CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S) / STATISTICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	208573
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Division/Office	Division of Hematology Products Office of Hematology and Oncology Products
Reviewer Names	Lori A. Ehrlich (Clinical) Qing Xu (Statistics)
Review Completion Date	March 14, 2016
Established Name	Venetoclax
(Proposed) Trade Name	Venclexta®
Applicant	AbbVie, Inc.
Formulations	Tablets: 10 mg, 50 mg, 100 mg
Dosing Regimen	20 mg daily for 7 days, 50 mg daily for 7 days, 100 mg daily for 7 days, 200 mg daily for 7 days, then 400 mg daily
Applicant Proposed Indication/Populations	Patients with relapsed or refractory chronic lymphocytic leukemia who have received at least one prior therapy, including those with 17p deletion
Recommendation on Regulatory Action	Accelerated Approval for revised indication
Recommended Indication/Population	For the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA-approved test, who have received at least one prior therapy

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Glossary

AE	adverse event
ALC	absolute lymphocyte count
BCL-2	B-cell lymphoma 2
BCRi	B-cell receptor inhibitor
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
CMC	chemistry, manufacturing, and controls
CR	complete remission
CRF	case report form
CRi	complete remission with inadequate marrow recovery
CSR	clinical study report
DCD	designated cohort dose
DLT	dose limiting toxicity
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EFS	event-free survival
FCR	fludarabine, cyclophosphamide, rituximab
FISH	fluorescent in situ hybridization
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug
IRB	institutional review board
IRC	independent review committee
IRT	Interdisciplinary Review Team
ITT	intent to treat
IW-CLL	International Workshop - CLL
LN	lymph nodes
MAED	MedDRA-Based Adverse Event Diagnostics
MedDRA	Medical Dictionary for Regulatory Activities

MRD	minimal residual disease
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCI-CWG	National Cancer Institute-CLL Working Group
NDA	new drug application
NHL	non-Hodgkin lymphoma
NME	new molecular entity
nPR	nodular partial remission
NR	no response, not reached
OCP	Office of Clinical Pharmacology
ORR	overall response rate
OS	overall survival
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PMA	pre-marketing application
PMC	post-marketing commitment
PMR	post-marketing requirement
PR	partial remission
PREA	Pediatric Research Equity Act
QSG	Quick Start Guide
REMS	risk evaluation and mitigation strategy
RPTD	recommended phase two dose
SAE	serious adverse event
SD	stable disease
SMQ	standardized MedDRA queries
SOC	system organ class
TEAE	treatment emergent adverse event
TLS	tumor lysis syndrome
TTNT	time to next treatment
TTP	time to progression
ULN	upper limit of normal
17p del	17p deletion

1 Executive Summary

1.1. Product Introduction

Venetoclax (also known as ABT-199 or GDC-0199) is a new molecular entity (NME), first-in-class BCL-2 protein inhibitor. The proposed proprietary name is Venclexta, and review by Division of Medication Error Prevention and Analysis (DMEPA) has determined the name to be conditionally acceptable. The proposed dosing schedule for patients with chronic lymphocytic leukemia (CLL) is initiation of therapy with venetoclax at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule (50 mg for 7 days, then 100 mg for 7 days, then 200 mg for 7 days), followed by the recommended daily dose of 400 mg. The dosage form is oral tablets provided at strengths of 10 mg, 50 mg, and 100 mg. Dosage for the ramp-up period is provided in a Starting Pack containing blister packs for the 20 mg, 50 mg, 100 mg, and 200 mg doses. Once the ramp-up period is completed, the 400 mg dose is achieved using 100 mg tablets supplied in bottles. Patients should continue venetoclax at 400 mg daily until disease progression or unacceptable toxicity. The Applicant's proposed indication is for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia who have received at least one prior therapy, including those with 17p deletion.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In this reviewer's assessment, the submitted evidence has provided substantial evidence for effectiveness for venetoclax for the treatment of patients with relapsed or refractory CLL with 17p deletion to support accelerated approval for this indication. The results in patients with R/R CLL with 17p deletion are from an interim analysis of a single-arm, phase 2 trial, M13-982, of venetoclax monotherapy in 107 patients (including 106 with 17p deletion). The regulatory endpoint of interest was the overall response rate in all patients enrolled in the main cohort. The ORR was 80% with a CR rate of 8%, which is an improvement over available therapy for patients with R/R CLL with 17p deletion.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Venetoclax is an oral, small molecule inhibitor of BCL-2 (B cell lymphoma protein 2) developed for the treatment of relapsed or refractory chronic lymphocytic leukemia (R/R CLL), including those with the 17p gene deletion. This reviewer recommends accelerated approval for the treatment of patients with relapsed or refractory CLL with 17p deletion based on the efficacy and safety information currently available.

Relapsed or refractory CLL is a serious and life-threatening disease with approximately 15,000 new cases per year, primarily in the elderly. The 17p gene deletion has been identified as a very poor prognostic factor with a survival duration generally less than 24 months. Several therapies are FDA-approved for the treatment of R/R CLL including combination therapy (fludarabine, cyclophosphamide, rituximab), ibrutinib, idelalisib with rituximab, and ofatumumab. However, the only FDA-approved therapy for patients with 17p deletion is ibrutinib which has an overall response rate of 48% in this disease population.

The efficacy of venetoclax for the treatment of R/R CLL with 17p deletion was evaluated in one single-arm, phase 2 trial, M13-982. The overall response rate in patients with 17p del in this trial was 80.2% with a complete response rate of 7.5%. Overall response rate is a surrogate endpoint in CLL for progression-free and overall survival. Venetoclax demonstrates an improvement over available therapies in patients with 17p deletion, and is eligible for accelerated approval. (b) (4)

The safety profile is characterized through three single-arm trials of single agent venetoclax for the treatment of patients with R/R CLL and supported by safety information from venetoclax in combination with other therapy and for the treatment of other cancers. The main safety concerns are the risk of tumor lysis syndrome and neutropenia. The risk of tumor lysis syndrome is mitigated through the use of venetoclax ramp-up dosing over 5 weeks, risk stratification based on tumor burden, and prophylaxis measures with hydration, anti-hyperuricemics, laboratory monitoring, and potential hospitalizations. The risks are communicated through the Prescribing Information including a Medication Guide, a Start Pack for dosing during the first 4 weeks of the ramp up period, and a Quick Start Guide provided with the Start Pack. Potential drug-drug interactions are identified in the prescribing information.

Venetoclax represents an additional oral therapeutic agent with a novel mechanism of action for the treatment of patients with relapsed or refractory CLL. The efficacy of venetoclax for the treatment of patients with R/R CLL with the 17p deletion is supported based on a surrogate endpoint of overall response rate. As such, it represents an improvement over available therapies. The safety in patients with R/R CLL is acceptable with rigorous management of the risk of tumor lysis syndrome which are addressed through appropriate labeling. Venetoclax is an important addition to the treatment armamentarium for patients with R/R CLL with 17p deletion.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CLL is a cancer of mature B lymphocytes, a type of white blood cell, which affects blood, bone marrow, lymph nodes, or spleen. • Approximately 15,000 new cases occur per year, predominately in older adults with about 70% occurring in patients older than 65 years. • CLL is typically a slowly progressing disease, and the percentage of patients surviving at 5 years is 81.7%. • The 17p gene deletion is an ultra-high risk poor prognostic factor that is more common in patients with relapsed or refractory disease. The median duration of survival for patients with 17p del is generally less than 24 months.	Relapsed or refractory CLL with 17p deletion is serious, life threatening, and rare in frequency. The median duration of survival for patients with 17p del is poor. Relapsed or refractory CLL generally affects the elderly.
Current Treatment Options	• For patients with relapsed or refractory CLL, treatment decisions are based on a patient's response to prior chemo- or chemoimmunotherapy, age, and presence of significant comorbidities. • FDA-approved therapies for the treatment of relapsed or refractory CLL include combination chemo-immunotherapy (fludarabine, cyclophosphamide, rituximab), ibrutinib, idelalisib with rituximab, and ofatumumab. • The response rates to standard therapies for patients with 17p del are significantly lower. • The only FDA-approved therapy for the treatment of patients with 17p deleted CLL is ibrutinib.	The standard of care for relapsed or refractory CLL is variable and can include re-treatment with a prior therapy though each successive treatment usually results in shorter response durations. Despite several new approvals for relapsed or refractory CLL, the disease remains incurable for most patients, and as such is an unmet medical need. The response rates in patients with 17p deletion are lower and the available therapies are much more limited.
Benefit	• The Phase 2, single-arm trial, M13-982, was venetoclax for the treatment of patients with relapsed or refractory CLL harboring the 17p deletion. The trial included 107 patients, and 106 patients had 17p deletion. • The primary endpoint was the overall response rate in the first 70 patients enrolled, but the response rate was evaluated for all patients enrolled. A response rate of >40% was considered clinically meaningful based on response rates to available therapies. • The overall response rate in 106 patients with 17p del was 80.2% (95% CI: 71.3, 87.3) with a complete remission rate of 7.5% (95% CI: 3.3, 14.3). • The phase 1, dose-escalation trial, M12-175, was venetoclax for the treatment of patients with relapsed or refractory CLL. This trial was designed to evaluate the safety of venetoclax	The phase 2 trial in patients with relapsed or refractory CLL with 17p deleletion met the primary endpoint of overall response rate. In this patient population, venetoclax is an improvement over available therapy with a better response rate and demonstration of complete responses which were not seen with ibrutinib. Overall response rate is considered a surrogate endpoint for progression-free or overall survival in CLL. Therefore, venetoclax is recommended for accelerated approval for patients with 17p del.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and to determine the recommended phase 2 dose. As such, the study was not powered to evaluate efficacy, and all efficacy evaluations were considered exploratory. The trial included 57 patients with relapsed or refractory CLL treated at the target dose of 400 mg daily. (b) (4)	(b) (4)
Risk	• Approximately 500 patients with cancer have been treated with venetoclax either as a single agent or in combination with other therapy. • In patients with CLL treated with single-agent venetoclax, 289 patients have been exposed with 240 patients exposed at the proposed target dose of 400 mg. • Although most patients treated with venetoclax had a treatment-emergent adverse reaction, only about 10% discontinued venetoclax due to an adverse reaction other than disease progression. Generally, the pattern of adverse reactions reflects events expected for a heavily pre-treated elderly population with R/R CLL with the exception of on-target effects of tumor lysis syndrome and neutropenia. • The risk assessment and prophylaxis for tumor lysis syndrome was modified in two major amendments to the venetoclax protocols. The dosing regimen for venetoclax was adjusted to include a ramp-up phase. The final estimated risk of tumor lysis syndrome was 6% and all events were limited to laboratory findings with limited clinical consequence. • The risk of neutropenia is significant both from underlying CLL and from treatment with venetoclax. The neutropenia is usually manageable with standard of care treatments including antibiotics and G-CSF. Importantly, no correlation was found between rates of neutropenia and infections. • Drug-drug interactions were seen with CYP3A inducers and inhibitors and P-gp inhibitors. • Venetoclax is metabolized by the liver, and a very limited number of patients with moderate hepatic impairment were treated with venetoclax. • Although venetoclax is not excreted by the kidney, and there was no difference in exposure in patients with renal impairment, there is an increased risk of tumor lysis syndrome in patients with renal impairment.	All safety information to date has been from single-arm trials, so contribution of the underlying disease is difficult to determine. However, no major safety concerns were identified except for the on-target events of tumor lysis syndrome and neutropenia. The confirmatory trial for venetoclax will be a randomized trial which will allow isolation of the contribution of venetoclax to the adverse reactions. A dedicated study of venetoclax in patients with hepatic impairment will be required to identify the specific risks in that patient population. Despite the known safety concerns, the risks are acceptable in patients with relapsed or refractory CLL who harbor the 17p deletion and require treatment for their disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The risk of tumor lysis syndrome is managed through ramp up dosing of venetoclax, risk assessment, and prophylaxis based on risk level. • Ramp up dosing for venetoclax is managed through a Start Pack which provides the first 4 weeks of dosing (20 mg, 50 mg, 100 mg, and 200 mg) in blister packs of 7 doses at each level. The final target dose of 400 mg is supplied in bottles containing 100 mg tablets. • Risk assessment is based on baseline lymph node size and absolute lymphocyte count. Prophylaxis for tumor lysis syndrome is provided through strict hydration guidelines (oral for low risk and oral with intravenous for medium- and high-risk patients), anti-hyperuricemics, close laboratory monitoring, and hospitalization if indicated. • Venetoclax is contraindicated with strong CYP3A inhibitors. Moderate CYP3A inhibitors, strong and moderate CYP3A inducers, P-gp inhibitors, and P-gp substrates with a narrow therapeutic index should be avoided or the dose of venetoclax should be adjusted appropriately. • Venetoclax should be taken with food which increases the bioavailability.	Labeling (including a Medication Guide and Quick Start Guide with the Start Pack) is adequate to address the safety issues associated with venetoclax.

2 Therapeutic Context

2.1. Analysis of Condition

Chronic lymphocytic leukemia (CLL) is a neoplasm of mature B cell lymphocytes in the peripheral blood, bone marrow, or lymphatic tissue. CLL is the most common leukemia of adults in Western countries, accounting for approximately 30% of all leukemias, but about 1% of cancers overall. Based on SEER data from 2008-2012 the age-adjusted incidence rate of CLL is approximately 4.5 per 100,000 men and women per year with the rate in men being approximately twice that of women. The incidence of CLL in white patients is about 1.5 times that of black patients and about 2 times more frequent in non-Hispanic patients than Hispanic patients in the US. From 2008-2012 the median age of diagnosis was 71 years of age with >65% of patients being diagnosed at age 65 or later[1].

The clinical course of CLL varies depending on risk stratification by the Rai staging system or Binet classification but it is typically a slowly progressing disease. The approximate 5 year survival rate for patients with CLL is 81.7%[1]. Due to infiltration of the bone marrow by CLL, the principal complication of CLL is immunodeficiency related to myelosuppression and as a result, infection is the major cause of death in patients with CLL[2]. Despite high response rates to initial treatment, relapse is common and relapsed or refractory disease is often characterized by resistance to chemotherapy, such as fludarabine or alkylating agents. The majority of CLL patients receive intermittent treatment with periods of remission or stable disease. With each successive treatment regimen, many patients become refractory to treatment with diminished response rates and shorter response durations[3]. Although advances have occurred in the treatment of CLL recently, it remains an incurable disease for most patients and as such, is still an unmet medical need.

Chromosomal abnormalities of 17p del, 11q del, and IGHV unmutated have been found to be markers of poor prognosis with a decrement in overall survival. Other markers of poor prognosis are β2-microglobulin >3.5 mg/L, lymphocyte doubling time <12 months, and age >60 years[4]. Treatment-related factors associated with poor prognosis include fludarabine refractoriness and relapse after 3 or more prior therapies[5].

The *TP53* tumor suppressor gene is located on the short arm of chromosome 17 (17p13). Deletion of 17p is a surrogate for deletion of the *TP53* gene and is a considered an ultra-high risk prognostic factor. Other *TP53* mutations have also been shown to be adverse prognostic factors independent of 17p deletion[4]. The 17p del is present in 5-7% of patients with early stage CLL[6], but increases to 20% with multiply relapsed disease and 40-50% in fludarabine-refractory disease[5]. Approximately 80% of patients with CLL with 17p deletion have a *TP53*

mutation on the other allele[5] which may be the reason for drug resistance[7].

The 17p deletion has been correlated in multiple clinical studies to have higher tumor burden, shorter progression-free survival, and shorter overall survival[5]. Higher rates of refractoriness to standard chemotherapies have been seen in this population. The median overall survival for patients with the 17p deletion mutation has been consistently observed as less than 24 months[5]. Because of the worse clinical course and refractoriness to standard therapies, patients with CLL requiring treatment who harbor the 17p deletion require consideration of alternative therapies for CLL including B cell receptor pathway inhibitors (BCRi), ibrutinib and idelalisib[4].

2.2. Analysis of Current Treatment Options

For patients with relapsed or refractory CLL, treatment decisions are based on a patient's response to prior chemo- or chemoimmunotherapy, age, and presence of significant comorbidities. NCCN Guidelines[8] suggest that patients with relapsed/refractory CLL could receive a variety of regimens including ibrutinib, idelalisib/rituximab, fludarabine/cyclophosphamide/rituximab, ofatumumab, obinutuzumab, lenalidomide/rituximab, and others. The therapies that are FDA-approved for treatment of patients with relapsed/refractory CLL are listed in Table 1. Other therapies or combinations used in this clinical setting are also listed in Table 1. With several new approvals in the last 5 years for relapsed/refractory CLL, the choice of therapy after first relapse can be quite variable[9].

Table 1: Available therapies for relapsed or refractory CLL

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Fludarabine, cyclo-phosphamide, rituximab (FCR)	Rituxan® (rituximab) is indicated, in combination with fludarabine and cyclo-phosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.	1997	Rituximab is given at 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2-6, in combination with fludarabine (25 mg/m^2/day) and cyclophosphamide (250 mg/m^2/day) on days 1-3, administered every 28 days	Rituximab PI: n=552; randomized 1:1 *PFS* FCR: 26.7 mo FC: 21.7 mo *ORR* FCR: 54% (95% CI: 48, 60) FC: 45% (95% CI: 37, 51) *CR* FCR: 9% FC: 3%	Rituximab has boxed warnings for: Fatal infusion reactions Severe mucocutaneous reactions Hepatitis B virus reactivation Progressive multifocal leukoencephalopathy Other warnings and precautions for rituximab include: Tumor lysis syndrome Infections Cardiac arrhythmias Bowel obstruction and perforation Live virus vaccines Cytopenias	This combination therapy is included in the rituximab prescribing information for patients with previously untreated CLL and relapsed/refractory CLL. The CR rate was not reported in the prescribing information, but a literature report of the same trial[10] reported CR rates for both arms. Safety issues listed are those in the rituximab prescribing information.
Ibrutinib	IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least	2013	420 mg taken orally once daily	Ibrutinib PI: Single-arm trial: n=48 ORR: 58% (95% CI: 43, 72) Randomized: n=391, randomized 1:1	Warnings and precautions for ibrutinib include: Hemorrhage Infections Cytopenias Atrial fibrillation Second primary malignancies	Efficacy results were as reported in the ibrutinib prescribing information.

	one prior therapy			*Median PFS* Ibrutinib: NR* Ofatumumab: 8.1 mo *ORR* Ibrutinib: 43% Ofatumumab: 4% *CR* Ibrutinib: 0% Ofatumumab: 0%	Tumor lysis syndrome Embryo-fetal toxicity	
Idelalisib, rituximab	Zydelig is indicated, in combination with rituximab, for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate therapy due to other co-morbidities	2014	Idelalisib: 150 mg orally, twice daily Rituximab: 8 doses (first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 every 2 weeks for 4 infusions and every 4 weeks for an additional 4 infusions)	<u>Idelalisib PI:</u> n=220, randomized 1:1 *Median PFS* Idela/ritux: NR* Placebo/ritux: 5.5 mo *ORR* Idela/ritux: 81% (95% CI: 71, 88) Placebo/ritux: 13% (95% CI: 6, 21) *CR* Idela/ritux: 0% Placebo/ritux: 0%	Idelalisib has boxed warnings for: Fatal/serious hepatotoxicity Fatal/serious diarrhea or colitis Fatal/serious pneumonitis Fatal/serious intestinal perforation Other warnings and precautions for idelalisib include: Severe cutaneous reactions Anaphylaxis Neutropenia Embryo-fetal toxicity	The only efficacy endpoint in R/R CLL reported in the idelalisib prescribing information for the combination of idelalisib and rituximab was PFS. The trial was stopped at the first interim analysis for an improvement in efficacy of the combination. Other efficacy endpoints were reported in the literature for the same clinical trial[11].

Alemtuzumab	Campath is indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL).	2001	Escalate to recommended dose of 30 mg/day three times per week for 12 weeks	Alemtuzumab PI: Three, single-arm trials: n=149 PR: 21-31% CR: 0-2%	Alemtuzumab has boxed warnings for: Serious, including fatal, cytopenias, infusion reactions, and infections Other warnings and precautions include: Cytopenias Infections	Initial accelerated approval for alemtuzumab in CLL was for patients with R/R CLL who have been treated with alkylating agents and who have failed fludarabine therapy based on the trial performed in that population. Efficacy data provided here is reported in the prescribing information as the results from three single-arm trials. The indication was later broadened to all patients with CLL. Campath is no longer marketed as of 09/04/12, but available to cancer patients free through the US Campath Distribution Program.
Ofatumumab	ARZERRA is indicated for the treatment of patients with CLL refractory to fludarabine and alemtuzumab	2009	300 mg initial dose, followed 1 week later by 2,000 mg weekly for 7 doses, followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses.	Ofatumumab PI: n=154, single arm ORR: 42% (99% CI: 26, 60) CR: 0% Median DOR: 6.5 mo	Ofatumumab has boxed warnings for: Hepatitis B virus reactivation Progressive multifocal leukoencephalopathy	Efficacy results were as reported in the ofatumumab prescribing information

Other Treatments (published)						
Bendamustine, rituximab	n/a	n/a	Bendamustine 70mg/m^2 on days 1 and 2 of each cycle. Rituximab 375 mg/m^2 on day 0 for the first course and 500mg/m^2 on day 1 for all subsequent courses. Treatment was administered every 28 days for up to six courses.	Lit report[12]: n=78, single arm ORR: 59% CR (CR+CRi): 9% median PFS: 15.2 mo	Warnings and precautions for bendamustine include: Myelosuppression Infections Anaphylaxis and infusion reactions Tumor lysis syndrome Skin reactions Other malignancies Extravasation injury Embryo-fetal toxicity	Bendamustine in combination with rituximab is approved for first-line treatment of patients with CLL, but is also used in the relapsed/refractory setting. The literature report was a study of 78 patients who had R/R CLL after 1-3 prior treatments. Safety issues listed are those in the bendamustine prescribing information.
*NR = not reached						

Only one agent, ibrutinib, has been approved in the US specifically for the 17p del subset of patients with CLL. The overall response rate for ibrutinib in the trial that led to its approval was 47.6% (vs. 4.7% in the control arm) with all responses categorized as partial remissions with no complete remissions by IRC assessment. Other regimens recommended in the NCCN guidelines for patients with relapsed/refractory CLL harboring the 17p del mutation include idelalisib ± rituximab, high-dose methylprednisone/rituximab, lenalidomide ± rituximab, alemtuzumab ± rituximab, ofatumumab, and chemoimmunotherapy such as oxaliplatin/fludarabine/cytarabine/rituximab. Though not approved specifically for the treatment of patients with 17p del in the US, the idelalisib/rituximab regimen is recommended for these patients in the NCCN guidelines and approved in Europe for first line treatment for patients with 17p del or *TP53* mutations unsuitable for chemo-immunotherapy. Common standard therapies used in relapsed CLL like fludarabine/cyclophosphamide/rituximab or bendamustine/rituximab have historically low response rates in patients with 17p del[12, 13]. Ofatumumab has been reported in the literature as used in patients with 17p deletion, but is not effective in patients with lymph nodes >5 cm[3]. Response rates from the literature for selected therapies used for patients with relapsed/refractory CLL with 17p del are shown in Table 2.

Table 2: Available therapies for relapsed or refractory CLL with 17p deletion

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Ibrutinib	IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion	2013	420 mg taken orally once daily	Ibrutinib PI: n=127, randomized 1:1 *ORR* Ibrutinib 47.6% Ofatumumab 4.7% *Median PFS* Ibrutinib NR Ofatumumab 5.8 mo (95% CI: 5.3, 7.9) Lit report[14]: n=28, single-arm ORR: 68% CR: 3.6%	See Table 1	In the ibrutinib prescribing information, the randomized trial for ibrutinib vs. obinutuzumab (results in Table 1) included 127 patients with 17p del. In the literature report, the trial was a single arm study of treatment with ibrutinib for patients with R/R CLL. A subset analysis includes 28 patients with 17p deletion.
Other Treatments (published)						
Fludarabine, cyclo-phosphamide, rituximab (FCR)	n/a	1997	Rituximab is given at 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2-6, in combination with fludarabine (25 mg/m^2/day) and cyclophosphamide (250 mg/m^2/day) on days 1-3, administered every 28 days	Lit report[13]: n=20, single-arm ORR: 35% CR: 0% Median PFS: 5 mo Median OS: 10.5 mo	See Table 1	In the literature report cited in Table 1, the single arm study of FCR was in 284 patients with R/R CLL. A subset analysis was done on 20 patients with chromosome 17 abnormalities.

Idelalisib, rituximab	n/a	2014	Idelalisib: 150 mg orally, twice daily Rituximab: 8 doses (first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 every 2 weeks for 4 infusions and every 4 weeks for an additional 4 infusions)	<u>EU SmPC[15]:</u> n=95, randomized 1:1 *ORR* Idela/ritux: 84.8% Placebo/ritux: 12.2% *Median PFS* Idela/ritux: NR* Placebo/ritux: 4.0 mo	See Table 1	The combination of idelalisib and rituximab is approved in the EU as first-line treatment for patients with 17p del or *TP53* mutations unsuitable for chemo-immunotherapy. Results listed are from a subset analysis of 46 patients with 17p del or *TP53* mutations (95 patients randomized 1:1) in a study of 220 patients with R/R CLL. Results were IRC-assessed.
Ofatumumab	n/a	2009	300 mg initial dose, followed 1 week later by 2,000 mg weekly for 7 doses, followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses.	<u>Lit report[3]:</u> n=17 in FA-ref arm ORR: 41% n=14 in BF-ref arm ORR: 14%	See Table 1	The literature report was a study of patients with CLL who were refractory to fludarabine and alemtuzumab (FA-ref, n=59) or refractory to fludarabine and not a good candidate for alemtuzumab due to bulky disease (LN >5 cm, BF-ref, n=79). A subset of patients had 17p deletion, 17 in the FA-ref arm and 14 in the BF-ref arm. Ofatumumab was not effective in patients with LN >5cm.

Alemtuzumab ± methyl-prednisolone	n/a	2001	Escalate to recommended dose of 30 mg/day three times per week for 12 weeks, given IV for 4 weeks, then SQ. Methylprednisolone: 1 gm/m^2/day for 5 days every 28 days for 4 cycles.	Lit report[16]: n=31, single-arm ORR: 39% Median PFS: 5.8 mo Median OS: 18.3 mo Lit report[17]: n=22 ORR: 77% CR+CRi rate: 14% Median PFS: 6.5 mo Median OS: 19.5 mo	See Table 1	The first report was for single agent alemtuzumab in patients refractory to fludarabine (n=103) with a subset analysis of 31 patients with 17p deletion. The second report was a study of 39 patients with 17p deletion in at least 20% cells. 17 patients were previously untreated, and 22 were previously treated.
Bendamustine, rituximab	n/a	2008	Bendamustine 70mg/m^2 on days 1 and 2 of each cycle. Rituximab 375 mg/m^2 on day 0 for the first course and 500 mg/m^2 for all subsequent courses. Treatment was administered every 28 days for up to six courses.	Lit report[12]: n=14, single-arm ORR: 7% CR rate: 7% Median PFS: 6.8 mo Median OS: 16.3 mo	See Table 1	In the literature report cited in Table 1, the single arm study of BR was in 78 patients with R/R CLL. A subset analysis was done on 14 patients with chromosome 17 abnormalities.
Lenalidomide, rituximab	n/a	2005	Rituximab: 375mg/m^2 on days 1, 8, 15, and 22 during cycle one then every 4 weeks. Lenalidomide: Started on day 9 of cycle one at	Lit report[18]: n=15, single-arm ORR: 53%	Lenalidomide has a boxed warning for embryo-fetal toxicity (with REMS), hematologic toxicity, and venous and arterial thromboembolism.	The literature report was a single-arm study of 59 patients with R/R CLL treated with lenalidomide and rituximab. A subset analysis was done on 15

			10 mg per day and administered continuously. Each cycle was 28 days for up to 12 cycles. Lenalidomide treatment could continue beyond cycle 12.		Lenalidomide has the following warnings and precautions: serious and fatal cardiac ARs, hepatotoxicity, allergic reactions, TLS, tumor flare reaction	patients with 17p deletion.
Oxaliplatin, fludarabine, cytarabine, rituximab	n/a	n/a	Oxaliplatin: IV 30 mg/m^2 daily on days 1 through 4 Rituximab: 375 mg/m^2 IV on day 3 of the first cycle and day 1 of subsequent cycles. Fludarabine: IV 30 mg/m^2 on days 2-5 Cytarabine: IV 0.5 gm/m^2 days 2-5 Cycles were every 4 weeks for maximum of 6 cycles	Lit report[19]: n=24, single-arm ORR: 8% Median survival: 12.6 mo	The most common AEs in the combination trial were cytopenias and infections.	In the literature report was a single arm study for the treatment of patients with Richter's syndrome or aggressive R/R CLL. Of those with aggressive R/R CLL, a subset analysis was done on 24 patients with 17p deletion.
* NR = not reached						

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Venetoclax is a new molecular entity (NME) and is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The trials for the treatment of patients with relapsed/refractory CLL were conducted under IND 110159, which was opened in the US on November 28, 2010. Due to tumor lysis syndrome resulting in deaths and renal failure requiring dialysis, the IND was placed on partial clinical hold on enrollment for studies in CLL on December 17, 2012. The hold was removed on May 3, 2013 after implementation of risk stratification and prophylaxis for TLS.

FDA granted Orphan Drug Designation (Designation #12-3756) to AbbVie on September 20, 2012 for venetoclax for the treatment of chronic lymphocytic leukemia.

At the End of Phase 2 meeting on July 2, 2014, FDA and AbbVie discussed and agreed up on the appropriate sample size for an initial registrational trial under accelerated approval for the treatment of patients with R/R CLL with 17p del. The primary efficacy endpoint of the phase 2 trial (M13-982) to be used for registration was after the first 70 patients, but FDA recommended at least 100 patients for a single arm trial for efficacy evaluation. At the EOP2 meeting, FDA also agreed that the Phase 3 study GO28667 (MURANO) could be used to confirm the clinical benefit of venetoclax assuming it first receives accelerated approval.

FDA granted Breakthrough Therapy designation on April 27, 2015 to venetoclax for the treatment of patients with relapsed/refractory CLL who harbor the 17p deletion cytogenetic abnormality.

This NDA was submitted under a rolling submission. The application qualified for this due to receiving Breakthrough Therapy designation. The initial part was submitted on September 15, 2015 and consisted of Quality and Nonclinical modules. The second part was submitted on October 29, 2015 and consisted of Clinical and the final Nonclinical modules. The Applicant requested Priority Review with the submission of the final portion of the NDA. FDA granted priority review December 23, 2015.

3.3. Foreign Regulatory Actions and Marketing History

Venetoclax is not currently available in any foreign markets.

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

4.1. Office of Scientific Investigations (OSI)

Clinical inspections were requested for Matthew Davids (Dana Farber Cancer Institute, Boston, MA), William Wierda (MD Anderson Cancer Center, Houston, TX), and Steven Coutre (Stanford Cancer Center, Palo Alto, CA). The sites for Matthew Davids and William Wierda were the highest enrolling US sites for study M12-175 (Phase 1), and both sites also included patients from study M13-982 (Phase 2). The site for Steven Coutre was the highest enrolling US site for study M13-982, which was the pivotal phase 2 trial included in this NDA. This site also had an overall response rate that was higher than expected (though difficult to determine with accuracy due to the small number of patients enrolled at any one site) and a protocol violation rate that was higher than expected for only six patients enrolled.

OSI inspections are still ongoing at the time of this review. The inspections of the Applicant (AbbVie) and Dr. Davids' sites were unremarkable. Dr. Wierda's site had minor regulatory deficiencies as preliminary information. The inspection of Dr. Coutre's site is pending.

4.2. Product Quality

The to-be-marketed venetoclax drug product will be provided as film-coated tablets containing 10, 50, or 100 mg of venetoclax per tablet with the following excipients: copovidone, polysorbate 80, colloidal silicon dioxide, anhydrous dibasic calcium phosphate, and sodium stearyl fumarate. The excipients used for the tablet core are commonly used pharmaceutical excipients that meet United States Pharmacopeia and The National Formulary (USP-NF) and European Pharmacopeia (Ph. Eur.) requirements.

Per the Applicant, primary stability lots and clinical lots for Phase I and Phase II studies were manufactured at the AbbVie, North Chicago site, using a process representative of the proposed commercial process. Three lots of each strength of venetoclax tablets were manufactured at the proposed AbbVie commercial site in Sligo, Ireland for use as commercial-site-specific stability lots. The composition of the tablets was unchanged throughout clinical development except for uncoated tablets used in early clinical studies changed to film-coated tablets used for the remainder of the development and to-be-marketed.

CMC is not planning inspections for this review because FDA has recently inspected the current manufacturing sites and found them to be adequate.

4.3. Clinical Microbiology

Clinical microbiology assessment is not applicable for this application.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical studies submitted in this NDA surpassed the requirements of the ICH S9 guideline for development in advanced cancers (b) (4) (D) (4). The pharmacokinetics of venetoclax was evaluated in mice, rats, New Zealand white rabbits, beagle dogs, cynomolgus monkeys and humans. An inactive, major human metabolite (M27) was identified in all species. Key findings in animal studies were decreased lymphocytes in peripheral blood and lymphoid tissues and decreased red blood cell mass in mice and dogs, testicular germ cell loss in dogs, and embryo-fetal toxicity in mice with no evidence of teratogenicity. A dedicated nonclinical carcinogenicity study was not completed.

In the repeat toxicology study in dogs, all doses caused microscopic findings in the testes and severe decreases in the number of germ cells in the testes. Mice did not have testicular changes. Embryo-fetal toxicology study in mice showed deleterious effects at the highest dose of 150 mg/kg/day with increased post-implantation loss and decreased fetal body weight. No embryo-fetal toxicity was seen in rabbits, but the plasma exposures are less by about 10-fold in rabbits even at higher doses.

Genetic toxicology studies (Ames and chromosomal aberration) for venetoclax and M27 were negative indicating a low genotoxic potential for venetoclax.

4.5. Clinical Pharmacology

A listing of clinical pharmacology studies is included in Table 4. These studies were reviewed in detail by the Office of Clinical Pharmacology (OCP). The findings described here are this reviewer's summary of the review by OCP.

4.5.1. Mechanism of Action

Resistance to apoptosis is a major mechanism of the development of cancer. One of the major regulators of apoptosis are Bcl-2 family proteins which include both anti-apoptotic proteins (Bcl-2, Bcl-X_L, and Mcl-1) and pro-apoptotic proteins (Bim, Bad, Bid, Noxa, Bak, and Bax). The anti-apoptotic proteins bind to and sequester the pro-apoptotic proteins to inhibit programmed cell death[20]. BCL-2 is overexpressed in some lymphoid malignancies and is associated with

increased resistance to chemotherapy. CLL cells are almost universally dependent on BCL-2; therefore, inhibition of BCL-2 can restore apoptosis in CLL cells[21]. Because BCL-2 is downstream of other survival signals such as p53, cells with p53 dysfunction or those resistant to other therapies could remain responsive to venetoclax.

Per the Applicant, *in vitro* studies showed that venetoclax binds with high affinity to Bcl-2 but >4,800-fold lower affinity to Bcl-X_L and >20,000-fold lower affinity to Bcl-w and Mcl-1. The M27 metabolite binds with a >220-fold lower affinity to Bcl-2 compared to venetoclax. Venetoclax did not cause inhibition of cell lines that were not dependent on Bcl-2 family members, but in a Bcl-2 dependent cell line, venetoclax rapidly induced apoptosis. In cell lines with 17p deletion, venetoclax was equally as potent.

4.5.2. Pharmacodynamics

There is no known pharmacodynamics endpoint. On-target effects of cytopenias are discussed in the review of safety in Section 8.

4.5.3. Pharmacokinetics

Study M13-363 was the mass balance/ADME study.

- Absorption: Exposure was increased 3- to 4-fold after a low- or high-fat meal, and venetoclax has been administered with food in all clinical studies. T_{max} occurs at a median of 5-8 hours, and PK is dose-proportional from 150 to 800 mg.
- Distribution: Venetoclax has high plasma protein binding and a large volume of distribution
- Metabolism: M27 is a major human metabolite that is inactive and inhibits BCL-2 at a 58-fold lower affinity. Venetoclax and M27 are predominantly metabolized by CYP3A4/5 with drug-drug interactions as noted below. Both venetoclax and M27 are substrates of efflux transporters P-gp and BCRP, but not substrates of uptake transporter OATP1B3 and OCT1.
- Excretion: Terminal elimination half-life was approximately 17 to 41 hours. >99.9% of the dose was recovered in feces and <0.1% in urine. The unchanged venetoclax was the main component in the plasma (72.6%), and the unchanged venetoclax accounted for 20.8% in the feces.

Venetoclax has strong potential for drug-drug interactions (DDI). As a substrate, venetoclax is predominantly metabolized by CYP3A4/5, and is a substrate of P-gp and BCRP. It is not a substrate of uptake transporter OATP1B1/3 and OCT1. As a perpetrator, venetoclax is not an inhibitor or inducer of major CYP enzymes at therapeutic concentrations. It is a weak inhibitor

of CYP2C8 and CYP2C9. Venetoclax is an inhibitor of P-gp and BCRP. Three dedicated DDI studies were completed and summarized here. A summary of recommended dose adjustments for DDI is shown in Table 3.

- M13-364: Interaction with ketoconazole, a strong CYP3A inhibitor. Coadministration resulted in a 2.3-fold increase in C_{max} and 6.4-fold increase in AUC. The use of strong CYP3A inhibitors is contraindicated during initiation of venetoclax and during the ramp up phase. If the use of moderate CYP3A inhibitors is required during the initiation or ramp up phase, then venetoclax dose should be reduced. During the steady daily dose of venetoclax, strong and moderate CYP3A inhibitors can be used with dose reductions of venetoclax.
- M14-497: Interaction with rifampin, a strong CYP3A inducer and P-gp inducer. Coadministration resulted in a 2.1-fold increase in C_{max} and 1.8-fold increase in AUC. Concomitant use of venetoclax with strong or moderate CYP3A inducers should be avoided. A PMR will be issued for a DDI study with a P-gp substrate.
- M15-065: Coadministration with warfarin. Warfarin levels increased by 18-28% with co-administration with venetoclax. INR should be monitored in patients requiring both warfarin and venetoclax.

Table 3: Clinical pharmacology summary of recommendations for dose adjustments for DDI

	Ramp up period	Stable dose period
CYP3A Inhibitor		
Weak	No dose adjustment	No dose adjustment
Moderate	Avoid or reduce venetoclax dose by 2-fold	Avoid or reduce venetoclax dose by 2-fold
Strong	Contraindicated	Avoid or reduce venetoclax dose by 4-fold
CYP3A Inducer		
Weak	No dose adjustment	No dose adjustment
Moderate	Avoid	Avoid
Strong	Avoid	Avoid
P-gp Inhibitors	Avoid	Avoid or reduce venetoclax dose by 2-fold
P-gp Substrates with narrow therapeutic index	Avoid	Avoid

Population pharmacokinetic (PopPK) analyses were completed across five studies in patients with cancer and three studies in healthy volunteers, which included doses from 10 mg to 1200 mg in 505 subjects. No effect was seen from age, race, sex, or body weight. No differences in

drug clearance were seen in patients with mild or moderate renal impairment, and no dose adjustments are suggested for mild or moderate renal impairment. No apparent differences in drug clearance were seen in patients with mild or moderate hepatic impairment, though the number of patients enrolled with hepatic impairment was very small (69 with mild impairment and 5 with moderate impairment). No dose adjustments are suggested for mild to moderate hepatic impairment, but a PMR will be issued for a dedicated hepatic impairment study.

4.6. Devices and Companion Diagnostic Issues

The initial development plan for venetoclax was for the study of patients with R/R CLL who had a deletion in the 17p which includes the *TP53* gene. Abbott Molecular developed a Vysis CLL FISH probe kit to detect the 17p deletion. This companion diagnostic provides information that is essential for the safe and effective use of venetoclax to identify patients who are most likely to benefit. A companion diagnostic will be required if venetoclax is approved only for patients with 17p deletion (b) (4) Abbott submitted a Pre-Marketing Application (PMA) (b) (4) for review by CDRH. CDER and CDRH reviews are being coordinated to take action on both applications concurrently.

4.7. Consumer Study Reviews

Venetoclax is administered orally and is dosed with a ramp-up period starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg, and 400 mg. To reduce medication errors, the first four dose levels will be provided in a Start Pack that will contain four 7-day blister packs corresponding to each week. The Start Pack comes with a Quick Start Guide (QSG), which is a reminder calendar for tablets and hydration. The Applicant conducted a Human Factors study to evaluate potential failures from the use of the Start Pack using a "worst case scenario" where patients were given no instructions on how to use the Start Pack and QSG. This reviewer's summary of the findings presented by the Applicant follows here. Participants were categorized as low risk where they received the Start Pack from the pharmacy and were asked to administer the drug at home or high risk where they imagined they returned home after a short hospitalization where they started their medication. In the final test group using the to-be-marketed materials, 30 participants were enrolled in the study, and 26 patients (87%) completed all critical and essential tasks of taking the correct dose, completed comprehension of hydration, contacting their healthcare provider, and what to do if they missed a dose. The most common error was only taking one of two tablets at the 20 mg dose in three patients, two of whom took the correct dose at the second dose without correction. Overall, this HF study validated the safe and effective use of the 4-week Start Pack.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 4 lists all clinical studies reviewed by the clinical and statistics reviewers. The Applicant also submitted interim analyses from studies of venetoclax in combination with other agents for supportive information. A listing of these additional studies can be found in Appendix 3 (Section 13.3).

Table 4: Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety							
M13-982	Phase 2, efficacy, safety. Open-label, single arm, monotherapy. To evaluate the efficacy and safety in patients with R/R CLL with 17p del.	Venetoclax tablet, daily, oral, lead-in period followed by 400 mg daily	Primary: ORR by IRC assessment in the first 70 patients Secondary: CR rate (CR + CRi), PR rate (nPR or PR), DOR, PFS, EFS, TTP, TTR, time to 50% reduction in ALC, OS, percent to HSCT Exploratory: TTNT, MRD, PRO, INV assessments of efficacy endpoints	Up to 2 years following last subject enrollment	145 (107 Main Cohort; 38 Safety Expansion Cohort)	Subjects with R/R or previously untreated CLL with 17p del ≥ 18 years of age	38 sites in 7 countries
M12-175	Phase 1, PK, safety, tolerability. Open-label, non-randomized, dose-finding. To assess the safety, PK, MTD, RPTD, and the lead-in period regimen for patients with R/R CLL and R/R NHL. Food effect in Cohorts 1-6 of Arm B.	Venetoclax tablet, daily, oral, lead-in period, followed by daily dose escalation cohorts to determine MTD (150 mg up to 1200 mg QD). Lead-in period followed by RPTD in the expanded safety portion of the study	Primary: safety , PK, MTD, RPTD, determine the lead-in period Exploratory: PFS, ORR (CR, CRi, nPR, PR), TTP, OS, DOR, and MRD.	Up to 2 years following last subject enrollment	222 (116 in Arm A; 106 in Arm B)	Arm A: Subjects with R/R CLL/SLL Arm B: Subjects with R/R NHL ≥ 18 years old	10 sites in 2 countries

Studies to Support Safety							
M14-032	Phase 2, efficacy, safety. Open-label, non-randomized. To evaluate the efficacy and safety of venetoclax in patients with CLL relapsed after or refractory to BCRi.	Venetoclax tablet, daily, oral lead-in period followed by venetoclax 400 mg daily	ORR by investigator assessment, safety, PK	Up to 2 years following last subject enrollment	28 (22 in Arm A; 6 in Arm B)	Subjects with R/R CLL Arm A: R/R to ibrutinib Arm B: R/R to idelalisib ≥ 18 years old	8 sites in 1 country
Other studies pertinent to the review of efficacy or safety (clinical pharmacological studies)							
M14-253	Phase 1, bioavailability. To compare the film-coated tablets with the uncoated tablets.	Tablet; 50 mg coated; 50 mg uncoated; single dose; oral	Oral bioavailability, safety in healthy subjects	Two single doses of ABT-199 with a washout interval of 7 days.	15	Healthy female subjects of non-childbearing potential, 18-60 years old	AbbVie Clinical Pharma-cology Research Unit (ACPRU)
M15-101	Phase 1, bioavailability. To compare the clinical trial formulation with the to-be-marketed formulation and to assess the effect of food (non-fasting vs. fasting conditions) on the PK	100 mg tablet, oral, single dose	Relative bioavailability, food effect on PK; safety and tolerability in healthy subjects	Four single doses of venetoclax with a washout interval of at least 7 days.	24	Healthy female subjects of non-childbearing potential, 18-60 years old	AbbVie Clinical Pharma-cology Research Unit (ACPRU)
M13-363	Phase 1, PK/mass balance. To investigate the disposition of [^{14}C]-venetoclax; safety and tolerability	200 mg solution, oral, single dose	Disposition of [^{14}C]-venetoclax	Single dose	4	Healthy female subjects of non-childbearing potential, 18- 60 years old	(b) (4)

M13-364	Phase 1, PK/DDI. To assess effect of ketoconazole on PK, evaluate safety	Venetoclax: 50 mg tablet, oral, single dose on days 1 and 8 Ketoconazole: 400 mg tablet, oral, daily on days 5-11	Effect of ketoconazole, a potent CYP3A inhibitor, on PK of venetoclax; safety	Per treatment regimen	12	R/R NHL, ≥ 18 years of age	3 sites in 1 country
M14-497	Phase 1, PK/DDI. To assess effect of rifampin on PK, evaluate safety	Venetoclax: 100 mg tablet, oral, single dose on Period 1 Day 1, Period 2 Day 1 and Period 2 Day 14 Rifampin: 600 mg capsule, oral, daily on Period 2 Day 1 and Period 2 Day 17	Effect of rifampin, a potent CYP3A inducer and OATP1B1 inhibitor, on PK of venetoclax; safety	Per treatment regimen	12	Healthy female subjects of non-childbearing potential, 18-60 years old	1 site
M15-065	Phase 1, PK/DDI. To assess effect of venetoclax on the PK of warfarin	Venetoclax:; 400 mg, oral, single dose on Period 2 Day 1 Warfarin: 5 mg tablet, oral, single dose of warfarin and vitamin K on Period 1 Day 1 and Period 2 Day 1	Effect of venetoclax on the PK of warfarin	Single dose of warfarin with vitamin K1 with a minimal washout of 14 days. One single dose of venetoclax.	8 (3 subjects took venetoclax and warfarin; 5 subjects took warfarin only)	Healthy female subjects of non-childbearing potential, 18-60 years old	AbbVie Clinical Pharma-cology Research Unit (ACPRU)

5.2. Review Strategy

The pivotal phase 2 study, M13-982, was submitted to support an indication for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy. (b) (4) (b) (4) (b) (4). One additional supportive study, M14-032, provides additional safety information for the treatment of patient with single-agent venetoclax at the proposed dose. A summary of the clinical studies used to support this submission is provided in Table 4.

Pertinent findings from the clinical pharmacology studies are summarized in this review, but are reviewed in detail by the Office of Clinical Pharmacology.

Section 6 contains a review of efficacy from (b) (4) M13-982 (b) (4). The statistical reviewer conducted the analyses independent of the Applicant's results except where indicated. Both the statistical and clinical reviewers provide commentary on the results. Exploratory analyses of pooled efficacy populations and pooled subset analyses were conducted by the clinical reviewer using JMP in Section 7. The clinical reviewer completed the safety review in Section 8. The analyses presented in Section 8 are those of the clinical reviewer using MAED and JMP except for a few areas where the Applicant's results were not independently verified where indicated.

In Section 6 of this review, the statistical reviewer focused on the efficacy results obtained from pivotal study M13-982. The primary source for this review will be based on the Clinical Study Report (CSR) shown in the following link:

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The supporting source of data for this review (e.g., datasets, define files and SAS program files) for study M13-982 can be found at:

\\CDSESUB1\evsprod\NDA208573\0000\m5

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. M13-982: Phase 2, Treatment of Subjects with Relapsed or Refractory CLL with 17p Deletion

6.1.1. Study Design

Overview and Objective

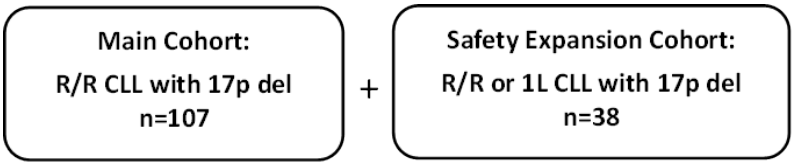
Study M13-982 is titled "A Phase 2 Open-Label Study of the Efficacy of ABT-199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia Harboring the 17p Deletion." The primary objective is to evaluate the efficacy of single-agent venetoclax in patients with R/R CLL with the 17p deletion. The primary efficacy outcome is overall response rate.

The secondary objectives were to evaluate the complete remission (CR) rate, partial remission (PR) rate, duration of response (DOR), progression-free survival (PFS), event-free survival (EFS), time to progression (TTP), time to first response, time to 50% reduction in ALC, overall survival (OS), and percent of subjects who moved on stem cell transplant.

Trial Design

M13-982 is a phase 2, single arm, multicenter study in relapsed/refractory or previously untreated CLL with the 17p deletion. A schematic of the trial is shown in Figure 1. This trial is ongoing, and the interim analysis is presented here with a data cutoff of April 20, 2015. The main cohort is provided for efficacy and safety and includes patients who have completed the scheduled 36-week disease assessment, have progressed prior to the 36-week disease assessment, or discontinued study drug for any reason. The safety expansion cohort is provided for safety data only. Patients who were previously untreated were allowed only in the safety expansion cohort. Patients remained on study until disease progression or unacceptable toxicity, and patients could continue the study drug if they are receiving benefit for up to two years. The duration of the study will be until up to two years after the final subject has enrolled on study. The study was designed to enroll approximately 100 patients in the main cohort and 50 patients in the safety expansion cohort. The numbers provided in the study design schema are the actual enrollment numbers at the data cutoff date.

Figure 1: Study design schema for M13-982



R/R=relapsed/refractory, 1L=first line. Modified from figure provided by Applicant.

Control group: There are no control groups in this study. Historical response rates were provided for common treatments for patients with R/R CLL with 17p deletion, as discussed in Table 2.

Diagnostic criteria: Patients must have the diagnosis of CLL that meets the 2008 Modified IWCLL NCI-WG Guidelines[22]. Patients had to have an indication for treatment based on the Guidelines and have clinical measurable disease (lymphocytosis >5 $x10^9$/L and/or palpable and measurable nodes and/or organomegaly by physical exam). Detection of the 17p deletion was performed by local laboratories (bone marrow or peripheral blood), and was confirmed in a central laboratory by the Vysis CLL FISH probe kit, identified by the loss of *TP53* locus (using peripheral blood).

Key inclusion/exclusion criteria (summary):

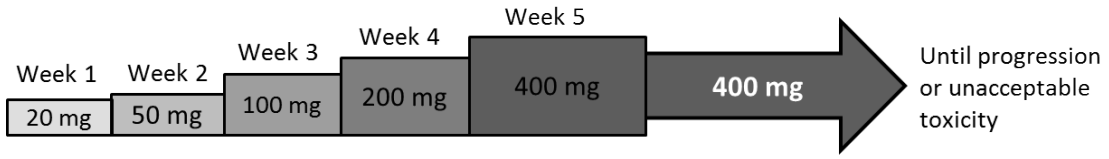
- ≥18 years of age
- R/R CLL after at least one prior line of therapy (either cohort) or previously untreated CLL (safety expansion only)
- 17p deletion assessed by local laboratory, confirmatory sample sent to the central laboratory
- ECOG performance score ≤2
- Adequate bone marrow function
    - ANC ≥1000/µL, may be with growth factor support
    - Platelets ≥40,000/mm^3, without transfusion in previous 14 days [≥30,000/mm^3 for the safety expansion cohort]
    - Hemoglobin ≥8.0 g/dL
- Adequate coagulation (aPTT and PT not to exceed 1.5x ULN)
- Creatinine clearance >50 mL/min
- AST and ALT ≤3x ULN, bilirubin ≤1.5x ULN (except for Gilbert's Syndrome)
- The following are excluded
    - Prior allogeneic stem cell transplant
    - Richter's transformation
    - Active and uncontrolled autoimmune cytopenias, including AIHA and ITP
    - Known to be positive for HIV
    - Known allergy to both xanthine oxidase inhibitors and rasburicase.

- Cardiovascular disability status of New York Heart Association Class ≥2
- Subject received any of the following within 7 days: CYP3A inhibitors, potent CYP3A inducers, or warfarin.

Dose selection: The dose of 400 mg was selected based on preliminary data in relapsed/refractory CLL/SLL subjects from the ongoing first-in-human Study M12-175. Additional information on dose selection is provided in Section 7.1.4.

Study treatments: Venetoclax is dosed with an initial 4-week ramp up schedule followed by the target dose. The dosing schedule is summarized in Figure 2. In protocol amendment 1, patients in the main cohort received the 20 mg dose as a single test dose while inpatient. If no significant electrolyte abnormalities or rapid change in lymphocyte count occurred in the first 24 hours, then the next dose was given at 50 mg. The 50 mg dose was continued for a week, and dose ramp-up continued as shown in the Figure. Any patient who had electrolyte or lymphocyte count changes after the first test dose at 20 mg, they would receive 20 mg for the first week. After protocol amendment 2, patients in the safety expansion cohort received the 20 mg initial dose for the entire first week regardless of laboratory monitoring. The second dose of venetoclax at 20 mg could be delayed for electrolyte abnormalities until resolution. Each dose is taken with approximately 240 mL of water within 30 minutes of a meal. Tumor lysis syndrome (TLS) risk stratification and prophylaxis guidelines were provided in this protocol. TLS is discussed in further detail in Section 8.5.1.

Figure 2: Dosing schedule for the safety expansion cohort in study M13-982



Modified from figure provided by Applicant.

Dose modification, dose discontinuation:
Dose reduction guidelines for neutropenia were provided. If grade 4 neutropenia occurred or grade 3 neutropenia with a declining ANC, G-CSF was recommended, and venetoclax treatment could continue. If grade 4 neutropenia persisted for more than 1 week despite optimal G-CSF, then venetoclax was interrupted until resolution to grade ≤2 or baseline. At the first occurrence, venetoclax could be re-initiated at the same dose. After the second occurrence of neutropenia within a month from the first occurrence, venetoclax was dose reduced per the Table 5. The dose could be gradually increased again to the target dose if the patient was

stable for 2 weeks at the lower dose. If the second occurrence was greater than one month after the first occurrence, then venetoclax could be restarted at the same dose.

Table 5: Dose Reduction Guidelines for Management of Neutropenia.

Venetoclax dose	Reduced Dose
400 mg	300 mg
300 mg	200 mg
200 mg	100 mg
100 mg	50 mg
50 mg	Re-challenge at 50 mg

Reproduced from table provided by the Applicant.

Dose modifications and discontinuations for TLS are discussed in Section 8.5.1.

Administrative structure: After approximately 20 subjects completed at least 12 weeks of study treatment in the main cohort, safety data was reviewed by an Independent Data Monitoring Committee (IDMC). Interim analysis results will be reviewed by the IDMC after approximately 20 subjects completed approximately 2 – 3 weeks of the lead-in period in the safety expansion cohort. Tumor response and disease progression assessments were made by individual investigators. An Independent Review Committee (IRC) reviewed the data for final determination of response or progression. The results from the IRC were not shared with the investigators.

Procedures and schedule (summary):

- Physical exams, vital signs, ECOG performance status: screening, day 1 of weeks 1-5, week 8 then every 4 weeks to week 36, and every 12 weeks thereafter; final visit, and 30-day safety follow up visit
- Laboratory tests
    - Chemistry and hematology: screening, within 72 hours prior to first dose of venetoclax, weeks 1-5 based on TLS management protocol (see Section 8.5.1 of this review), day 1 of week 8, then every 4 weeks to week 36, and every 12 weeks thereafter; final visit, 30-day safety follow-up visit, and as needed throughout study.
    - Coagulation panel: Screening, day 1 of weeks 12 and 24; final visit, 30-day safety follow-up visit.
    - Urinalysis: screening, day 1 of week 24, and final visit
    - Quantitative immunoglobulins (IgA, IgG, and IgM): Screening, day 1 of weeks 12 and 24, final visit, 30-day safety follow-up visit
    - Lymphocyte enumeration (B- and T-cell subpopulations): Screening, day 1 of weeks 4 or 5, 12, 24, and 36, and every 12 weeks thereafter; final visit

- Electrocardiogram: screening, final visit, and as clinically indicated
- Left ventricular ejection fraction (Echo or MUGA): screening and as clinically indicated
- Disease assessments (2008 modified IW-CLL NCI-WG Guidelines)
    - Clinical laboratory values (hematology) and physical exam: screening, day 1 of week 4 or 5, week 8, then every 4 weeks through Week 36, and every 12 weeks thereafter; no earlier than 8 weeks after the CR, CRi, or PR criteria were first met (if applicable), and the final visit.
    - CT (or MRI) neck, chest, abdomen, and pelvis:
        - within 35 days prior to study drug administration
        - when a response (PR or CR) was determined by clinical criteria (laboratory tests and physical exam), no earlier than 8 weeks later for confirmation of PR or CR; bone marrow biopsy also required after confirmation of CR or CRi
        - at 36 weeks for all subjects (regardless of disease status)
        - for any patient with clinical signs of possible disease progression (increased liver, spleen, or LN) without an increase in lymphocytes meeting PD criteria
    - Bone marrow aspirate and biopsy: screening, as soon as possible after confirmation of CR or CRi (2 scans separated by 8 weeks) or for patients who met criteria for CR/CRi except for node(s) that were approximately <2 cm
    - MRD assessment by flow cytometry: in peripheral blood and bone marrow at time of bone marrow aspirate after confirmation of CR/CRi/PR with nodes <2 cm, then in peripheral blood every 12 weeks after the first assessment until MRD negativity is achieved in the peripheral blood; once MRD negativity was achieved in the peripheral blood, repeat bone marrow aspirate was collected

Dietary restrictions/instructions: Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or the subject's first meal of the day. Patients should not consume grapefruit, Seville oranges, or star fruit due to possible CYP3A mediated interactions.

Concurrent medications: Subjects should receive full supportive care during study participation, including hematopoietic growth factors (G-CSF support is strongly recommended for subjects with Grade 4 neutropenia [ANC < 500/µL]), transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate. Anti-infective prophylaxis for lymphopenia is at the investigator's discretion and considering potential for drug-drug interactions. Steroid therapy for anti-neoplastic intent was not allowed. Limited corticosteroid treatment (i.e., for approximately 21 days with rapid taper) was allowed for significant active autoimmune cytopenias (AIHA or ITP).

Treatment compliance: A calendar/diary was collected from all patients, and they were asked to record the date and time each dose of the study drug was taken. Patients were also asked to record adverse events and concomitant medications. Patients were instructed to return all unused tablets and/or containers, even if empty, to the study coordinator at scheduled study visits, and the study coordinator questioned the subjects regarding adherence. Compliance was monitored and documented by the study coordinator. Compliance below 80% required counseling of the subject by study site personnel.

Rescue medications: The study drug was continued until disease progression or unacceptable side effects. No additional disease-directed therapy was allowed while on study.

Subject completion, discontinuation, or withdrawal: Subjects were allowed to withdraw at any time. The investigator could remove subjects from the trial if they believed it was in the best interest of the subject, for disease progression, or unacceptable toxicity.

Study Dates

Key study dates for this report are as follows:

- First subject first visit: 27 June 2013
- First subject first dose: 09 July 2013
- Last subject last visit: Not available; projected to be in May 2017 (2 years after last subject enrolls)
- Data cutoff date for this report: 30 April 2015

Study Endpoints

Primary endpoints: Overall response rate (ORR) defined as the proportion of subjects with an overall response (complete remission (CR), plus complete remission with incomplete bone marrow recovery (CRi), plus nodular partial remission (nPR), plus partial remission (PR)) per the NCI-CWG guidelines as assessed by the Independent Review Committee (IRC) in the first 70 subjects enrolled treated in the main cohort.

Secondary endpoints: CR rate (CR + CRi), PR rate (nPR or PR), duration of overall response, progression-free survival, event free survival, time to progression, time or response, time to 50% reduction in ALC, overall survival, and percent of subjects who move on to stem cell transplant.

Exploratory efficacy analyses: Time to next anti-CLL treatment (TTNT), rate of MRD negativity, Health Economic and Patient Reported Outcome measures, and a sensitivity analysis of the investigator assessment of ORR, CR rate, PR rate, DOR, PFS, and TTP in the first 70 subjects treated and all subjects treated in the main cohort.

Reviewer Comment: It is to be noted that time to event endpoints such as, progression-free survival, event-free survival, time to progression, and overall survival are not interpretable in a single-arm study.

Disease response assessments: Evaluated using the 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response[22] with the addition of CT imaging. Treatment management was based on the investigator assessment. To be assigned a status of a CR or PR, the response must be confirmed no earlier than 8 weeks after the clinical criteria for response are first met. Response and progression assessments were also reviewed by an Independent Review Committee.

Complete Remission (CR), requires all of the following:

- Peripheral lymphocytes <4000/µL
- No lymphadenopathy >1.5 cm by physical examination and CT scan
- No hepatomegaly or splenomegaly by physical examination and CT scan (if indicated)
- Absence of disease or constitutional symptoms
- Blood counts above the following laboratory values:
    - Neutrophils >1500/µL (without growth factors support)
    - Platelets >100,000/µL (without platelet transfusion or growth factors)
    - Hemoglobin >11 g/dL (without blood transfusions or exogenous erythropoietin)
- Bone marrow normocellular, <30% lymphocytes, no lymphoid nodules

Complete Remission with Incomplete Marrow Recovery (CRi):

Subjects who fulfill the criteria for CR (including bone marrow) but who have persistent cytopenia (anemia or thrombocytopenia or neutropenia) apparently unrelated to CLL but related to drug.

Nodular Partial Remission (nPR):

Subjects who are otherwise in a complete remission, but bone marrow nodules can be identified histologically. Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells, B lymphocytes other than CLL cells, or CLL cells.

Partial Remission (PR):
At least two of the following must be met:

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

AND at least one of the following criteria must be met:

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

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

Progressive Disease (PD):
At least one of the following:

- Any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. An increase by 50% or more in greatest determined diameter of any previous site and >1.5 cm.
- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per microliter. The increase should be assessed against the best response while on study.
- Transformation to a more aggressive histology (e.g., Richter's Syndrome).
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL only if confirmed by a bone marrow assessment showing unequivocal progression.

Stable Disease (SD):

Patients who have not achieved a CR or a PR, or who have not exhibited PD, will be considered to have stable disease.

Statistical Analysis Plan

For the primary efficacy analyses, statistical significance was determined by a two-sided p value <0.05 (one-sided <0.025). The assessment of ORR was performed once 70 subjects in the main cohort completed the scheduled 36-week disease assessment, progressed prior to the 36-week disease assessment, discontinued study drug for any reason, or after all treated subjects discontinued venetoclax, whichever was earlier. The ORR for venetoclax was tested to reject the null hypothesis of 40%. If the null hypothesis is rejected and the ORR is higher than 40%, then venetoclax has been shown to have an ORR significantly higher than 40%. The ninety-five percent (95%) confidence interval for ORR was based on binomial distribution (Clopper-Pearson exact method). Per the recommendation of FDA, the timing of the efficacy analysis for the main cohort was modified to occur after at least 100 subjects had completed the 36-week disease assessment.

Sample Size and Power

Approximately 100 subjects were planned to be enrolled in the main cohort to assess the safety and efficacy of venetoclax in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) harboring the 17p deletion. Performing the efficacy analyses at 70 subjects provides at

least 90% power (at two-sided alpha of 5%) to reject the null hypothesis of 40% ORR in favor of an alternative hypothesis of 60% ORR.

Reviewer Comment: According to the Applicant, a therapy providing a significant benefit in overall response rate over a standard rate of 40% would be considered clinically meaningful. The pre-specified primary efficacy analysis was based on the first 70 subjects. However, during the FDA-Sponsor meeting dated Oct 29, 2014, the FDA commented:

> *"We do not agree that your proposed plan to submit interim efficacy data on 70 patients to support an accelerated approval is acceptable, given the recent regular approval of ibrutinib in this indication. Your application will be stronger with a complete final study report containing efficacy data on at least 100 patients."*
>
> *During the meeting discussion, the Agency commented:*
> *"The Agency stated that the current advice to submit the complete IRC-assessed 107 patient datasets in the NDA is related to the recent approval of ibrutinib in the 17pdel CLL indication. The ABT-199 NDA submission will be stronger by waiting until they have data on all of these patients, given the approval of a new available therapy."*

Therefore, the final sample size used in this report was 107 subjects. Even though testing hypothesis was pre-specified based on a null hypothesis of 40%, no inference can be made based on a single arm study; estimate of treatment activity based on ORR with 95% confidence interval will be described.

Analysis Populations

Efficacy and safety analyses were performed for the following analysis sets:

- All treated subjects: All subjects who received at least one dose of venetoclax in either the main cohort or safety expansion cohort. This analysis set was only for safety analyses.
- All treated subjects in Main cohort: All subjects who received at least one dose of venetoclax in the main cohort. This analysis set was used for the efficacy and safety assessments.
- All treated subjects in main cohort with 17p deletion CLL: All subjects who received at least one dose of venetoclax in the main cohort and have a confirmation of 17p deletion based on the central laboratory test. This analysis set was for the efficacy assessment.
- Primary efficacy subjects: The first 70 subjects who received at least one dose of venetoclax in the main cohort and have a confirmation of 17p deletion based on the central laboratory. The analysis set served as the analysis set for the primary efficacy endpoint of ORR only.

- Safety expansion subjects: All subjects who received at least one dose of venetoclax in the safety expansion cohort. This analysis set was used for the summary of subjects treated in the safety expansion cohort for safety assessments.

Protocol Amendments

Three amendments were issued during the conduct of this study as of the study cutoff date. The amendment changes are briefly summarized below. No subjects were enrolled under the original protocol. See Section 8.5.1 for further details on protocol amendments regarding TLS.

Protocol Amendment 1 (10 May 2013): 107 subjects (comprising the main cohort) were enrolled under this Amendment. The main purpose of the amendment was to implement more stringent measures for prophylaxis and management of TLS, including modification to the dosing regimen with a starting dose of 20 mg and ramp up of 4-5 weeks, and to introduce TLS risk assessment with prophylaxis and monitoring according to the risk as well as intensive laboratory monitoring.

Protocol Amendment 2 (25 July 2014): 36 subjects (all in the safety expansion cohort) were enrolled under this Amendment. The main purpose of the amendment was to introduce revised measures for prophylaxis and management of TLS in response to an extensive analysis among the CLL studies, including 58 subjects that demonstrated a substantial reduction in the frequency and severity of laboratory TLS and no events of clinical TLS.

Protocol Amendment 3 (19 December 2014): As of the data cutoff date for this interim report, total of two subjects (in the safety expansion cohort) were enrolled under this Amendment. The main purpose of the amendment was to allow enrollment of subjects with previously untreated CLL harboring 17p deletion in the safety expansion cohort, as there are no standard treatments for these patients.

Data Quality and Integrity: Sponsor's Assurance

Per the Applicant, the AbbVie monitor or designee monitored the study site throughout the study. A source document review was performed against entries on the eCRFs, and a QA check was performed to ensure that the investigator was complying with the protocol and regulation. Data entered into eCRFs were electronically transferred to the sponsor and imported into the database using validated software throughout the study. Computer logic checks were run to identify such items as inconsistent study dates. Any necessary corrections were made to the eCRF.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with Good Clinical Practices including review of the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study by an Independent Ethics Committee or Institutional Review Board (IEC/IRB).

Financial Disclosure

A summary of the financial disclosures for Study M13-982 is provided in Appendix 2 (Section 13.2). Four investigators and two sub-investigators were identified to have financial disclosures; one disclosure was for proprietary or financial interest in the product tested in the clinical study, and five disclosures were for significant payments having total value in excess of $25,000 from AbbVie or Genentech/Roche. The sites enrolled (b) (6) subjects. With the small number of patients enrolled at any site, the enrollment of patients by these investigators is not expected to bias the outcome of the study results. Removal of the (b) (6) patients enrolled at these sites from the main cohort analysis resulted in a similar overall response rate.

Patient Disposition

At the time of the data cutoff for this NDA submission, 30 April 2015, 151 patients were enrolled. Of those patients, 145 had the opportunity to complete the 5-week dose ramp-up period and were evaluable for this report. The 145 patients includes 107 in the main cohort and 38 in the safety expansion cohort. In the main cohort, 104 achieved the target dose of 400 mg, and 3 subjects discontinued during the ramp-up period. In the safety expansion cohort, 36 achieved the target dose of 400 mg, 1 subject discontinued during the ramp-up period, and 1 subject was still in the ramp-up period at the data cutoff.

In the main cohort, 37 patients discontinued venetoclax at the data cutoff. This included 11 patients for disease progression, 9 for disease progression with Richter's, 2 for an AE related to disease progression, 9 for AE not related to disease progression, 2 withdrew consent, 1 for non-compliance, and 3 for stem cell transplantation. In the safety expansion cohort, 5 patients discontinued venetoclax at the data cutoff. This included 3 for disease progression, 2 for disease progression with Richter's, and 1 for AE not related to disease progression.

Protocol Violations/Deviations

Per the Applicant, protocol deviations were defined in accordance with ICH guidelines and included, but were not limited to: inclusion/exclusion criteria violations, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdraw, and use of prohibited concomitant medications. Table 6 shows a summary of medically significant protocol deviation in the main cohort.

Table 6: Summary of protocol deviations in the main cohort of M13-982

Protocol deviations	Number of patients
Inclusion/exclusion	1
Prohibited concomitant medication	15
Incorrect dose of venetoclax	2
Treatment compliance	6
Failure to discontinue subjects	1
Other Good Clinical Practices	3

Of the use of prohibited concomitant medications, most were strong or moderate CYP3A inhibitors. Six patients were poorly compliant with treatment, but none with less than 80% compliance. Per the Applicant's assessment, none of the protocol deviations were considered to have affected the study outcome or interpretation of the study results or conclusions.

The Applicant reviewed protocol deviations pertaining to TLS prophylaxis independent of other protocol violations. The most frequent deviation regarding TLS prophylaxis was missing essential chemistry panel (potassium, phosphorus, uric acid and calcium) in 61 subjects with 31 subjects missing one time point and 14 subjects missing two time points (all 4 or only 1 or 2 electrolytes missing).

Table of Demographic Characteristics

The demographics of the patients from study M12-982 are summarized in Table 7. The median age and sex of the patients enrolled in this study generally reflects the demographics of patients with relapsed/refractory CLL. Although CLL occurs more frequently in whites than other races (see Section 2.1), patients who are black or Asian are underrepresented in this clinical trial. The main cohort and safety expansion cohort had similar demographics.

Table 7: M13-982, Demographic characteristics of the primary analysis

Demographic Parameters	Treatment Group n=145		Total n=145 n (%)
	Main Cohort n=107 n (%)	Safety Expansion n=38 n (%)	
Sex			
Male	70 (65.4)	22 (57.9)	92 (63.4)
Female	37 (34.6)	16 (42.1)	53 (36.6)
Age			
Mean years (SD)	65.7 (9.9)	66.9 (10.3)	66.0 (10.0)
Median (years)	67	68	67
Min, max (years)	37, 85	29, 83	29, 85
Age Group			
< 17 years	0	0	0
≥ 17 - < 65 years	46 (43.0)	12 (31.6)	58 (40.0)
≥ 65 years	61 (57.0)	26 (68.4)	87 (60.0)
> 65 - < 75 years	41 (38.3)	18 (47.4)	59 (40.7)
≥ 75 years	20 (18.7)	8 (21.1)	28 (19.3)
Race			
White	103 (96.3)	37 (97.4)	140 (96.6)
Black or African American	3 (2.8)	0	3 (2.1)
Asian	0	0	0
Other[1]	1 (0.9)	1 (2.6)	2 (1.4)
Ethnicity			
Hispanic or Latino	0	2 (5.3)	2 (1.4)
Not Hispanic or Latino	0	0	0
Other[2]	107 (100)	36 (94.7)	143 (98.6)
Region			
United States	17 (15.9)	15 (39.5)	32 (22.1)
Rest of the World[3]	90 (84.1)	23 (60.5)	133 (77.9)
Canada	1 (0.9)	1 (2.6)	2 (1.4)
Europe	79 (73.8)	15 (39.5)	94 (64.8)

[1] Data on race were missing in 2 patients, both enrolled in France.

[2] Data on two patients were reported as Hispanic or Latino; all other patients were not reported.

[3] No patients were enrolled in South America, Asia, or Africa

Other Baseline Characteristics

One patient in the main cohort (subject (b) (6)) was enrolled without meeting the 17p assay cutoff of >7% deleted. This patient's sample was switched with another subject when it was sent to the central laboratory for testing. The error was discovered after the patient had initiated study drug, and the patient remained on study. He discontinued the study after 15 days after rapid deterioration, and the patient died on day 21.

Amendment 2 allowed patients to be enrolled in the safety expansion cohort with local laboratory testing of the peripheral blood or bone marrow or from results previously obtained. A confirmatory sample was sent to the central laboratory at the screening visit. The results in Table 8 reflect the central laboratory testing for 17p deletion status. In 7 patients (18%), the central testing showed 17p was not deleted. This discordance highlights the conflicting results among non-standardized tests for 17p deletion status. Of the patients with available data, 72.8% (83/114) had *TP53* mutations on the other allele which is similar to the literature reported rate (see Section 2.1).

In the safety expansion cohort, the inclusion criteria were expanded to include patients with previously untreated disease with >5 x 10^9 B-lymphocytes/L in the peripheral blood. Two patients (subjects 11051 and 11052) had previously untreated CLL, but both had prior prostate cancer, and their anti-hormonal treatments were reported as prior treatments.

The baseline characteristics regarding other high-risk categories other than 17p deletion had a large amount of missing data. The amount of missing data makes subset analyses in these categories difficult. The baseline disease characteristics generally reflect that of patients in the community setting who have relapsed or refractory CLL.

Table 8: M13-982, Baseline characteristics of the primary analysis

Baseline Parameters	Treatment Group n=145		Total n=145 n (%)
	Main Cohort n=107 n (%)	Safety Expansion n=38 n (%)	
Number of prior therapies			
Median (min, max)	2 (1, 10)	2 (1, 6)[1]	2 (1, 10)
1	29 (27.1)	16 (42.1)	45 (31.0)
2	25 (23.4)	8 (21.1)	33 (22.8)
3	21 (19.6)	6 (15.8)	27 (18.6)
4 or more	32 (29.9)	8 (21.1)	40 (27.6)
17p deletion status			
Deleted	106 (99.1)	31 (81.6)	137 (94.5)
Not deleted	1 (0.9)	7 (18.4)	8 (5.5)
***IGVH* mutation[2]**			
Unmutated	30 (28.0)	10 (26.3)	40 (27.6)
Mutated	7 (6.5)	4 (10.5)	11 (7.6)
Missing	70 (65.4)	24 (63.2)	94 (64.8)
Fludarabine Refractory			
Yes	34 (31.8)	7 (18.4)	41 (28.3)
No	57 (53.3)	30 (78.9)	87 (60.0)
Missing	16 (15.0)	1 (2.6)	17 (11.7)
***TP53* mutation**			
Yes	60 (56.1)	23 (60.5)	83 (57.2)
No	17 (15.9)	8 (21.1)	25 (17.2)
Indeterminate	6 (5.6)	0	6 (4.1)
Missing	24 (22.4)	4 (18.4)	31 (21.4)
Baseline absolute lymphocyte count			
$< 25 \times 10^9$/L	53 (49.5)	21 (55.3)	74 (51.0)
$\geq 25 \times 10^9$/L	54 (50.5)	17 (44.7)	71 (49.0)
$< 100 \times 10^9$/L	83 (77.6)	34 (89.5)	117 (80.7)
$\geq 100 \times 10^9$/L	24 (22.4)	4 (10.5	28 (19.3)
Baseline LDH			
0 to 1 x ULN	44 (41.1)	15 (39.5)	59 (40.7)
> 1 x ULN	63 (58.9)	23 (60.5)	86 (59.3)
Baseline ECOG			
0 to 1	98 (91.6)	36 (94.7)	134 (92.4)
2	9 (8.4)	2 (5.3)	11 (7.6)

Bulky Disease by PI			
Lymph nodes <5 cm	50 (46.7)	24 (63.2)	74 (51.0)
Lymph nodes ≥5 cm	57 (53.3)	14 (36.8)	71 (49.0)
Prior stem cell transplant			
Yes	3 (2.8)	0	3 (2.1)
No	104 (97.2)	38 (100)	142 (97.9)

[1] 2 patients had previously untreated CLL. Prior therapy reported for both patients was hormonal therapy for prostate cancer.

[2] *IGVH* mutation status, unmutated if ≤2% mutation detected

For labeling purposes, we removed the one patient who did not have 17p deletion. Rates of high-risk categories were based on 106 patients regardless of the amount of missing data for any given category.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No subject was less than 80% compliant over the course of the study. Five subjects (Subjects (b) (6)) were determined to be less than 80% compliant with their venetoclax dosing regimen for single or collective periods ≥ 25 days.

To mitigate the risk of TLS, subjects were to receive hydration (IV or oral) and anti-hyperuricemics; therefore, the most common concomitant medications were IV fluids (83.4%), allopurinol (94.5%), and rasburicase (51.0%). As noted in protocol deviations, some patients received strong or moderate CYP3A inhibitors, which were prohibited. One subject received rituximab due to autoimmune thrombocytopenia. See Section 8.5.2 for the use of growth factors for treatment of or prophylaxis for neutropenia or febrile neutropenia.

Efficacy Results – Primary Endpoint

The primary endpoint was the ORR (CR+CRi+nPR+PR) as assessed by the IRC in the first 70 patients in the main cohort, and for all 107 patients enrolled in the main cohort. The efficacy results for all 107 patients are shown in Table 9 for both the investigator assessments and the IRC assessment. Overall, per IRC assessment, the majority of subjects (85 subjects; 79.4%) achieved an overall response. Complete remission (CR+CRi) was reported in 8 (7.5%) subjects, including for 6 subjects achieving CR and 2 subjects achieving CRi. Per investigator assessment, the overall response was reported in 79 (73.85%) subjects. Complete remission (CR+CRi) was reported in 17 (15.9%) subjects, including 14 subjects achieving CR and 3 subjects achieving CRi. An additional analysis was performed to summarize the ORR for the first 70 subjects (see Table 9 below; ORR=77.1% [54/70], 95% CI (65.6, 86.3) per IRC assessment).

Table 9: Efficacy results for M13-982

	M13-982 (17p del) n=107 n (%)		M13-982 (17p del) n=70 n (%)	
	IRC	Investigator	IRC	Investigator
ORR (95% CI)[a]	85 (79.4) (70.5, 86.6)	79 (73.8) (64.4, 81.9)	54 (77.1) (65.6, 86.3)	52 (72.9) (60.9, 82.8)
CR rate (CR/CRi)	8 (7.5) (6/2)	17 (15.9) (14/3)	5 (7.1)	8 (11.4)
nPR	3 (2.8)	4 (3.7)	2 (2.9)	8 (11.4)
PR	74 (69.2)	58 (54.2)	47 (67.1)	3 (4.3)
No response	22 (20.6)	28 (26.2)	16 (22.9)	19 (27.1)

[a] 95% CI was based on Clopper-Pearson exact method

Reviewer Comment: In general, we do not accept the hypothesis testing for a single arm study. (b) (4) .

The point estimate of ORR by IRC assessment and Investigator assessment were both above 70%. The ORR by IRC assessment was higher than that by investigator assessment. According to the Applicant, this was a result of differences in interpretation of splenomegaly and hepatomegaly, which may have been affected by subjectivity in the assessment of the CT scans. There were 4 subjects who were assessed as having ORR by the study investigator were not considered ORR by IRC assessment (Table 10).

Table 10 Discordance in ORR between IRC and Investigator assessment

ORR Status	Investigator Assessment: Yes	Investigator Assessment: No
IRC Assessment: Yes	75	10
IRC Assessment: No	4	22

There were 10 subjects who were assessed as having complete remission by the study investigator who were not considered CR by IRC assessment (Table 11). According to the Applicant, the PR assessments by the IRC were mainly based on node size>15 mm that may not have actually been representative of residual CLL.

Table 11: Discordant in CR between IRC and Investigator assessment

CR Status	Investigator Assessment: Yes	Investigator Assessment: No
IRC Assessment Yes	7	1
IRC Assessment No	10	89

For labeling purposes, the one patient without 17p deletion (subject (b) (6)) was removed from the analysis since this is a single-arm trial without need for an intent-to-treat analysis. With 106 patients with 17p deletion, the ORR by IRC was 80.2% (85/106, 95% CI: 71.3, 87.3) and CR+CRi rate was 7.5% (8/106) (Table 12).

Table 12: Efficacy results for M13-982 removing patient without 17p deletion

Subject Response n (%)	IRC Assessment n=106 n (%) (95% CI)[a]	Investigator Assessment n=106 n (%) (95% CI)[a]
Overall response rate	85 (80.2) (71.3, 87.3)	79 (74.5) (65.1, 82.5)
Complete remission rate (CR+CRi)	8 (7.5) (3.3, 14.3)	17 (16.0) (9.5, 24.2)
Partial remission (nPR+PR)	77 (72.6) (63.1, 80.9)	62 (57.9) (48.0, 67.4)

[a] 95% CI was based on Clopper-Pearson exact method

Data Quality and Integrity – Reviewers' Assessment

The quality of the original data submission was adequate to evaluate and review the submission, in general. However, it was difficult to interpret the subgroup results for some of the baseline characteristics due to the missing data. See the details in the subgroup analysis section.

Efficacy Results – Secondary and other relevant endpoints

With a median follow-up time of 32 months, the median duration of response has not yet been reached for this study. An estimated durable response rate (Kaplan-Meier estimate) at 12 months was 84.7% (95% CI: 74.5, 91.0) per IRC assessment (Table 13). This DOR per IRC assessment was evaluated in 85 subjects in the main cohort who had a record of response (CR, CRi, PR, or nPR).

Per investigator assessment, an estimated durable response rate (Kaplan-Meier estimate) at 12 months was 89.1% (95% CI: 79.2, 94.4) (Table 13). This DOR per investigator assessment was evaluated in 79 subjects in the main cohort who had a record of response (CR, CRi, PR, or nPR).

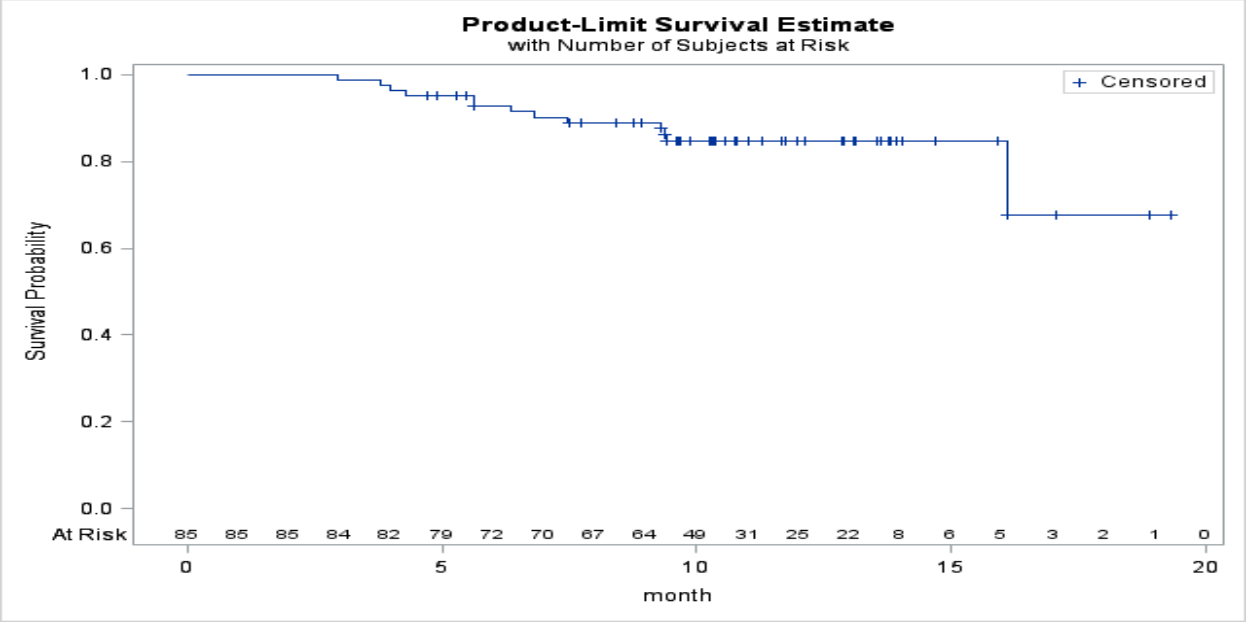
Table 13 Summary of Duration of Overall Response Rate

	IRC Assessment n=85 n (%)	Investigator Assessment n=79 n (%)
Event	13 (15.3)	10 (12.7)
Censor	72 (84.7)	69 (87.3)
Duration of ORR (month)[a]		
25th percentile (95% CI)	16.2 (9.4, NR)	15.9 (14.7, NR)
Median (95% CI)	NR (16.1, NR)	NR (15.9, NR)
Estimated ORR at month 12 (95% CI)[a]	84.7 (74.5, 91.0)	89.1 (79.2, 94.4)

[a] Based on the Kaplan-Meier estimate
NR = not reached

Figure 3 shows the Kaplan-Meier plot of duration of overall response based on IRC assessment.

Figure 3 Kaplan-Meier plot of Duration of Response per IRC assessment



The median duration of progression free-survival has not been reached. Based on IRC assessment, the Kaplan-Meier estimate of the proportion of subjects with PFS at 12 months was 72.0% (95% CI: 61.8, 79.8). Based on investigator assessment, the Kaplan-Meier estimate of the proportion of subjects with PFS at 12 months was 74.6% (95% CI: 64.9, 81.9).

The median duration of time to tumor progression has not been reached. Per IRC assessment, the Kaplan-Meier estimate of the proportion of subjects without progression at 12 months was 76.9% (95% CI: 67.0, 84.2). 24 subjects experienced disease progression per IRC assessment while on study. Per investigator assessment, the Kaplan-Meier estimate of the proportion of subjects without progression at 12 months was 78.4% (95% CI: 68.7, 85.3). 25 subjects experienced disease progression per investigator assessment while on study.

At the data cutoff date, 17 (15.9%) subjects in the main cohort died, and 90 (84.1%) subjects in the main cohort were still alive. The Kaplan-Meier estimate of the proportion of subjects surviving at 12 months was 86.7% (95% CI: 78.6, 91.9).

Reviewer Comment: *In general, time to event analyses cannot be evaluated based on single-arm studies. The results from Kaplan-Meier estimates of these secondary endpoints are for information only,* (b) (4)

MRD results: The protocol procedures stated that patients who achieved a CR, CRi, or PR with lymph nodes <2 cm should have an MRD assessment by 4- or 6-color flow cytometry. Of the 21 patients, meeting those criteria, 4 patients are missing MRD assessments. Other patients with an investigator-assessed response of PR had MRD assessments. Initially, assessments were performed by local laboratories, but the quality of the data was not acceptable for some samples. The later assessments were changed to regional laboratories. After removal of the low-quality data, 45 had MRD assessments that were evaluable with a cutoff of 10^{-4}. The majority of assessments were from the peripheral blood. Of the 45 evaluable MRD samples, 18 (40%) were MRD negative in the peripheral blood (7 were CR/CRi by the investigator and the remaining were PR by the investigator). Ten of those 18 patients had bone marrow MRD assessments, and 6 of the 10 were MRD negative in the bone marrow. The MRD negative rate based on the total enrolled patients in this study was 17% (18/107).

MRD data was available for 10 of 11 patients that had IRC assessments of CR, CRi, or nPR. Of those 11 patients, 5 were MRD negative (45%) with the following breakdown by IRC-assessed response category.

- CR (n=6) – 3 (50%) MRD neg
- CRi (n=2) – 2 (100%) MRD neg
- nPR (n=3) – 0 MRD neg

Analysis of Subpopulations

Table 14 shows the analysis results for the primary efficacy endpoint by demographics. No outliers were observed among these subgroups.

Table 14 Subgroup analysis of IRC assessed ORR by demographics

Subgroup	Number of patients	IRC assessment n (%) (95% CI)[a]	Investigator assessment n (%) (95% CI)[a]
Age <65 years	46	40 (87.0) (73.7, 95.1)	34 (73.9%) (58.9, 85.7)
Age ≥65 years	61	45 (73.8) (60.9, 84.2)	45 (73.8) (60.9, 84.2)
Male	70	56 (80.0) (68.7, 88.6)	49 (70.0) (57.9, 80.4)
Female	37	29 (78.4) (61.8, 90.2)	30 (81.1) (64.8, 92.0)
White	103	81 (78.6) (69.5, 86.1)	76 (73.8) (64.2, 82.0)
Black	3	3 (100.0)	3 (100.0)
Other	1	1 (100.0)	0
United States	17	13 (76.5) (50.0, 93.2)	13 (76.5) (50.1, 93.2)
European Union	79	63 (79.8) (69.2, 88.0)	58 (73.4) (62.3, 82.7)
Rest of world	11	9 (81.8) (48.2, 97.7)	8 (72.7) (39.0, 94.0)

[a] 95% CI was based on Clopper-Pearson exact method

Table 15 shows the analysis results for the primary efficacy endpoint by baseline disease characteristics. No outliers were observed among these subgroups.

Table 15 Subgroup analysis of IRC assessed ORR by baseline disease characteristics

	Number of patients	IRC assessment n (%) (95% CI)[a]	Investigator assessment n (%) (95% CI)[a]
Fludarabine refractory status (Yes)	34	29 (85.3) (68.9, 95.0)	27 (79.4) (62.1, 91.3)
Fludarabine refractory status (No)	57	47 (82.5) (70.1, 91.3)	41 (71.9) (58.5, 83.0)
Ig V_H Mutation Status (Yes)	7	5 (71.4) (29.0, 96.3)	4 (57.1) (18.4, 90.1)
Ig V_H Mutation status (No)	30	25 (83.3) (65.3, 94.4)	26 (86.7) (69.3, 96.2)
Lymph nodes <5 cm	50	41 (82.0) (68.6, 91.4)	37 (74.0) (59.7, 85.4)
Lymph nodes ≥5 cm	57	44 (77.2) (64.2, 87.3)	42 (73.7) (60.3, 84.5)
Prior therapy=1	29	27 (93.1) (77.2, 99.2)	26 (89.7) (72.6, 97.8)
Prior therapy=2	25	19 (76.0) (54.9, 90.6)	15 (60.0) (38.7, 78.9)
Prior therapy=3	21	17 (81.0) (58.1, 94.6)	18 (85.7) (63.7, 97.0)
Prior therapy=4	14	9 (64.3) (35.1, 87.2)	9 (64.3) (35.1, 87.2)
Prior therapy ≥5	18	13 (72.2) (46.5, 90.3)	13 (72.2) (46.5, 90.3)
LDH ≤1x ULN	44	37 (86.0) (69.9, 93.4)	34 (77.3) (62.2, 88.5)
LDH >1x ULN	63	48 (76.2) (63.8, 86.0)	45 (71.4) (58.7, 82.1)
ECOG Grade=0	42	36 (85.7) (71.5, 94.6)	32 (76.2) (60.5, 87.9)
ECOG Grade ≥1	65	49 (75.4) (63.1, 85.2)	47 (72.3) (59.8, 82.7)
ALC <25x10^9/L	53	43 (81.1%) (68.0, 90.56)	38 (71.1%) (57.7, 83.2)
ALC ≥25x10^9/L	54	42 (77.8%) (64.4, 88.0)	41 (75.9%) (62.3, 86.5)

[a] 95% CI was based on Clopper-Pearson exact method
LDH = lactate dehydrogenase; ULN = upper limit of normal; ALC = absolute lymphocyte count

Reviewer Comment: All subgroup analyses are considered exploratory. There are missing assessments for some of the baseline disease characteristics. There are 24 (22.4%) subjects missing TP53 *mutation status, 48 (44.9%) subjects missing ZAP-70 status, 31 (29.0%) subjects missing CD38, 70 (65.4%) subjects missing* IGVH *mutation status, and 16 (15.0%) subjects missing fludarabine refractory status. Therefore, it is difficult to interpret the subgroup results based on those baseline characteristics because of these high rates of missing data.*

Dose/Dose Response

The venetoclax dosage selection was evaluated in the exposure-response analysis using all data included in this submission from two studies (Studies M13-982 and M12-175), and is discussed in detail in Section 7.1.4.

Durability of Response

See analysis of primary efficacy endpoints section.

Persistence of Effect

The study is still ongoing and the current analysis was conducted with a cutoff date of 30 April 2015 for the purpose of filing a regulatory submission. The median duration of follow-up was 32 months. The results are based on interim results with limited follow-up. Whether the observed efficacy persists after longer follow up time cannot be assessed definitively at this time. See analysis of primary and secondary efficacy sections.

Additional Analyses Conducted on the Individual Trial

See analysis of primary efficacy section for the analysis of discordance on ORR and CR between IRC assessment and investigator assessment.

6.2. M12-175: Phase 1, Safety and Pharmacokinetics in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

6.2.1. Study Design

Overview and Objective

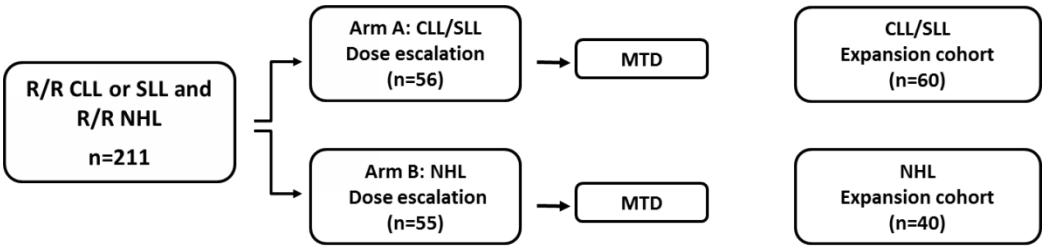
Study M12-175 is titled "A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma." The primary objectives were to assess the safety and PK, to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RPTD), and to determine the lead-in period regimen of ABT-199. Food effect was studied in the dose-escalation portion in patients with NHL.

Reviewer Comment: The primary objective of this study was to evaluate the safety and PK. ORR was not the primary efficacy endpoint and the study was not powered based on the ORR. Therefore, the analysis results of ORR from this study are exploratory (b) (4)

Trial Design

M12-175 is a phase 1, single arm, multicenter study evaluating the safety and PK of treatment of patients with relapsed or refractory CLL (Cohort A) and NHL (Cohort B). A schematic of the trial is shown in Figure 4. This trial is fully enrolled and ongoing, and the interim analysis is presented here with a data cutoff of February 10, 2015. Results from patients in Arm A and the CLL/SLL expansion cohort are presented here. The dose escalation phase utilized a 3+3 study design and evaluated target doses between 150 mg and 1200 mg daily after an initial dose ramp-up phase. The expansion cohort was treatment at the 400 mg target dose. The efficacy evaluation was not a pre-specified evaluation and consisted of patients in the dose escalation cohort treated at 400 mg and patients in the expansion cohort with CLL who had baseline disease assessments. Safety data was provided for all patients including those with NHL and at all doses. Patients remained on study until disease progression or unacceptable toxicity, and patients could continue the study drug if they are receiving benefit for up to two years. The duration of the study will be until up to two years after the final subject has enrolled on study.

Figure 4: Study design schema for M12-175



R/R=relapsed/refractory. Modified from figure provided by Applicant.

Control group: There are no control groups in this study. Historical response rates were provided for common treatments for patients with R/R CLL with 17p deletion, as discussed in Table 2.

Diagnostic criteria: Patients in Arm A must have the diagnosis of relapsed or refractory CLL or SLL. Patients had to have an indication for treatment based on the opinion of the investigator.

Key inclusion/exclusion criteria (summary):

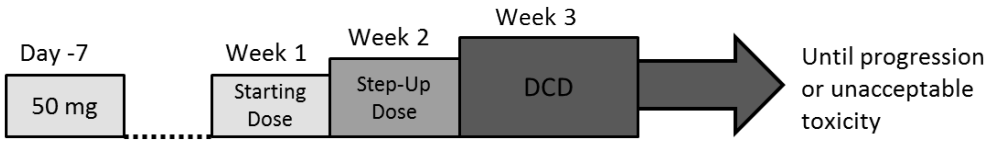
- ≥18 years of age
- (Arm A) CLL or SLL, relapsed or refractory to standard treatments such as fludarabine based regimens (F, FC, FR, FCR) or alkylator (chlorambucil, bendamustine) based regimens, with no other curative options and exhausting options considered standard of care.
- ECOG performance score ≤1
- Adequate bone marrow function
    - ANC ≥1000/µL, may be with growth factor support if bone marrow heavily infiltrated with underlying disease
    - Platelets ≥30,000/mm^3, without transfusion in previous 14 days
    - Hemoglobin ≥8.0 g/dL
- Adequate coagulation (aPTT and PT not to exceed 1.2x ULN)
- Creatinine clearance ≥50 mL/min
- AST and ALT ≤3x ULN, bilirubin ≤1.5x ULN (except for Gilbert's Syndrome)
- The following are excluded
    - Prior allogeneic or autologous stem cell transplant
    - Active and uncontrolled autoimmune cytopenias, including AIHA and ITP
    - Known to be positive for HIV
    - Cardiovascular disability status of New York Heart Association Class ≥2
    - Patient requiring the use of warfarin
    - Subject received any of the following within 7 days: CYP3A inhibitors, potent CYP3A inducers.

Dose selection: The initial start dose in Cohort 1 for the CLL/SLL arm was 200 mg based on pharmacology/toxicology studies in mice and dogs. The recommended phase 2 dose for patients with R/R CLL was determined in this study to be a target dose of 400 mg, and patients in the expansion cohort were enrolled at this target dose. Additional information on dose selection is provided in Section 7.1.4.

Study treatments: The first three patients were treated at 100 mg or 200 mg of venetoclax. Following events of tumor lysis, the starting dose was lowered to 50 mg and a ramp-up schedule was established as shown in Figure 5. The starting dose was later lowered to 20 mg. After the clinical hold due to fatal events of tumor lysis, the ramp-up period was extended to 5 weeks, initially with a single test dose of 20 mg and finally with the recommended schedule of 20 mg for one week with a 5 week ramp up period as described in trial M13-982 above, see Figure 2 above.

Each dose is taken with approximately 240 mL of water within 30 minutes of a standard, low-fat breakfast. Tumor lysis syndrome (TLS) risk stratification and prophylaxis guidelines were provided in this protocol. TLS is discussed in further detail in Section 8.5.1.

Figure 5: Dosing schedule for the dose escalation in study M12-175



DCD = designated cohort dose. Modified from figure provided by Applicant.

Intra-subject dose escalation was allowed after at least 12 weeks at the assigned designated cohort dose.

Dose modification, dose discontinuation: The dose modification and discontinuation guidelines were the same as in study M13-982, see Section 6.1.1

Administrative structure: Tumor response and disease progression assessments were made by individual investigators. An Independent Review Committee (IRC) reviewed the data for final determination of response or progression for patients who were assigned to a target dose of 400 mg. The IRC reviewed ORR, CR rate, PR rate, DOR, duration of PFS, and TTP. The results from the IRC were not shared with the investigators.

Procedures and schedule: Study procedures and schedule for the safety expansion cohort are summarized here.

- Physical exams, vital signs, ECOG performance status: screening, day 1 of weeks 1-8, 12, 16, 20, and 24 then every 12 weeks thereafter; final visit, and 30-day safety follow up visit
- Laboratory tests
    - Chemistry and hematology: screening, within 72 hours prior to first dose of venetoclax, weeks 1-4 or 5 based on TLS management protocol (see Section 8.5.1 of this review), day 1 of week 5-8, 12, 16, 20, and 24 then every 12 weeks thereafter; final visit, 30-day safety follow-up visit, and as needed throughout study including 8 weeks after CR, CRi, or PR to tumor response confirmation.
    - Coagulation panel: Screening, day 1 of week 4, then every 4 weeks until week 24, and every 12 weeks thereafter; final visit, 30-day safety follow-up visit.
    - Urinalysis: Screening, day 1 of week 4, then every 4 weeks until week 24, and every 12 weeks thereafter; final visit, 30-day safety follow-up visit.
    - Quantitative immunoglobulins (IgA, IgG, and IgM): Screening, day 1 of week 12 and every 12 weeks thereafter, final visit, 30-day safety follow-up visit
    - Lymphocyte enumeration (B- and T-cell subpopulations): Screening, day 1 of week 1, 4, and 24, and every 12 weeks thereafter; final visit
- Electrocardiogram: screening, final visit, and as clinically indicated. Additional ECGs were obtained for patients in the dose escalation cohort for evaluation of QTc.
- Left ventricular ejection fraction (Echo or MUGA): screening and final visit
- Disease assessments (2008 modified IW-CLL NCI-WG Guidelines)
    - CT (or MRI) neck, chest, abdomen, and pelvis: Screening, day 1 of week 6, 16, 24, 36, and 48; at least 8 weeks after CR, CRi, or PR tumor response criteria are met; every 24 weeks after achieving CR or CRi; final visit
    - Bone marrow aspirate and biopsy: screening, day 1 of week 24, within 2 months of meeting criteria for CR.
    - MRD assessment by flow cytometry or ASO-PCR: in peripheral blood or bone marrow at time of bone marrow aspirate at least 8 weeks after CR/CRi criteria were first met or PR with LN <2 cm, then in peripheral blood every 12 weeks after the first assessment until MRD negativity is achieved in the peripheral blood; once MRD negativity was achieved in the peripheral blood, repeat bone marrow aspirate was collected

Dietary restrictions/instructions: Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of a standard low-fat breakfast. Patients should not consume grapefruit, Seville oranges, or star fruit due to possible CYP3A mediated interactions.

Concurrent medications: Steroid therapy for anti-neoplastic intent was not allowed. Limited corticosteroid treatment (i.e., for approximately 21 days with rapid taper) was allowed for significant active autoimmune cytopenias (AIHA or ITP). Best supportive care was allowed including antiemetics, antibiotics, transfusions, nutritional support, and pain control. Hematopoietic growth factors (G-CSF, GM-CSF, and erythropoietin) were allowed per ASCO guidelines. Anti-infective prophylaxis for lymphopenia is at the investigator's discretion and considering potential for drug-drug interactions.

Treatment compliance: A calendar/diary was collected from all patients, and patients were asked to record the date and time each dose of the study drug was taken. Patients were also asked to record adverse events and concomitant medications. Patients were instructed to return all unused tablets and/or containers, even if empty to the study coordinator at scheduled study visits, and the study coordinator questioned the subjects regarding adherence. Compliance was monitored and documented by the study coordinator. Compliance below 80% required counseling of the subject by study site personnel.

Rescue medications: The study drug was continued until disease progression or unacceptable side effects. No additional disease-directed therapy was allowed while on study.

Subject completion, discontinuation, or withdrawal: Subjects were allowed to withdraw at any time. The investigator could remove subjects from the trial if they believed it was in the best interest of the subject, for disease progression, unacceptable toxicity.

Study Endpoints

The primary objectives for this phase 1 study were to assess the safety and PK, to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RPTD), and to determine the lead-in period regimen of ABT-199.

Other exploratory efficacy objectives were PFS, ORR (CR+CRi+nPR+PR), TTP, OS, DOR, and MRD. Responses Disease response assessments were evaluated by investigators and an IRC using the 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response[22] with the addition of CT imaging. Response criteria are summarized in Section 6.1.1. To be assigned a status of PR or CR changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 2 months after the criteria for response is first met.

Dose limiting toxicity (DLT) was defined as any of the following events, which cannot be attributed to a clearly identified cause such as tumor progression, underlying illness, concurrent illness, or concomitant medications:

- Grade 4 neutropenia lasting more than 7 days (while receiving growth factor support)
- Grade 3 or Grade 4 neutropenia with fever

- Grade 4 thrombocytopenia
- Grade 2 or higher bleeding associated with thrombocytopenia
- Unexpected Grade 2 toxicity which requires dose modification or delay of ≥ 1 week, will be considered a DLT (e.g., peripheral neuropathy)
- Clinical TLS will be considered a DLT
- Laboratory TLS will be considered a DLT if the metabolic abnormalities do not resolve within 72 hours despite protocol required management
- All other Grades 3, 4 or 5 adverse events will be considered a DLT with the exception of the following:
    - Grade 3 thrombocytopenia that does not result in bleeding
    - Grades 3, 4 lymphopenia
    - Grades 3, 4 leukopenia
    - Grade 3 nausea, vomiting and/or diarrhea unless unresponsive to treatment
    - Grade 3 or 4 hyperuricemia or hypocalcemia or Grade 3 hyperkalemia, if transient (i.e., lasting < 48 hours) and without manifestations of clinical tumor lysis syndrome (i.e., creatinine ≥ 1.5 × ULN, cardiac arrhythmias, sudden death, or seizures)

Statistical Analysis Plan

M12-175 was a dose-escalation study, and the sample size was estimated to be 56 subjects with R/R CLL or SLL. Sixty additional subjects with R/R CLL or SLL were enrolled at the MTD or RPTD for safety evaluation. All efficacy endpoints were descriptive without a formal statistical analysis plan.

Protocol Amendments

There were 10 amendments and 3 administrative changes made to the original protocol. None of the study subjects were enrolled under the original protocol. Important changes are summarized below. Amendments regarding TLS are summarized in Section 8.5.1.

Amendment 1 (13 December 2010): Three subjects enrolled. Clarified definitions of R/R CLL, allowed enrollment of SLL, clarified DLT definitions.
Amendment 2 (31 May 2011): Two subjects (both in Arm A) enrolled. The primary purpose of amendment 2 was to add a second arm (Arm B). Arm A included patients with CLL or SLL. Arm B included patients with NHL.
Amendment 3 (19 July 2011): 21 subjects in Arm A and 9 subjects in Arm B enrolled. Added primary objective to include determination of the ramp-up period regimen and adjusted period dose-escalation.

Amendment 4 (20 December 2011): 18 subjects in Arm A and 19 subjects in Arm B enrolled. Added implementation of G-CSF for the management of neutropenia at the investigator's discretion.
Amendment 5 (27 April 2012): No subjects were enrolled under Protocol Amendment 5.
Amendment 6 (14 June 2012): 12 subjects in Arm A and 4 subjects in Arm B enrolled. Increased the maximum dose of venetoclax from 600 mg/day to 1200 mg/day.
Amendment 7 (20 November 2012): No subjects were enrolled under Protocol Amendment 7. Added MRD assessment in subjects with CLL who have achieved CR or CRi status.
Amendment 8 (30 April 2013): 54 subjects in Arm A and 43 subjects in Arm B enrolled. Clarified that the MRD assessment was to be collected as needed throughout the study, and provided better guidance on how to manage neutropenia.
Amendment 9 (23 December 2013): 6 subjects in Arm A and 31 subjects in Arm B enrolled. Further defined intra-subject dose escalation, added to CT scans (or MRI, PET, PET-CT) that once a subject achieves a CR/CRi.
Amendment 10 (07 January 2015): No subjects were enrolled under Protocol Amendment 10.

Data Quality and Integrity: Sponsor's Assurance

Per the Applicant, the AbbVie monitor or designee monitored the study site throughout the study. A source document review was performed against entries on the eCRFs, and a QA check was performed to ensure that the investigator was complying with the protocol and regulation. Data entered into eCRFs were electronically transferred to the sponsor and imported into the database using validated software throughout the study. Computer logic checks were run to identify such items as inconsistent study dates. Any necessary corrections were made to the eCRF.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with Good Clinical Practices including review of the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study by an IEC/IRB.

Financial Disclosure

A summary of the financial disclosures for Study M12-175 is provided in Appendix 2 (Section 13.2). One investigator and two sub-investigators were identified to have financial disclosures. The investigator had proprietary or financial interest, and both sub-investigators had significant equity interest in AbbVie. The investigator's site enrolled (b) (6) patients across both arms of the

study, and the sub-investigators enrolled (b) (6) and (b) (6) patients, respectively. With the small number of patients enrolled at any site, the enrollment of patients by these investigators is not expected to bias the outcome of the study results. Removal of the (b) (6) patients enrolled at these sites from the 400 mg cohort analysis resulted in a similar overall response rate.

Patient Disposition

At the data cutoff date, 116 patients with R/R CLL/SLL were enrolled in Arm A, 56 in the dose escalation and 60 in the dose expansion cohort. Of those, 7 patients in the dose escalation and all patients in the dose expansion cohort were treated at a target dose of 400 mg after the ramp-up period.

The dose escalation cohorts consisted of 8 cohorts ranging from 150 mg to 1200 mg. Seven patients did not reach their designated cohort dose (DCD), and 19 subjects escalated above their DCD as allowed after 12 weeks at the DCD. Of the patients in the 400 mg cohorts, 10/67 escalated to 600 mg. Dose-response analysis is discussed in Section 7.1.4.

Fifty-six patients were still active on treatment at the data cutoff of February 10, 2015. The primary reason for discontinuation were disease progression (31%, 36/116 including Richter's transformation for 15 of the 36), adverse events (11.2%, 13/116), withdrew consent (1/116, 0.9%), and other reasons (10/116, 9%). Seven of the 10 other reasons were for bone marrow transplantation, and one each subject choice after achieving MRD negative CR, the need for long-term warfarin, and deterioration secondary to diabetes mellitus.

Reviewer Comment: See Section 8.5.3 regarding the rate of Richter's transformation.

Protocol Violations/Deviations

Protocol deviations were defined in accordance with ICH guideline s and included, but were not limited to: inclusion/exclusion criteria violations, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdraw, and use of prohibited concomitant medications. Table 16 below shows a summary of medically significant protocol deviation in the main cohort.

Table 16: Summary of protocol deviations in M12-175

Protocol deviations	Number of patient n=222[a]
Inclusion/exclusion	11
Prohibited concomitant medication	19
Incorrect dose of venetoclax	7
Treatment noncompliance	3
Failure to discontinue subjects	1
Other Good Clinical Practices	4

[a] Includes patients with both CLL and NHL

Only 4 of the inclusion/exclusion deviations were for patients with CLL, and these were use of a CYP3A inhibitors with less than the required 7 day wash-out period or an anti-neoplastic agents with less than 30 day wash-out (21 days for one patient), an ANC <1000/μL, and a platelet transfusion within 14 days of the first dose. The majority of the prohibited concomitant medications were strong or moderate CYP3A inhibitors. Only one patient with CLL was non-compliant, and is discussed below under treatment compliance. Per the Applicant's assessment, none of the protocol deviations were considered to have affected the study outcome or interpretation of the study results or conclusions.

The Applicant reviewed protocol deviations pertaining to TLS prophylaxis independent of other protocol violations. The most frequent deviation regarding TLS prophylaxis was missing essential chemistry panel (potassium, phosphorus, uric acid, and calcium) in 17 subjects. No clinical consequences were reported in the 20 patients with protocol deviations related to TLS prophylaxis in the 60 patients enrolled after the first major amendment (see Section 8.5.1).

Table of Demographic Characteristics

Patients were enrolled in the US or Australia. The demographics of the study at all doses are displayed in Table 17 for patients treated at 400 mg and the total patient population in patients with R/R CLL/SLL. Note that 67 patients were enrolled at a target dose of 400 mg, but 10 patients were excluded from efficacy analysis, 8 had SLL and 2 did not have baseline disease assessments. The characteristics of the patients treated at 400 mg were the same as patients treated at all doses. The demographics generally reflect the demographics patients with relapsed/refractory CLL except for an underrepresentation of non-white races.

Table 17: M12-175, Demographic characteristics of the primary analysis

Demographic Parameters	400 mg[1] n=57 n (%)	Total n=116 n (%)
Sex		
Male	43 (75.4)	89 (76.7)
Female	14 (24.6)	27 (23.3)
Age		
Mean years (SD)	64.2 (9.0)	64.5 (9.6)
Median (years)	66	66
Min, max (years)	42, 84	36, 86
Age Group		
< 17 years	0	0
≥ 17 - < 65 years	27 (47.4)	52 (44.8)
≥ 65 years	30 (52.6)	64 (55.2)
> 65 - < 75 years	22 (38.6)	47 (40.5)
≥ 75 years	8 (14.0)	17 (14.7)
Race		
White	52 (91.2)	104 (89.7)
Black or African American	1 (1.8)	5 (4.3)
Asian	1 (1.8)	2 (1.7)
Other[2]	3 (5.3)	5 (4.3)
Ethnicity		
Hispanic or Latino	2 (3.5)	3 (2.6)
Not Hispanic or Latino	0	0
Other[3]	55 (96.5)	113 (97.4)
Region		
United States	38 (66.7)	74 (63.8)
Rest of the World[4]	19 (33.3)	42 (36.2)

[1] Excludes 8 patients with SLL and 2 patients with CLL without baseline data for efficacy analysis

[2] Data on race were missing in 5 patients.

[3] Data on three patients were reported as Hispanic or Latino; all other patients were not reported.

[4] Patients were enrolled in either the US or Australia.

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

17p deletion status and other baseline disease characteristics were determined by local laboratories and not confirmed by central laboratory evaluation. As noted in Section 6.1.2, there is a significant amount of discordance between local laboratories and central laboratory evaluation for 17p deletion. Significant missing data occurred in the baseline disease characteristics which can weaken the reliability of subset analyses.

Table 18: M12-175, Baseline characteristics of the primary analysis

Baseline Parameters	400 mg[1] n=57 n (%)	Total n=116 n (%)
Number of prior therapies		
Median (min, max)	3 (1, 11)	3 (1, 11)
1	12 (21.1)	19 (16.4)
2	12 (21.1)	25 (21.6)
3	5 (8.8)	15 (12.9)
4 or more	28 (49.1)	57 (49.1)
17p deletion status		
Deleted	12 (21.1)	31 (26.7)
Not deleted	40 (70.2)	60 (51.7)
Indeterminate	4 (7.0)	8 (6.9)
Missing	1 (1.8)	17 (14.7)
***IGVH* mutation[2]**		
Unmutated	21 (36.8)	46 (39.7)
Mutated	11 (19.3)	17 (14.7)
Missing	25 (43.9)	53 (45.7)
Fludarabine Refractory		
Yes	43 (75.4)	70 (60.3)
No	14 (24.6)	44 (37.9)
Missing	0	2 (1.7)
***TP53* mutation**		
Yes	12 (21.1)	30 (25.9)
No	32 (56.1)	60 (51.7)
Missing	13 (22.8)	26 (22.4)
Baseline absolute lymphocyte count		
$< 25 \times 10^9$/L	37 (64.9)	81 (69.8)
$\geq 25 \times 10^9$/L	20 (35.1)	35 (30.2)
$< 100 \times 10^9$/L	53 (93.0)	106 (91.4)
$\geq 100 \times 10^9$/L	4 (7.0)	10 (8.6)
Baseline LDH		
0 to 1 x ULN	32 (56.1)	58 (50.0)
> 1 x ULN	25 (43.9)	58 (50.0)
Baseline ECOG		
0 to 1	54 (94.7)	113 (97.4)
2	1 (1.8)	1 (0.9)
Missing	2 (3.5)	2 (1.7)
Bulky Disease by PI		
Lymph nodes < 5 cm	19 (33.3)	45 (39.1)
Lymph nodes ≥ 5 cm	38 (66.7)	70 (60.9)
Prior stem cell transplant		
Yes	5 (8.8)	6 (5.2)
No	52 (91.2)	110 (94.8)

[1] Excludes 8 patients with SLL and 2 patients with CLL without baseline data for efficacy analysis
[2] *IGVH* mutation status, unmutated if ≤2% mutation detected

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Three subjects were less than 80% compliant with venetoclax dosing, 1 with CLL and 2 with NHL. The patient with CLL was non-compliant during one week during dose escalation, but reached the designated cohort dose.

To mitigate the risk of TLS, subjects with CLL/SLL were to receive hydration (IV or oral) and anti-hyperuricemics; therefore, the most common concomitant medications were IV fluids (86.2%) and allopurinol (94.8%). Patients also frequently received concomitant medications for infectious prophylaxis such as acyclovir (53.4%), sulfamethoxazole/trimethoprim (50.9%), valaciclovir (28.4%), human immunoglobulin (24.1%), and levofloxacin (20.7%). See Section 8.5.2 for the use of growth factors for treatment of or prophylaxis for neutropenia or febrile neutropenia.

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Handling of Missing Data

Subjects who only had a baseline tumor assessment but no post-baseline tumor assessments were classified as incomplete data, and were included in the analyses.

Dose/Dose Response

The venetoclax dose selection was evaluated in the exposure-response analysis using data included in this submission from two studies (M13-982 and M12-175) and is discussed in detail in Section 7.1.4.

Persistence of Effect

The primary objective of this study was to evaluate the safety and PK. ORR was not the primary efficacy endpoint and the study was not powered based on the ORR. The sample size is small, and whether the observed efficacy persists cannot be assessed definitively for this study.

Additional Analyses Conducted on the Individual Trial

See analysis of efficacy section for the analysis of discordance on ORR between IRC assessment and investigator assessment.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Efficacy evaluation was a primary endpoint in the phase 2 study M13-982 in patients with R/R CLL with 17p deletion. Efficacy was descriptive only in the phase 1 study M12-175. Despite this, the enrollment criteria were similar for both studies, and efficacy results could be combined for evaluation of all patients with relapsed/refractory CLL treated at 400 mg (n=164, 107 in M13-982 and 57 in M12-175) and all patients with R/R CLL with 17p del treated at 400 mg (n=118, 106 in M13-982 and 12 in M12-175). Additional patients were treated at higher or lower target doses in the phase 1 study, but these patients are not evaluated in this review for brevity. Efficacy results were also provided for patients enrolled in study M14-032 which was venetoclax monotherapy for the treatment of patients relapsed or refractory to a B cell receptor inhibitor (BCRi; ibrutinib or idelalisib). Those patients were not included in this reviewer's evaluation because the trial design was not reviewed in depth due to the limited number of evaluable patients at the data cutoff date. All analyses in the pooled analyses are considered exploratory.

Clinically important demographic and baseline disease parameters for the combined efficacy analysis are presented in Table 21. There is a significant amount of missing data for *IGVH* mutation status (n=95, 57.9%), fludarabine refractory status (n=16, 9.8%), and *TP53* mutation status (n=37, 22.6%; and 6 patients indeterminate). Demographics and baseline disease characteristics were nearly identical in the R/R CLL with 17p del population compared to all R/R CLL population. The notable differences are that the 17p del population had slightly less patients who were fludarabine refractory and slightly more patients with *TP53* mutations.

Table 21: Demographic and baseline disease parameters for combined efficacy analysis

Demographic Parameters	All R/R CLL n=164 n (%)	R/R CLL with 17p del n=118 n (%)
Sex		
Male	113 (68.9)	79 (66.9)
Female	51 (31.1)	39 (33.1)
Age		
Median (min, max)	66 (37, 85)	66 (37, 83)
Age Group		
< 65 years	73 (44.5)	64 (54.2)
≥ 65 years	91 (55.5)	54 (45.8)
Number of prior therapies		
Median (min, max)	3 (1, 11)	3 (1, 11)
17p deletion status		
Deleted[1]	118 (72.0)	118 (100)
Not deleted	41 (25.0)	0
***IGVH* mutation**		
Unmutated	51 (31.1)	35 (29.7)
Mutated	18 (11.0)	10 (8.5)
Fludarabine Refractory		
Yes	77 (47.0)	45 (38.1)
No	71 (43.3)	57 (48.3)
***TP53* mutation**		
Yes	72 (43.9)	66 (55.9)
No	49 (29.9)	20 (16.9)
Baseline absolute lymphocyte count		
< 25 x 10^9/L	90 (54.9)	62 (52.5)
≥ 25 x 10^9/L	74 (45.1)	56 (47.5)
Bulky Disease by PI		
Lymph nodes < 5 cm	69 (42.1)	53 (44.9)
Lymph nodes ≥ 5 cm	95 (57.9)	65 (55.1)

[1] 17p del status was indeterminate in 4 patients (2.4%) in the all R/R CLL group

IRC-assessed response rates for the pooled analysis are shown in Table 22 for all R/R CLL treated at 400 mg and R/R CLL with 17p del treated at 400 mg.

Table 22: IRC-assessed response rates for pooled analysis

	All R/R CLL n=164 n (%)	R/R CLL with 17p del n=118 n (%)
ORR (95% CI)[1]	127 (77.4) (70.5-83.2)	93 (78.8) (70.6-85.2)
CR rate (CR/CRi)	12 (7.3) (8/4)	8 (6.8) (6/2)
nPR	3 (1.8)	3 (2.5)
PR	112 (68.3)	82 (69.5)
No response	37 (22.6)	25 (21.2)

[1] 95% CI varied slightly from Applicant's analysis, score method

7.1.2. Secondary and Other Endpoints

Pooled analyses were not conducted on other endpoints than those discussed in Section 7.1.1. The differences in timing of assessments across trials make analysis of time-to-event endpoints limited and are not interpretable in single-arm studies. Also, the median duration of response, PFS, and OS were not reached.

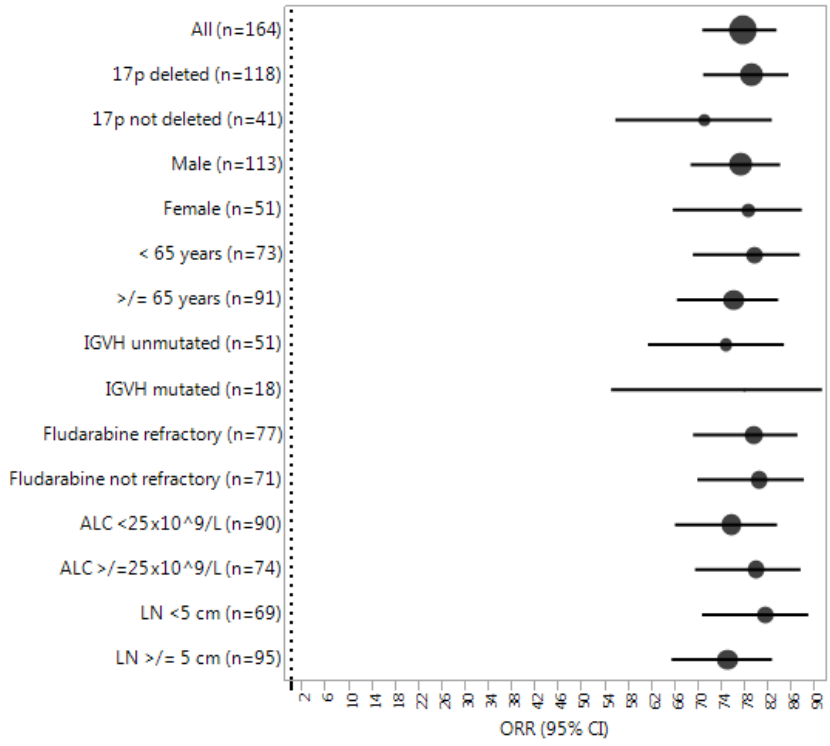
7.1.3. Subpopulations

The overall response rates and 95% CI for each subgroup are represented in Table 23 and the forest plot representation in Figure 6. The studies included >90% patients that were white, so a subgroup analysis based on race was not performed. No outliers were observed among these subgroups.

Table 23: Response rates based on IRC assessment in population subsets

Subset	No. of patients	ORR n (%) (95% CI)	CR rate n (%) (CR/CRi)	nPR n (%)	PR n (%)	No response n (%)
All	164	12 (77.4) (70.5-83.2)	12 (7.3) (8/4)	3 (1.8)	112 (68.3)	37 (22.6)
17p deleted	118	93 (78.8) (70.6-85.2)	8 (6.8) (6/2)	3 (2.5)	82 (69.5)	25 (21.2)
17p not deleted	41	29 (70.7) (55.5-82.4)	3 (7.3) (2/1)	0	26 (63.4)	12 (29.3)
Male	113	87 (77.0) (68.4-83.8)	5 (4.4) (3/2)	2 (1.8)	80 (70.8)	26 (23.0)
Female	51	40 (78.4) (65.4-87.5)	7 (13.7) (5/2)	1 (2.0)	32 (62.7)	11 (21.6)
< 65 years	73	58 (79.5) (68.8-87.1)	7 (9.6) (6/1)	0	51 (69.9)	15 (20.5)
≥ 65 years	91	69 (75.8) (66.1-83.5)	5 (5.5) (2/3)	3 (3.3)	61 (67.0)	22 (24.2)
IGVH unmutated	51	38 (74.5) (61.1-84.5)	3 (5.9) (2/1)	0	35 (68.6)	13 (25.5)
IGVH mutated	18	14 (77.8) (54.8-91.0)	1 (5.6) (1/0)	1 (5.6)	12 (66.7)	4 (22.2)
Fludarabine refractory	77	61 (79.2) (68.9-86.8)	7 (9.1) (3/4)	1 (1.3)	53 (68.8)	16 (20.8)
Fludarabine not refractory	71	57 (80.3) (69.6-87.9)	3 (4.2) (3/0)	1 (1.4)	53 (74.6)	14 (19.7)
ALC <25 $x10^9$/L	90	68 (75.6) (65.8-83.3)	6 (6.7) (4/2)	1 (1.1)	61 (67.8)	22 (24.4)
ALC ≥25 $x10^9$/L	74	59 (79.7) (69.2-87.3)	6 (8.1) (4/2)	2 (2.7)	51 (68.9)	15 (20.3)
Lymph nodes <5 cm	69	56 (81.2) (70.4-88.6)	10 (14.5) (6/4)	3 (4.3)	43 (62.3)	13 (18.8)
Lymph nodes ≥ 5 cm	95	71 (74.7) (65.2-82.4)	2 (2.1) (2/0)	0	69 (72.6)	24 (25.3)

Figure 6: Overall response rate (95% CI) of population subsets



Reviewer Comment: While the ORR or CR rates were not substantially different for any subgroup evaluated, the CR rate tended to be higher in patients with lymph nodes <5 cm and in women. There was no known difference in exposure between men and women, so the higher CR rate could be due to random chance in low samples size with CR. Patients with lower disease burden (lymph nodes <5 cm or ALC <25 x10^9/L) typically have better response rates with any CLL-directed treatment.

7.1.4. Dose and Dose-Response

Review of the data to support the dose selection and the dose-response evaluation were performed by OCP. The findings are summarized here. Doses in the M12-175 study ranged from 150-1200 mg. 400 mg was designated as the recommended phase 2 dose and the recommended marketing dose based on a plateau in the overall response rate in the dose escalation phase as shown in Figure 7. This evaluation includes all patients with CLL and SLL who were enrolled in the dose escalation and dose expansion cohorts in M12-175. Assignments to cohorts were based on the patient's designated cohort dose. Where allowed, some subjects in M12-175 escalated above their DCD, including 7 patients in the 400 mg cohort

who escalated to 600 mg. Patients with SLL were also included in this analysis. For comparison, the response rates for patients with CLL with 17p deletion from M13-982 are included in the figure for comparison. The analysis was based on investigator assessments only because IRC-assessment was only available for the 400 mg cohort. Overall response rate plateaus at 400 mg, but the CR rate shows a potential increase with doses above 400 mg.

Figure 7: Dose-response evaluation

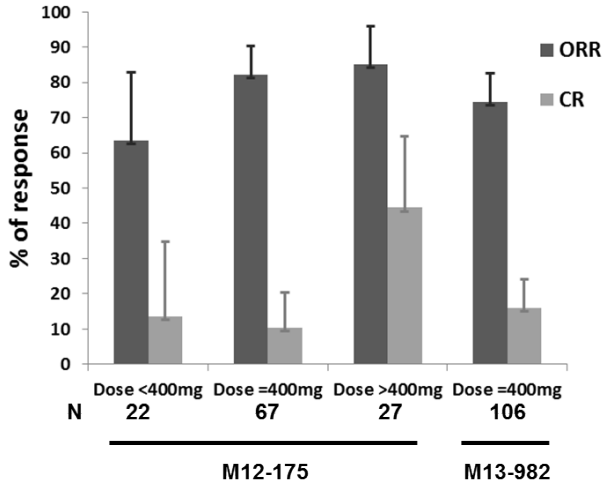


Figure provided by OCP

Reviewer Comment: The overall response rate is the relevant efficacy endpoint in CLL. While CR is desirable, the achievement of a CR does not alter treatment decisions. The potential increase in CR with higher doses is inconclusive due to the patients being allowed to escalate above their designated cohort dose which were not adjusted for in this evaluation. In addition, this evaluation was based on the investigator's evaluation of responses. The rate of CR was significantly lower on IRC assessment for the 400 mg cohort dose and was not evaluated in other doses. No apparent exposure-response relationship was identified for safety.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

In study M13-982, the majority of first disease responses were seen at the first visit after initiation of treatment. Confirmation of response was required 8 weeks after the first response was observed. Per the Applicant's evaluation, the median time to first response was 0.8 months (range 0.1-8.1 months) in patients who achieved a CR, CRi, nPR, or PR. Venetoclax should be continued until intolerable side effects or progression of disease. The persistence of efficacy with continual treatment is discussed in Section 6.1.2 regarding duration of response. The persistence of response after discontinuation of therapy is not known.

Reviewer Comment: Further studies could be considered to evaluate durability of efficacy after discontinuation of venetoclax for patients who have achieved an MRD-negative CR. However, there is currently no evidence to support discontinuation of venetoclax for patients who have a favorable response.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The demographics of the patients studied in both clinical trials generally reflect the demographics of patients with relapsed/refractory CLL. The subset analyses did not identify a population of patients with significantly lower efficacy. While blacks and patients >80 years old were underrepresented, there is no indication that efficacy in these populations would be lower.

While the phase 1 trial was limited to patients who have exhausted available therapies, the phase 2 trial enrolled patients who were not as heavily pre-treated. The development of 17p deletion is often later in the disease, so use in the earlier disease setting in 17p deletion will likely be somewhat limited. The best sequence of therapies for CLL also requires further study. It is unknown if early therapy with venetoclax could lead to resistance to other drugs that could be prior to venetoclax or vice versa.

Compliance in the outpatient setting is difficult to predict, and the effect of poor compliance on disease response is no known. When in remission, CLL can have relatively few disease-related symptoms which could potentially lead to poor compliance. There is no data available to indicate that poor compliance could lead to early resistance to venetoclax treatment, but it does remain a theoretical risk. Concerns for safety with poor compliance are discussed in Section 8.8.2.

7.2.2. Other Relevant Benefits

After the ramp up stage when TLS risk has decreased, the burden of administration is low. The use of a daily oral medication for disease control does not require clinic visits for administration, with physician evaluation only for monitoring of side effects and efficacy.

7.3. Integrated Assessment of Effectiveness

In this reviewer's assessment, the submitted evidence has provided substantial evidence for effectiveness for venetoclax for the treatment of patients with relapsed or refractory CLL with 17p deletion. Evidence of efficacy was provided in the pivotal phase 2 study, M13-982. Patients were required to have received at least one prior CLL-directed therapy, and were

required to have the ultra-high risk 17p del mutation. The primary endpoint was overall response rate in the first 70 patients enrolled based on the IRC-assessment. Response rate evaluations were also conducted for the entire enrolled population of 107 patients based on both investigator and IRC assessments. While the CR rate was lower in the IRC assessment, the ORR results were robust and consistent over all subgroups analyzed.

The primary endpoint of overall response rate is a surrogate endpoint for CLL. While durable ORR has been accepted for regular approval, the interim analysis of this single arm trial does not provide a direct comparison with available therapy or information on durability of response. Because CLL is an indolent disease, the preferred endpoint for regulatory action is progression free survival, whereas demonstration of overall survival may not be required. The use of a surrogate endpoint makes this potentially approvable using the accelerated approval pathway. Accelerated approval requires the evidence to provide a meaningful advantage over available therapies. For patients with R/R CLL with 17p deletion, the available therapies are limited to ibrutinib which has a 48% ORR (0% CR) in patients with 17p deletion or the use of other chemo-immunotherapies that are not labeled for this population and have historically low response rates in exploratory analyses in patients with 17p deletion. In study M13-982, venetoclax monotherapy after a ramp-up phase with a target ongoing dose of 400 mg achieves an ORR of 80% and a CR rate of 8% in patients with 17p deletion based on the IRC-assessment which is a substantial improvement over ibrutinib. Proposed labeling for venetoclax for the treatment of patients with R/R CLL with 17p del is reviewed in Section 10.1. The efficacy results presented in the proposed label reflect only study M13-982.

Venetoclax provides a novel mechanism of action for the treatment of CLL. Targeting the anti-apoptotic protein BCL-2 could potentially overcome resistance to other therapies. The Applicant has an ongoing phase 2 trial, M14-032 which will address the efficacy of venetoclax after failure of B cell receptor inhibitors.

The oral route of administration and convenience of once daily dosing provide an advantage to patients with R/R CLL. After the initial ramp-up phase, the routine visits to the treating oncologist for safety and efficacy monitoring required will be low compared to treatments that require IV administration.

8 Review of Safety

8.1. Safety Review Approach

Three studies were included in the safety database for single agent venetoclax; see Table 4 for details. M13-982 was a phase 2 study for the treatment of patients with R/R CLL with 17p deletion with 107 patients in the main cohort and 38 patients in the safety expansion cohort. M12-175 was a phase 1, dose escalation study for the treatment of patients with R/R CLL/SLL and NHL with 7 patients in the dose escalation part and 60 patients in the safety expansion part treated at 400 mg. 116 patients with R/R CLL/SLL were treated with any dose of venetoclax in the phase 1 study. SLL is the same biological entity as CLL except with disease primarily in the lymph nodes for SLL compared to the bone marrow for CLL. For safety, patients with SLL were included. Study M14-032 is an ongoing phase 2 study of the treatment of patients with R/R CLL who have failed a B cell receptor inhibitor (BCRi; ibrutinib or idelalisib). This study provides safety information for the treatment of patients with R/R CLL with single agent venetoclax. The safety profile for patients with 17p del or who have failed a BCRi is not expected to be different from all patients with R/R CLL. Studies M13-982 and M12-175 were reviewed for efficacy and safety while study M14-032 was reviewed for safety only. The contribution of each study to the safety database is listed in Table 24.

Table 24: Safety database for the treatment of patients with R/R CLL with single agent venetoclax.

	R/R CLL patient treated at 400 mg	R/R CLL patient treated at All doses
M13-982	145	145
M12-175	67	116
M14-032	28	28
Total	240	289

In addition, study M12-175 enrolled 106 patients with NHL treated with single agent venetoclax at doses between 200 mg and 1200 mg daily including a safety expansion cohort at 1200 mg daily. A separate safety evaluation was performed on NHL patients.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The overall exposure of patients to treatment with venetoclax includes patients with R/R CLL enrolled in the single arm studies, as stated in 8.1. The Applicant also submitted data from clinical pharmacology trials in normal volunteers (58 volunteers exposed) and patients with NHL (12 patients exposed). The Applicant also provided safety data from three ongoing single arm trials of venetoclax in combination with other chemo- or immunotherapies (rituximab, bendamustine/rituximab, or obinutuzumab; n=88).

Table 25: All patients who have received venetoclax

Safety Database for Venetoclax Individuals exposed to the study drug in this development program for the indication under review	
Clinical Trial Groups	Venetoclax (n=553)
Normal Volunteers	58
Trials conducted for this indication[1]	289
All other than trials conducted for this indication[2]	88
Controlled trials conducted for other indications[3]	118

[1] patients with R/R CLL with single-agent venetoclax, includes all doses
[2] patients with R/R CLL/SLL treated in combination trials, includes all doses
[3] includes patients with NHL included in M12-175 (n=106) and one clinical pharmacology study (ketoconazole with venetoclax, n=12). Patients in the clinical pharmacology study were not pooled in the safety evaluation for patients with NHL.

In the pooled dataset of patients with R/R CLL/SLL treated at 400 mg venetoclax, the median exposure was 10.3 months (average 9.1 mo), and a maximum of 34.1 months. Many patients were still ongoing on study drug at the time of this interim analysis. Of note, seven subjects in the 400 mg cohort of the phase 1 trial (M12-175) exceeded the dose of 400 mg as allowed per the study protocol. All seven patients escalated to 600 mg.

Table 26: Duration of exposure in patients with R/R CLL/SLL treated with venetoclax at 400 mg

Number of patients exposed to the study drug:		
≤24 weeks	24-48 weeks	≥48 weeks
N=88	N=42	N=110

Reviewer Comment: The Applicant included safety data from patients with CLL treated with venetoclax combination therapy. Due to the variety of backbone chemotherapies used in the combination trials which confound the safety findings in single arm trials, this safety information was not reviewed. Review of safety from clinical pharmacology studies in normal volunteers was also not included.

While venetoclax treatment can be long-term in patients who have ongoing remissions, CLL is a life-threatening condition. Therefore, the ICH-E1A guidelines for the extent of population exposure do not apply.

8.2.2. **Relevant characteristics of the safety population:**

Demography information for patients enrolled in Studies M13-982 and M12-175 are listed in Table 21 for the combined efficacy analysis. The demographics of those trials generally represent the expected demographics of patients with R/R CLL. The addition of 28 patients from study M14-032 did not significantly change the demographic profile in the pooled analysis.

The number of patients enrolled with renal impairment and hepatic impairment is shown in Table 27. Patients with severe renal or hepatic impairment were excluded from both trials.

Table 27: Patients with renal and hepatic impairment in the safety database at 400 mg

	Definition	R/R CLL patient treated at 400 mg
Renal impairment		
Normal	CrCl ≥90 mL/min	45
Mild	CrCl ≥60 to <90 mL/min	102
Moderate	CrCl <60 mL/min)	85[a]
Hepatic impairment		
Normal	total bili ≤1 mg/dL and AST ≤40 U/L	198
Mild	total bili ≤1 mg/dL and AST >40 U/L, or total bili >1 to ≤1.5 mg/dL and any AST	37
Moderate	total bili >1.5 to ≤3 mg/dL and any AST	5

[a] Includes one subject with CrCl <30 mL/min

8.2.3. Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions. Because the data are all from single arm trials, the contribution of the underlying disease to adverse reactions is difficult to estimate. Patients with R/R CLL are elderly with significant comorbidities and concomitant medications. However, this population is a good representation of the US population. The adverse reactions were evaluated over all doses of venetoclax, but the majority of patients were treated at the target dose of 400 mg. The duration of treatment is adequate to allow assessment of adverse reactions over time, and all trials in the current review are still ongoing.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of the safety data submitted was adequate to allow substantial primary review. The Applicant provided analysis-ready datasets for each individual study as well as an integrated dataset reporting AEs in all patients treated with venetoclax monotherapy. The Applicant also provided narratives for all patients with AEs resulting in death, SAEs, AEs leading to discontinuation of the study, and AEs of interest.

8.3.2. Categorization of Adverse Events

For all studies, AEs and SAEs were defined according to ICH E2A guidelines. The severity of events was rated using the NCI CTCAE, version 4.0. A TEAE was defined as any event with onset after the first dose of venetoclax and no more than 30 days after the last dose of venetoclax. AEs were coded using MedDRA dictionary version 17.1.

AEs of special interest (AESIs) identified as important known or potential risks to venetoclax treatment included tumor lysis syndrome, neutropenia, and infection including opportunistic infections. The Applicant evaluated the AESI by the following search criteria:

- Tumor lysis syndrome: standardized MedDRA queries (SMQ) of tumor lysis syndrome (narrow search)
- Neutropenia: Preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis
- Infection: system organ class (SOC) of infections and infestations

For accurate rates of cytopenias, the preferred terms were combined as neutropenia/neutrophil count decreased, thrombocytopenia/platelet count decreased, anemia/hemoglobin decreased, and lymphopenia/lymphocyte count decreased.

Safety data coding was evaluated by comparing the verbatim term and the MedDRA version 17.1 preferred term. Adverse events were assessed by frequency (i.e., events per patient).

There were some areas of splitting of preferred terms, but the splitting did not impact the results to the point that combining these split events would have increased the incidence of the broader event term to be considered for the frequent AE tables. For example, pruritus/generalized pruritus, pneumonia/viral pneumonia/bacterial pneumonia, and upper respiratory tract infection/viral upper respiratory tract infection were separate categories. These categories contributed to the common ARs, and evaluation by preferred term and high level terms to combine these categories is reported in Section 8.4.5. SMQ analysis was also performed using MAED, and no additional safety signals were revealed.

8.3.3. Routine Clinical Tests

See Sections 6.1.1 and 6.2.1 for the frequency of clinical tests for Studies M13-982 and M12-175, respectively. The testing was adequate to assess the risks of serious safety events such as tumor lysis syndrome and cytopenias as discussed in detail below.

8.4. Safety Results

8.4.1. Deaths

The most common cause of death from an AE in the safety population was disease progression (n=13). In patients with R/R CLL treated at all doses (n=289), 8 patients had death from an AE after AEs of malignant neoplasm progression were removed from the evaluation. Note that the Applicant determined that two patients with a reported AE of multi-organ failure were due to disease progression. Each of the remaining deaths was a single event of the following: hemorrhagic stroke, hepatic function abnormal, septic shock, cardiopulmonary failure, sudden death, small intestine obstruction, pneumonia viral, and death (not otherwise specified). All deaths were considered not related or probably not related to study drug by the investigator except for the event of sudden death. The patient with sudden death (patient (b) (6) in study M12-175) experienced fatal tumor lysis syndrome after escalating to 1200 mg and is discussed further in Section 8.5.1. The other causes of death are consistent with elderly population with advanced CLL.

Additional non-treatment emergent deaths due to an AE (those occurring >30 days after treatment discontinuation) were pneumonia, complications of bone marrow transplantation, myelodysplastic syndrome, and cardiorespiratory arrest.

8.4.2. Serious Adverse Events

Serious adverse events in patients with R/R CLL treated with single agent venetoclax at 400 mg are shown in Table 28. The most common SAE of febrile neutropenia is discussed in further detail in Section 8.5.2. Tumor lysis syndrome is discussed in further detail in Section 8.5.1. Investigators determined that cases of febrile neutropenia, pyrexia, TLS, and AIHA were

considered to have a reasonable possibility of being related to venetoclax while pneumonia and atrial fibrillation were considered not related in most cases.

Table 28: Serious Adverse Reactions occurring in ≥2% of patients in patients with R/R CLL treated at 400 mg.

	Pooled studies at 400 mg Total n=240
Any SAE	106 (44)
Pneumonia	12 (5)
Febrile neutropenia	11 (5)
Pyrexia	8 (3)
Autoimmune Hemolytic Anemia	7 (3)
Tumor Lysis Syndrome	5 (2)
Anemia	5 (2)
Atrial Fibrillation	4 (2)
Thrombocytopenia	4 (2)

Of the patients treated at 400 mg, 85 patients had moderate renal impairment defined as creatinine clearance <60 mL/min (one patient was <30 mL/min). SAEs in this subgroup are shown in Table 29.

Reviewer Comment: Venetoclax is not excreted by the kidney, as discussed in Section 4.5.3. Despite that, the rate of SAE was slightly higher in patients with moderate renal impairment (53%) compared to the overall population (44%). This could be impacted by the underlying CLL in patients with renal impairment such as the increased risk of TLS.

Table 29: SAEs in patients with moderate renal impairment

	Moderate renal impairment in pooled studies at 400 mg Total n=85 n (%)
Any SAE	45 (53)
Febrile neutropenia	5 (6)
Pneumonia	5 (6)
Autoimmune hemolytic anemia	4 (5)
Atrial fibrillation	3 (4)
Pyrexia	3 (4)
Abdominal pain	2 (2)
Anemia	2 (2)
Breast cancer	2 (2)
Deep vein thrombosis	2 (2)
Dyspnea	2 (2)
Lower respiratory tract infection	2 (2)
Tumor lysis syndrome	2 (2)

Of the patients treated at 400 mg, only 5 patients had moderate hepatic impairment defined as total bilirubin >1.5 to ≤3 mg/dL and any AST. Due to the small number of patients, a subgroup analysis was not performed.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Of the patients with R/R CLL treated with venetoclax at 400 mg, 21 patients (9%) discontinued venetoclax due to an AE other than disease progression. The most common reasons for discontinuation were autoimmune hemolytic anemia (AIHA) and thrombocytopenia, occurring in two patients each. In the subset of 85 patients with moderate renal impairment treated at 400 mg (n=85), nine patients (11%) discontinued venetoclax due to an AE other than disease progression, all with single events.

Dosage reductions due to adverse reactions occurred in 23 patients (10%). The most frequent adverse reactions leading to dose adjustments were neutropenia (n=7), febrile neutropenia (n=3), and thrombocytopenia (n=3). Of these 23 patients, 8 were able to re-escalate to 400 mg.

Dosage discontinuations due to adverse events occurred in 21 patients (9%), including 6 deaths (see Section 8.4.1). The most frequent adverse reactions leading to drug discontinuation were autoimmune hemolytic anemia (AIHA) in 2 patients and thrombocytopenia in 2 patients. Only 4

events were classified as at least possibly related to study drug by the investigator, two events of thrombocytopenia, one of AIHA, and one event of diarrhea and vomiting.

8.4.4. Significant Adverse Events

Grade ≥3 adverse events defined by NCI-CTCAE in patients with R/R CLL treated with single agent venetoclax at 400 mg are shown in Table 30.

Table 30: Grade ≥3 AEs occurring in ≥10% of patients in patients with R/R CLL treated at 400 mg.

	Pooled studies at 400 mg Total n=240
Any Grade ≥3 AE	177 (74)
Neutropenia	87 (36)
Anemia	42 (18)
Thrombocytopenia	32 (13)

Reviewer Comment: The most common grade ≥3 AEs were cytopenias, which can be managed with growth factors for neutropenia, concomitant medications for thrombocytopenia, or transfusions for anemia and thrombocytopenia. See Section 8.5.2 for further discussion of neutropenia. The majority of cytopenias occurred in the first 90 days of venetoclax treatment.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

All grade adverse events in patients with R/R CLL treated with single agent venetoclax at 400 mg are shown in Table 31. The majority of patient (236, 98%) had an AE. Neutropenia is the most common event and is discussed further in Section 8.5.2. Otherwise, gastrointestinal upset (diarrhea, nausea, vomiting), and other cytopenias were the most common events. The majority of the AEs are consistent with an elderly population with CLL.

Table 31: All Grade AEs occurring in ≥10% of patients in patients with R/R CLL treated at 400 mg.

	Pooled studies at 400 mg Total n=240 n (%)
Any AE	236 (98)
Neutropenia	94 (39)
Diarrhea	85 (35)
Nausea	80 (33)
Anemia	68 (28)
Upper respiratory tract infection	52 (22)
Fatigue	51 (21)
Thrombocytopenia	45 (19)
Pyrexia	38 (16)
Headache	36 (15)
Hyperphosphatemia	35 (15)
Vomiting	35 (15)
Constipation	33 (14)
Cough	32 (13)
Hypokalemia	29 (12)
Edema peripheral	26 (11)
Back pain	24 (10)

For labeling purposes, the Applicant combined neutropenia/neutrophil count decreased (n=109, 45%), anemia/hemoglobin decreased (n=70, 29%), and thrombocytopenia/platelet count decreased (n=52, 22%).

To evaluate for the impact of splitting of MedDRA preferred terms to the overall evaluation, the list of common AEs grouped by higher level term (HLT) is presented in Table 32. No new safety signals were identified by this analysis.

Table 32: Common AEs grouped by HLT occurring in ≥15% patients in patients treated at 400 mg

	Pooled studies at 400 mg Total n=240 n (%)
Any AE	236 (98)
Neutropenias	99 (41)
Nausea and vomiting symptoms	93 (39)
Diarrhea (excluding infective)	85 (35)
Upper respiratory tract infections	82 (34)
Anemias NEC	68 (28)
Asthenic conditions	60 (25)
Thrombocytopenias	49 (20)
Phosphorus metabolism disorders	48 (20)
Potassium imbalance	44 (18)
Lower respiratory tract and lung infections	43 (18)
Musculoskeletal and connective tissue pain and discomfort	43 (18)
Gastrointestinal atonic and hypomotility disorders NEC	39 (16)
Coughing and associated symptoms	38 (16)
Febrile disorders	38 (16)
Headaches NEC	37 (15)

Of the 240 patients with R/R CLL in the safety database who were treated at 400 mg, 160 patients had 17p deletion. The majority of the patients (137) with 17p deletion were from the M13-982 phase 2 trial and per protocol had their deletion status verified by central laboratory evaluation. The remaining patients had 17p deletion evaluations done at their local laboratory. The common AEs seen patients with 17p deletion is shown in Table 33, and is nearly identical to the whole population of patients with R/R CLL. No unique safety signals were identified in patients with 17p del.

Table 33: All grade AEs occurring in ≥10% of patients in patients with 17p deletion.

	17p del treated at 400 mg Total n=160 n (%)
Any AE	156 (98)
Neutropenia	63 (39)
Diarrhea	52 (33)
Nausea	46 (29)
Anemia	44 (28)
Fatigue	32 (20)
Thrombocytopenia	31 (19)
Pyrexia	25 (16)
Upper respiratory tract infection	24 (15)
Headache	20 (13)
Hypokalemia	20 (13)
Nasopharyngitis	20 (13)
Vomiting	20 (13)
Constipation	19 (12)
Hyperphosphatemia	19 (12)
Back pain	16 (10)

The safety profile of single agent venetoclax was also evaluated in patients with R/R CLL treated at all doses (150 mg-1200 mg, n=289) and in the phase 1 arm of the trial for patients with NHL (n=106). Common AEs in those cohorts are shown in Table 34 and Table 35, respectively.

Table 34: All grade AEs occurring in ≥10% of patients in patients with R/R CLL treated at all doses.

	Pooled studies at 400 mg Total n=289 n (%)
Any AE	284 (98)
Neutropenia	118 (41)
Diarrhea	108 (37)
Nausea	107 (37)
Anemia	76 (26)
Upper respiratory tract infection	76 (26)
Fatigue	75 (26)
Thrombocytopenia	55 (19)
Pyrexia	51 (18)
Cough	48 (17)
Headache	47 (16)
Constipation	43 (15)
Vomiting	43 (15)
Hyperphosphatemia	37 (13)
Hypokalemia	33 (11)
Edema peripheral	32 (11)
Arthralgia	28 (10)

Table 35: All grade AEs occurring in ≥10% patients in patients with NHL treated at all doses

	NHL patients treated at all Doses Total n=106 n (%)
Any AE	103 (97)
Nausea	51 (48)
Diarrhea	45 (42)
Fatigue	42 (40)
Vomiting	21 (20)
Decreased appetite	20 (19)
Anemia	19 (18)
Constipation	18 (17)
Back pain	17 (16)
Headache	17 (16)
Cough	16 (15)
Neutropenia	16 (15)
Upper respiratory tract infection	14 (13)
Thrombocytopenia	13 (12)
Dyspnea	12 (11)
Pyrexia	12 (11)
Dizziness	11 (10)
Hypomagnesemia	11 (10)
Edema peripheral	11 (10)

Reviewer comment: The rate of neutropenia is lower in patients with NHL indicating that the rate of neutropenia in CLL is at least partially due to the underlying disease. Additionally, electrolyte abnormality AEs were less common in NHL reflecting the disease burden and on-target effects of venetoclax in CLL.

8.4.6. Laboratory Findings

Chemistry laboratory findings generally reflect the risk of tumor lysis syndrome in patients treated with venetoclax which is discussed further in Section 8.5.1. After the current protocol amendment which uses TLS stratification, monitoring, and prophylaxis at the final recommendations, 66 patients were treated and the most common laboratory AE was hyperkalemia in 20%, hyperphosphatemia in 15%, hypocalcemia in 9%, and hyperuricemia in 6%.

8.4.7. Vital Signs

Potentially clinically significant post-baseline systolic blood pressure, defined as value ≥160 mmHg, was seen in 24.5% of patients with R/R CLL treated at 400 mg. Post-baseline diastolic blood pressure ≥100 mmHg was seen in 10% of patients. Hypertension was reported as an AE in 5% of patients and was ≥ grade 3 in 2%. All other changes in vital signs occurred in <5% of patients.

8.4.8. Electrocardiograms (ECGs)

ECGs were obtained in the phase 2 studies (M13-982 and M14-032) at baselines and at the final visit. In the phase 1 study (M12-175), ECGs were obtained at baseline and steady state. Two patients had grade 1 treatment-emergent abnormal ECG findings, one with abnormal T wave and one with sinus tachycardia.

8.4.9. QT

The phase on study (M12-175) included a thorough QT study. ECGs were measure at baseline, 2, 4, 6, and 8 hours with first dose administration and at steady state (weeks 3, 6, or 7) in both patients with R/R CLL and NHL. 176 patients had QTc data available with doses ranging from 100 to 1200 mg daily. The mean QTcF change from baseline was <5 ms at all times points and doses in both disease settings. The FDA Interdisciplinary Review Team (IRT) for QT Studies reviewed the thorough QT study. IRT found no effect of venetoclax on QTc interval and no relationship between venetoclax exposure and changes in QTc interval.

8.4.10. Immunogenicity

Immunogenicity is not applicable to this small molecule drug.

8.5. Analysis of Submission-Specific Safety Issues

Based on non-clinical data or early clinical trial data, the Applicant identified several AEs of special interest. Tumor lysis syndrome occurred early in clinical development from on-target killing of CLL cells with venetoclax treatment, and two deaths and one patient with renal impairment requiring dialysis were seen. This is the most serious safety issue and is discussed in detail below. Cytopenias were seen in pre-clinical studies as well as studies of the non-selective BCL-2 inhibitor, navitoclax. Patients with CLL often have disease-related cytopenias that can increase the risk. Worsening cytopenias can lead to an increased risk of infections or bleeding which were also collected as AEs of special interested. Other AEs of special interest collected in these studies, Richter's transformation, second primary malignancy, and drug-related hepatic disorders are described below.

8.5.1. Tumor Lysis Syndrome

The first three patients enrolled on the phase 1 study, M12-175, experienced laboratory tumor lysis after the first dose of venetoclax at 100 mg or 200 mg. The protocol was amended (Amendment 3, July 19, 2011) to lower the starting dose to 50 mg and to establish a 2- to 3-week ramp-up period with a maximum designated cohort dose of 1200 mg. Oral hydration and uric acid reducers were also introduced. Amendment 5 of M12-175 (April 27, 2012) added mandatory hospitalization for Day 1 and more stringent TLS prophylaxis.

In December 2012, 2 fatal events and 1 event of renal failure requiring dialysis occurred from TLS in patients with high tumor burden. Patient (b) (6) in study M13-365 (Phase 1b study of venetoclax + rituximab in R/R CLL/SLL) died from TLS within 24 hours of the first dose of 50 mg. Patient (b) (6) in M12-175 died from TLS within 48 hours of dose escalation to 1200 mg. Patient (b) (6) n study M12-175 had acute renal failure requiring dialysis after the first dose of 50 mg without appropriate prophylaxis. These events resulted in a Sponsor-initiated partial clinical hold with no enrollment of new subjects and reduction in the dose of venetoclax to 600 mg for existing subjects.

In May 2013, the partial clinical hold was removed under Amendment 8 for M12-175 and Amendment 2 for M13-982 which lengthened the ramp-up dosing period to be over 5 weeks, starting with a single test dose of 20 mg and with a final target dose of 400 mg. The amendments provided enhanced monitoring and TLS prophylaxis measures including oral and IV hydration, a uric acid reducing agent, and hospitalization for the first doses at 20 mg and 50 mg with intensive laboratory monitoring in all patients.

TLS risk categories based on disease bulk were introduced under the amendments.

- Low risk: requires all lymph nodes all <5 cm AND ALC <25 $x10^9$/L.
- Medium risk: any LN ≥5 cm to <10 cm OR ALC ≥25 $x10^9$/L.
- High risk: any LN ≥10 cm OR ALC ≥25 $x10^9$/L AND any LN ≥5 cm. 58 subjects with R/R CLL treated with venetoclax monotherapy at 400 mg were enrolled under these amendments.

Laboratory monitoring:

- 72 hours prior to first dose, correct as needed
- Hour 0 (pre-dose), 8, and 24 hours of first dose at each dose level for low and medium risk patients
- Hour 0 (pre-dose), 4, 8, 12, and 24 hours of first dose at each dose level for high risk patients
- Aggressive correction of electrolyte abnormalities at any time point
- Give next dose only when electrolytes have been stable without treatment for at least 24 hours

In May 2014 after review of the 58 subjects enrolled post-May 2013, the final TLS risk stratification and prophylaxis measures were introduced under Amendment 3 for M13-982. The risk stratification was unchanged from the prior amendments. All subjects started at 20 mg for 1 week. Low and medium risk patients were treated as outpatient with electrolyte monitoring at baseline and 8 and 24 hours with real-time monitoring of results. High-risk patients were hospitalized for first dose at 20 mg and 50 mg, and then treated as an outpatient for subsequent dose ramp-up. Oral uric acid reducing agents and oral fluids were initiated 72 hours prior to dosing with venetoclax. Additional IV fluids were given for medium- and high-risk patients. Rasburicase was recommended for high-risk patients, especially those with high baseline uric acid. Reassessment of tumor burden on current ALC with adjustment of TLS risk categorization was allowed for high-risk patients at subsequent dose levels.

A summary of the number of patients enrolled in the venetoclax development under each step of TLS monitoring and prophylaxis is summarized in Table 36.

Laboratory tumor lysis was defined using the Howard criteria[23] which is ≥2 of the following criteria within 24 hours of each other: K >6 mmol/L, UA ≥ 476 µmol/L, Ca ≤1.75 mmol/L, or Phos > 1.5 mmol/L. Other tumor lysis was defined as laboratory abnormalities that did not meet the Howard criteria. Clinical tumor lysis was defined as laboratory tumor lysis with an associated increase in serum creatinine level of 0.3 mg/dL (or a single value >1.5x ULN if no baseline was available) or the presence of oliguria (average urine output of <0.5 mL/kg/hr for 6 hours), (2) cardiac arrhythmias or sudden death, (3) seizure. Other reported TLS include patients who had a TEAE reported of TLS, but the laboratory findings did not meet the criteria for laboratory TLS.

The rate of TLS reported prior to the May 2013 amendment was 11.7% (9/77) with 6.5% clinical tumor lysis, including the deaths and dialysis discussed above. After the May 2013 amendments, the rate of tumor lysis was 4.3% (10/234) with no clinical tumor lysis. After the May 2014 amendment, the rate of tumor lysis was 6.1% (4/66) with no clinical tumor lysis. The results in these subsets are summarized in Table 36.

Table 36: Number of patients and rates of TLS with each major amendment

	Patients with CLL treated with monotherapy or combination therapy at any dose	Rate of any TLS n (%)	Rate of clinical TLS n (%)
Pre-May 2013 Amendment	77	9 (11.7)	5 (6.5)
After 1st Major Amendment (May 2013)	234	10 (4.3)	0
After 2nd Major Amendment (May 2014)	66	4 (6.1)	0
Total	377	23 (6.1)	5 (1.3)

The final tumor lysis risk stratification, monitoring, and prophylaxis were conveyed in the prescribing information in tabular format; see Section 10.1.

Dose modification and discontinuation guidelines for TLS: At any dose level, the subsequent dose of venetoclax was held for any clinically significant electrolyte abnormalities until the abnormality resolved. Aggressive management of electrolyte abnormalities are required including hydration, potassium chelators or other reducing agents, phosphate binders, anti-hyperuricemics, or calcium replacement. After resolution of the electrolyte abnormalities, venetoclax dosing could be resumed after re-assessment of risk (including tumor burden status). All subjects must receive the intended dose for at least 7 days before increasing to the next higher dose.

Reviewer Comment: The data in this section is a review of the Applicant's analysis which was not independently verified by the clinical reviewer because the TLS analysis spanned all trials of venetoclax in patients with CLL including combination trials that were not reviewed as part of this submission.

8.5.2. Neutropenia

Neutropenia is a common toxicity seen in patients with CLL who have received multiple prior therapies and can be due to bone marrow infiltration by CLL or reduced bone marrow reserves after therapy. In the safety cohort treated at 400 mg of venetoclax, 27.5% had low neutrophil count at baseline. Further analysis was completed by the Applicant to pool preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis. With this grouping of AEs, 46.7% (112/240) had AE of neutropenia. These AEs were grade ≥3 in 42.1% (101/240) and reported as an SAE in 5.8% (14/240). Dose reduction due to an AE of neutropenia occurred in 4.2% (10/240). Despite the

common occurrence of neutropenia, most cases resolved with standard of care treatment of antibiotics and G-CSF when indicated. The risk of neutropenia decreases over time during treatment with venetoclax.

In study M13-982, thirty-nine of 145 subjects (26.9%) received filgrastim, 17.9% received pegfilgrastim, 8.3% received lenograstim, and 4.8% received G-CSF for treatment of or prophylaxis for neutropenia or febrile neutropenia. In study M12-175: Forty-seven (40.5%) subjects received granulocyte colony stimulating factor (G-CSF) for treatment of or prophylaxis for neutropenia or febrile neutropenia.

Even with the high rate of neutropenia, only 5.4% (13/240) reported febrile neutropenia, and the occurrence of neutropenia or febrile neutropenia did not correlate with infections.

8.5.3. **Richter's Syndrome**

Richter's Syndrome or Richter's Transformation is the transformation of CLL into an aggressive lymphoma, most commonly diffuse large B cell lymphoma (DLBCL)[24]. Incidence of Richter's in CLL difficult to estimate because it is included in the definition of progressive disease, and is often reported as only progressive disease without further detail. The incidence of Richter's transformation is estimated at 2-10%[25] with some reports as high as 20%[26].

In patients treated with single-agent venetoclax at all doses, 10.0% (29/289) patients discontinued venetoclax for Richter's transformation. Thirteen of those reports of Richter's were within 6 months of initiating venetoclax which could indicate that the Richter's transformation could have initiated prior to starting the drug. The rate of Richter's transformation in patients treated with single-agent venetoclax is within the expected rate of Richter's transformation in patients with CLL, though this warrants ongoing monitoring.

Reviewer Comment: In the safety database of 289 patients, 61 patients had progressive disease. Twenty-nine of the 61 patients (48% of progressions) were due to Richter's transformation. The overall rate of Richter's (10%) is in line with literature reported rates, but a randomized trial will further inform of any potential increased risk due to venetoclax treatment.

8.5.4. **Infections**

Infections are a common complication in patients with CLL due to bone marrow involvement of their CLL, previous cancer-directed therapies. Heavily pre-treated patients are at highest risk. The majority of infections in untreated CLL are bacterial, predominately lower respiratory tract infections, where fungal and opportunistic infections are less common[27].

In patients with R/R CLL treated with venetoclax at 400 mg, infections were reported in 65.4% (157/240) of subjects and were grade 1 or 2 for the majority of these subjects (114/157). Serious infections AEs occurred in 43 patients (18%). The most common reported infections were upper respiratory tract infection, nasopharyngitis, pneumonia, and urinary tract infections. The most common serious infections were pneumonia (5%) and upper respiratory tract infection (1%). Two deaths were reported in the infections SOC, one with pneumonia due to influenza A and one with septic shock with grade 4 neutropenia. No clear association was seen between the rates of infection and the rates of neutropenia, and higher doses of venetoclax did not correlate with higher rates of infections.

For comparison, the rates of infections in patients with NHL treated with venetoclax, most at higher doses, was only 36% (38/106) subjects with infection SAEs in 10% (11/106). Therefore, a significant proportion of infections seen in patients with CLL are due to the underlying immune compromise and not the initiation of venetoclax treatment.

8.5.1. **Other AEs of Special Interest**

The Applicant evaluated the following AEs of special interest:

- Second primary malignancy: Due to immune impairment, patients with CLL are at higher risk of second primary malignancies, most commonly skin cancers, and also including soft tissue sarcomas, colorectal cancer, and lung cancer[28]. Review of MAED SMQ of malignant tumors and myelodysplastic syndrome, excluding reports of CLL progression, indicated 28 patients (12%) with a second primary malignancy, some patients had more than one event. Squamous cell skin cancer occurred in 14 patients and basal cell carcinoma occurred in 7 patients. Breast cancer occurred in 2 patients. All other events were single occurrences of various malignancies without a specific pattern.
- Bleeding AEs: Due to the high incidence of patients who are on baseline concomitant anticoagulation due to the high risk of cardiovascular disorders (i.e. stroke or TIA) in the elderly patient population with CLL, bleeding adverse events were collected as an AESI. Of all patients with CLL treated with venetoclax at 400 mg, 101 patients (42%) were receiving anticoagulation and/or antiplatelet medications (except warfarin which was excluded). The SMQ of Hemorrhage (narrow) indicated 33 patients (14%) had an AE in this category. Six of these events were considered serious, and all serious events were considered not related to the study drug by investigators. Nine events were ≥grade 3, and of these 9 patients, 6 had underlying ITP. The remaining three subjects had AEs that were considered unrelated the study drug by investigators (fatal hemorrhagic stroke after DVT, gastric ulcer hemorrhage from massive infiltration by Richter's transformation, and upper GI hemorrhage with reflux esophagitis).

- Drug-related hepatic disorders: Ten patients (4%) with R/R CLL treated at 400 mg had an AE in the hepatobiliary SOC. One event was an SAE of fatal hepatic function abnormality in a patient with underlying fatty liver and multiple concomitant medications. This event was considered to have no reasonable possibility of being related to venetoclax by the investigator. There were no reports of drug-induced liver injury, and no patients met Hy's law criteria (ALT >3x ULN and TBL >2x ULN without notable increase ALP (<2xULN); see also the FDA Guidance for Industry Drug-Induced Liver Injury).

8.6. Specific Safety Studies/Clinical Trials

No specific safety studies were performed.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

A formal human carcinogenicity was not conducted for venetoclax. Review of the development of second primary malignancies is found in Section 8.5.1. MAED SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps) included events in 58 patients (20%) in patients with CLL treated at all doses of venetoclax. The majority of these events were CLL progression or non-melanoma skin cancers as discussed above.

8.7.2. Human Reproduction and Pregnancy

No pregnancies were reported in the safety database for patients with R/R CLL treated with single agent venetoclax. Two pregnancies have been reported in other studies with venetoclax use. One pregnancy was in the partner of a (b) (6) male who was taking venetoclax in the MURANO trial. A live infant was born with no congenital anomalies or neonatal complications. One pregnancy was reported in a female patient with systemic lupus erythematosus (SLE) in study M13-093. A live infant was born with no congenital anomalies or neonatal complications.

Nonclinical findings of decreased sperm count are reviewed in Section 4.4.

8.7.3. Pediatrics and Assessment of Effects on Growth

The Applicant was granted Orphan Designation for venetoclax for the treatment of patients with CLL and therefore is exempt from pediatric studies under the Pediatric Research Equity Act (PREA).

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There have been no reported cases of overdose of venetoclax in the CLL clinical studies. Venetoclax does not have abuse potential because of its toxicity profile.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Venetoclax is not currently marketed in the US or foreign markets.

8.8.2. Expectations on Safety in the Postmarket Setting

The main safety concern that could pose a significant risk in the post-marketing setting is tumor lysis syndrome. As discussed in Section 8.5.1, early deaths were seen, particularly in patients with bulky disease, treated with venetoclax. The risks were mitigated with initiation of the ramp up dosing and clear guidelines for risk assessment, stratification, monitoring, and prophylaxis. The ramp up packaging and instructions and TLS guidelines were clearly outlined in the prescribing information. There are no important differences in how the drug was administered in the clinical trial compared to the expected post-marketing setting. However, in the post-marketing setting, non-compliance with the ramp up dosing or non-adherence to the TLS guidelines could increase the risk of serious events from TLS.

8.9. Additional Safety Issues From Other Disciplines

No additional safety issues were identified by other disciplines.

8.10. Integrated Assessment of Safety

In this reviewer's assessment, the submitted evidence has provided substantial evidence for the safe use of venetoclax for the treatment of patients with relapsed or refractory CLL. Evidence of safety was provided from all patients with R/R CLL and SLL treated at all doses of venetoclax in the pivotal phase 2 study, M13-982, and the supportive studies, M12-175 and M14-032. Although most patients treated with venetoclax had a treatment emergent AE, only about 10% discontinued venetoclax due to AE other than disease progression. Generally, the pattern of adverse reactions reflects events expected for a heavily pre-treated elderly population with R/R CLL with the exception of on-target effects of tumor lysis syndrome and neutropenia. In these single arm trials, the contribution of the drug compared to the contribution of the underlying disease is difficult to determine.

TLS risk is well described above. TLS events resulted in a partial clinical hold early in development. The risk assessment and prophylaxis were modified in two major iterations, and the final guidelines used in the clinical trial reflect the guidelines to be used in the post

marketing setting. The final risk of TLS was 6% and all events were limited to laboratory finding and with low clinical consequence. The ramp up dosing can be burdensome to some patients, but overall is fairly manageable with the Start Pack, Quick Start Guide, and Patient Labeling described below.

The risk of neutropenia is significant both from underlying CLL and from treatment with venetoclax. The neutropenia is usually manageable with standard of care treatments including antibiotics and G-CSF. Importantly, no correlation was found between rates of neutropenia and infections. Anemia and thrombocytopenia were less common and could be managed with red blood cell or platelet transfusions.

The overall rate of Richter's transformation was within the range of that seen with underlying CLL, so the added risk of treatment with venetoclax is not clear.

Other than TLS and neutropenia, venetoclax is generally a well-tolerated drug. Gastrointestinal upset (nausea, vomiting, and diarrhea) occurs, but is typically low grade and did not lead to dose interruptions. The other adverse reactions seen were generally within that expected for elderly patients with CLL and heavy pretreatment with CLL-directed therapies.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting is not planned for this application because the Division of Hematology Products is familiar with the trial design and clinical trial endpoints. We did not consult special government employees (SGEs) because this application was conducted on an expedited timeline due to its Breakthrough Therapy designation.

10 Labeling Recommendations

10.1. Prescribing Information

1 INDICATIONS AND USAGE: TRADENAME is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate.

Reviewer Comment: (b) (4)

(b) (4)

2 DOSAGE AND ADMINISTRATION: The ramp up phase was described in tabular format as shown in Table 37.

Table 37: Dosing Schedule for Ramp-Up Phase

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

(b) (4)

For clarity and to minimize the risk to patients, the TLS risk categories and recommended prophylaxis was included in tabular format with defined recommendations based on the clinical trials, as shown in Table 38.

Table 38: Tumor Lysis Syndrome Risk Categories and Recommended Prophylaxis Based on Clinical Trial

(b) (4)


(b) (4)

Dose modifications were recommended in the following table. The references to Table 3 in the label are the same as Table 5 in this review.

Table 39: Recommended Dose Modifications for Toxicities

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 3) *[see Dosage and Administration (2.3)]*.
		For any events of clinical TLS, resume at a reduced dose following resolution (see Table 3) *[see Dosage and Administration (2.3)]*.
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt TRADENAME. Once the toxicity has resolved to Grade 1 or baseline level, TRADENAME therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt TRADENAME. Follow dose reduction guidelines in Table 3 when resuming treatment with TRADENAME after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia) *[see Warnings and Precautions (5.2)]*	1st occurrence	Interrupt TRADENAME. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with TRADENAME if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, TRADENAME therapy may be resumed at the same dose.
	2nd and subsequent occurrences	Interrupt TRADENAME. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 3 when resuming treatment with TRADENAME after resolution. A larger dose reduction may occur at the discretion of the physician.
Consider discontinuing TRADENAME for patients who require dose reductions to less than 100 mg for more than 2 weeks.		

4 CONTRAINDICATIONS: Concomitant use of TRADENAME with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated, as discussed in Section 4.5.3 of this review.

5 WARNINGS AND PRECAUTIONS: Tumor lysis syndrome, neutropenia, and immunizations.

6 ADVERSE REACTIONS: Common adverse reactions were listed by body system for any grade and grade 3/4. The common AEs are listed in Section 8.4.5 of this review.

7 DRUG INTERACTIONS: Dose adjustment recommendations for moderate CYP3A inhibitors, P-gp inhibitors, and CYP3A inducers was included as described in Section 4.5.3 of this review.

8 USE IN SPECIFIC POPULATIONS: There is no human data on the risks of venetoclax on the fetus. Animal data showing embryo-fetal risk in mice is described as in Section 4.4 of this review. Safety database in geriatric patients was described from the three clinical trials. No differences in overall safety were seen in the geriatric population.

14 CLINICAL STUDIES: The planned accelerated approval will be in patients with R/R CLL with 17p deletion. Only study M13-982, the phase 2 study for patients with 17p deletion, was included in the label. (b) (4)

(b) (4)

17 PATIENT COUNSELING INFORMATION: Information is provided to the prescriber to counsel patients regarding TLS, neutropenia, drug interactions, immunizations, and pregnancy/lactation. Patients are also advised to take venetoclax with a meal at approximately the same time every day.

10.2. Patient Labeling

A Medication Guide was included in the prescribing information by the Applicant. It conveys the risks, signs and symptoms of TLS, and the importance of hydration. The medication guide also conveys the importance of potential drug-drug interactions.

Dosing during the ramp up period will be with the use of the Starting Pack and Quick Start Guide as described in Section 4.7.

10.3. Nonprescription Labeling

Venetoclax will be provided with a prescription only.

11 Risk Evaluation and Mitigation Strategies (REMS)

The risks of venetoclax including TLS can be adequately managed in the post-market setting through product presentation and labeling. Presentation for tablets for the ramp-up period will be in a Starting Pack which contains four 7-day wallets and a Quick Start Guide with recommended hydration. The package insert will also include a Medication Guide. There are no additional risk management strategies required beyond the recommended packaging and labeling. Therefore, the subsequent subsections are not applicable for this review and have been omitted.

12 Post-marketing Requirements and Commitments

The following Post-marketing Requirements are planned for this application:

- Confirmatory Trial: Conduct a randomized, phase 3 trial comparing venetoclax and rituximab versus bendamustine and rituximab in patients with relapsed or refractory CLL (including 17p del). (b) (4) The title of this trial is: 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." (b) (4)
- Drug-drug interaction Study with a P-gp substrate: To investigate the effect of single dose venetoclax on the pharmacokinetics of a P-gp substrate.
- Hepatic Impairment Study: To evaluate the pharmacokinetics of venetoclax in subjects with varying degree of hepatic impairment.

13 Appendices

13.1. References

1. Howlader N, et al., *SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.*
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11. Furman, R.R., et al., *Idelalisib and rituximab in relapsed chronic lymphocytic leukemia.* N Engl J Med, 2014. **370**(11): p. 997-1007.
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13.2. Financial Disclosure

Covered Clinical Study: M13-982

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 58 investigators, 316 sub-investigators		
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): 4 investigators, 2 sub-investigators		
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: 5 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in 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): 0		
Is an attachment provided with the reason: n/a	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: M12-175

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 12 investigators with 105 sub-investigators		
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): 1 investigator, 2 sub-investigators		
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: 1 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 2		
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): 0		
Is an attachment provided with the reason: n/a	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: M14-032

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 14 investigators, 144 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 [1 had a spouse who was an employee]		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 investigator, 3 sub-investigators		
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: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in 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): 0		
Is an attachment provided with the reason: n/a	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: M13-365

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 7 investigators, 70 sub-investigators		
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): 1		
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: 0 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in 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): 0		
Is an attachment provided with the reason: n/a	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Table of other trials submitted

Table 40: List of trials submitted for venetoclax in combination with other therapy

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Other submitted studies (combination trials)							
GP28331	Phase 1b, safety/ tolerability of combination therapy of venetoclax with obinutuzumab in R/R CLL and previously untreated CLL. Open-label, single arm, dose-finding and safety expansion	Venetoclax tablet, daily, oral. Lead-in period followed by venetoclax dose escalation cohorts (100 mg up to 400 mg). Obinutuzumab: 1000 mg IV; 3 doses during Cycle 1 (first dose over 2 consecutive days: 100 mg on Day 1 and 900 mg on Day 2), then every 28-days for up to 6 cycles.	Primary: MTD of venetoclax in combination with obinutuzumab; safety, tolerability Secondary: PK/PD of combination, preliminary efficacy by ORR, DOR, CR rate, PFS, and OS Exploratory: potential biomarkers, MRD, anti-therapeutic antibodies to obinutuzumab	Combination therapy: ~6 months, venetoclax: up to 1 year following last subject enrollment	20 at data cutoff Planned 90	R/R or previously untreated CLL ≥18 years of age	8 sites in 2 countries

GO28440	Phase 1b, safety/ tolerability of combination therapy of venetoclax with bendamustine and rituximab in R/R CLL and previously untreated CLL. Open-label, dose-finding and safety.	Venetoclax tablet, daily, oral. Lead-in period followed by venetoclax dose escalation cohorts (100 mg up to 400 mg). Bendamustine 70 mg/m^2 IV for R/R CLL or 90 mg/m^2 IV for previously untreated CLL on 2 consecutive days each 28-day cycle for 6 cycles Rituximab: 375 mg/m^2 IV during Cycle 1 and 500 mg/m^2 IV during Cycles 2 – 6	Primary: MTD and schedule of venetoclax in combination with bendamustine and rituximab Secondary: PK/PD, preliminary efficacy	Combination therapy: ~6 months, venetoclax: up to 1 year following last subject enrollment	19 at data cutoff Planned 90	R/R or previously untreated CLL ≥18 years of age	10 sites in 3 countries

M13-365	Phase 1b, safety/ tolerability of combination therapy of venetoclax with rituximab in R/R CLL. Open-label, non-randomized, dose-finding and safety.	Venetoclax tablet, daily, oral. Lead-in period followed by venetoclax dose escalation (200 up to 600 mg) Rituximab: 375 mg/m^2 IV on Day 1 of Month 1, followed by either 5 or 7 doses at 500 mg/m^2 IV over a period of approximately 6 months	Primary: safety, MTD, RPTD of venetoclax in combination with rituximab; tolerability, optimal lead-in period Secondary: PK, exploratory efficacy by ORR, DOR, TTP Exploratory: PD, pharmacogenetics, MRD	Up to 2 years following last subject enrollment	49 (41 Dose Escalation Cohorts, 8 Safety Expansion Cohort) Planned up to 50 (30 in dose escalation and 20 in safety expansion)	Subjects with relapsed CLL or SLL ≥18 years of age	6 sites in 2 countries

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CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Hematology Products
April 10, 2015

Summary Box

1. IND 110159
2. Sponsor: AbbVie, Inc.
3. Drug: Venetoclax (ABT-199)
4. Indication: For the treatment of patients with relapsed or refractory (R/R) chronic (b) (4) leukemia who harbor the 17p deletion (17p del) cytogenetic abnormality (17p del CLL)
5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition? Yes.
6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints? Yes, Ventoclax has the potential to provide a substantial improvement over available therapies for the treatment of patients with 17p del CLL with preliminary evidence of complete disease responses.

Division: Division of Hematology Products
Medical officer: Lori Ehrlich
Clinical Team Leader: Virginia Kwitkowski

1. Brief description of the drug

Venetoclax is a Bcl-2 family protein inhibitor. Bcl-2 is an oncogenic protein that is overexpressed in some lymphoid malignancies and is associated with increased resistance to chemotherapy. CLL cells are almost universally dependent on Bcl-2; therefore, inhibition of Bcl-2 could restore apoptosis in CLL cells. Because Bcl-2 is downstream of other survival signals such as p53, it is anticipated that cells with p53 dysfunction or those resistant to other therapies will remain responsive to venetoclax.

2. Brief description of the disease and intended population

CLL is a neoplasm composed of monomorphic small, round to slightly irregular, mature B cell lymphocytes in the peripheral blood, bone marrow or lymphatic tissue. CLL is the most common leukemia of adults in Western countries. Based on SEERS data from 2004-2008 the age adjusted incidence rate of CLL is approximately 4.2 per 100,000 men and women per year with the rate in men being approximately twice that of women. From 2004-2008 the median age of diagnosis was 72 years of age with approximately 70% of patients being diagnosed at age 65 or later.

The clinical course of CLL varies depending on risk stratification by the Rai staging system or Binet classification but it is typically a slowly progressing disease. Chromosomal abnormalities such as del 17p and 11q are associated with a significantly poorer prognosis. 17p del is present in 5-7% of patients with early stage CLL[1] and has been correlated in multiple clinical studies to have higher tumor burden, shorter progression-free survival, and shorter overall survival[2]. Higher rates of refractoriness to standard chemotherapies have been seen in this population. The median overall survival for patients with the 17p deletion mutation has been consistently observed as less than 24 months[2].

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

In support of their Breakthrough Therapy Designation Request, the Sponsor reports the best overall response rate with rates of complete responses and partial responses. They have provided supporting information on minimal residual disease and safety.

For their ongoing phase 2 trial, M13-982, the primary endpoint is overall response rate. The secondary endpoints are complete response rate, partial response rate, duration of response, progression free survival, time to progression, overall survival, and percent of subjects proceeding to allogenic stem cell transplant.

In CLL, the ultimate clinical benefit endpoint is overall survival, but the long duration of studies needed to reach median overall survival is often limiting in this disease. The division has previously accepted progression free survival for regular approval or overall response rate with a long duration of response for accelerated approval. Rate of complete responses and evidence of negative minimal residual disease have been provided as supporting information.

4. Brief description of available therapies (if any)

Only one agent, ibrutinib, has been approved in the US specifically for the 17p del subset of patients with CLL. The overall response rate for ibrutinib in the trial that led to its approval was 47.6% (vs. 4.7% in the control arm) with all responses categorized as partial and no complete responses. Idelalisib is approved in combination with rituximab for the treatment of patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. Though not approved specifically for the treatment of patients with 17p del, this regimen is recommended for these patients in the NCCN guidelines and approved in Europe for first line treatment for patients with 17p del or TP53 mutations unsuitable for chemo-immunotherapy. The response rate for idelalisib in combination with rituximab was 78.3% with no complete responses. Common standard therapies of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab have historically low response rates of 35% and 7%, respectively. See Table 1 for a summary of the currently available therapies for 17p del CLL.

Table 1: Treatment Options for 17p del CLL

Trial	Product (s)	N	Response Rate in del17p CLL	% Complete Response
Ibrutinib vs. ofatumumab	Ibrutinib*	127 (63 on ibrutinib)	47.6% vs. 4.7%	0%
Rituximab ± idelalisib	Idelalisib + Rituximab	46	78.3%	0%
Single arm (Badoux 2011 Blood)[3]	Fludarabine + Cyclophosphamide + Rituximab	20	35%	0%
Single arm (Fischer 2011 JCO)[4]	Bendamustine + Rituximab	14	7%	7%

* FDA approved specifically for patients with 17p del CLL

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

Ibrutinib (Imbruvica) was previously granted Breakthrough Therapy Designation for 17p del CLL, and has since been approved for that indication. Obinutuzumab (Gazyva), ofatumumab (Arzerra), and idelalisib (Zydelig) have been granted BTD for CLL.

6. Description of preliminary clinical evidence

Patient information was submitted from two ongoing trials of venetoclax in relapsed and refractory CLL. The first was a phase 1 trial, M12-175, for determination of the recommended phase 2 dosing. This trial enrolled 56 patients with CLL in the dose-finding portion and 60 patients in a safety expansion cohort. Of those, 8 patients had 17p del CLL and were treated at the target dose of 400 mg daily. The second trial was a phase 2 study, M13-982, open-label single-arm trial of single-agent venetoclax for the treatment of relapsed/refractory 17p del CLL with a planned enrollment of 107 patients in the main study and 50 in an safety expansion cohort. Of those enrolled on that trial, 25 patients have completed the 36-week response assessment or have discontinued the study. For the total 33 patients, the median time on study was 10.1 months (range 1.3-17.0 months) with a median number of prior treatment regimens of 4, and 37.5% of patients were fludarabine refractory.

A summary of the best responses for these patients are shown in Table 2. An overall response rate of 82% was seen with 9% complete responses and 6% complete responses with incomplete marrow recovery (CRi). Partial responses were seen in an additional 67% of patients, and stable disease was seen in 18%. At the time of reporting, of the 25 subjects in Study M13-982, 19 remain on study, 4 discontinued for progressive disease, 1 discontinued for an adverse event, and 1 proceeded to allogeneic transplant after achieving a nodular PR and is still disease-free 6 months after transplant. For the 8 subjects in Study M12-175, 5 remain on study and 3 discontinued for progressive disease.

Table 2: Best Response for Patients with 17p del CLL Treated with Venetoclax

Response Category	M13-982 N=25	M12-175 N=8	Total N=33
ORR	84%	75%	82%
CR	12%	0	9%
CRi	8%	0	6%
nodular PR	8%	0	6%
PR	56%	75%	61%
SD	16%	25%	18%
PD	0	0	0

Of the 25 patients from trial M13-982, 8 had testing for minimal residual disease (MRD) at the time of complete remission. Two of the 8 patients achieved MRD negativity with a sensitivity of <10-4 cells. Three of the remaining patients have had sequential MRD assessments, and the MRD level continues to decrease.

The Sponsor submitted a summary of safety information for 279 patients who have received venetoclax as monotherapy or in combination with rituximab. The most common adverse reactions were nausea (36%), diarrhea (36%), neutropenia (30%), fatigue (25%), and anemia (24%).

The serious safety risks identified to date are neutropenia and tumor lysis syndrome (TLS). Tumor lysis syndrome was identified as an on-target effect that occurred soon after initiating therapy with venetoclax and in subjects with high tumor burden. The TLS rate from the initial dose-ranging studies was 19.6%, including two deaths and one occurrence of acute renal failure requiring dialysis. Upon intensification of monitoring and prophylactic treatments, the rate of TLS has been reduced to 9.3% and 1.7%, in the main cohort of study M13-982 and the safety expansion cohort of study M12-275, respectively. No further deaths or events requiring dialysis have occurred. The Division believes that the current dose escalation, intensive monitoring, and prophylactic measures for patients to be treated with venetoclax is adequate at this time.

Severe (grade 3-4) neutropenia is reported in 42% of patients with relapsed/refractory CLL receiving venetoclax. Neutropenia with venetoclax appears to be responsive to dose interruptions and granulocyte colony stimulating factor. The rate of grade ≥3 infections in this R/R CLL population at the 400 mg proposed dose of venetoclax was approximately 16%, which is consistent with the historical rates for patients in this setting[5].

Deaths due to adverse events in studies of venetoclax range from 0-8.4%. This compares with 4.6% in the ibrutinib CLL trial (PCYC-1112-CA) and 2.7% in the idelalisib CLL trial (312-0116).

7. Division's recommendation and rationale

DHP recommends that venetoclax be granted Breakthrough Therapy Designation for Relapsed or Refractory CLL harboring the 17p deletion mutation. The disease is a serious condition, and preliminary clinical evidence indicates a substantial improvement over available therapy for the following reasons:

- New mechanism of action, targets Bcl-2
- Venetoclax provides Complete Responses in patients with 17p del CLL (other therapies do not)
- Venetoclax provides a higher Overall Response Rate than available therapies
- Safety profile appears different than available therapies (possibly better)

8. Division's next steps and sponsor's plan for future development

AbbVie intends to submit an application for accelerated approval in August 2015 based on 107 patients with CLL that harbor the 17p deletion mutation. They are developing a companion diagnostic for the assay to determine 17p del status in CLL patients.

They have (b) (4) planned Phase 3 trial (b) (4)

- R/R CLL (incl. 17p del): Venetoclax/rituximab vs. bendamustine/rituximab (Trial MURANO)

(b) (4)

9. References (if any)

1. Zenz, T., et al., *Chronic lymphocytic leukemia and treatment resistance in cancer: the role of the p53 pathway.* Cell Cycle, 2008. **7**(24): p. 3810-4.
2. Stilgenbauer, S. and T. Zenz, *Understanding and managing ultra high-risk chronic lymphocytic leukemia.* Hematology Am Soc Hematol Educ Program, 2010. **2010**: p. 481-8.
3. Badoux, X.C., et al., *Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL.* Blood, 2011. **117**(11): p. 3016-24.
4. Fischer, K., et al., *Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group.* J Clin Oncol, 2011. **29**(26): p. 3559-66.
5. Thurmes, P., et al., *Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia.* Leuk Lymphoma, 2008. **49**(1): p. 49-56.

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LORI A EHRLICH
04/09/2015

VIRGINIA E KWITKOWSKI
04/09/2015

Briefing Document
Breakthrough Therapy Designation request for ABT-199 under IND# 110159
Adam George Pharm.D., Clinical Reviewer
Division of Hematology Products
Office of Hematology and Oncology Products
July 08, 2013

1. Executive Summary

AbbVie Inc. has submitted a request for Breakthrough Therapy designation for ABT-199 for the treatment of patients with previously treated 17p deletion mutation-positive CLL as detected by an FDA-approved test. ABT-199 is an orally available, small molecule Bcl-2 family protein inhibitor. This reviewer concludes that the Sponsor has not met one of the two key requirements (FDASIA § 902) for Breakthrough Therapy designation. The Sponsor has met the requirement that the disease is serious and life-threatening. The Sponsor has not met the requirement for preliminary clinical evidence that indicates the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effect observed early in clinical development.

2. Rationale for the use of drug for proposed indication

ABT-199 is a Bcl-2 family protein inhibitor. The Bcl-2 protein family includes both proapoptotic and antiapoptotic proteins, and the interplay between these 2 groups regulates the intrinsic apoptotic pathway. Bcl-2 overexpression is commonly found in some lymphoid malignancies and is associated with increased resistance to chemotherapy.

3. Background: in proposed indication

CLL is a neoplasm composed of monomorphic small, round to slightly irregular, mature B cell lymphocytes in the peripheral blood, bone marrow or lymphatic tissue. Immunophenotyping is critical in diagnosing CLL as B cells typically express CD5, CD20, and CD23. CLL is the most common leukemia of adults in Western countries. Based on SEERS data from 2004-2008 the age adjusted incidence rate of CLL is approximately 4.2 per 100,000 men and women per year with the rate in men being approximately twice that of women. It is estimated that 15,680 men and women will be diagnosed with CLL in 2013.[1] From 2004-2008 the median age of diagnosis was 72 years of age with approximately 70% of patients being diagnosed at age 65 or later.

The clinical course of CLL varies depending on risk stratification by the Rai staging system or Binet classification but it is typically a slowly progressing disease. Chromosomal abnormalities such as del 17p and 11q are associated with a significantly poorer prognosis. An article by Dohner reported that in 325 patients with various stages of CLL 7% (23) had a 17p chromosomal aberration. Dohner evaluated the clinical implications of this chromosomal aberration compared to patients with a normal karyotype and found that at a median follow-up of 70 months patients

1. Cancer Statistics Reference for 2013: Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2013. CA Cancer J Clin. 2013; 63: 11-30.

with del 17p had a median survival of 32 months compared to 111 months for patients with normal karyotype.[2]

Currently there are no drugs approved specifically for the treatment of patients that have received prior treatment for CLL and who harbor deletion 17p. There are, however regimens commonly used for the treatment of patients with CLL which are also used to treat patients with 17p deletion CLL (Table 1). The rates of overall response are variable mainly due to the fact that the results are based on small subgroups of 17p deletion patients that were included in the broader trial population.

Table 1 Treatment options for relapsed/refractory CLL with 17p deletion

Trial	Regimen	Response Data in 17p deletion CLL	Response Data in broad CLL population
Single arm, open label (Wierda 2010, JCO) n=59 FA, n=79 BF n=17, 17p del FA group n=14, 17p del BF group	Ofatumumab	ORR 41% (FA) ORR 14% (BF) CR rate not published	ORR 58% (FA) ORR 47% (BF) CR rate 0%(FA) CR rate 1% (BF)
Single arm, open label (Fischer 2011, JCO) n=78 r/r CLL n=14, 17p del	Bendamustine + rituximab (BR)	ORR 7% CR rate 7%	ORR 59% CR rate 9%
Single arm, open label (Badoux 2011, Blood) n=80 r/r CLL n=14, 17p del	Cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR)	ORR 29% CR rate 14%	ORR 65% CR rate 29%
Single arm, open label (Stilgenhauer 2009, JCO) n=103 fludarabine refractory CLL n= 31, 17p del	Alemtuzumab	ORR 39% CR rate not published	ORR 34% CR rate not published
Single arm, open label (Pettitt 2012, JCO) n=39, 1st line and prior tx. 17p del n=22, prior tx CLL 17p del	Alemtuzumab + methylprednisolone	ORR 77% CR rate 14%	ORR 82% CR rate 36%

FA=fludarabine and alemtuzumab refractory, BF=fludarabine refractory only due to bulky disease (>5 cm)

4. Clinical trial experience with drug

Dosing of ABT-199

At this phase of the development process the Sponsor is trying to determine the safest dose and schedule to administer ABT-199 in order to mitigate the risk of a serious toxicity of tumor lysis syndrome (TLS) which has lead to the death of 2 patients with relapsed/refractory CLL. As a result of these fatal events the IND was put on partial clinical hold. This serious toxicity is discussed in greater detail in the safety section of the briefing document.

[2] Dohner et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-6.

Prior to clinical hold ABT-199 was administered at a starting test dose of 50 mg and the dose was increased incrementally using a step-up approach until the patient reached the final cohort assigned dose.

- 50 mg x 1 day → no dosing x 6 days → 50 mg x 7 days → 100 mg x 7 days → dose ~25% of final assigned cohort dose x 7 days → final cohort assigned dose (max 1,200 mg daily)

Following the partial clinical hold the Sponsor proposed a revised step-up approach for administering ABT-199.

- (b) (4)

Efficacy

To support the request for Breakthrough Therapy designation the Sponsor provided preliminary data for the ongoing first in human trial M12-175 titled "A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma." Currently, there were 17 patients enrolled with relapsed or refractory CLL that have the 17p deletion mutation. As of a data cut-off of April 4, 2013 16 of the 17 patients were evaluable for efficacy. The one patient who is not evaluable for efficacy did not yet have the first (Week 6) tumor evaluation conducted at the time of the data cut-off. The ORR (CR+CRi+PR) rate in the 16 patients evaluable for efficacy was 81% (13/16) [Table 2].

(b) (4)

Table 2 Disposition and response information for 17p deletion CLL patients M12-175

Subject Disposition	No. of Subjects
Achieved a Partial Response (PR)	11
Achieved a Complete Response (CR)	1
Achieved a Complete Response with incomplete bone marrow recovery (CRi)	1
Achieved a response of Stable Disease (SD)	1
Achieved a response of Progressive Disease (PD)	1
Discontinued prior to the Week 6 assessment	1
Had not reached Week 6 assessment and therefore non-evaluable at time of reporting	1

The median duration of response in the 16 evaluable patients receiving ABT-199 monotherapy and expressing the 17p deletion mutation is 13 months. The median time on trial for 17 patients (includes responders and non-responders) is approximately 7 months with 4 of the 17 being on trial for > 1 year. Twelve subjects remain active on trial. Given the available information we are

unable to confirm the Sponsor's claimed duration of response (b) (4) We suspect there is an error in the duration of response.

Safety

In December of 2012 the IND was put on partial clinical hold, prohibiting further enrollment of patients with CLL. This was due to the fact that the Division of Hematology Products (DHP) received reports of fatal events of tumor lysis syndrome (TLS) which occurred in 2 patients with relapsed/refractory CLL. In addition to the 2 fatal events of TLS, there were 7 serious events of TLS which required the patient's to be hospitalized. Of these 7 serious events 5 met the Cairo-Bishop criteria for clinical TLS. Clinical TLS is a serious medical condition that even if treated can result in death. In 4 out of the 5 cases of clinical TLS 4 occurred after the patient received their first dose of ABT-199. Of the 5 cases of clinical TLS 2 occurred in patients that harbor the 17p deletion mutation.

Subject (b) (6) *in Study M12-175*

On (b) (6) a 55 year old male patient with relapsed CLL enrolled in trial M12-175 suffered a fatal event. Based on the information provided by the Sponsor this patient did not harbor the 17p deletion but did have bulky disease (a 10 cm nodal mass). The patient received his first dose of ABT-199 at 50 mg on (b) (6) The patient then received 7 days of dosing with 50 mg and 7 days of dosing on 150mg ABT-199. He received his first dose of 1200mg on (b) (6). The following laboratory abnormalities suggestive of TLS were observed at 8 hours and 24 hours after receiving the 1200 mg dose; elevated serum phosphate, elevated uric acid and an increase in serum creatinine (observed at 24 hours). These laboratory changes met Cairo-Bishop criteria for TLS. The subject received a second dose of 1200mg on (b) (6) (b) (6). Subsequently, the subject was found dead that night at home. The cause of death was not confirmed.

Subject (b) (6) *in Study M13-365*

On (b) (6) a 58 year old male patient with relapsed CLL enrolled in trial M13-365 with bulky abdominal lymphadenopathy (14 x 18 cm) developed clinical tumor lysis syndrome (TLS) with elevations in potassium and phosphate following his first dose of 50 mg of ABT-199. The subject died of cardiac arrest secondary to hyperkalemia. The subject had a cardiac history of atrial flutter with subsequent cardioversion. Based on the information provided by the Sponsor in the response to clinical hold, this patient harbored the 17p deletion.

The Sponsor submitted a response to clinical hold which made changes to the protocols under partial clinical hold that may mitigate the risk of tumor lysis syndrome in patients with CLL. These changes were acceptable and the IND was removed from partial clinical hold in May 2013. To date the Agency does not yet have any data to determine if these changes mitigate risk of TLS.

The Sponsor submitted combined safety data for the broad population of patients with relapsed/refractory CLL enrolled in trial M12-175. As of a data cutoff of April 4, 2013 there were 56 patients enrolled in this trial which includes the patients with 17p deletion. The most commonly reported treatment emergent adverse events are diarrhea (23 patients, 41%); neutropenia (22 patients, 39%); nausea (21 patients, 37%); fatigue (16 patients, 29%); and upper

respiratory tract infection (15 patients, 27%). The most common Grade ≥3 adverse events ≥10% are neutropenia 37% (n=21) and tumor lysis syndrome 11% (n=6). A total of 3 patients with CLL/SLL in Study M12-175 have experienced adverse events that led to death: multi-organ failure, sudden death and mental status change each occurring in one patient.

5. Regulatory Considerations

Relapsed/refractory CLL is a serious and life threatening disease. Clinical outcomes in patients with CLL that harbor the 17p deletion mutation are significantly worse than the outcomes compared to the broader population of patients with CLL that do not harbor the 17p deletion. Currently there are no drugs that have FDA approval for the treatment of patients with relapsed/refractory CLL with 17p deletion. There are however drugs which are approved for the treatment of lymphoma that are used off label which have activity in patients with 17p deletion. In analyses of small subsets of patients with 17p deletion included in clinical trials in patients with CLL, ORRs ranged from 7-77% (Table 1). In clinical trial M12-175 investigating the use of ABT-199 in patients with relapsed or refractory CLL the ORR in 16 patients with the 17p deletion evaluable for efficacy was 81%. While this response rate indicates that ABT-199 maybe highly active in patients with CLL that harbor the 17p deletion, the number of patients (n=16) included in this analysis is too small to reliably conclude that ABT-199 may demonstrate substantial improvement over existing therapies.

Drug development plan

Under IND 110159 AbbVie is currently conducting multiple early stage Phase 1 trials evaluating the maximum tolerated dose of ABT-199 in various hematologic malignancies. At this time the Sponsor has the following later stage clinical trials planned for the development of ABT-199:

- A Phase 2 single-arm trial of ABT-199 monotherapy in subjects with a diagnosis of relapsed/refractory CLL with chromosome 17p deletion (Study M13-982)
- A randomized Phase 3 trial investigating ABT-199 combined with rituximab versus a combination of bendamustine with rituximab in subjects with a diagnosis of relapsed/refractory CLL (Study GO28667).

Both studies are anticipated to be initiated in 2013.

Recommendation

At this time DHP is recommending that the request for Breakthrough therapy designation for ABT-199 for the treatment of patients with previously treated 17p deletion mutation-positive CLL as detected by an FDA-approved test be denied for the following reasons:

- There is limited data with which to conclude that ABT-199 may demonstrate substantial improvement over existing therapies.
- Data on activity at the dose/schedule that the Sponsor proposes to take forward is not available.
- It is unclear whether the changes to the dose/schedule will improve safety and/or reduce activity.

References: provided throughout document

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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07/08/2013

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