

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208573Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	04/04/16
From	Virginia E. Kwitkowski, MS, ACNP-BC
Subject	Cross-Discipline Team Leader Review
NDA #	208573
Applicant	AbbVie, Inc.
Date of Submission	Rolling Submission Final 10/29/15
PDUFA Goal Date	06/29/16
Proprietary Name / Non-Proprietary Name	Venclexta / venetoclax
Dosage form(s) / Strength(s)	Tablets / 10, 50, and 100 mg
Applicant Proposed Indication(s)/Population(s)	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
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Table 1

Venetoclax Review Team		
Discipline	Primary Reviewer	Team Leader/Supervisor
Clinical	Lori Ehrlich	Virginia Kwitkowski
Statistics	Qing Xu	Yuan Li Shen
Clinical Pharmacology	Clin Pharm-Guoxiang Shen (DCPV) Pharmacometrics-Lian Ma (DPM)	Clin Pharm-Bahru Habtemariam (DCP5) Pharmacometrics-Nitin Mehrotra

	Pharmacometrics -Justin Earp (DPM) Genomics-Sarah Dorff (GTTG)	(DPM) Genomics-Rosane Charlab Orbach (GTTG) Division Director-Nam Atiqur Rahman (DCPV)
Pharmacology / Toxicology	Ramadevi Gudi Emily Place, PhD, MPH	Christopher Sheth (Supv, TL) John Leighton (Division Director)
CMC	Rajiv Agarwal (Drug Product & EA) Monica Cooper (Drug Substance) Gerlie Gieser (Biopharm) Ruth Moore (Facility) Peter Guerrieri (Process)	Tracey Rogers (Application Technical Lead)
DMEPA	Nicole Garrison Kevin Wright	Yelena Maslov
DRISK	Mona G Patel	Cynthia LaCivita
Patient Labeling	Rowe Medina	LaShawn Griffiths
Office of Scientific Investigations	Anthony Orenca	Janice Pohlman

Table of Tables

Table 1 1

Table 2 FDA Approved Treatments for CLL 11

Table 3 Recommended Regimens for Relapsed or Refractory CLL 13

Table 4 Available Therapies for Relapsed/Refractory CLL 14

Table 5 Dose Recommendation for Patients Taking CYP3A Modulators 24

Table 6 M13-982, Demographic characteristics of the primary analysis 30

Table 7 M13-982, Baseline disease characteristics of the primary analysis 31

Table 8 M13-982, Efficacy Results 33

Table 9 M13-982, Efficacy Results removing patient without 17p deletion 33

Table 10 Trials Included in Pooled Efficacy Analysis 38

Table 11 IRC-Assessed Response Rates for Pooled Efficacy Analysis	38
Table 12 Efficacy Results for M12-175	40
Table 13 Components of safety database for single-agent venetoclax therapy	41
Table 14 Serious Adverse Reactions occurring in at least 2% of patients with R/R CLL treated at 400 mg	43
Table 15 All Grade Adverse Reactions Occurring in at Least 10% of patients with R/R CLL treated at 400 mg	44

Table of Figures

Figure 1 Cairo-Bishop definition of laboratory tumor lysis syndrome	9
Figure 2 Cairo-Bishop definition of clinical tumor lysis syndrome	10
Figure 3 Response Definitions for CLL (2008 IWCLL NCI Working Group).....	10
Figure 4 M13-982 Trial Schema.....	25
Figure 5 Dosing schedule for the safety expansion cohort in Study M13-982	26
Figure 6 Study Schema for Trial M12-175.....	39

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Venetoclax is an orally available, small molecule inhibitor of BCL-2 (B cell lymphoma protein 2) that has been studied in patients with relapsed or refractory Chronic Lymphocytic Leukemia (CLL), including those with the 17p deletion, which is typically less responsive to treatment than those without this gene deletion. The Applicant has submitted data from single-arm studies that demonstrate that the overall response rate (with durability of response) is higher than the available therapy (ibrutinib) for patients with the 17p deletion. For this reason, accelerated approval is recommended for the following indication: *“VENCLEXTA 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.”*

There are an estimated 15,000 new cases of CLL per year in the United States. CLL occurs primarily in the elderly. Patients with CLL and the 17p deletion have a very poor prognosis, with survival duration of less than 2 years. There is only one drug approved at this time, specifically for this 17p deletion subset. This drug is ibrutinib (Imbruvica) and in a similar patient population with 17p deletion, it had a 48% Overall Response

Rate.

The efficacy of venetoclax for the treatment of R/R CLL with 17p deletion was evaluated in a 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 recommended dose of venetoclax is 400 mg daily that is achieved by a lower starting dose followed by a ramp-up, to reduce the risk of a life-threatening condition called tumor lysis syndrome (TLS). Patients who take venetoclax will be evaluated for their specific risk of TLS, and hydrated (with oral or intravenous fluids) and given medications that reduce their uric acid levels, in addition to slowly increasing the dose to the target dose of 400 mg daily. Close monitoring of their blood tests will be needed during the early treatment to detect cases of TLS.

The most frequent (>25%) Adverse Reactions in patients with R/R CLL were neutropenia (39%), diarrhea (35%), nausea (33%), and anemia (28%).

Venetoclax represents an additional oral therapeutic agent with a novel mechanism of action for the treatment of patients with relapsed or refractory CLL with 17p deletion. The efficacy of venetoclax for the treatment of patients with R/R CLL with the 17p deletion is supported by a surrogate endpoint of overall response rate. The higher response rate for venetoclax over ibrutinib 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 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	<ul style="list-style-type: none"> • 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, predominantly in older adults with about 70% occurring in patients older than 65 years. • CLL is typically a slowly progressing disease, and the percentage of 	<p>Relapsed or refractory CLL with 17p deletion is serious, life threatening, and rare in frequency. The duration of survival for patients with 17p del is poor. Relapsed or refractory CLL generally affects the elderly.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>patients surviving at 5 years is 81.7%.</p> <ul style="list-style-type: none"> 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. 	
<p><u>Current Treatment Options</u></p>	<ul style="list-style-type: none"> 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. 	<p>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.</p> <p>The response rates in patients with 17p deletion are lower and the available therapies are much more limited.</p>
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> 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 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 	<p>The phase 2 trial in patients with relapsed or refractory CLL with 17p deletion 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.</p> <p style="text-align: right;">(b) (4)</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>refractory CLL treated at the target dose of 400 mg daily. (b) (4)</p>	(b) (4)
<p><u>Risk</u></p>	<ul style="list-style-type: none"> • 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 	<p>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 safe dose and specific risks in that patient population.</p> <p>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.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>difference in exposure in patients with renal impairment, there is an increased risk of tumor lysis syndrome in patients with renal impairment.</p>	
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> • 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. 	<p>Labeling (including a Medication Guide and Quick Start Guide with the Start Pack) is adequate to address the safety issues associated with venetoclax.</p>

2. Background

On October 29, 2015, AbbVie, Inc. submitted the final portion of NDA 208573 for their BCL-2 family protein inhibitor, venetoclax. This application was submitted as a rolling submission with the first sequence submitted on September 15, 2015 (Module 1 Administrative, Module 2 Summaries (2.3, 2.4, 2.6.1 through 2.6.7), Module 3 Quality, and Module 4 Nonclinical Study Reports. The 2nd sequence was submitted on 10/29/15 and included Module 1 Administrative, Module 2 Summaries (2.5, 2.7.1 through 2.7.6), and Module 5 Clinical Study Reports. A rolling submission was acceptable to the Agency because venetoclax was granted Breakthrough Therapy Designation on 04/27/15 for the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukemia who harbor the 17p deletion (17p del) cytogenetic abnormality (17p del CLL).

AbbVie and Genentech/Roche are co-developing venetoclax in CLL and other hematologic malignancies.

Venetoclax (ABT-199 and GDC-0199), a new molecular entity (NME), is a novel, orally bioavailable, small-molecule Bcl-2 family inhibitor in the biarylacylsulfonamide chemical class. Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in various hematologic and solid tumor malignancies. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in a variety of B-cell and other hematologic malignancies.

There is no previously established pharmacologic class for venetoclax. Venetoclax is provided as a tablet for oral use in strengths of 10, 50, and 100mg.

Tumor lysis syndrome was identified as a risk of venetoclax treatment in Phase I studies. Because of this risk, the proposed dosing regimen is on a ramp-up schedule starting with one week of 20mg daily, one week of 50 mg daily, one week of 100 mg daily, one week of 200 mg daily, followed by 400 mg daily thereafter. Venetoclax is to be taken with water and a meal. Due to the risk of tumor lysis syndrome (TLS), dosing should not be started until hydration (oral or intravenous) and antihyperuricemics (allopurinol and/or rasburicase) are given based upon an assessment of the patient's individual risk of TLS.

The Applicant seeks the following indication: *Venetoclax is indicated 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.*

Disease Background

Chronic Lymphocytic Leukemia (CLL) is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes. CLL is categorized as a mature B-cell lymphoma and it represents approximately 7% of newly diagnosed cases of Non-Hodgkin Lymphoma (NHL) (The Non-Hodgkin's Lymphoma Classification Project, 1997). CLL is the

most common adult leukemia in Western countries with 14,620 new cases and 4,650 new deaths estimated for 2015 in the United States (Siegel, Miller, & Jemal, 2015). CLL and small lymphocytic lymphoma (SLL) are different manifestations of the same disease and are managed in much the same way (Alizadeh & Eisen, 2000). The major difference is that in CLL, a significant number of the abnormal lymphocytes are predominantly found in the lymph nodes (Tsimberidou AM, 2007).

CLL is typically asymptomatic at diagnosis and is often initially identified by routine hematology testing. When symptoms are present, they include weight loss, fevers, and night sweats (called B-symptoms). Patients also often present with symptomatic anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and have a predisposition to repeated infections. Patients who are diagnosed with CLL are usually managed with a “watchful waiting” approach, and only receive treatment when indicated. Indications for initial treatment include: 1) significant disease-related symptoms; 2) threatened end organ function; 3) progressive bulky disease; 4) progressive anemia or thrombocytopenia.

Tumor lysis syndrome (TLS) is a potentially life-threatening complication of anticancer therapy that is characterized by metabolic and electrolyte abnormalities caused by the sudden release of intracellular contents into the peripheral blood resulting from rapid tumor lysis induced by anticancer therapy. CLL is a tumor that is known to be at high risk for inducing TLS; approximately 10% of patients with CLL in a compassionate use trial of rasburicase developed TLS (Coiffier, Altman, Pui, & al., 2008). It most frequently occurs within 12 to 72 hours after the start of anticancer therapy. If untreated, TLS can induce cardiac arrhythmias, seizures, loss of muscle control, acute renal failure (requiring hemodialysis), and death. (Coiffier, Altman, Pui, & al., 2008) TLS risk can be reduced by preventive hydration and maintaining a normal uric acid level through use of rasburicase and/or allopurinol prior to the initiation of chemotherapy. Frequent monitoring of electrolytes and renal function (every 6 to 8 hours), with interventions for hyperkalemia and hyperphosphatemia, and cardiac ECG monitoring to identify early electrolyte-related cardiac abnormalities are important to reduce the risk of morbidity and mortality associated with TLS.

There are two classifications of TLS; laboratory and clinical. The Cairo-Bishop criteria were published in 2004 (Cairo & Bishop, 2004).

Figure 1 Cairo-Bishop definition of laboratory tumor lysis syndrome

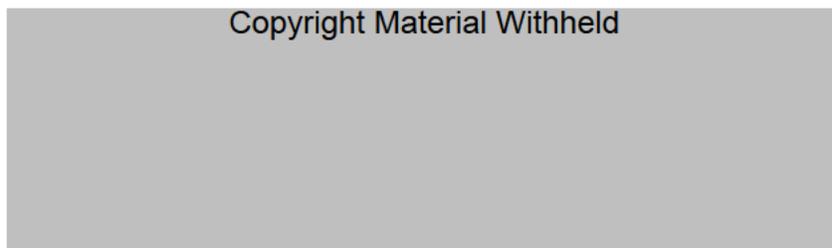
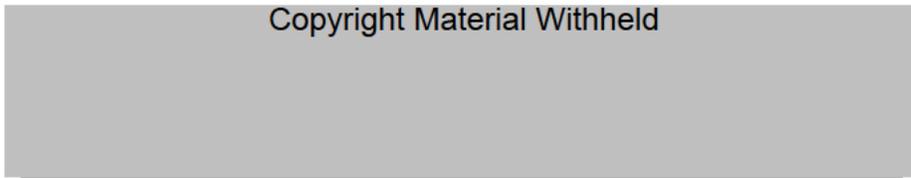


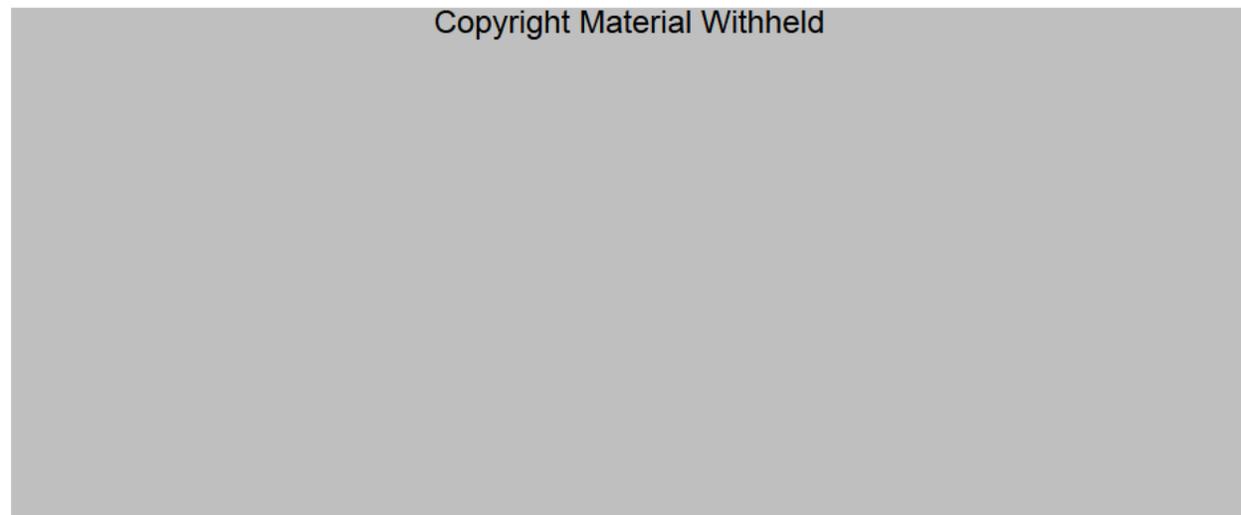
Figure 2 Cairo-Bishop definition of clinical tumor lysis syndrome



Response Assessment of CLL

After treatment, response to therapy for CLL is most often assessed by the National Cancer Institute-sponsored Working Group (NCI-WG) published guidelines for the diagnosis and management of CLL, most recently updated in 2008. In the clinical practice setting, response assessment involves both physical examination and evaluation of blood parameters. Per the NCI-WG criteria, CT scans are desirable in clinical trials for evaluations of adenopathy and organ involvement. The response is assessed at least 2 months after treatment completion. The response categories are listed in Figure 3 below (Hallek, et al., 2008).

Figure 3 Response Definitions for CLL (2008 IWCLL NCI Working Group)



The use of small molecule inhibitors of BCR-signaling pathway (ibrutinib and idelalisib) was known to result in an initial transient increase in lymphocytosis resulting from the redistribution or release of leukemic cells from the lymph node compartment to the peripheral blood. Considering these findings, for patients receiving idelalisib and ibrutinib, the revised response criteria recently proposed by Cheson et al allow for a new response category, “PR with lymphocytosis”, to include those with a clinical response (reduction in lymph nodes and splenomegaly) with persistent lymphocytosis (in the absence of other indicators or progressive disease) (Cheson, Byrd, & Rai, 2012).

Minimal residual disease (MRD) negativity determined in the peripheral blood is presently being evaluated as a predictor of treatment efficacy in CLL (Kovacs, Boettcher, Bahlo, & al., 2014).

Prognostic Information

The typical immunophenotype for CLL/SLL is CD5+, CD10-, CD19+, and CD20 dim, surface immunoglobulin dim, CD23+, CD43+/-, and cyclin D1-. Complex karyotype (3 or more unrelated chromosomal abnormalities in more than one cell on conventional karyotyping of stimulated CLL cells) is associated with an unfavorable prognosis (ref 9-11). Over the past decade, there have been numerous factors identified in patients with CLL, which appear to provide prognostic information. One cytogenetic abnormality that can be detected by FISH is del(17p), which is present in approximately 7% of patients with previously untreated CLL and 20% of previously treated patients. The del(17p) abnormality is more frequently observed in treated patients, making it likely that treatment-driven clonal selection may occur during therapy (ref 51). Del(17p), which reflects the loss of the TP53 gene and is frequently associated with mutation in the remaining Tpa53 allele, is associated with worst outcomes, with short treatment-free interval, short median survival (32 months), and poor response to chemotherapy (ref 19). The German CLL Study Group conducted a randomized Phase 3 trial comparing fludarabine + cyclophosphamide ± rituximab in patients with previously untreated patients with CLL. In this trial del(17p) was a significant independent predictor of poor survival outcomes, irrespective of the treatment arm. The 3 year PFS rate was only 18% in this subgroup (Hallek, Fischer, Fingerle-Rowson, & al., 2010).

Initial Treatment of CLL

Prior to treatment, patients with CLL are staged using either the Rai or Binet staging systems. These staging systems rely on physical exam (presence of lymph node enlargement and hepatosplenomegaly) and blood parameters (presence of anemia or thrombocytopenia) to assess the degree of tumor burden. The modified Rai classification stratifies newly diagnosed patients into three risk groups: Low-risk, Stage 0 with a median survival of 150 months; Intermediate-risk, Stage I-II with a median survival of 71-101 months; and High-risk, Stage III-IV with a median survival of 19 months (Rai, Sawitsky, Cronkite, & al., 1975). The Binet staging system is based on the number of involved areas and the level of hemoglobin and platelets, similar to the Rai staging system; and also provides meaningful correlation with clinical outcomes (PFS and OS) (Binet, Auquier, Dighiero, & al., 1981).

Although many treatments are approved for the treatment of CLL, it is considered incurable. Table 2 below lists the current FDA-approved treatments for CLL (Food and Drug Administration).

Table 2 FDA Approved Treatments for CLL

Year of Initial Approval	Proprietary Name (non-proprietary name)/ Current Type of Approval	Specific Indication
1957	Leukeran (chlorambucil) / Traditional	CLL (unspecified)
1959	Cytosan (cyclophosphamide)/ Traditional	CLL (unspecified)
1991	Fludara (fludarabine)/	For the treatment of adult patients with B-

	Traditional	cell CLL who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. Benefit in treatment-naïve or nonrefractory CLL patients is not established.
2007	Campath (alemtuzumab)/ not currently marketed as of 09/04/12, but available to patients with cancer for free through “US Campath Distribution Program”.	Treatment of B-cell CLL
2008	Treanda (bendamustine)/ Traditional	Treatment of patients with CLL. Efficacy relative to first line therapies other than chlorambucil has not been established.
2009	Arzerra (ofatumumab)/ Traditional	In combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate
2010	Rituxan (rituximab)/ Traditional	In combination with fludarabine and cyclophosphamide for the treatment of patients with previously untreated and previously treated CD20-positive CLL
2013	Gazyva (obinutuzumab)/ Traditional	Obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
2014	Imbruvica (ibrutinib)/ Traditional	--Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy. --Chronic lymphocytic leukemia with 17p deletion.
2014	Zydelig (idelalisib)/ Traditional	-Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. -Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

The initial treatment of CLL is determined by stage, karyotype, and fitness for standard chemoimmunotherapy. In many trials, fitness is determined by use of the Chronic Illness Rating

Scale (CIRS). For younger and more fit patients with Low, Intermediate, and High risk CLL and without del(11q) or del(17p)/TP53 mutations, the standard first-line therapy is chemoimmunotherapy with the FCR regimen (fludarabine, cyclophosphamide, and rituximab). Patients without del(17p) or del(11q) and considered unfit for standard chemoimmunotherapy often receive obinutuzumab OR ofatumumab OR rituximab with chlorambucil.

Patients with CLL with del(17p) have historically low response rates with chemoimmunotherapy and have different standard first-line therapies. The NCCN Guideline (National Comprehensive Cancer Network) recommendations for first-line treatment of del(17p)/TP53 mutation CLL in order of preference include ibrutinib, followed by high-dose methylprednisolone (HDMP) + rituximab, followed by FCR, followed by FR, followed by obinutuzumab + chlorambucil, followed by alemtuzumab ± rituximab. Should these patients experience a response to therapy, those with complex karyotypes should be considered for allogeneic stem cell transplant or a clinical trial.

Relapsed or Refractory Disease

Patients with CLL that is refractory to initial therapy or relapses after initial therapy are recommended for clinical trial participation or the following second-line regimens primarily based upon the presence or absence of del(11q) or del(17p) and fitness for standard dose chemoimmunotherapy. The NCCN recommendations are described below in Table 2 (National Comprehensive Cancer Network, Inc. 2016).

Table 3 Recommended Regimens for Relapsed or Refractory CLL

<i>Age ≥ 70 and younger patients with significant morbidities</i>		<i>Age <70 y without significant morbidities</i>	
<i>Without del(11q) or del(17p)</i>	<i>With del(11q)</i>	<i>Without del(11q) or del(17p)</i>	<i>With del(11q)</i>
Ibrutinib	Ibrutinib	Ibrutinib	Ibrutinib
Idelalisib ± rituximab	Idelalisib ± rituximab	Idelalisib ± rituximab	Idelalisib ± rituximab
Chemoimmunotherapy -Bendamustine ± rituximab -Reduced-dose FCR ^a -Reduced dose PCR ^b -HDMP ^c + rituximab	Chemoimmunotherapy -Bendamustine ± rituximab -Reduced-dose FCR -Reduced dose PCR -HDMP + rituximab -Rituximab + chlorambucil	Chemoimmunotherapy -FCR -PCR -Bendamustine ± rituximab -Fludarabine + alemtuzumab -RCHOP ^d -OFAR ^e	Chemoimmunotherapy -FCR -PCR -Bendamustine ± rituximab -Fludarabine + alemtuzumab -OFAR
Ofatumumab	Ofatumumab	Ofatumumab	Ofatumumab
Obinutuzumab	Obinutuzumab	Obinutuzumab	Obinutuzumab
Lenalidomide ± rituximab	Lenalidomide ± rituximab	Lenalidomide ± rituximab	Lenalidomide ± rituximab
Alemtuzumab ± rituximab	Alemtuzumab ± rituximab	Alemtuzumab ± rituximab	Alemtuzumab ± rituximab
Dose-dense rituximab	Dose-dense rituximab	HDMP + rituximab	HDMP + rituximab

^a FCR=fludarabine, cyclophosphamide, rituximab

^b PCR=prednisolone, cyclophosphamide, rituximab

^c HDMP=high dose methylprednisolone

^d RCHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

^e OFAR= oxaliplatin, fludarabine, cytarabine, and rituximab

Patients with relapsed or refractory CLL **with** del(17p)/TP53 mutation have the following recommended treatment regimens (according to NCCN):

- Ibrutinib
- Idelalisib ± rituximab
- HDMP + rituximab
- Lenalidomide ± rituximab
- Alemtuzumab ± rituximab
- Ofatumumab
- OFAR

The only drug specifically FDA-approved for treatment of patients with del(17p) CLL is Imbruvica (ibrutinib). Because the Applicant is seeking accelerated approval, venetoclax must be better than ibrutinib for the treatment of patients with CLL who harbor the del(17p) mutation. Ibrutinib is the only approved available therapy for this del(17p) CLL indication.

The efficacy of ibrutinib was evaluated in 127 patients with del(17p) CLL who were randomized 1:1 to ibrutinib or ofatumumab. The median patient age was 67 and all patients had a baseline ECOG score of 0-1. The median PFS for patients randomized to ibrutinib was not reached whereas the median PFS for patients randomized to ofatumumab was 5.8 months. The hazard ratio (95% CI) for the PFS analysis was 0.25 (0.14, 0.45). The overall response rate in patients randomized to ibrutinib was 47.6% as compared to 4.7% for patients randomized to receive ofatumumab (Pharmacyclics). The analysis of whether venetoclax is better than available therapy for patients with 17pdel CLL is to be based upon this data.

(b) (4)

Regulatory History

Regulatory Milestones for Venetoclax		
Date	Event	Notes
11/28/10	IND 110159 opened in US	
09/20/12	Orphan Drug Designation # 12-3756 granted for treatment of CLL	
12/17/12	Partial clinical hold due to Tumor Lysis Syndrome deaths in CLL	
05/03/13	Clinical hold lifted after implementation of risk stratification and prophylaxis for TLS	

07/02/14	End of Phase 2 Meeting	Agreement reached upon acceptable sample size for initial registrational trial under AA for 17p del CLL. Agency recommended at least 100 patients with 17pdel. PMR trial (MURANO) discussed.
04/27/15	FDA Granted Breakthrough Therapy Designation for “the treatment of patients with relapsed/refractory CLL who harbor the 17p deletion cytogenetic abnormality”.	
09/15/15	Initial Module of Rolling NDA Submitted	Contents of submission included: -Module 1-Admin. -Module 2-Summaries 2.3, 2.4, and 2.6.1-2.6.7 -Module 3-Quality Module 4-Nonclinical Study Reports
09/22/15	Pre-NDA Meeting	Discussed submission plan, proposed content and format of NDA; no agreements for late submissions were requested or granted; a complete application was expected.
10/29/15	Final Module of NDA submitted	Contents of submission included: -Module 1-Admin. -Module 2-Summaries (2.5, 2.7.1 – 2.7.6 -Module 4- Nonclinical Study Reports (R&D/10/421) -Module 5-Clinical Study Reports

3. Product Quality

The product quality (CMC) review was archived on 04/04/16. Tracey Rogers was the CMC Lead.

NDA 208573 for Venclexta™ (venetoclax) tablets is recommended for approval by the Office of Pharmaceutical Quality. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “approve” recommendation was entered into Panorama 04-04-2016.

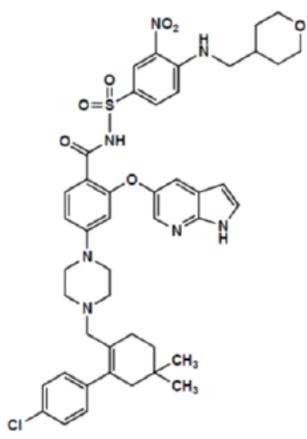
Based on the adequate totality of stability data at 24 months at long term storage conditions, 24 months of expiration dating may be granted for this product when stored at or below 30°C.

General Product Quality Considerations

The chemical name for the drug substance is:

4-(4-{{2-(4-Chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo [2,3-b]pyridin-5-yloxy)benzamide.

The molecular structure is:



Venetoclax drug substance is a light yellow to dark yellow powder with a melting point onset of approximately 138°C. Venetoclax is not hygroscopic (b) (4)

(b) (4)

(b) (4) is manufactured by multiple suppliers, (b) (4) used by the supplier (b) (4) was provided. Starting materials are fully characterized. The description of the drug substance manufacturing process and controls for starting materials, solvents, reagents, (b) (4) are adequate. Adequate in process controls are in place for the critical quality attributes during the drug substance manufacturing process.

The drug substance is packaged in an (b) (4) and (b) (4). Stability data is provided for the drug substance in this packaging configuration. Long term and accelerated stability study results show no significant changes. Based on 24 months of long term data provided, a (b) (4) retest date for venetoclax drug substance is acceptable when stored in (b) (4) at or below 30°C.

Product Stability and Expiry

Based on the adequate totality of stability data at 24 months at long term storage conditions, 24 months of expiration dating may be granted for this product when stored at or below 30°C.

Drug Product

Venetoclax tablets are available in 10, 50, or 100 mg strengths (b) (4). Drug product is supplied as pale yellow or beige tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient. Each tablet is debossed with “V” on one side and “10”, “50” or “100” corresponding to the tablet strength on the other side.

Excipients include copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic.

The tablet coating contains polyethylene glycol, talc, polyvinyl alcohol, titanium dioxide and either iron oxide yellow (for the 10 mg and 100 mg tablet) or iron oxide yellow, red and black (for the 50 mg tablet).

(b) (4)

The commercial primary packaging configurations are either 120-count of 100 mg tablets in a 200 cc HDPE bottle with induction-sealed, (b) (4) cap, or 1 tablet in a blister (b) (4) for (b) (4), 50, and 100 mg tablets. The stability studies on primary stability batches showed that 10 mg tablets packaged in the (b) (4), and 50 and 100 mg tablets packaged in the blister are physically and chemically stable during storage. In addition, the packaging configurations provide adequate protection of the product from (b) (4) such that the (b) (4) will be maintained below the proposed commercial shelf life limit over the duration of the shelf life.

The expiration-dating period of 24 months may be granted for the drug product packaged in either bottles or blisters and stored at or below 30°C.

Drug substance and drug product manufacturing facilities were reviewed and all have “approve” as final recommendations (see primary review for details).

Based on the review of the application, inspection documents and compliance history of the drug substance and drug product manufacturing facilities, and the control testing laboratories, there are no significant outstanding risks that impact their ability to perform the functions listed in this application. All facilities are recommended for approval.

Biopharmaceutics

1. BCS Designation: N/A
 - Drug Substance: low solubility (< 0.0042 mcg/mL dissolves in pH 4 and pH 7.4 at 25 °C); low-to-moderate permeability (In Mass-Balance Study, at least 20% radioactivity could be recovered as unchanged drug in the feces. Absolute BA study cannot be done (b) (4)
 - Drug Product: (b) (4)
2. Biowaivers/Biostudies
 - Biowaiver Requests - none
 - PK studies – refer to the Clinical Pharmacology review
 - IVIVC - none

From a Biopharmaceutics perspective, the NDA is recommended for approval. The following dissolution method and acceptance criteria should be used for routine QC testing of venetoclax tablets.

USP Apparatus	Dips per min	Medium/ Volume/Temperature	Acceptance Criteria
3	20 ± 5%	250 mL of 50 mM sodium phosphate buffer, pH 6.8 ± 0.05 with 0.4% sodium dodecyl sulfate (SDS) and 3 small drops of antifoaming agent per vessel at 37 ± 0.5°C	10 mg: Q = (b) (4)% in 1.5 h Q = (b) (4)% in 2 h 50 mg: Q = (b) (4)% in 2 h Q = (b) (4)% in 3 h 100 mg: Q = (b) (4)% in 3 h Q = (b) (4)% in 4 h

Impurities

The applicant described the critical steps, process controls, and intermediate specifications which ensure that the synthesis and impurity profiles are controlled throughout the venetoclax drug substance manufacturing process.

Environmental Assessment

The Applicant requested a Categorical Exclusion from the requirement to prepare an EA under 21CFR § 25.31 (b) for the active pharmaceutical ingredient (API), venetoclax. The CMC reviewer stated in the primary review that: “No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). This drug is manufactured using a synthetic process and is not known to be derived from any wild sourced plant and/or animal material 21 CFR 25.21(b). Granted.”

Microbiology

Per Pete Guerrieri and concurrence by Jennifer Maguire, the proposed manufacturing process and controls assure acceptable microbial quality of the final drug product.

Carton and Container Labeling

As of 3/31/16, the information contained in the PI, primary, and secondary container closure labels is adequate.

4. Nonclinical Pharmacology/Toxicology

The primary pharmacology/toxicology review was conducted by Rama Gudi and Emily Place. Their review was archived on 03/21/16. The Pharm/Tox review recommends the approval of venetoclax. The Pharm/Tox team participated in revisions to the proposed labeling.

[Source: Executive Summary of the Primary Pharm/Tox review.]

Nonclinical pharmacology studies conducted in vitro and in vivo demonstrated that venetoclax inhibits Bcl-2, an anti-apoptotic protein regulator. In a series of biochemical assays conducted to characterize binding affinity, venetoclax demonstrated selectivity to Bcl-2 ($K_i < 0.1$ nM) relative to other anti-apoptotic and pro-apoptotic complexes. In vitro studies using knockout (Bak^{-/-} Bax^{-/-}) murine embryonic fibroblasts demonstrated that venetoclax-mediated cell death requires the key effector proteins Bax and/or Bak, indicating activation of intrinsic pathway of apoptosis. Venetoclax showed selectivity in cell killing in tumor cells dependent on Bcl-2 for survival relative to tumor cells dependent on other anti-apoptotic family members (Bcl-XL cells). Increased sensitivity to venetoclax-mediated cell death was observed in leukemia and lymphoma cells harboring the t(14;18) translocation that overexpress Bcl-2. Venetoclax-induced apoptotic cell death was associated with release of mitochondrial intermembrane protein cytochrome C, caspase activation and the externalization of phosphatidylserine at the cell membrane. Venetoclax promotes cell death in a variety of hematological

tumor cell lines including CLL cells derived from patients with an average EC50 of 6 nM (n=35). Venetoclax induced cell death in CLL samples bearing the 17p deletion derived from patients, with an average EC50 of 8 nM (n = 5). Additionally in SCID (Severe Combined Immunodeficiency) mice models of human xenografts expressing high levels of Bcl-2, treatment with venetoclax resulted in reduction of tumor volume.

In this section, you should emphasize or expand upon any issue from the Pharmacology/ Toxicology review as relevant. Particular attention should be paid to any potential clinical safety concern emanating from nonclinical studies, including but not limited to results of acute or chronic toxicity studies, genotoxicity or carcinogenicity studies, or reproductive toxicology studies, or any issue that has a potential relevance to labeling.

Venetoclax treatment had no toxicologically significant effects on safety pharmacology endpoints including those from mouse (respiratory or neurological) and dog (cardiovascular) studies.

After oral dosing, bioavailability of venetoclax was 27% in the mouse and 28% in the dog. Tissue distribution was extensive following administration of oral venetoclax in rats. The highest exposure (by Cmax or AUC) was in the liver, lymph nodes, small intestine, adrenal glands, kidney cortex, kidney, and the pancreas. The metabolism of venetoclax was similar in both mice and dogs following oral exposure; the metabolites in both mouse and dog plasma account for less than 13% of total drug related materials. The most prominent human metabolite “M27” was detected in both species (0.21% in dogs, 0.79% in mouse). The main route of elimination is the hepatobiliary system. Approximately 90% of elimination occurred in the feces, and less than 1% in the urine in both mouse and dog. The elimination half-life after oral dosing in nonclinical species ranged from 3 to 14.5 hours. Based on the data collected in general toxicology studies, there were no gender differences in exposure, and increase in Cmax and AUC values were dose proportional.

The toxicity of repeated daily doses of oral venetoclax was assessed by conducting 26-week (6-month) and 39-week (9-month) toxicity studies in mice and dogs, respectively. In both mice and dogs, the major target organs of venetoclax toxicity included the lymphatic system, and male reproductive organs (dogs). Toxicities in mice and/or dogs included:

- Dose-related body weight reductions (up to 15%) correlated with decreased food consumption in dogs.
- Dose-responsive decrease in lymphocyte (up to -75% in mice, and -81% in dogs) and red blood cell mass decreases in mice and dogs. Decrease in lymphocytes correlated with microscopic findings in lymphoid organs including the mandibular and mesenteric lymph nodes, and spleen, and gut-associated lymphoid tissue (GALT).
- Male reproductive systems (decreased prostate weights, dose dependent bilateral testicular seminiferous tubule degeneration/atrophy, reduced testicular weight) in dogs.
- Epithelial single cell necrosis (gallbladder, exocrine pancreas, prostate, epididymides, and stomach) in dogs.

- Hair discoloration correlated microscopically with decreased pigment in the hair follicle bulbs in the scapular region in dogs.

Venetoclax was not phototoxic to hairless mice when administered orally daily for three days up to 825 mg/kg followed by UV exposure.

Venetoclax did not induce mutations in the bacterial mutagenesis (Ames) assay, and was not clastogenic in both the in vitro chromosome aberration assay using human peripheral blood lymphocytes and the in vivo bone marrow mouse micronucleus assay. Carcinogenicity studies have not been conducted and are not necessary for the proposed indication. M27 was negative in the Ames assay and in the vitro chromosome aberration studies.

In fertility and early embryonic development studies conducted in male and female mice, venetoclax had no effect on male fertility, or female fertility parameters (e.g. estrous cycling, mating, or early embryonic development).

The embryo-fetal development effects of venetoclax were studied in mice and rabbits. Venetoclax produced decreases in implantations, litter size, live fetuses, fetal body weights, increases in both dead or resorbed conceptuses/litter and number of post implantation losses in mice. These effects are supported by scientific literature indicating the role of BCL-2 in oocyte and embryonic development. In addition, BCL-2 knockout mice exhibited adverse developmental effects, such as renal failure.^{1, 2,3 ,4,5.} Thus, administration of venetoclax during pregnancy may cause embryo-fetal toxicities and a statement under the Warnings and Precautions of the label is warranted.

Venetoclax was not teratogenic in mice. Of note, the human metabolite M27, present at nearly 30% in patients at the recommended dose of 400 mg/day was present in minor amounts in the mouse (0.8%). In rabbits, venetoclax was maternally toxic based on mortality (4/20) and reductions in net body weight gain (57% of the control), most evident at the high dose. While no embryo-fetal effects were observed in rabbits, this species may not predict adverse embryo-fetal effects in humans because the exposure to the parent drug was very low (0.2 times the human exposure) and metabolite M27 is not present in rabbits.

The dose of 150 mg/kg/day of venetoclax in mice resulted in exposures (AUC) of approximately 1.2 times (AUC 37.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in mice) and the dose of 300 mg/kg/day of venetoclax in rabbits resulted in exposures (AUC) of approximately 0.2 times (AUC 4.9 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in rabbits), the human exposure (AUC 31.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$) at the recommended dose of 400 mg daily.

5. Clinical Pharmacology

The primary Clinical Pharmacology reviewer was Guoxiang Shen, from DCPV. The Pharmacometrics co-reviewers were Lian Ma and Justin Earp. The Genomics reviewer was Sarah Dorff.

The consolidated clinical pharmacology review, archived on 03/14/16, recommends approval.

They have recommended two post-marketing requirements (refer to Section 13 of this review).

Summary of Clinical Pharmacology: [Source: Clinical Pharmacology Review]

Route of Administration: Venetoclax is an orally bioavailable, small molecule inhibitor of anti-apoptotic protein Bcl-2.

ADME

Venetoclax PK is linear over the dose range of 150 to 800 mg. After oral administration, the median time to reach C_{max} was 5 to 8 hours. The half-life of venetoclax is estimated to be 26 hours. Venetoclax is highly bound to plasma protein independent of concentrations. The population estimated apparent volume of distribution ($V_{d_{ss}}/F$) of venetoclax ranged from 256 to 321 L in patients with CLL/SLL and NHL.

Venetoclax has a food effect; exposure is increased by 3 to 5-fold when administered with low- or high-fat meals. In vitro studies indicated that venetoclax is predominantly metabolized by CYP3A4/5 to form a major metabolite M27, which is considered pharmacologically inactive. In the human mass balance study, approximately 100% of the administered radioactive dose was recovered in the feces, with 21% as unchanged venetoclax.

Intrinsic Factors Impacting Elimination

Renal and Hepatic Impairment: The applicant has not conducted dedicated organ impairment studies to evaluate the effect of organ (hepatic or renal) impairment on venetoclax PK. Based on the population PK (popPK) analyses, no dose-adjustment is needed for patients with mild or moderate hepatic or renal impairment. However, there was a trend of increased incidence of TEAEs in these patients, tighter safety monitoring and dose-modification based on toxicity during the dose ramp-up period may be needed. The recommended dose for patients with severe hepatic or renal impairment has not been determined.

Gender: PopPK analyses indicated that gender did not have a clinically significant effect on venetoclax exposure.

Age: PopPK analyses indicated that age did not have a clinically significant effect on venetoclax exposure (median age: 65 years, range: 25/88). Pediatric studies have not been conducted with venetoclax.

Race: PopPK analyses indicated that race did not have a clinically significant effect on venetoclax exposure.

Weight: PopPK analyses indicated that weight did not have a clinically significant effect on venetoclax exposure.

Drug-Drug Interactions:

Venetoclax is predominantly metabolized by CYP3A4/5, and a substrate of efflux transporters Pgp and BCRP. Co-administration of ketoconazole (a strong CYP3A, P-gp and BCRP inhibitor) increased venetoclax C_{max} and AUC_∞ by 2.3- and 6.4-fold, respectively. Co-administration of moderate CYP3A4/5 inhibitors showed a smaller effect on venetoclax exposure (40 to 60% increase in C_{max} and AUC₀₋₂₄). Venetoclax exposure also increased (C_{max} ↑ 106%, AUC_∞ ↑ 78%) after co-administration of single dose of rifampin, presumably due to the inhibition of P-gp by rifampin. However, venetoclax C_{max} and AUC_∞ were reduced by 42% and 71%, respectively, after multiple doses of rifampin due to the predominant effect of CYP3A4/5 induction. Based on these results, the applicant's proposed dose recommendations for patients taking CYP3A modulators are considered acceptable and shown in Table 5. In addition, co-administration of Pgp inhibitors should also be avoided during the ramp-up phase and requires 2-fold reduction of venetoclax dose during the stable dose phase.

As a perpetrator, venetoclax increased CYP2C9 substrate warfarin exposure by 18% for C_{max} and 28% for AUC_∞. As an inhibitor of P-gp, venetoclax also have DDI potential with P-gp substrates in the gut at therapeutic dose levels.

Table 5 Dose Recommendation for Patients Taking CYP3A Modulators

A large rectangular area of the document is redacted with a solid grey fill. In the top right corner of this redacted area, the text "(b) (4)" is printed in a small font.

Cardiac Electrophysiology

The QT/QTc prolonging potential of venetoclax was in study M12-175, a clinical study that included patients with relapsed/refractory CLL and NHL. ECG measurements were collected in triplicate at baseline and at steady state dose of venetoclax ranging from 150 to 1200 mg. The results Venetoclax had no large effect on QTc interval (i.e., > 20 ms) and there was no relationship between venetoclax exposure and change in QTc interval.

6. Clinical Microbiology

Not relevant to an oral anti-cancer agent.

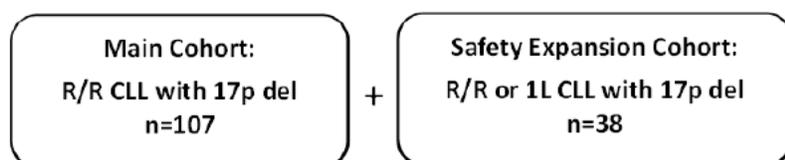
7. Clinical/Statistical- Efficacy

The efficacy data in this section is broken up into two sections. First, the efficacy data for patients with relapsed/refractory CLL with 17pdel mutation, the population recommended for accelerated approval, will be presented. (b) (4)

Relapsed Refractory CLL with 17pdel Mutation

The efficacy of venetoclax in patients with CLL who harbor the 17pdel mutation was evaluated in trial M13-982, conducted by the Applicant in 38 sites across 7 countries. In this trial, 107 patients with relapsed/refractory CLL (including 106 with the 17p del mutation) were treated with single-agent venetoclax. The trial title was: “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 trial also contained a “safety expansion cohort” of 38 patients who were evaluable only for safety.

Figure 4 M13-982 Trial Schema



R/R=relapsed/refractory, 1L=first line. Modified from figure provided by Applicant (Source: Primary Clinical/Stats review).

Key Inclusion/Exclusion Criteria (Source: Primary Clinical/Stats Review)

Diagnostic Criteria

Patients must have the diagnosis of CLL that meets the 2008 Modified IWCLL NCI-WG Guidelines (Hallek, et al., 2008). Patients had to have an indication for treatment based on the Guidelines and have clinical measurable disease (lymphocytosis $>5 \times 10^9/L$ 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 $\geq 1000/\mu\text{L}$, may be with growth factor support
 - Platelets $\geq 40,000/\text{mm}^3$, without transfusion in previous 14 days [$\geq 30,000/\text{mm}^3$ 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 $\leq 3x$ ULN, bilirubin $\leq 1.5x$ 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.

In this study, venetoclax was dosed with an initial 4-week ramp-up schedule followed by the target dose. In amendment 1, patients each received a 20mg dose on Day 1, they were observed for tumor lysis syndrome (via laboratory monitoring) for 24 hours, and if no signs of TLS were observed, they went on to receive 50 mg daily for a week followed by weekly increments to 100mg, 200mg, and then to the final 400 mg target dose. If there were signs of TLS, the rest of the week would be dosed at 20mg daily. Venetoclax was to be taken with 240mL of water within 30 minutes of a meal. Patients were instructed to avoid consuming grapefruit, Seville oranges, or starfruit due to possible CYP3A mediated interactions.

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.

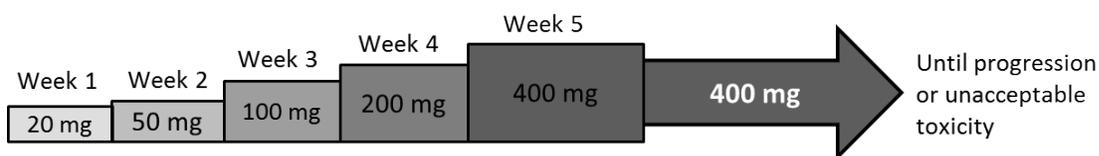


Figure 5 Dosing schedule for the safety expansion cohort in Study M13-982

Amendment 2 revised the protocol to have all patients dosed at 20mg for the first week; with the 2nd dose delayed for signs of TLS. After the first week of 20 mg dosing, the ramp-up was the same as previously described in Amendment 1 (weekly increments to 50mg, 100mg, 200mg, and finally to the 400 mg target dose). Figure 5, above, shows the ramp-up plan for dosing in Study M13-982 implemented with Amendment 2.

Before venetoclax dosing began, patients were assessed for their baseline risk of tumor lysis syndrome based upon lymph node burden and absolute lymphocyte count. Depending on their risk, they received TLS prophylaxis. Since this topic is more relevant to safety, see Section 8.

Dose reductions occurred for toxicity and GCSF was administered for Grade 4 neutropenia. Patients were also to receive typical supportive care such as transfusions, antibiotics, fluids and electrolyte replacements, where appropriate. Limited corticosteroid treatment (i.e., for approximately 21 days with rapid taper) was allowed for significant active autoimmune cytopenias (AIHA or ITP).

Efficacy Assessments

Disease assessments were according to the 2008 modified IW-CLL NCI-WG Guidelines. Clinical laboratory tests (hematology) and physical exam occurred at 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 then at the final visit.

Radiographic testing (CT or MRI of neck, chest, abdomen, and pelvis) occurred at baseline (within 35 days prior to study drug), when a response was determined by clinical criteria (PR or CR) [no earlier than 8 weeks later for confirmation of PR or CR], at 36 weeks for all subjects (regardless of disease status), and for any patient with clinical signs of disease progression (increased liver/spleen/Lymph Nodes) without an increase in lymphocytes meeting PD criteria.

Bone Marrow aspirate and biopsy were to occur at screening, to confirm CR or CRi, and for patients who met CR/CRi criteria except for nodes that were approximately <2cm.

Minimal Residual Disease by flow cytometry (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 this occurred, repeat marrow aspirate MRD assessment was done.

Study Endpoints

The primary endpoint was Overall Response Rate in the first 70 patients by Independent Review Committee. The secondary endpoints included CR rate (CR+CRi), PR rate (nPR or PR), Duration of Response, Progression Free Survival, Event Free Survival, Time to Progression, Time to Response, Time to 50% reduction in ALC, Overall Survival, and percent to HSCT (hematopoietic stem cell transplantation). Exploratory endpoints included Time to Next Treatment, Minimal Residual Disease, Patient Reported Outcomes, and Investigator assessments of efficacy endpoints.

Statistical Plan (Source: Primary Clin/Stats Review)

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.

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.

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:

See primary clinical/statistics review for full details of protocol amendments.

No subjects were enrolled under the original protocol version. All 107 of the patients in the main cohort were enrolled under Amendment 1 which was made to implement more stringent prophylaxis and management of Tumor Lysis Syndrome. This included modification of the ramp-up schedule periods. Almost the entire safety expansion cohort (36/38) was treated under protocol amendment 2 which further revised the prophylaxis and management of TLS. The last 2 patients in the safety expansion cohort were enrolled under Amendment 3 which allowed the enrollment of treatment naïve CLL patients with 17pdel, as there was no standard treatment for these patients.

Study Dates

First subject visit: 06/27/13

First subject dosed: 07/09/13

Last subject visit: Projected to be in May 2017

Data Cutoff Date for Clinical Study Report submitted: 04/30/15

Financial Disclosure

The Applicant provided financial disclosures for Study M13-982. There were 4 Investigators and 2 Sub-investigators who reported financial interests. These were determined to not be the source of bias because the study used an Independent Review Committee (the basis for the primary analysis) and analysis of the results with these patients removed did not impact the overall results.

Study Results

Trial M13-982 appears to have been conducted in accordance with good clinical practices and under Independent Ethics Committees or IRBs. Review of financial disclosures indicates that financial interests reported did not appear to introduce bias into the study results. The reported protocol violations did not appear to have affected the study outcome or interpretation of the study results or conclusions.

Demographics

Table 6 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

*Disease Baseline Characteristics***Table 7 M13-982, Baseline disease 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 mutation²			
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 x 10 ⁹ /L	53 (49.5)	21 (55.3)	74 (51.0)
≥ 25 x 10 ⁹ /L	54 (50.5)	17 (44.7)	71 (49.0)
< 100 x 10 ⁹ /L	83 (77.6)	34 (89.5)	117 (80.7)
≥ 100 x 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)

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. This patient was removed from the analysis for labeling purposes since he did not have the 17p deletion.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

[Source: Primary Clinical/Stats Review]

No subject was less than 80% compliant over the course of the study. Five subjects (Subjects 10601, 11907, 40101, 50801, and 60206) 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.

Efficacy Results – Primary Endpoint [Source: Primary Clinical/Statistical Review]

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 8 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 8 M13-982, Efficacy Results

	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)

Discordance between INV and IRC:

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 a response by the study investigator were not considered as a responder by IRC assessment. There were 10 subjects who were assessed as having complete remission by the study investigator who were not considered CR by IRC assessment. 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.

FDA Revised Analysis

One patient was removed from the analysis because they did not have the 17p deletion. The adjusted results for this analysis are below. This is the analysis that was proposed by the review team for inclusion in labeling.

Table 9 M13-982, Efficacy Results 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)

Efficacy Results—Secondary and other endpoints

Secondary Endpoints

Duration of Response

With a median follow-up time of 32 months, the median duration of response had not been reached. An estimated durable response rate (Kaplan-Meier estimate) at 12 months was 84.7% (95% CI: 74.5, 91) per IRC assessment. This analysis was conducted in 85 subjects in the main cohort who had a recorded response of CR, CRi, PR, or nPR.

Progression Free Survival

The median PFS duration has also 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). PFS is not evaluable from single-arm trials (b) (4)

Event Free Survival

The median duration of event-free survival has not yet been reached. The Kaplan-Meier estimate of the proportion of patients with event-free survival as 12 months was 70% (95% CI: 60.0%, 77.9%), per IRC assessment. Event-free survival is not evaluable from single-arm trials (b) (4)

Time to Progression

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). Twenty-four (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.

Time to Response

Responders are defined as having achieved a clinical response (CR or PR), confirmed after at least 8 weeks by radiologic assessment (for CR or PR) and bone marrow biopsy (for CR only). The median time to response (for responders only) was 0.8 months (range: 0.1 to 8.1 months). Of the subjects reporting a CR/CRi, the median time to CR/CRi was 8.2 months (range: 3.0 to 16.3 months).

Time to 50% Reduction in ALC

Lymphocytosis (Absolute lymphocyte count of $>5 \times 10^9/L$) was present in 81.3% of the patients at baseline. Of these 87 patients, 85 had a 50% reduction in ALC, occurring on average within the first week of treatment (median 0.3 months [range: 0.1 to 0.9 months]). Lymphocyte count normalization occurred in 53 patients by week 4. Of the two patients who did not achieve an ALC reduction of 50%, one withdrew consent after 1 day of treatment with venetoclax, and the other patient had a best response of stable disease and progressed after Week 20.

Overall Survival

In the main cohort, 17 (15.9%) of patients died; leaving 90 patients (84.1%) alive at the data cutoff date. The Kaplan-Meier estimate of the proportion of patients surviving at 12 months was 86.7% (95% CI: 78.6%, 91.9%). Overall survival (a time to event analysis) is not interpretable from a single-arm trial [REDACTED] (b) (4).

Percent to HSCT

As of the data cutoff for this report, 3 patients (2.8%) went on to receive a stem cell transplant. These patients have remained disease free after 2 months, 1 month, and 11 months after the transplant, respectively.

Exploratory Endpoints

Time to Next Treatment

TTNT was defined as the number of days from the first dose of venetoclax to the date of first dose of new anti-CLL treatment or death from any cause. Twenty-five (23.4%) patients received a new anti-CLL treatment. The median time to next treatment was not reached.

Minimal Residual Disease

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

Patient Reported Outcomes

Patient-reported health related QoL measures were identified as exploratory efficacy endpoints for this study, including MDASI, EORTC QLQ-C30, EORTC QLQ-CLL16,

EQ-5D-5L, and EQ VAS.

Comment: Per the *FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, “open-label clinical trials, where patients and investigators are aware of assigned therapy, are rarely adequate to support labeling claims based on PRO instruments. Patients who know they are in an active treatment group may overestimate benefit whereas patients who know they are not receiving active treatment may underreport any improvement actually experienced.” Study M13-982, was a single-arm (open-label) trial and the patient reported outcomes were exploratory endpoints without control of the Type I error rate; therefore they are not adequate to support labeling claims. The results of the PRO endpoints are presented here for completeness.

MDASI

The MDASI evaluates 13 core symptom severity items and 6 symptom interference items. A negative change in score from Baseline represents an improvement in symptoms. The smallest difference that is considered clinically important can be a specified difference (the minimum important difference [MID]). The MID for the MDASI ranged from 0.98 to 1.21 and the lower bound (0.98) was used for MID acceptance. Subjects experienced early improvement in symptom severity and symptom interference at Weeks 4, 12, and 36, but the change from Baseline did not reach MID. Since most patients had low baseline scores for symptom severity and interference (1.6 and 2.1, respectively), and the MID is 0.98, approximately a 50% reduction in these scores would need to be achieved to reach MID. While subjects achieved a 25% improvement at 4 weeks for symptom severity and a 29% improvement in symptom interference, the MID of 0.98 was not met.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

The EORTC QLQ-C30 consists of a global health status/QoL scale, a financial difficulties scale, 5 functional scales (cognitive, social, physical, emotional, and role functioning), and 8 symptom scales/items (fatigue, insomnia, appetite loss, pain, constipation, diarrhea, dyspnea, and nausea and vomiting). A positive change on the functional scales and global QoL scales means that patients have better functioning or QoL, where as a negative change on the symptom and financial difficulties scales means an improvement in symptoms. Changes of 5 – 10 points are considered "a little" change to patients and the lower bound (5 points) was used for MID acceptance.

Patients reported changes that exceeded the MID in the Global Health Status and functioning scores (Role, Emotional, and Social). Improvements in Physical Functioning were improved at Week 12 and exceeded the MID (6.6), but were not consistently maintained. Patients reported improvements in fatigue and dyspnea at the first assessment (Week 4) which exceeded the MID (-6.7 and -8.1 respectively). The largest improvement in fatigue and dyspnea were noted at Week 36 and Week 12, respectively. At Week 36, patients reported a worsening in diarrhea, but no differences noted at other time points. Insomnia was reported as improved at Weeks 4, 12, 36, and 48 and the difference exceeded the MID. For nausea, vomiting, pain, appetite loss, or constipation there were no changes from baseline.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chronic Lymphocytic Leukemia 16 (EORTC QLQ-CLL16)

The EORTC QLQ CLL16 module includes 16 items, consisting of 4 multi-item scales (fatigue, treatment side effects, disease symptoms, and infection) and 2 single items (social problems and future health worries). A negative change in score from baseline represents an improvement in symptoms. Changes of 5 – 10 points are considered "a little" change to patients and lower bound (5) was used for MID acceptance.

The most improved parameter in the EORTC-QLQ-CLL16 was for Future Health, which is a question about “worry” which is not proximal to the treatment effect of venetoclax. Items related to social problems (also not proximal to the treatment effect of venetoclax) had moderate improvements beginning at Week 4. Fatigue improved and exceeded the MID at the first assessment at Week 4 and for each following assessment. Other disease effects (feeling ill, bruising, night sweats, and abdominal discomfort), treatment side effects (weight loss, dry mouth, change in temperature, and skin problems), and items on the Infection Scale (trouble with infections and use of antibiotics) were also noted to improve. The Disease Effects and Infection Scale improvements that exceeded the MID were seen at Week 4, and improvements in Treatment Side Effects only exceeded MID at Week 36.

European Quality of Life 5 Dimensions-5 Levels Questionnaire (EQ-5D-5L)

This instrument has 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are measured on a 5-level scale (no problems, slight problems, moderate problems, severe problems, and extreme problems). A positive change in overall Health Index score from baseline represents an improvement in symptoms. The MID for EQ-5D in cancer patients is 0.06—0.09 and the lower bound (0.06) was used for MID acceptance. The improved responses at Week 12 met the MID but this was not sustained.

European Quality of Life 5 Dimensions Visual Analogue Scale (EQ VAS)

This instrument includes the five dimensions of EQ-5D-5L, but uses a visual analogue scale to assess the subject’s overall health. A positive change in score from baseline represents an improvement in symptoms. The MID for the EQ VAS is 7.0. Based on the EQ VAS, patients reported improvement in their overall health, that exceeded the MID at their first assessment (Week 4), and maintained these improvements in subsequent assessments.

Conclusions on Patient Reported Outcomes Data:

- Patients reported an improvement in symptoms and QoL on venetoclax compared to baseline values.
- Some of the differences exceeded the MID (minimally important difference).
- Fatigue improved on two measures (EORTC-QLQ-30 and EORTC-QLQ-CLL16).
- These results should be interpreted with caution because they were designed as exploratory endpoints and are collected in an open-label, single-arm trial, which is subject to bias from knowledge of treatment assigned.

Investigator assessments of efficacy endpoints (discussed earlier with each relevant endpoint)

Integrated Review of Effectiveness

Exploratory pooled analyses were conducted where the studies below were pooled to evaluate efficacy in a larger group of patients treated at 400 mg daily with R/R CLL and in those with 17pdel:

Table 10 Trials Included in Pooled Efficacy Analysis

Trials	Number of Patients with R/R CLL	Number of Patients with R/R CLL and 17pdel
Phase 2 Study M13-982	164	106
Phase I Study M12-175	57	12

For the details of demographics and baseline disease characteristics, please refer to the Primary Clinical/Stat review, Table 21.

Table 11 IRC-Assessed Response Rates for Pooled Efficacy Analysis

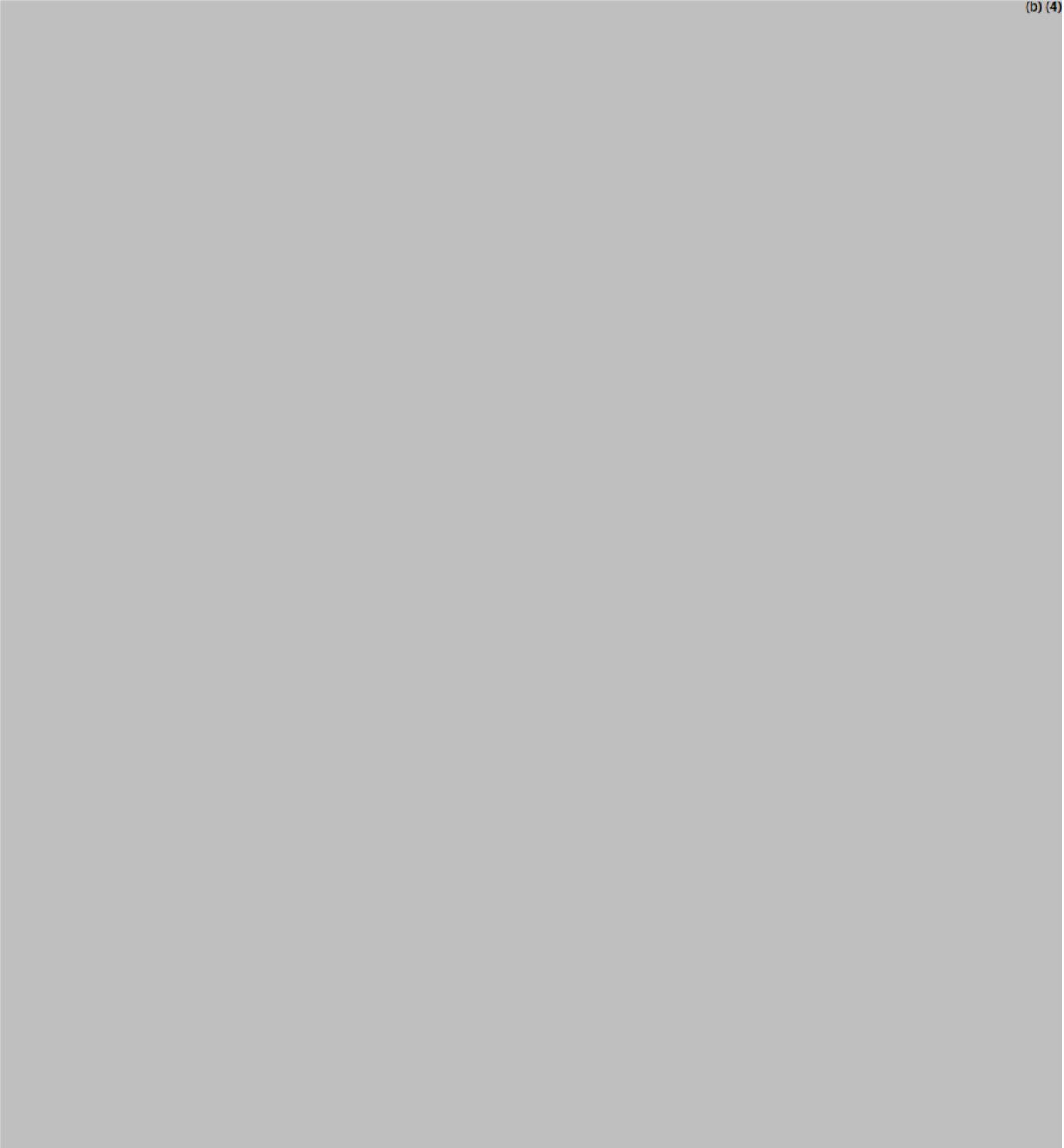
	All R/R CLL n=164 n (%)	R/R CLL with 17p del n=118 n (%)
ORR (95% CI) ¹	127 (77.4) (70.5-83.2)	93 (78.8) (70.6-85.2)
CR rate CR/CRi)	12 (7.3) (8/4)	8 (6.8) (6/2)
nPR	3 (1.8)	3 (2.5)
PR	112 (68.3)	82 (69.5)
No response	37 (22.6)	25 (21.2)

¹ 95% CI varied slightly from Applicant's analysis, score method
[Source: Primary Clinical/Stats Review]

Comment: The pooled analyses results were quite similar to the primary analysis and do not provide additional information.

Subgroup analyses were conducted by the primary review team. The ORR and 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. I agree with the Primary Review team's conclusion that the differences could be due to random chance in groups with low sample sizes. Because >90% of the patients enrolled were white, subgroups of race were not performed.

No other pooled efficacy endpoint analyses were conducted due to the differences in timing of assessments across trials and the lack of interpretability of time-to-event analyses in single-arm trials.



(b) (4)

(b) (4)



Summary of Efficacy Conclusions:

The accelerated approval provisions of FDASIA in section 506(a) of the FD&C Act provide that FDA may grant accelerated approval to:

- A product for a serious or life-threatening disease or condition
- Upon determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

For drugs granted accelerated approval, post-marketing confirmatory trials have been required to verify and describe the anticipated effect on IMM or other clinical benefit.

Chronic lymphocytic leukemia is a serious and life-threatening disease.

Overall response rate is an acceptable surrogate endpoint that can be measured earlier than IMM for CLL indications. Progression-free survival is considered an acceptable endpoint for traditional or regular approval for CLL indications because the chronic nature of the disease precludes waiting for overall survival data.

I concur with the Primary Review Team conclusion that the evidence submitted by AbbVie demonstrates the efficacy of venetoclax for the treatment of patients with relapsed/refractory CLL with 17p deletion. This evidence was from the Phase 2, single-arm trial M13-982 that enrolled patients who had received at least 1 prior CLL-directed therapy and had the ultra-high risk 17p del mutation as detected by the Vysis CLL FISH Probe Kit. The results support an accelerated approval because they demonstrate an improvement over available therapy (ibrutinib is the only other product with the 17pdel CLL indication). The data that supported the approval of ibrutinib in patients with 17pdel CLL was an overall response rate of 48%, compared to the 80.2% ORR with venetoclax. I also concur that venetoclax being available as another oral

therapy for patients with 17pdel CLL is advantageous in that it will require less medical visits (after the initial ramp-up phase and reduced risk of TLS) than an infusional therapy.

The primary endpoint of interest in CLL for accelerated approval is Overall Response Rate. An improvement in Progression-Free Survival will be needed to receive Traditional or Regular Approval. The Applicant has agreed to a Post-Marketing Requirement trial (MURANO) to verify and describe the clinical benefit of venetoclax in patients with relapsed/refractory CLL. The title of the trial is: A Study of GDC-0199 (ABT-199) Plus MabThera/Rituxan (Rituximab) Compared With Bendamustine Plus MabThera/Rituxan (Rituximab) in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia". The trial is Sponsored by Hoffman-La Roche.

(b) (4)

8. Safety

The safety of single-agent venetoclax was evaluated in a broader population than the efficacy evaluation because the presence or absence of a 17pdel should not impact the safety of a product. The primary clinical reviewer, Lori Ehrlich, included patients from three studies in the safety analysis:

- M13-982 (Phase 2 study of patients with R/R CLL and 17pdel) [n=145]
- M12-175 (Phase 1 study of patients with R/R CLL/SLL and NHL) [n=67]
- M14-032 (Phase 2 study of patients with 17pdel or who have failed a BCRi)

The safety profile for patients without 17p del or who have failed a BCRi is not expected to be different from all patients with 17pdel R/R CLL.

Table 13 Components of safety database for single-agent venetoclax therapy

	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 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.

I concur with Dr. Ehrlich's conclusion that while venetoclax treatment can be long-term in patients who have ongoing remissions, CLL is a life-threatening condition. Therefore, the ICH-E1A ICH Guideline for the extent of population exposure does not apply.

I also concur with Dr. Ehrlich's conclusion that the size of the safety database is adequate to provide a reasonable estimate of adverse reactions.

For all studies, AEs and SAEs were defined according to ICH E2A guidelines and the grading for severity used the NCI CTCAE, version 4.0. All 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.

Deaths

The most common cause of death within 30 days of venetoclax treatment from an AE was disease progression (n=13). Among patients treated with R/R CLL treated at all doses (n=289), 8 patients died from AEs after AEs of malignant neoplasm progression were removed. There were single events of death due to AE from the following causes: hemorrhagic stroke, hepatic function abnormal, septic shock, cardiopulmonary failure, sudden death, small intestine obstruction, pneumonia viral, and death (NOS). All deaths were considered "not related" or "probably not related" to study drug by the investigator, except for the single event of "sudden death". This patient experienced fatal tumor lysis syndrome after escalating to 1200 mg. The other causes of death are consistent with an elderly CLL patient population with frequent comorbidities.

Serious Adverse Reactions

The most common SAE in the safety population was febrile neutropenia. Table 14 below lists the most frequently reported SAEs for single-agent venetoclax in the R/R CLL population treated at

400 mg. There were 85 patients with moderate renal impairment among the 240 patients treated at 400 mg. The rates of SAEs were slightly higher in patients with moderate renal impairment (53% vs. 44%) than those with normal renal function, despite the understanding that venetoclax is not excreted by the kidneys (see Table 29 in the Primary Clinical/Stats review for a list of SAES in patients with renal impairment). There were too few patients enrolled with hepatic impairment to conduct a subgroup analysis.

Table 14 Serious Adverse Reactions occurring in at least 2% of 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)

Dropouts and Discontinuations

The discontinuation rate due to AEs for patients with R/R CLL was 9%. The most common reasons for discontinuation were autoimmune hemolytic anemia (AIHA) and thrombocytopenia, in two patients each.

Dose-reductions due to AEs occurred in 10% of patients with the most frequent AE reported as neutropenia (n=7), febrile neutropenia, and thrombocytopenia (3 each). Of the 23 patients who experienced dose-reductions, 8 were able to later re-escalate to the 400 mg dose.

Severe Adverse Reactions

Grade 3 or higher adverse reactions were reported in 74% of the patients with neutropenia in 36%, anemia in 18%, and thrombocytopenia in 13%. Hematologic toxicities like these are frequently observed in therapies for the treatment of CLL and are managed through use of growth factors (GCSF) and transfusions for thrombocytopenia and anemia when needed.

Treatment Emergent Adverse Reactions

Adverse reactions of any grade were reported in 98% of patients with R/R CLL treated at 400 mg daily. The most frequent (>25%) AR was neutropenia (39%), diarrhea (35%), nausea (33%), and anemia (28%).

Table 15 All Grade Adverse Reactions Occurring in at Least 10% of 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)

Because hematologic adverse reactions are often underreported by investigators in hematologic malignancy trials, for labeling purposes the following combined analyses of laboratory reports and adverse reactions were conducted:

- Neutropenia/neutrophil count decreased: 45%
- Anemia/hemoglobin decreased: 29%
- Thrombocytopenia/platelet count decreased: 22%

To evaluate for the impact of splitting MedDRA preferred terms, an analysis of common AEs by higher level term (HLT) was conducted by the Primary Clinical Reviewer. No new safety signals were identified by this analysis (Primary Clinical/Stats Review, Table 32). An analysis was also conducted limiting the safety population to the 17p del CLL population. This analysis was nearly identical to the broader R/R CLL population (without regard to 17pdel) [Primary Clinical/Stats Review, Table 33].

Safety Conclusions

The size of the safety population was adequate to identify common, but not rare, adverse reactions. The safety evaluations that were performed in the trials submitted were appropriate for this product and these patient populations. The safety assessment of venetoclax is limited by the single-arm nature of the submitted trials because the impact of underlying medical conditions cannot be evaluated without a control-arm. The ongoing randomized MURANO trial will be useful to fully evaluate the safety profile of venetoclax. Based upon OSI clinical site inspections

that were conducted, the data appear reliable. The safety data were adequately categorized using MedDRA.

Death occurred within 30 days of venetoclax treatment (not due to disease progression) in 8 patients due to adverse reaction from the following causes: hemorrhagic stroke, hepatic function abnormal, septic shock, cardiopulmonary failure, sudden death, small intestine obstruction, viral pneumonia, and death (NOS) in one patient each. All deaths were considered either “not related” or “probably not related”, except for the single case of sudden death, as this patient experienced fatal tumor lysis syndrome after escalating to a dose of 1200 mg.

The most frequently reported adverse reactions (>25%) of any grade are neutropenia, diarrhea, nausea, and anemia. The most frequently reported SAEs (>10%) include neutropenia, anemia, and thrombocytopenia. The toxicities of venetoclax appear to be rather manageable through transfusions, growth factor support, anti-emetics, and anti-diarrheals; drug discontinuation occurred in 9% of patients and dose-reductions occurred in 10% of patients.

The primary safety issue that can be life-threatening if patients are not appropriately screened, provided with adequate prophylaxis, and monitored, is tumor lysis syndrome. Oncologists/hematologists who manage patients with CLL are aware of this risk with cytotoxic therapies in patients with bulky CLL. It is a well-known oncologic emergency. This risk is mitigated with venetoclax by the implementation of baseline risk screening, a low starting dose with a dose ramp-up, prophylaxis with hydration (oral or IV depending upon risk), and uric acid reducing agents (allopurinol or rasburicase depending upon risk).

The product will be provided with a MedGuide to enhance the education of the patients regarding this risk and the need to hydrate and closely adhere to the dose ramp-up instructions. The Applicant has also submitted for review a Quick Start Guide. The Patient Labeling group provided review and recommended revisions of the Medication Guide and Quick Start Guide. DMEPA reviewed the human factors validation study that was conducted on the proposed wallet and blister packs, as well as the wallet/blister pack labels, PI, and quick start guide.

9. Advisory Committee Meeting

Venetoclax was not selected for presentation at an Oncology Drug Advisory Committee Meeting because the Division is familiar with the trial design and study endpoints. We also did not consult Special Government Employees because this application was reviewed on an expedited timeline due to its Breakthrough Designation status and the need to get this therapy out to patients who have limited treatment options.

10. Pediatrics

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).

11. Other Relevant Regulatory Issues

Companion Diagnostic

The initial development and early clinical trials were in patients with CLL who harbor the 17p deletion. The Applicant was advised that they would need to work with a diagnostic company to develop a companion diagnostic to detect the 17p deletion for therapy selection. The Applicant worked with Abbott Molecular to develop the Vysis CLL FISH probe kit to detect the 17p deletion. Abbott submitted a Pre-Marketing Application (PMA) (b) (4) for review by CDRH. CDRH is reviewing the device and our intention is to take action on the diagnostic and drug simultaneously. Because the clinical indication will be (b) (4) patients with CLL who harbor the 17p deletion, the companion diagnostic will be required to identify patients who are most likely to benefit from venetoclax therapy.

Financial disclosures

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 [Source: Lori Ehrlich's Primary Clinical Review]

I agree that the results of trial M13-982 are not likely to be due to bias associated with financial gain.

Office of Scientific Investigations (OSI) audits

Dr. Anthony Orenca, OSI archived his review on 03/10/16. Three clinical sites and the Sponsor site were inspected in support of the NDA. He concludes that the data submitted by the inspected sites appear acceptable and reliable in support of this specific indication.

Division of Risk Management

The Applicant submitted a Medication Guide and proposed pharmacovigilance plan. Mona Patel (DRISK) archived her review on 03/15/16. In the Executive Summary, she concludes that she agrees with DHP that a REMS is not needed to ensure that the benefits of venetoclax outweigh its risks and that the risks will be communicated through labeling.

12. Labeling

Prescribing Information

Revisions to the Applicant's Submitted Prescribing Information are described by Section:

All Sections: Revised text (b) (4)
(b) (4) to "patients with CLL". The proprietary name of "VENCLEXTA" was deemed

“conditionally acceptable” on 12/16/15 by DMEPA. The clinical team did not object to this proprietary name.

Highlights of Prescribing Information

- [REDACTED] (b) (4)
- Added the companion diagnostic information to the indication statement
- Revised the “immunization” warning to include the word “attenuated” and to add the third time period in which live attenuated vaccines should be avoided (after treatment).
- Revised the drug interactions for brevity, and added P-gp inhibitors and substrates

Indications and Usage

- [REDACTED] (b) (4)
- Added the companion diagnostic information to the indication statement

Dosage and Administration

- The proposed dose (including starting dose, target dose, and ramp-up plan) was acceptable to the review team and supported by the clinical studies submitted in the NDA.
- Added Section 2.1 “Patient Selection”, upon recommendation from CDRH to describe the method for selecting patients with 17p deletion.
- Provided significant revisions to this section to organize the information in a way that is more useful to prescribers.
- Replaced [REDACTED] (b) (4) describing assessment of TLS risk and recommended prophylaxis with a table that more clearly summarizes this information.
- Revised to reflect active voice.
- Recommended that the Applicant add a footnote to the table titled “Recommended Dose Modifications for Toxicities” describing that “adverse reactions were graded using NCI CTCAE version 4.0”.
- Recommended that the Applicant define TLS as a footnote to the same table [REDACTED] (b) (4)
- Asked the Applicant to clarify the footnote “a” which states [REDACTED] (b) (4) ; because according to the protocol, this appears to have only been done during the rampup phase.
- In subsection 2.5, we moved the most important information to the beginning (contraindication for use of strong CYP3A inhibitors at initiation of venetoclax and during rampup phase).
- Added [REDACTED] (b) (4) “P-gp inhibitors” to the sentence recommending avoidance of concomitant use of venetoclax.
- A table was added to summarize the dose modifications needed for venetoclax with CYP3A and P-gp inhibitors
- It was discussed as to how to provide the risk assessment for TLS, prophylaxis recommendations, and dose-ramp-up information and what should go in Section 2 vs. Section 5 (W&P). After mocking up dividing this information between two sections, it

was preferred by the review team to leave it all in Section 2 for ease of location by prescribers.

Dosage Forms and Strengths

No revisions to this section were proposed.

Contraindications

Italicized the word “strong” before CYP3A inhibitors... to call attention to the fact that it’s not all CYP3A inhibitors that are contraindicated.

Warnings and Precautions

5.1 Tumor Lysis Syndrome: Added “and renal failure requiring dialysis” to further describe the events of TLS seen in clinical trials. Added “and P-gp inhibitors” to the list of concomitant drugs that may increase venetoclax exposure and the risk of TLS during initiation and ramp-up.

5.2 Neutropenia: Added “(b) (4) with TRADENAME (b) (4)” to indicate that these events were treatment emergent; revised existing language to active voice; deleted the word (b) (4) from “use of growth factors” because the trial data did not support this recommendation; and deleted (b) (4)

Adverse Reactions

- Revised the introduction that described the studies included in the safety population. (b) (4)
- Added a statement listing the most frequent ARs that led to dose adjustments.
- In the AR table, revised the column headings to clinically relevant terms ((b) (4) (b) (4) to Body System and (b) (4) (b) (4) to “Adverse Reaction”.
- To the AR table, added a footnote identifying how the ARs were graded (i.e., using CTCAE).
- (b) (4) (b) (4); sent the Applicant a comment that only ARs as defined in 21CFR201.57©(7), should be included in labeling.

Drug Interactions

- Added statement that strong CYP3A inhibitors are contraindicated during ramp-up phase of venetoclax treatment.
- Provided instructions on dose-modifications of venetoclax after rampup phase is completed and concomitant use of strong CYP3A inhibitors.
- Added statement that use of concomitant P-gp substrates should be avoided.

Use in Specific Populations

Section 8.1 Pregnancy was revised to be consistent with the PLLR final rule, PLLR guidance, and current preferred terminology for this section.

Section 8.4 Pediatric Use was revised to include the preferred statement regarding the lack of efficacy/safety data in children.

Section 8.5 Geriatric Use was revised (b) (4)

Section 8.6 Renal Impairment was revised to include the most important information first (patients with reduced renal function are at increased risk of TLS).

Section 8.7 Hepatic Impairment was revised to add the data that the human mass balance study showed that venetoclax undergoes hepatic elimination.

Overdosage

(b) (4). A comment was given to the Applicant: *“This section should describe the amount of drug in a single dose associated with symptoms of drug overdose that is likely to be life-threatening; whether the drug is dialyzable; signs, symptoms, and laboratory findings of overdose; complications that can occur with overdose (e.g., organ toxicity, delayed acidosis); concentration of drug in biologic fluids associated with toxicity or death; physiologic variables that influence the excretion of drug; and general treatment procedures and specific measure for support of vital functions (e.g. antidotes, gastric lavage, forced diuresis). See 21CFR201.57(c)(11).”*

Description

No revisions to this section.

Clinical Pharmacology

12.1 MOA: Deleted statement (b) (4)

(b) (4),” Because it appeared promotional. Deleted the word “ (b) (4),” in the statement “Venetoclax is a (b) (4), selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein.” (b) (4)

12.2 PD Replaced (b) (4) with “hematologic malignancies (b) (4) (b) (4)

12.3 PK Added “under fed conditions” in sentence that described absorption. Added “Elimination” and “Excretion” subheadings. Moved data on half-life to elimination subsection. Added statement to the excretion subsection that states “indicating that hepatic elimination is responsible for the clearance of venetoclax from the systemic circulation”.

Deleted (b) (4)

To Renal Impairment subsection, added specific method of how creatinine clearance was measured.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

None of the review disciplines has recommended a REMS for venetoclax. I agree that the known safety issues with venetoclax can be effectively communicated through labeling and the MedGuide. No REMS is planned.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The Applicant has agreed to the following Subpart H PMR:

Clinical

Venetoclax is recommended for approval under Subpart H (the accelerated approval provisions). The approval is subject to a Postmarketing Requirement to verify and describe the clinical benefit of venetoclax. The agreed upon PMR description is:

PMR #1 Description: Submit the complete final report and data from trial GO28667, a randomized, phase 3 trial comparing venetoclax and rituximab with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL), including CLL with deletion 17p

PMR Schedule Milestones:	Final Protocol Submission:	Completed
	Study Completion:	<u>05/2018</u>
	Final Report Submission:	<u>05/2019</u>

The Clinical Pharmacology PMRs are agreed upon:

Clinical Pharmacology

The Clinical Pharmacology review team has recommended the following post-marketing requirements to enable complete dosing information for patients with hepatic impairment and to further evaluate drug-drug interactions:

PMR #2 Description: Evaluate the effect of hepatic impairment on the pharmacokinetics and safety of venetoclax compared to subjects with normal hepatic function. Submit a complete final study report with all supporting datasets for trial M15-342 entitled, “A Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment”.

PMR Schedule Milestones:	Final Protocol Submission:	<u>03/2016</u>
	Study/Trial Completion:	<u>03/2017</u>
	Final Report Submission:	<u>12/2017</u>

PMR # 3 Description: Evaluate the effect of venetoclax co-administration on pharmacokinetics of a probe substrate of P-gp. Submit a complete final study report with all supporting datasets.

Final Protocol Submission:	08/2016
Study/Trial Completion:	11/2016
Final Report Submission:	06/2017

14. Recommended Comments to the Applicant

None.

Bibliography

- Alizadeh, A., & Eisen, M. D. (2000). Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*, 503-511.
- Binet, J., Auquier, A., Dighiero, G., & al., e. (1981). A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer*, 198-206.
- Cairo, M., & Bishop, M. (2004). Tumour lysis syndrome: new therapeutic strategies and classification. *British Journal of Haematology*, 3-11.
- Cheson, B., Byrd, J., & Rai, K. (2012). Novel targeted agents and the need to refine clinical endpoints in chronic lymphocytic leukemia. *J Clin Oncol*, 2820-2822.
- Coiffier, B., Altman, A., Pui, C., & al., e. (2008). Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*, 2767-2778.
- Food and Drug Administration. (n.d.). *Drugs@FDA*. Retrieved March 25, 2016, from [Drugs@FDA: FDA Approved Drug Products: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)
- Hallek, M., Cheson, B., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., Dohner, H., et al. (2008). Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute Working Group 1996 Guidelines. *blood*, 5446-5456.
- Hallek, M., Fischer, K., Fingerle-Rowson, G., & al., e. (2010). Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*, 1164-1174.
- Kovacs, G., Boettcher, S., Bahlo, J., & al., e. (2014). Value of Minimal Residual Disease (MRD) Negative Status at Response Evaluation in Chronic Lymphocytic Leukemia (CLL): Combined Analysis of Two Phase III Studies of the German CLL Study Group. *Blood*, Abstract 23.
- National Comprehensive Cancer Network, Inc. 2016. (n.d.). *NCCN Guidelines Version 2.2016 Non-Hodgkin's Lymphomas*. Retrieved January 6, 2016, from http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf
- Pharmacocyclics. (n.d.). *Imbruvica Approved Prescribing Information*. Retrieved Feb 15, 2016, from [Drugs@FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s0021bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s0021bl.pdf)
- Rai, K., Sawitsky, A., Cronkite, E., & al., e. (1975). Clinical staging of chronic lymphocytic leukemia. *Blood*, 219-234.
- Siegel, R., Miller, K., & Jemal, A. (2015). Cancer Statistics, 2015. *CA CANCER J CLIN*, 5-29.
- The Non-Hodgkin's Lymphoma Classification Project. (1997). A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Bood*, 3909-3918.
- Tsimberidou AM, W. S. (2007). Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center. *J Clin Oncol*, 4648-4656.

APPEARS THIS WAY ON ORIGINAL

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

/s/

VIRGINIA E KWITKOWSKI
04/04/2016