high proportion of patients remained progression free after 24 months indicating that the benefit of VEN+G was maintained over time, despite cessation of therapy after a maximum of 12 cycles.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Completion rates for EORTC QLQ-C30 and MDASI-CLL questionnaires were similar between the treatment arms throughout treatment (consistently above 90%) and follow-up (consistently above 85% until month 30).

Baseline levels of physical functioning and role functioning as measured by EORTC QLQ-C30 were maintained with no clinically meaningful change (improvement or deterioration) observed for either arm during treatment and follow-up. The GHS/QoL scale demonstrated clinically meaningful improvement ($\geq$8 points, Cocks et al. 2012) starting at Cycle 3 in the VEN+G arm and Cycle 8 in the GClb arm that was maintained throughout the remainder of treatment and follow-up. Additional exploratory analyses conducted with the social, cognitive and emotional functioning scales of the EORTC QLQ-C30 corroborate that HRQoL was maintained, with no meaningful change observed in either arm during the trial.

Across CLL symptom scale, core cancer symptom scale, and symptom interference scales measured by the MDASI-CLL, there was no clinically meaningful change (improvement or deterioration) observed for either arm during treatment and follow-up. Additional exploratory analyses with the symptom scales of the EORTC QLQ-C30 corroborate that patients in both arms experienced low symptom burden with no clinically meaningful deterioration observed in any scale and clinically meaningful improvement in mean insomnia and fatigue scores (≥9 points) starting at cycle 3 in the VEN+G arm and Cycle 4 and 6, respectively, in the GClb arm that were maintained during the remainder of treatment and follow-up in both arms. Clinically meaningful improvements in mean scores (≥9 points) were observed in dyspnea in the VEN+G arm during treatment starting at Cycle 3, but not maintained during follow-up.

Additional Analyses Conducted on the Individual Trial

Additional MRD Analyses

MRD Measured by ASO-PCR and Progression Free Survival

Pre-specified exploratory landmark analyses showed that patients who achieved MRD-negativity at EOT assessment had a longer duration of PFS compared with patients who did not. Similar observations were noted for MRD assessments performed in peripheral blood and bone marrow (Figure 4, Figure 5).

In addition, landmark analyses showed that patients who achieved a PR with peripheral blood MRD-negativity had a PFS outcome similar with that of patients who achieved CR with peripheral blood MRD-negativity (see Figure 8 and Figure 10 of CSR BO25323).

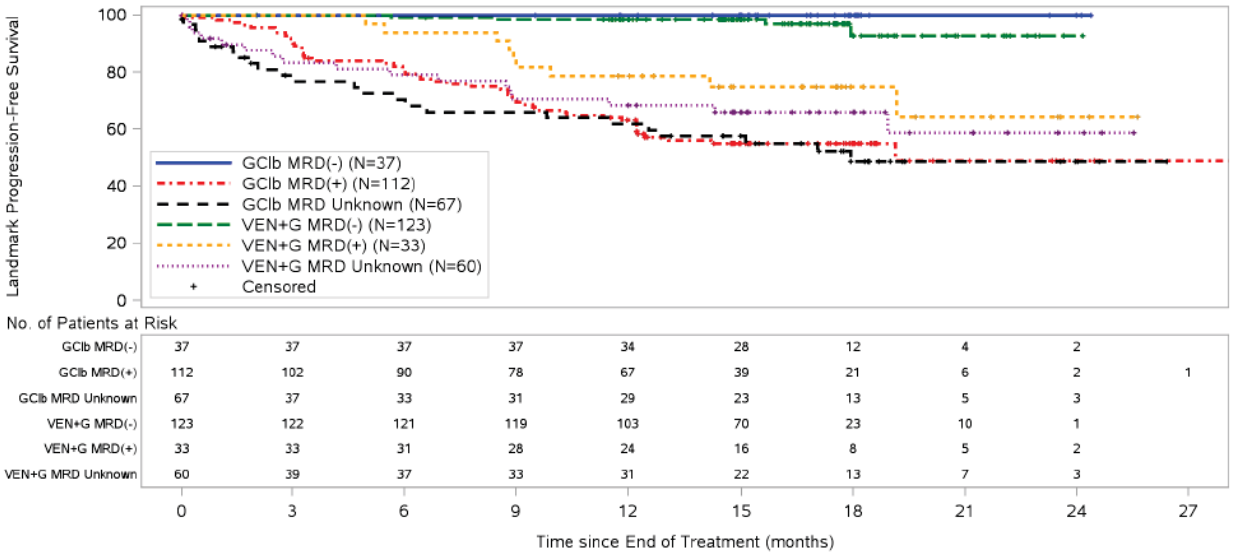
Persistence of MRD Negativity

Analysis of MRD over time showed that the difference of MRD-negativity rate between the two arms was maintained beyond treatment completion. At one year after treatment completion assessment (follow-up month 12, the last visit for which complete data were available prior to CCOD), the MRD negativity rate in peripheral blood was maintained at 58.3% in the VEN+G arm while it had dropped to 9.3% in the GClb arm (difference: 49.07 [95% CI: 41.20, 56.95]).

MRD by Next-Generation Sequencing

Pre-specified exploratory analysis of MRD by Adaptive ClonoSeq NGS showed that the EOT MRD results using a cut-off of 10^{-4} were consistent with the MRD by ASO-PCR at EOT assessment (Table 6). Furthermore, MRD-negativity rate remained significantly higher in the VEN+G arm than in the GClb arm at EOT assessment with 10^{-5} cutoff and 10^{-6} cutoff (Table 6), indicating a 1- to 2-log increase in the depth of response achieved with VEN+G treatment to a much greater extent than those treated with GClb.

Figure 4: Kaplan-Meier Plot of Investigator-Assessed PFS Status (Bone Marrow) at the End of Treatment (ITT Population)



The Landmark period runs from the Last Treatment date to the date of the PFS Event.
MRD Negative < 10^-4.
MRD bone marrow response status is based on ASO-PCR results.
Program: /opt/BIOSTAT/prod/cdt3709a/k25323d/g_ef_km_ldmk.sas Output: /opt/BIOSTAT/prod/cdt3709a/k25323d/reports/g_ef_km_ldmk_PFSIBMPCR_NSFRFL_323_IT.pdf
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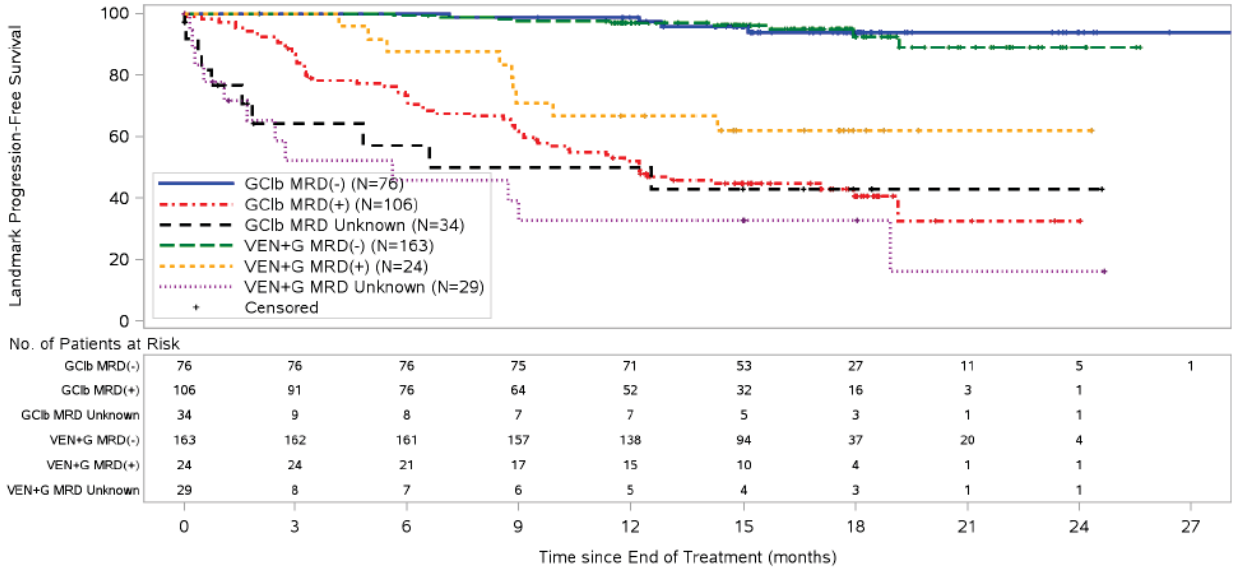
Figure 5: Kaplan-Meier Plot of Investigator-Assessed PFS Status (Peripheral Blood) at the End of Treatment (ITT Population)



The Landmark period runs from the Last Treatment date to the date of the PFS Event.
MRD Negative < 10^-4.
Program: /opt/BIOSTAT/prod/cdt3709a/k25323d/g_ef_km_ldmk.sas Output: /opt/BIOSTAT/prod/cdt3709a/k25323d/reports/g_ef_km_ldmk_PFSIBLPCR_NSFRFL_323_IT.pdf
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Table 6: NGS: End of Treatment MRD $<10^{-4}$, 10^{-5}, 10^{-6} Response (Peripheral Blood; ITT Population)

Parameter	GClb (N 216)	VEN+G (N 216)
MRD-Negativity Rate at EOT Assessment – NGS, $<10^{-4}$		
MRD negative (at 10^{-4})	74 (33.3%)	168 (77.8%)
95% CI	[27.95, 41.00]	[71.64, 83.14]
Difference in MRD negative rates [95% CI]	43.52 [34.85, 52.18]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate at EOT Assessment – NGS, $<10^{-5}$		
MRD negative (at 10^{-4})	42 (19.4%)	142 (65.7%)
95% CI	[14.39, 25.36]	[59.00, 72.05]
Difference in MRD negative rates [95% CI]	46.30 [37.80, 54.79]	
P-value (CMH test)	p<0.0001	
MRD-Negativity Rate at EOT Assessment – NGS, $<10^{-6}$		
MRD negative (at 10^{-4})	9 (4.2%)	67 (31.0%)
95% CI	[1.92, 7.76]	[24.92, 37.65]
Difference in MRD negative rates [95% CI]	26.85 [19.89, 33.8]	
P-value (CMH test)	p<0.0001	

Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted.

Integrated Review of Effectiveness

The FDA's Assessment:

FDA agrees with the applicant's position for the majority of primary analysis and secondary analyses. However, FDA does not agree with the following items:

1. FDA considers the PFS by IRC as the primary outcome of the study. The results of PFS by IRC are summarized in the following table.
2. The estimated 1-year and 2-year PFS rates are exploratory. Point estimate of event rates at a fixed time point for time-to-event endpoint can be misleading because it does not represent the entire effect size of the treatment.
3. For the analyses of duration of responses, the estimated HZ are exploratory and the p-values are considered to nominal, because these analyses are not conducted based on the randomized population.
4. Since there is no pre-specified statistical testing procedure to control the type I error, all of the PRO analyses are considered to be exploratory. No claims can be made based these analyses. The applicant cannot claim for clinically meaningful difference based on observations at certain cycles for certain QoL scales. The observed values can only be used for hypothesis generating.
5. The number of events in overall survival (OS) result is low. The estimates can be unreliable and HR reported is subject to uncertainty.
6. The denominator in MRD in CR in bone marrow and peripheral blood results should be the number of CRs in each arm. The results should be reported as:

	VENCLEXTA + Obinutuzumab	Obinutuzumab + Chlorambucil
MRD negativity rate in patients with CR		
N	100	47
Bone marrow, n (%)	69 (69)	21 (45)
95% CI	(59, 78)	(30, 60)
p-value[a]	0.0048	
Peripheral blood, n (%)	87 (87)	29 (62)
95% CI	(79, 93)	(46, 75)
p-value[a]	0.0005	
CI = confidence interval; CR = complete remission. [a]p-value based on Chi-square test		

7.1.3 Assessment of Efficacy Across Trials

The Applicant's Position:
This application is based primarily on efficacy from Study BO25323. Supportive efficacy data from patients with first-line CLL are provided from Phase Ib Study GP28331 (see Section 6 of CSR GP28331) and were consistent with the results from Study BO25323.

The FDA's Assessment:
FDA agrees with the applicant's position.

7.1.4 Integrated Assessment of Effectiveness

The Applicant's Position:
Study BO25323 is an ongoing, prospectively planned, adequately controlled, multi-center, international, and centrally randomized, open-label, Phase III study. The study was well designed, adequately powered, and conducted according to ICH E6 Guideline for GCP; source documents were verified and PFS results were confirmed by an IRC. Overall, the design and results of Study BO25323 are in accordance with the criteria for establishing efficacy within a single trial as described in the FDA Guidance (1998). The study results are statistically significant, clinically meaningful and compelling for use in patients with first-line CLL.

Results from Study BO25323 showed that VEN+G, a chemotherapy-free regimen given over a fixed-duration, significantly improved PFS and response rates, with high rates of MRD negativity, compared with a current standard of care (GClb) in patients with first-line CLL and coexisting medical conditions.

The clinically meaningful and statistically significant improvement in PFS (assessed by the investigator and IRC) by VEN+G was seen across high-risk and low-risk subgroups. This, along with other important endpoints of overall response in the vast majority of treated patients with

particularly high rates of complete remissions, provides meaningful clinical benefit to patients by significantly extending the time without disease progression and its associated symptoms.

The achievement of MRD negativity at 10^{-4} cutoff is an independent predictor of PFS and OS as demonstrated by several randomized Phase III studies in the first-line setting. The high rate of MRD negativity ($<10^{-4}$) observed in BO25323, which was maintained even after the cessation of treatment, assured the fixed-duration of treatment was feasible, while other novel therapies needed to be continued up to progression which, in the setting of first-line CLL, may be many years and associated with potential long-term toxicity. Moreover, MRD response assessed by NGS in Study BO25323 showed high rates of MRD negativity below 10^{-5} and 10^{-6} in the VEN+G arm, further demonstrating the deep response in these patients with 1 year fix-duration treatment.

The benefits of VEN+G over GClb were achieved without any apparent detrimental effects on overall health-related QoL, an important consideration for CLL patients, particularly the elderly population.

The totality of the efficacy data from Pivotal Study BO25323 show that the chemotherapy-free regimen of VEN+G, given for a defined period of 1 year, represents a significant advancement for the treatment of first-line patients with CLL. Additionally, in Supportive Study GP28331, the efficacy data including PFS, response rates (ORR and CR/CRi) and achievement of MRD negativity from patients with first-line CLL, including those patients considered 'fit' are consistent with the data from the Study BO25323 study and support the conclusions drawn.

The FDA's Assessment:
FDA agrees with the applicant's position.

7.2 Review of Safety

The Applicant's Position:
The safety profile of VEN+G in previously untreated patients with CLL was assessed in Study BO25323, a pivotal randomized, open-label Phase III study (in comparison to GClb), and in Phase Ib Study GP28331 providing supportive data.

The key safety findings from the main, randomized phase of Study BO25323 are presented in the following sections, with a CCOD of 17th August 2018. The safety profile associated with VEN+G combination therapy was consistent with the individual established safety profiles of venetoclax and obinutuzumab, and no new safety concerns were identified.

7.2.1 Safety Review Approach

The Applicant's Position:
The safety profile of individual study drugs, venetoclax and obinutuzumab, are well established

in the CLL patient population. The focus of the safety review in Study BO25323 was therefore to establish the safety profile of these drugs when used in combination in previously untreated patients with CLL and co-morbidities (as defined by a CIRS of >6 and/or creatinine clearance <70 ml/min).

Analysis presented hereafter is of TEAEs (i.e. any event not present prior to the initiation of study treatment, or any event already present that worsened in either intensity or frequency following exposure to study treatment).

The safety profile of VEN+G was assessed by analyzing the frequency of AEs, SAEs (including Grade 5 AEs), adverse events of special interest (AESIs)/selected AEs, AEs leading to discontinuation, AEs leading to dose modification (dose reduction or interruption), vital sign measurements and clinical laboratory assessments.

All AEs were to be reported until 28 days after the last dose of study treatment (venetoclax, chlorambucil, or obinutuzumab); Grade 3-4 AEs were to be reported for 6 months after the last dose of study treatment, Grade 3-4 infections were to be reported for 2 years after the last dose of study treatment, irrespective of causality, unless the patient developed disease progression and received next leukemic treatment. Before disease progression, all SAEs (including Grade 5 AEs) were reported during safety follow-up, regardless of causality, whereas after disease progression, only related SAEs (including Grade 5 AEs) and second primary malignancies were required to be reported by Investigators.

To assess clinically meaningful differences between treatment groups, incidence rates with <5% difference between treatment arms for any AEs (including Grade ≥ 3), and incidence rates with <2% difference between treatment arms for SAEs were considered comparable.

To assess potential new adverse drug reactions (ADRs), two algorithms were used:

1. All-Grade AEs with an incidence of >10% in either arm, with a difference of >5% higher in the VEN+G arm, and
2. Grade 3-4 AEs with a difference of >2% higher in the VEN+G arm

The FDA's Assessment:
The FDA agrees with the Applicant's position.

7.2.2 Review of the Safety Database

Overall Exposure
The Applicant's Position:
The safety population in Study BO25323 included any patient who received at least one dose of study treatment. Of 216 patients randomized in the main phase of the study to receive VEN+G, the safety-evaluable population consisted of 212 patients (who received at least one dose of study treatment).

The safety population definition was updated in SAP Version 2 post-unblinding. Patients randomized to the VEN+G arm who received only obinutuzumab were analyzed in the VEN+G arm rather than the GClb arm, which was stated in the original version 1. This change affected 9 patients who would have been analyzed in the GClb arm, but were ultimately analyzed in the VEN+G arm to which they were randomized, despite only receiving obinutuzumab treatment. Review of the listings for AEs and SAEs (including Grade 5 AEs) for these 9 patients suggests that including these patients in the VEN+G arm for the safety analysis did not unduly impact the safety profile reported and represented a more conservative approach for safety analysis by ensuring AEs caused by obinutuzumab were reflected in the data from the VEN+G arm.

Safety data from Study BO25323 and supportive Study GP28331 were not analyzed with results presented in a pooled fashion, as agreed with the Agency; instead, pooled datasets have been provided to the Agency. Pooling was not considered to be appropriate in view of the different study eligibility criteria and study schedules.

The FDA's Assessment:
The FDA agrees with the Applicant's position and has provided further supportive information below.

The number of patients exposed to study treatment was adequate for safety review.

Exposure in Study BO25323 is summarized in Table 7. The median exposure duration for venetoclax was 10.5 months (11 cycles) with a range of 1 day to 13.5 months. For the 189 patients that reached the target dose of 400 mg, the median relative dose intensity (RDI) was 98% (range 14 to 100%). For patients receiving chlorambucil, the median exposure duration was 12 cycles (range 1 to 12 cycles) and a median relative dose intensity of 95% (range 4 to 111%). The median exposure and dose intensity of obinutuzumab were similar in both treatment arms. The use of primary and secondary granulocyte colony stimulating factory were similar between treatment arms (Table 7)

Table 7: Exposure in the BO25323 Safety Population

Variable		GClb (N = 214)		VEN+G (N = 212)	
Cycles received	Median (range)	12	(1, 12)	11	(1,14)
RDI					
Venetoclax	Mean (SD)	-	-	86%	(22%)
	≥ 90%[a]	-	-	126	(62%)
Chlorambucil	Mean (SD)	83%	(27%)	-	-
	≥ 90%	137	(64%)	-	-
Obinutuzumab	Mean (SD)	93%	(21%)	92%	(23%)
	≥ 90%	183	(86%)	180	(85%)
		N = 216		N = 216	
GCSF Prophylaxis	Primary	23	(11%)	19	(9%)
	Secondary	84	(39%)	81	(38%)

GCSF: Granulocyte colony stimulating factor, RDI: Relative dose intensity, SD: Standard deviation
[a]Based on 203 patients receiving at least one dose of venetoclax
Source: FDA analysis of ADEX dataset and CSR Section 8.2

Relevant characteristics of the safety population:

The Applicant's Position:
The demographics and baseline characteristics of the patient population were mostly well balanced between treatment arms, and are described in Section 7.1.2.

The median CIRS score at baseline was 8.0 in the GClb group (range 0-23.0) and 9.0 (range 1.0-28.0) in the VEN+G group. Most patients in each treatment arm had comorbidities in 4-8 organ systems (82.9% in both arms). Overall, 39.4% of patients in the GClb arm and 44.9% of patients in the VEN+G arm had a severity score of ≥3 in one or two organ systems.

In the breakdown by different organ systems (body system as per CIRS), a higher percentage of patients in the VEN+G group had involvement of cardiac systems (46.8% in the VEN+G arm and 38.4% in the GClb arm) and hypertension (75.0% and 64.8%, respectively). Other organ systems with a higher percentage of patients with involvement in the VEN+G arm were respiratory organ system (40.3% in the VEN+G arm and 34.7% in the GClb arm), lower gastrointestinal organ system (30.1% and 21.8%, respectively), and endocrine/metabolic system (47.2% and 41.2%, respectively). Neurological involvement was reported in a higher percentage of patients in the GClb arm (29.2% in the GClb arm compared with 24.1% in the VEN+G arm).

The FDA's Assessment:
The FDA agrees with the Applicant's position.

The baseline characteristics of the BO25323 safety population and primary efficacy population are nearly identical, as the safety population has 2 less patients in the GClb arm and 4 less patients in the VEN+G arm. See Table 2 and Table 3.

Adequacy of the safety database:

The Applicant's Position:
The safety profiles of venetoclax and obinutuzumab as single agents are well established. An estimated 3,751 subjects have been exposed to at least one dose of venetoclax, including 1,072 subjects exposed for greater than 12 months in company-sponsored interventional clinical trials as of 04 December 2018. An estimated 1,327 patients have been exposed to venetoclax for the indication of CLL/ SLL. Venetoclax has an estimated cumulative exposure of 6,518.2 patient-treatment years in the postmarketing setting (4,000.4 in the US), from 01 April 2016 through 30 November 2018.

An estimated total of 5,202 patients have received obinutuzumab in clinical trials (from 13 August 2007 through 31 August 2018), with an estimated 1,776 patients for the indication of CLL. An estimated cumulative total of 37,294 patients have received obinutuzumab from post-marketing experience (01 November 2013 through 31 October 2018), of which 6,832 have received obinutuzumab for first-line CLL in the US.

The size of the safety database for Study BO25323 (N=212), supported by supplemental data from the Phase Ib Study GP28331 (N=32 first-line patients) is considered adequate to support

the benefit-risk assessment for the use of VEN+G in patients with previously untreated CLL, and adequately represents the target patient population.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

7.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
No issues relating to data integrity or quality were identified for Study BO23523.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Categorization of Adverse Event

The Applicant's Position:
For classification purposes, lower level terms were assigned by the Sponsors to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0) terminology for AEs and diseases. AEs were then presented by preferred term (PT) and system organ class (SOC).

For the analysis of selected AEs in this study, the following search criteria (MedDRA Preferred Term [PT], AE Group Term [AEGT], Standard MedDRA Query [SMQ], or MedDRA System Organ Class) were applied:

- Grade ≥3 thrombocytopenia: PTs Thrombocytopenia, Platelet Count Decreased;
- Grade ≥3 neutropenia: PTs Neutropenia and Neutrophil Count Decreased. The following MedDRA PTs were used to identify Grade ≥3 events of 'extended search neutropenia': Neutropenia, Neutrophil count decreased, Febrile neutropenia, Agranulocytosis, Neutropenic infection, and Neutropenic sepsis.
- Grade ≥3 infusion-related reaction (IRR): Events from Sponsor-specific AEGT Infusion-Related Reactions/Hypersensitivity occurring during infusion or within 24 h after end of infusion;
- TLS: SMQ Tumor Lysis Syndrome (Narrow)
- Grade ≥3 infection and serious infection: SOC Infections and Infestations.
- Second primary malignancies: SMQs: Malignant tumours, Myelodysplastic syndrome.

In addition to evaluating AEs of TLS, laboratory data were also reviewed to identify laboratory abnormalities that met Howard criteria for TLS, but that were not reported by the Investigator as AEs.

The FDA's Assessment:
The FDA agrees with the Applicant's position. Adverse events were graded according to

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. For increased sensitivity, the FDA and Applicant used agreed upon custom groupings of preferred term as defined in Appendix 17.4.

Routine Clinical Tests

The Applicant's Position:
Further detail on study assessments is provided in Section 4.5 of the study protocol (including Section 4.5.14 for laboratory assessments). The Schedule of Assessments (SoA) is provided in Appendices 1-3 of the study protocol.

Key assessments included routine clinical laboratory tests (hematology, chemistry), vital sign assessments, pregnancy tests and TLS lab-based risk assessments.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

7.2.4 Safety Results

Deaths
The Applicant's Position:
Overall, there were 17 deaths in the GClb arm (7.9%) compared with 20 deaths in the VEN+G arm (9.3%) in the ITT population. One patient in the GClb arm died prior to receiving study treatment, hence in the safety-evaluable population, there were 16 deaths (7.5%) in the GClb arm.

Disease progression was responsible for 5 deaths in the GClb arm compared with 3 deaths in the VEN+G arm. Three patients in the GClb arm, and 1 patient in the VEN+G arm died with reason reported as 'other' (GClb: reported as respiratory sepsis, sepsis and unknown; VEN+G: reported as natural cardiac death). Per protocol, these were non-reportable adverse events as they occurred following disease progression, after which only causally related events were to be reported as SAEs.

The frequency of fatal AEs was numerically higher in the VEN+G arm (n=16, 7.5%) vs. the GClb arm (n=8; 3.7%). The incidence of fatal AEs with onset during treatment (or within 28 days of the last study drug) was comparable in both arms (5 patients [2.4%] in the VEN+G arm vs. 4 patients [1.9%] in the GClb arm); all events that occurred during the treatment period, occurred during the combination treatment period; no fatal AE was reported during the single agent treatment period.

The incidence of fatal AEs with onset during the post-treatment follow-up period (after 28 days following the last dose of study treatment), was numerically higher in the VEN+G arm (11 patients in the VEN+G vs. 4 patients in the GClb arm). Review of these deaths confirmed that causal association with venetoclax was unlikely for most of these events due to the long latency

period from the last dose of study drug (in the post-treatment period, from 73 to 575 days after the last dose of venetoclax), relevant pre-existing medical conditions (e.g., cardiovascular risk factors/disease), and other confounding factors.

Individual medical review was conducted of the fatal AEs. Assessment by SOC revealed that the main differences between treatment groups were found with infections and cardiac disorders:

- There were 8 patients with fatal AEs of infection in the VEN+G arm; 4 occurred with onset of AE during the treatment period (of which 1 patient had not received venetoclax, and another death occurred following Richter's transformation), and 4 with onset of AE in the post-treatment period (of which 1 patient developed T-cell lymphoma and died following other anti-leukemic therapy). There were 3 patients with fatal infection in the GClb arm, all occurred with onset of AE during the treatment period.
- There were 4 patients with fatal AEs related to cardiac disorders in the VEN+G arm compared with 1 in the GClb arm. All occurred with onset in the post-treatment period, and all had relevant previous medical history or cardiovascular risk factors.

Infections are a common cause of morbidity and mortality in patients with CLL, and deaths due to a variety of causes in an elderly patient population are to be expected. An in-depth review of the fatal AEs was conducted by the Applicant to assess the causality of VEN+G and fatal AEs. Three of the 16 reported fatal AEs in the VEN+G arm were assessed by the Applicant to be possibly related to VEN+G (1.4%), compared with 3 of the 8 fatal AEs possibly related in the GClb arm (1.4%).

In summary, while the fatal AEs were reported with greater frequency in the VEN+G arm, the overall number of deaths, and fatal AEs with onset during treatment were balanced. The rate of deaths in the VEN+G arm is consistent with the rates of death observed in other studies of anti-CLL therapies in elderly, co-morbid patients (Goede et al. 2014; Moreno et al. 2018).

The FDA's Assessment:
Upon review of patient narratives and adverse event datasets for all deaths occurring during Study BO25323, the FDA agrees with the Applicant's position.

Serious Adverse Events
The Applicant's Position:
The incidence of SAEs was higher in the VEN+G arm (49.1%) compared with the GClb arm (42.1%). This was largely driven by differences in the Infection and Infestations SOC (18.9% VEN+G vs. 14% GClb), and the biggest difference within this SOC was noted for the PT of sepsis (2.8% VEN+G vs. 0.9% GClb).

The higher rate of SAEs in the VEN+G arm appeared to be driven by more events in the post-treatment period, i.e. more than 28 days after the last dose of study drug. The rate of SAEs in this study period was 21.3% in the VEN+G arm, compared with 15.4% in the GClb arm. No individual PTs or medical concepts were identified to drive these differences. The rates of SAEs in the combination treatment period (28.8% with VEN+G vs. 31.8% with GClb) and in the single

agent treatment period (12.6% with VEN+G vs. 11.1% with GClb) were comparable.

The most frequently reported individual PTs across all systems were IRR (6.1% GClb vs. 4.2% VEN+G), pneumonia (4.2% GClb vs. 4.7% VEN+G), febrile neutropenia (3.7% GClb vs. 5.2% VEN+G) and pyrexia (3.3% GClb and 3.8% VEN+G). No other individual PTs were reported with a frequency of ≥2% overall.

Assessment of SAEs by grouped PTs was conducted in order to identify trends in SAE rates across medical concepts rather than individual PT. There were no SAEs identified with a ≥ 2% difference, higher in the VEN+G arm, as assessed by grouped PTs.

The FDA's Assessment:
The FDA agrees with the Applicant's position and has provided supplemental information on SAEs below.

Table 8: Serious Adverse Events (≥2%) in Study BO25323

Event	GClb (N = 214)		VEN+G (N = 212)	
	n	%	n	%
Any grade ≥ 3 SAE	75	35%	91	43%
Any grade ≥ 4 SAE	26	12%	36	17%
Any SAE	90	42%	104	49%
SAE in ≥ 2% by System Organ Class				
Infections and infestations	30	14%	40	19%
Blood and lymphatic system disorders	17	8%	19	9%
Injury, poisoning and procedural complications	22	10%	16	8%
Neoplasms benign, malignant and unspecified	12	6%	15	7%
General disorders and administration site conditions	9	4%	12	6%
Respiratory, thoracic and mediastinal disorders	9	4%	12	6%
Nervous system disorders	5	2%	9	4%
Cardiac disorders	12	6%	8	4%
Gastrointestinal disorders	4	2%	8	4%
Metabolism and nutrition disorders	7	3%	7	3%
Vascular disorders	3	1%	5	2%
Investigations	4	2%	4	2%
Musculoskeletal and connective tissue disorders	4	2%	1	<1%
Skin and subcutaneous disorders	4	2%	0	0%
SAE in ≥ 2% by Preferred Term or Grouped Preferred Term				
Pneumonia	11	5%	13	6%
Febrile neutropenia	8	4%	11	5%
Infusion related reaction	13	6%	9	4%

Event	GClb (N = 214)		VEN+G (N = 212)	
	n	%	n	%
Pyrexia	7	3%	8	4%
Sepsis	5	2%	8	4%
Thrombocytopenia	5	2%	2	1%
Transaminase increased	4	2%	2	1%
Tumor lysis syndrome	4	2%	1	<1%

Source: FDA analysis of AAE dataset
Includes all-cause events reported up to 28 days after last dose of venetoclax, chlorambucil, or obinutuzumab.
Bolded categories are involved ≥ 2.0% more in the VEN+G arm.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Per protocol, patients were to discontinue study treatment if they were non-compliant, became pregnant, or experienced disease progression or AEs of Grade 4 IRR or Grade 4 TLS.

AEs leading to withdrawal of any study treatment were balanced in both treatment groups (16% VEN+G vs. 15.4% GClb). Regardless of causality, withdrawal of venetoclax due to AEs was reported in 12.7% of patients. The most common AEs that resulted in withdrawal of venetoclax were neutropenia (2.4%), sepsis (0.9%), and asthenia (0.9%).

Withdrawal of obinutuzumab due to AEs was balanced in both treatment groups (7.1% VEN+G vs. 7.5% GClb). AEs reported more than once in either treatment arm resulting in withdrawal of obinutuzumab were neutropenia (0.5% VEN+G vs. 0.9% GClb), thrombocytopenia (0.9% VEN+G vs. 0.5% GClb), anemia (0.9% GClb), and infusion-related reaction (0.9% both arms).

Withdrawal of chlorambucil due to AEs was reported in 14.5% of patients. The most common AEs that resulted in withdrawal of chlorambucil were neutropenia (2.3%), neutrophil count decreased (0.9%) and infusion-related reaction (0.9%).

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Certain toxicities, including Grade≥3 neutropenia, were to be managed by dose interruptions, followed by dose reduction on resumption of study drug (per protocol, this was mandated for venetoclax only).

Dose interruption of any study treatment was reported in 73.6% of patients in VEN+G arm compared to 68.2% in GClb arm. AEs leading to dose interruption of venetoclax were reported

in 57.1% of patients, most commonly due to neutropenia (40.6%). AEs leading to dose interruption of obinutuzumab were reported in 56.1% of patients in the VEN+G arm and 52.3% of patients in the GClb arm, mostly due to IRR (23.6% VEN+G, 26.6% GClb) and neutropenia (26.4% VEN+G, 22.9% GClb). AEs leading to dose interruption of chlorambucil were reported in 56.5% of patients, mostly due to neutropenia (38.8%).

Dose reduction of any study treatment was reported in 20.8% of patients in VEN+G compared with 8.4% in GClb. AEs leading to dose reduction of venetoclax were reported in 20.3% of patients, again primarily due to neutropenia (13.2%). Dose reductions of obinutuzumab were not allowed per protocol, although a small number of dose reductions were reported regardless (5 patients in total). Dose reductions of chlorambucil were permitted according to local guidelines, and were reported in 7.9% of patients due to AEs (neutropenia being the primary cause, 6.1%).

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Significant Adverse Events
The Applicant's Position:
The incidence of Grade 3 or 4 AEs (by NCI-CTCAE grading) was similar in both arms (78.8% VEN+G vs. 76.6% GClb). Individual PTs (Grade 3-4) reported with an incidence at least 2% higher in the VEN+G arm were neutropenia (52.8% VEN+G vs. 48.1% GClb arm), hyperglycemia (3.8% VEN+G vs. 1.4% GClb), diarrhea (4.2% VEN+G vs. 0.5% GClb) and hypertension (2.8% VEN+G vs. 0.5% GClb). These are discussed further in the following section.

The FDA's Assessment:
The FDA agrees with the Applicant's position and has provided supplemental information on Grade 3 or 4 AEs below.

Table 9: Grade 3 or 4 Adverse Events in Study BO25323

Event	GClb (N = 214)		VEN+G (N = 212)	
	n	%	n	%
Any grade 3 or 4 AE	163	76%	167	79%
Any grade 4 AE	71	33%	86	41%
Grade 3 or 4 AEs in ≥ 2% by Preferred Term or Grouped Preferred Term				
Neutropenia	112	52%	119	56%
Thrombocytopenia	33	15%	32	15%
Infusion related reaction	22	10%	19	9%
Anemia	14	7%	17	8%
Pneumonia	10	5%	11	5%
Febrile neutropenia	8	4%	11	5%
Diarrhea	1	<1%	9	4%
Leukopenia	11	5%	8	4%

Event	GClb (N = 214)		VEN+G (N = 212)	
	n	%	n	%
Hyperglycemia	3	1%	8	4%
Hypertension	1	<1%	6	3%
Fatigue	3	1%	5	2%
Dyspnea	1	<1%	5	2%
AST increased	7	3%	5	2%
ALT increased	7	3%	4	2%
Syncope	4	2%	4	2%
Atrial fibrillation	3	1%	4	2%
Tumor lysis syndrome	5	2%	3	1%
Lymphopenia	5	2%	3	1%
Hypotension	5	2%	2	1%

Source: FDA analysis of AAE dataset
Includes all-cause events reported up to 28 days after last dose of venetoclax, chlorambucil, or obinutuzumab.
Bolded categories are involved ≥ 2.0% more in the VEN+G arm.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

ADRs were identified in Study BO25323 using two algorithms.

1. AEs occurring in >10% of patients, with >5% frequency higher in the VEN+G arm, were diarrhea (27.8% VEN+G vs. 15% GClb) and pyrexia (22.6% VEN+G vs. 15.4% GClb).
2. Grade 3-4 AEs occurring with a >2% difference, higher in the VEN+G arm, were neutropenia (52.8% VEN+G vs. 48.1% GClb), hyperglycemia (3.8% VEN+G vs. 1.4% GClb), diarrhea (4.2% VEN+G vs. 0.5% GClb) and hypertension (2.8% VEN+G vs. 0.5% GClb).

Neutropenia and diarrhea are known ADRs of both venetoclax and obinutuzumab as single agents. Medical review of pyrexia was conducted; causality with venetoclax is considered unlikely, given that this symptom appeared to occur mostly in the context of IRRs or infection.

Review of hyperglycemia revealed that most of these AEs occurred in the context of previous medical history of diabetes, and/or administration of steroid medication prior to obinutuzumab infusion.

Hypertension AEs were found to occur mostly in patients with a previous history of hypertension or in the context of concurrent conditions that temporarily raised the blood pressure (only one case had hypertension ongoing at the time of CCOD).

The FDA's Assessment:

The FDA agrees with the Applicant's position and has provided supplemental information on treatment emergent AEs below.

Event	GClb (N = 214)		VEN+G (N = 212)	
	n	%	n	%
Any grade TEAE	213	99%	200	94%
TEAEs in ≥ 7% by Preferred Term or Grouped Preferred Term				
Neutropenia	132	62%	128	60%
Infusion related reaction	110	51%	95	45%
Diarrhea	32	15%	59	28%
Thrombocytopenia	52	24%	59	28%
Pyrexia	33	15%	48	23%
Fatigue	50	23%	44	21%
Nausea	46	21%	40	19%
Anemia	43	20%	36	17%
Cough	28	13%	36	17%
Upper respiratory tract infection	36	17%	35	17%
Constipation	19	9%	28	13%
Headache	21	10%	24	11%
Dizziness	20	9%	22	10%
Back pain	20	9%	21	10%
Vomiting	18	8%	21	10%
Transaminitis	23	11%	20	9%
Pruritus	9	4%	19	9%
Pneumonia	14	7%	18	8%
Edema	20	9%	17	8%
Arthralgia	18	8%	16	8%
Hyperglycemia	9	4%	16	8%

Source: FDA analysis of AAE dataset
Includes all-cause events reported up to 28 days after last dose of venetoclax, chlorambucil, or obinutuzumab.
Bolded categories are involved ≥ 2.0% more in the VEN+G arm.

Reviewer comment: The overall safety profile, including the increased incidences diarrhea and vomiting compared to GClb, is consistent with current labeling for venetoclax.

Laboratory Findings

The Applicant's Position:

Shift tables were used to identify treatment-emergent laboratory abnormalities that were new or worsening, or worsening from baseline unknown. The following Grade ≥ 3 abnormalities were reported with an incidence >5% higher in the VEN+G arm compared with the GClb arm: low calcium (9.0% VEN+G vs. 3.7% GClb), low lymphocyte count (57.1%VEN+G vs. 50.5% GClb), low neutrophil count (63.2% VEN+G vs. 55.6% GClb) and low white blood cell count (45.8% VEN+G vs. 40.7% GClb). These are all known ADRs of venetoclax; no new changes in chemistry or hematological parameters were identified as a result of VEN+G therapy, on review of laboratory abnormalities. The incidence of neutropenia (low neutrophil count) is consistent

with other studies of venetoclax in CLL. Further information is available in Section 8.13.2 of the CSR.

When assessing changes in laboratory parameters over time, no marked differences between the GClb and VEN + G treatment arms were observed in the mean change from baseline data for hematology or blood chemistry laboratory parameters. Of note, at baseline, the median lymphocyte count was 55 x 10^9 cells/L in both arms. On Cycle 1 Day 15, the median count had decreased to 1.27 x 10^9 cells/L (range 0.2-83.7 x 10^9 cells/L) in the VEN+G arm and 1.03 x 10^9 cells/L (range 0.2-43.4 x 10^9 cells/L) in the GClb arm.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Vital Signs
The Applicant's Position:
There were no clinically meaningful changes from baseline in either treatment arm or differences between treatment arms in weight, blood pressure (including diastolic and systolic values), heart rate or body temperature.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Electrocardiograms (ECGs)
The Applicant's Position:
ECGs were conducted at baseline for all patients, and then as clinically indicated during the study. Three patients in the VEN+G arm, and 1 patient in the GClb arm, were reported to have post-baseline abnormal ECGs (clinically significant); none were reported as specific conduction AEs, however all patients had preexisting cardiac disease or other cardiac AEs that could reasonably account for ECG abnormalities.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

QT
The Applicant's Position:
No QT studies were performed as part of Study BO25323.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Immunogenicity
The Applicant's Position:
No immunogenicity assessments were conducted as part of Study BO25323.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

7.2.5 Analysis of Submission-Specific Safety Issues

The Applicant's Position:
Selected AEs were identified as requiring more thorough evaluation based on the known identified and potential risks of venetoclax, mechanism of action of venetoclax and obinutuzumab, known class effects, previous clinical experience, and the underlying disease:

Tumor Lysis Syndrome
Both venetoclax and obinutuzumab cause rapid cell breakdown after initial dosing of patients with CLL; administration of both agents individually has been associated with events of laboratory and/or clinical TLS. TLS risk assessment to stratify patient management was conducted by investigators; close blood count monitoring was required, as well as prophylactic measures including hydration and uric acid reducers, with elective hospital admission for patients at highest risk.

AEs of TLS were reported in 3 patients in the VEN+G arm (1.4%) and 5 patients in the GClb arm (2.3%). All AEs in the VEN+G arm occurred prior to the first dose of venetoclax and were associated with obinutuzumab treatment. One case in each treatment arm was associated with clinical manifestations, but neither case met Howard laboratory criteria of TLS. All cases resolved and study treatment was restarted.

In addition to evaluating AEs of TLS, laboratory data were also reviewed to identify laboratory abnormalities that met Howard criteria for laboratory TLS, but that were not reported by the Investigator as AEs of TLS. In the VEN+G arm, 12 patients experienced laboratory abnormalities consistent with Howard criteria in Cycles 1 or 2, and 6 patients were identified in the GClb arm. These events do not appear to have resulted in any dose modifications of venetoclax or required other treatment to be given; they were not considered medically significant such that they should be reported as AEs.

TLS remains a known risk with the VEN+G regimen; TLS prophylaxis measures and risk assessment are essential to mitigate the risk of TLS, as is vigilance during the initiation and ramp-up of venetoclax in this patient population.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Reviewer Comment: The risk of TLS is mitigated by delayed initiation of venetoclax (Day 22, Cycle 1) and completion of the 5-week ramp-up.

Grade ≥ 3 Neutropenia
The Applicant's Position:
The rate of Grade ≥ 3 neutropenia (including extended search neutropenia) was similar in both

treatment groups, as was the use of GCSF.

The percentage of patients with Grade 3 or 4 neutropenia events (reported AEs of neutropenia or neutrophil count decreased) was similar in both arms (52.3% in the GClb arm and 56.1% in the VEN+G arm). No Grade 5 neutropenia events were reported. Febrile neutropenia was reported in 5.2% of patients in the VEN+G arm compared with 3.7% in the GClb arm.

Venetoclax and chlorambucil dose interruptions due to all-grade neutropenia were reported in 40.6% in the VEN+G arm and 38.8% in the GClb arm. A similar proportion of patients received GCSF for the indication of neutropenia (38.9% in the GClb arm and 37.5% in the VEN+G arm).

Taken together, these results indicated that VEN+G did not unduly increase the risk of Grade ≥ 3 neutropenia compared with GClb, and was managed according to standard of care (dose modification and colony stimulating factors) in both groups.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Grade ≥ 3 Thrombocytopenia
The Applicant's Position:
The rate of Grade ≥ 3 thrombocytopenia was similar in both treatment groups, as was the rate of Grade ≥3 hemorrhage.

The percentage of patients with Grade 3 or 4 thrombocytopenia events (reported AEs of thrombocytopenia or platelet count decreased) was similar in both arms (15.4% in the GClb arm and 15.1% in the VEN+G arm). No Grade 5 thrombocytopenia events were reported.

Of all patients with Grade ≥ 3 thrombocytopenia, Grade ≥ 3 AEs of hemorrhage were reported in 6.1% of these patients in the GClb arm, and 6.3% of these patients in the VEN+G arm. Dose interruptions in venetoclax and chlorambucil due to thrombocytopenia were reported in 2.8% of patients and 5.6%, respectively.

VEN+G did not increase the risk of Grade ≥ 3 thrombocytopenia or hemorrhage compared to GClb, and was managed with standard of care measures, including dose modification, equally in both groups.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Grade ≥ 3 Infections and Serious Infections
The Applicant's Position:
The incidence of Grade ≥ 3 infection was comparable, but the incidence of serious infection was different between treatment groups.

The rate of Grade ≥ 3 infection was 16.4% in the GClb arm and 19.3% in the VEN+G arm. The most frequently reported Grade ≥ 3 infection was pneumonia (4.2% in the GClb arm and 4.2% in the VEN+G arm). An imbalance was observed in the number of sepsis events (0.9% in the GClb arm compared with 3.3% in the VEN+G arm). Five of the sepsis events in the VEN+G arm were fatal, 3 of which occurred in the post-treatment period.

The frequency of serious infections was higher in the VEN+G arm (18.9%) compared with GClb (14%). This was driven by a difference in reported AEs of sepsis. Analysis of serious infections by treatment period did not reveal a difference in incidence in any particular time period. Also, the majority of serious infections did not appear to occur in the context of neutropenia, in both treatment groups.

Serious infection is a known risk with CLL and CLL therapies, particularly in an older, co-morbid population (Hilal et al. 2018). This is primarily due to disease-related (inherent immune dysfunction caused by the disease process, affecting both humoral and cell-mediated immunity, and complement activity) and therapy-related elements (most anti-CLL treatments are responsible for causing lymphopenia, either B-cell or T-cell, and/or neutropenia to some degree). Vigilance is required by medical practitioners to monitor for signs of infection and treat accordingly, and this has been highlighted in the label (within the Warnings and Precautions section of the USPI).

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Reviewer Comment: Due to the risk of serious infections (incidence 19% in VEN+G), including fatal cases of sepsis (3%, 6/212), a Warning and Precaution for infections was added to the venetoclax prescribing information. For grade 3 or higher infection, interruption of venetoclax is recommended.

Second Primary Malignancies
The Applicant's Position:
The rate of second primary malignancies was comparable in both groups (13.7% VEN+G vs. 10.3% GClb), with no clear patterns of malignancy by type or geographical region identified. The most common malignancies seen in this patient population were squamous cell carcinoma and basal cell carcinoma.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Richter's Syndrome
The Applicant's Position:
Two patients in the VEN+G arm and 1 patient in the GClb arm developed Richter's syndrome. All 3 transformations were to diffuse large B-cell lymphoma.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

7.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
Overall, the COA results suggest that, with regard to the patient-relevant concepts assessed, VEN+G is tolerable from the patients' perspective:

- In both the VEN+G and GClb arms, mean scores on the CLL symptom, core cancer symptom, and symptom interference scales of the MDASI-CLL did not meaningfully change from baseline and were comparable between arms throughout treatment and follow-up. Similarly, with the exception of three symptom scales on the EORTC QLQ-C30 that demonstrated clinically meaningful improvement (≥9 points) in one (dyspnea) or both arms (fatigue, insomnia), baseline symptom levels were maintained. No evidence of difference was observed between the arms at any point during the trial.

The FDA's Assessment:
The COA analyses does not have a pre-specified analysis plan. Therefore, all results are considered to be exploratory and hypothesis generating. No claim can be made based on these results.

7.2.7 Safety Analyses by Demographic Subgroups

The Applicant's Position:
The safety of the VEN+G regimen was investigated according to age, sex, race, geographic region, and organ (hepatic or renal) impairment. The safety profile was consistent with the overall safety profile in all subgroups analyzed, with no major differences between treatment groups. The percentage of patients with an SAE or Grade 3-4 AE was higher for those aged ≥ 65 years than for those aged < 65 years, in both treatment groups; older patients are more susceptible to AEs in clinical trials, which can be expected given the higher levels of comorbidity among older cancer patients, and the decline in physiological reserve with age (Williams et al. 2016). No specific pattern of AEs by SOC was identified and no clinically meaningful differences were observed between older and younger patients in either study arm.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

7.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:
No specific studies were conducted to evaluate safety concerns.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

7.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Patients with CLL, particularly elderly patients with previous comorbidities, are at risk of developing second primary malignancies due to underlying immune impairment. However, analysis of second primary malignancies reported in BO25323 has not identified any particular safety concerns with VEN+G, compared with GClb.

The rate of all-grade second malignancies by SMQ, was comparable in both groups (13.7% VEN+G vs. 10.3% GClb), with no clear patterns of malignancy by type or geographical region identified. The most common malignancies seen in this patient population were squamous cell carcinoma (3.3% VEN+G vs. 3.7% GClb) and basal cell carcinoma (2.8% in both arms).

SAEs within this SOC Neoplasms benign, malignant and unspecified (including cysts and polyps) were reported in 7.1% in VEN+G and 5.6% in GClb. No individual PT was reported with a difference of > 2 patients with serious malignancy.

The rate of death within the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps) was balanced in both treatment groups (3 patients each: VEN+G PTs of myelodysplastic syndrome, metastatic malignant melanoma and bladder cancer; GClb PTs of squamous cell carcinoma, sarcoma of skin and acute myeloid leukemia). In both treatment arms, 1 fatal AE had onset during the treatment period, and 2 had onset in the post-treatment period.

Discontinuations due to malignancy were balanced in both groups, with 3 patients withdrawing from venetoclax (Bowen's disease, myelodysplastic syndrome and prostate cancer metastatic), 2 patients withdrawing from chlorambucil (skin squamous cell carcinoma metastatic and squamous cell carcinoma of skin), and 2 patients withdrawing from obinutuzumab (myelodysplastic syndrome VEN+G, squamous cell carcinoma of skin GClb).

Taken together, there is no evidence to suggest increased risk of malignancy with the VEN+G regimen, considering the underlying risk of malignancy in an elderly population with CLL.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

The Applicant's Position:

No pregnancies were reported during the study.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth
The Applicant's Position:
Not applicable.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
The Applicant's Position:
No reports of overdose were obtained during the study.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

7.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Position:
No change to the benefit-risk profile of venetoclax is recommended following the most recent Periodic Safety Updated Report (PSUR), which reports postmarket safety assessments through 04 Dec 2018. Similarly, no change to the benefit-risk profile of obinutuzumab is recommended following the most recent Periodic Benefit-Risk Evaluation Report (PBRER) (through to 31 October 2018).

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting
The Applicant's Position:
Not applicable; there is considerable postmarket experience with both venetoclax and obinutuzumab already available.

The FDA's Assessment:
Based upon the established safety profile of venetoclax and obinutuzumab, it is expected that safety issues can be adequately managed through labeling and routine postmarketing surveillance.

7.2.11 Integrated Assessment of Safety

The Applicant's Position:
The safety profile of VEN+G was found to be consistent with the individual established safety profiles of venetoclax and obinutuzumab, with no new safety concerns identified.

TLS is a known risk of both venetoclax and obinutuzumab. It occurred at low frequency during Study BO25323 and was balanced across treatment groups. No AEs of TLS were reported after

venetoclax initiation in the main, randomized phase of the study, which suggests that the current risk mitigation for TLS (including dose ramp-up, risk assessment and prophylaxis measures) are adequate to manage this risk.

Neutropenia is another known risk of both venetoclax and obinutuzumab. It was managed in the study with dose modifications and GCSF administration, mirroring clinical practice and guidance provided in the protocol. No significant differences between treatment groups were identified. There was no observed relationship between serious infections and neutropenia. Most immunomodulatory drugs used to treat CLL result in some degree of either neutropenia and/or lymphopenia, owing to the mechanism of action of these drugs (Hilal et al. 2018); this can be managed though close monitoring of blood counts, prophylactic treatment with GCSF if required, and prompt treatment with antibiotics or antifungal agents if infection should arise.

Elderly patients with CLL are at increased risk of infection compared with the general population, and infection is a known risk of venetoclax and obinutuzumab. Serious infection was seen at a higher rate in the VEN+G arm, including infection leading to death; of note however, the risk of developing serious infection whilst on treatment was balanced in both treatment groups. Given the results from this study, vigilance of infection is required in this population following VEN+G treatment. Physicians will be alerted to this risk through the product label (serious infection added in the Warnings and Precautions section of the USPI).

The incidence of fatal AEs was higher in the VEN+G arm, driven by infection and cardiovascular events. Careful review of these cases revealed that causality with VEN+G was not likely, given the latency between last dose of study treatment and onset of AE, confounding factors and previous medical history.

In light of these results, and bearing in mind the patient population of the study (elderly CLL patients with comorbid conditions), the safety profile of VEN+G is considered acceptable, and aligned with the known safety profiles of venetoclax and obinutuzumab. No new safety concerns were identified, and given the superior efficacy over GClb, the benefit-risk profile is considered positive. Additionally, the safety profile in the 32 first-line patients from Study GP28331 was consistent with that observed in Study BO25323.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

SUMMARY AND CONCLUSIONS

7.3 Statistical Issues

The FDA's Assessment:
The results of the primary analysis showed that VEN+G statistically significantly prolonged PFS compared with GClb. The results of secondary points also support this finding.

7.4 Conclusions and Recommendations

The FDA's Assessment:

The BO25323/CLL14 trial, a randomized, open-label, actively controlled trial of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in 432 patients with untreated CLL demonstrated that treatment with venetoclax plus obinutuzumab resulted in longer progression-free survival, higher complete remission and overall response rates, and improved minimal residual disease negativity rates at the completion of treatment compared to chlorambucil plus obinutuzumab. The evaluation of safety of venetoclax plus obinutuzumab demonstrated an acceptable safety profile in patients with newly diagnosed CLL, and the overall safety profile is consistent with current labeling for venetoclax and obinutuzumab. Therefore, the benefit-risk assessment supports regular approval of venetoclax for the treatment of adult patients with CLL or SLL.

X X

Weishi Yuan, PhD
Primary Statistical Reviewer

Jingjing Ye, PhD
Statistical Team Leader

X X

Nicholas Richardson, DO, MPH
Primary Clinical Reviewer

R. Angelo de Claro, MD
Clinical Team Leader

8. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not presented to an advisory committee or external consultants because it did not raise significant efficacy or safety issues for the proposed indication.

9. Pediatrics

The Applicant's Position:
Not applicable, as the applicant has not proposed any changes to the pediatric sections of the VENCLEXTA label.

The FDA's Assessment:
VENCLEXTA is exempt from pediatric study requirements in 21 CFR 314.55 for patients with CLL. FDA granted Orphan Drug Designation for VENCLEXTA for the following indication (date of designation): Treatment of chronic lymphocytic leukemia (20 September 2012).

10. Labeling Recommendations

10.1 Prescription Drug Labeling

The Applicant's Position:
The compelling data presented in the dossier from patients in Study BO25323 and supported by the data from patients with first-line CLL in Study GP28331, which included patients considered fit enough to receive chemo-immunotherapy, demonstrates the benefits of VEN+G to the broad patient population in clinical practice (i.e., patients with co-morbidities, but also fitter patients with better performance status).

The Applicant recommends that venetoclax, in combination with obinutuzumab, as a fixed-duration chemotherapy-free regimen, should be made available to patients with previously untreated CLL with the following indication:
"VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)"

The FDA's Assessment:
The following are recommendations for the VENCLEXTA prescribing information based on this review.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section (USPI)	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1.1 Indications and Usage, CLL/SLL	(b) (4) the use of VENCLEXTA in combination with obinutuzumab for adult patients with (b) (4) CLL	Treatment of adult patients with CLL or SLL
2.1 Recommended Dosage	Included dosing information for VENCLEXTA in combination with obinutuzumab	FDA agrees with Applicant's

	(See Section 5.2.2.1 of the present document)	proposal
5.2 Warnings and Precautions, Neutropenia	Streamlined to present ranges across CLL studies. *(See Sections 7.2.4 and 7.2.5 of the present document)*	FDA agrees with Applicant's proposal
5.3 Warnings and Precautions, Serious Infection	Included new identified risk and recommendations. *(See Section 7.2.5 of the present document)*	FDA agrees with Applicant's proposal
6.1 Adverse Reactions, Clinical Trial Experience with CLL/SLL	Included information from Study BO25323 (CLL14). *(See Section 7.2.4 of the present document)*	FDA agrees with Applicant's proposal
6.1 Adverse Reactions, Clinical Trial Experience with CLL/SLL	Included the ADR 'Sepsis' under Other Adverse Reactions for Study GO28667 (MURANO) in connection with the update to Section 5.3 referenced above.	FDA agrees with Applicant's proposal
6.1 Adverse Reactions, Clinical Trial Experience with CLL/SLL *Important Adverse Reactions – Tumor Lysis Syndrome*	Included information from Study BO25323 (CLL14). *(See Section 7.2.5 of the present document)*	FDA agrees with Applicant's proposal
8.5 Use in Specific Populations, Geriatric Use	Modified language to incorporate outcomes from Study BO25323 (CLL14). *(See Section 7.2.7 of the present document)*	FDA agrees with Applicant's proposal
14.1 Clinical Studies, CLL/SLL	Included information from Study BO25323 (CLL14). *(See Section 7.1.2 of the present document)*	FDA agrees with Applicant's proposal

11. Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:

Venetoclax and obinutuzumab have been utilized in the postmarket setting for a number of years. The product label details sufficient advice for prescribers, to mitigate against known risks of TLS, neutropenia and serious infection. No additional REMS is required in addition to the product label.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The clinical review team does not recommend a REMS. Based on the risk/benefit profile of VEN+G, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

12. Postmarketing Requirements and Commitment

The FDA's Assessment:
The clinical review team determined that a safety PMR or PMC was not warranted based upon this review.

13. Division Director (OB)

X

Thomas Gwise, PhD

14. Division Director (Clinical)

Summary Review of the Supervisory Associate Division Director:

This section was derived in part from the review of the CDTL (Angelo de Claro, MD).

Background: AbbVie, Inc. submitted S-13 for NDA 208573 on February 6, 2019 in which they requested approval of venetoclax (Venclexta) for the following indication: treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). They based this request on a single open label actively controlled trial in which over 400 patients with previously untreated CLL were randomized between venetoclax plus obinutuzumab (VEN + G) and chlorambucil plus obinutuzumab (GClb).

Efficacy Results: A statistically significant increase was observed in progression-free survival [hazard ratio 0.33 (95%CI 0.22, 0.51), P-value <0.0001], overall response rate (85% vs 71%, P-value 0.0007), complete remission (CR) and complete remission with incomplete marrow recovery rate (50% vs 23%, P-value <0.0001), and minimal residual disease (MRD) negative rate at the end of treatment (ITT population: bone marrow 57% vs 23%, P-value 0.0001).

Safety Results: The VEN+G and GClb arms had similar incidences of treatment emergent fatal toxicities (2% per arm) as well as similar incidences of serious adverse events and grade 3 or 4 adverse events. No new safety signals were identified.

Benefit Risk: The VEN+G arm exhibited significant improvement and superiority to the comparator arm (GClb) without an increase in toxicity. Of special interest was an MRD negativity rate among CRs of 69% vs 45% in the bone marrow (P-value <0.0001).

Regulatory recommendation: Approval.

X

Albert Deisseroth, MD, PhD

15. Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

16. Appendices

16.1 References

The Applicant's References:

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List of Referenced Studies

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BO25323 (CLL14), GP28331 - Population PK Analysis for Venetoclax in Combination with Obinutuzumab in Previously Untreated and Relapsed or Refractory Patients with Chronic Lymphocytic Leukemia. Report no. 1092220. Feburary 06 2019.

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Study GO28667/MURANO: A Multicenter, Phase III, Open-Label, Randomized Study in Relapsed/Refractory Patients with Chronic Lymphocytic Leukemia to Evaluate The Benefit of GDC-0199 (ABT-199) Plus Rituximab Compared with Bendamustine plus Rituximab.

Study GP28331: A Phase Ib Multicenter Dose-Finding and Safety Study of Venetoclax and Obinutuzumab in Patients with Relapsed or Refractory or Previously Untreated Chronic Lymphocytic Leukemia.

Study M12-175: A Phase I Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma.

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

Study M13-982: A Phase 2 Open-Label Study of the Efficacy of ABT-199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia Harboring the 17p Deletion.

Study M14-032: A Phase 2 Open-Label Study of the Efficacy and Safety of Venetoclax (ABT-199/GDC-0199) in Chronic Lymphocytic Leukemia Subjects with Relapse or Refractory to B-Cell Receptor Signaling Pathway Inhibitor Therapy

The FDA's References:
The FDA agrees with the Applicant.

16.2 Financial Disclosure

The Applicant's Position:
See Section 7.1.2 for Financial Disclosure Information from the Applicant.

The FDA's Assessment:
The FDA agrees with the Applicant's position and has completed the table below based on the provided data.

Covered Clinical Study (Name and/or Number): BO25323/CLL14 and GP28331

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1,406		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 11		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 11 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 24		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3 FDA Grouped Preferred Terms

Grouped PT	Included
Abdominal pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort
Anemia	Anemia, Hemoglobin decreased
Arrhythmia	Arrhythmia, Atrial fibrillation, Bradycardia, Sinus bradycardia, Tachycardia, Ventricular arrhythmia, Ventricular tachycardia, Atrial flutter, Cardiac flutter, Heart rate irregular, Sinus arrhythmia, Sinus tachycardia, Supraventricular tachycardia
Candidiasis	Candida infection, Oral candidiasis, Esophageal candidiasis
Chest pain	Chest discomfort, Chest pain, Noncardiac chest pain
Cough	Cough, Productive cough, Upper airway cough syndrome

Grouped PT	Included
Dizziness	Dizziness, Dizziness exertional, Vertigo
Dyspnea	Dyspnea, Dyspnea exertional, Dyspnea at rest
Edema	Face edema, Fluid overload, Edema Peripheral, Peripheral swelling, Generalized edema
Fatigue	Asthenia, Fatigue, Lethargy
Gastritis	Gastritis, Gastritis viral, Helicobacter gastritis
Gastroenteritis	Gastroenteritis, Gastroenteritis norovirus, Gastroenteritis rotavirus, Gastroenteritis viral, Gastrointestinal infection, Gastroenteritis salmonella
Gastrointestinal hemorrhage	Gastrointestinal hemorrhage, Hematemesis, Hematochezia, Melena, Rectal hemorrhage
Headache	Headache, Head discomfort
Hepatitis	Hepatitis, Hepatocellular injury
Herpes virus infection	Herpes pharyngitis, Herpes simplex, Herpes simplex otitis externa, Herpes virus infection, Herpes zoster, Nasal herpes, Ophthalmic herpes zoster, Oral herpes, Varicella zoster virus infection, Herpes zoster cutaneous disseminated
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia
Hyperglycemia	Hyperglycemia, Blood glucose increased
Hyperkalemia	Blood potassium increased, Hyperkalemia
Hypersensitivity	Drug hypersensitivity, Urticaria, Urticaria papular
Hypertension	Hypertension, Blood pressure increased
Hyperuricemia	Blood uric acid increase, Hyperuricemia
Hypogammaglobulinemia	Blood immunoglobin G decreased, Hypogammaglobulinemia, Immunoglobins decreased
Hypokalemia [a]	Hypokalemia, Blood potassium decreased
Hypotension	Hypotension, Orthostatic hypotension, Blood pressure decreased
Hypoxia	Hypoxia, Oxygen saturation decreased
Live function analysis	Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Transaminases increased
Lower respiratory tract infection	Bronchitis, Bronchitis chronic, Lower respiratory tract infection, Lung infection
Lymphopenia	Lymphopenia, lymphocyte count decreased
Mucositis	Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, Stomatitis

Grouped PT	Included
Musculoskeletal pain	Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity
Myocardial ischemia or infarction	Acute myocardial infarction, Angina pectoris, Myocardial infarction, Acute coronary syndrome
Neuropathy peripheral	Neuralgia, Neuropathy peripheral, Peripheral sensory neuropathy, Peripheral motor neuropathy
Neutropenia	Neutropenia, Neutrophil count decreased
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease
Pneumonia	Atypical pneumonia, Lung consolidation, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia influenza, Pneumonia legionella, Pneumonia streptococcal, Pneumonia fungal, Pneumonia respiratory syncytial viral, Pneumonia viral
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease, lung infiltration
Pruritus	Pruritus, Pruritus generalized
Psychiatric disorder	Affective disorder, Anger, Anxiety, Delirium, Depressed mood, Depression, Emotional distress, Amnesia
Rash	Dermatitis, Dermatitis allergic, Dermatitis contact, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash vesicular, Transient acantholytic dermatosis, Dermatitis acneiform Rash pruritic
Renal insufficiency	Acute kidney injury, Renal failure, Renal impairment
Respiratory tract infection	Respiratory tract infection + specific types (e.g., respiratory tract infection viral, respiratory syncytial virus infection)
Sepsis	Sepsis, Septic shock, specific types of sepsis or bacteremia (e.g. Staphylococcal), Neutropenic sepsis, Pulmonary sepsis, Urosepsis
Skin infection	Cellulitis, Erysipelas, Skin infection, Impetigo
Thrombocytopenia	Thrombocytopenia, Platelet count decreased
Thrombosis or thromboembolism	Deep vein thrombosis, Portal vein thrombosis, Pulmonary embolism, Intracardiac thrombus, Thrombosis
Upper respiratory tract infection	Laryngitis, Nasopharyngitis, Pharyngitis, Pharyngotonsillitis, Rhinitis, Upper respiratory tract infection, Viral upper respiratory tract infection
Urinary tract infection	Cystitis, Urinary tract infection + specific types (e.g. Escherichia UTI)
Visual impairment	Diplopia, Vision blurred, Visual acuity reduced, Visual impairment
Xerosis	Dry skin, Dry eye, Dry mouth, Xerosis

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/s/

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