Advisory Committee Briefing Document

Venetoclax for the Treatment of Pediatric Patients with Relapsed/Refractory Cancers

AbbVie Inc./Genentech/Roche

Oncologic Drugs Advisory Committee
Pediatric Subcommittee

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Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations and Definitions of Terms

ABC	Activated B-Cell
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia or Acute Lymphocytic Leukemia
AML	Acute Myelogenous Leukemia or Acute Myeloid Leukemia
ASD	Amorphous Solid Dispersion
AST	Aspartate Aminotransferase
AUC	Area Under The Curve
AUC_{SS}	Area Under The Curve at Steady State
BCL-2	B-Cell Lymphoma 2
BIM	Bcl-2-Interacting Mediator of Cell Death
BTD	Breakthrough Therapy Designation
CCSK	Clear Cell Sarcoma of the Kidney
CLL	Chronic Lymphocytic Leukemia
C_{max}	Maximum Concentration
CNS	Central Nervous System
COG	Children's Oncology Group
CR	Complete Remission
CRi	Complete Remission With Incomplete Marrow Recovery
CrCL	Creatinine Clearance
CSF	Cerebral Spinal Fluid
CT	Computerized Axial Tomography
CTCAE	Common Terminology Criteria For Adverse Events
CYP	Cytochrome P450
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitor Board
ECG	Electrocardiogram
EFS	Event Free Survival
EMA	European Medicines Agency
FDA	Food And Drug Administration
FL	Follicular Lymphoma
GCB	Germinal Center B-Cell
GLP	Good Laboratory Practice

IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IWG	International Working Group
MCL	Mantle Cell Lymphoma
MDS	Myelodysplastic Syndrome
MLL	Mixed Lineage Leukemia
MM	Multiple Myeloma
MRD	Minimal Residual Disease
mRNA	Messenger Ribonucleic Acid
NBL	Neuroblastoma
NHL	Non-Hodgkin Lymphoma
ODAC	Oncologic Drug Advisory Committee
ORR	Objective Response Rate
QD	*quaque die*, Once Daily
OS	Osteosarcoma
QTcF	Fridericia's Correction Formula
PD	Progressive Disease
PDX	Patient Derived Xenograft
PET	Positron Emission Tomography
P-GP	Permeability Glycoprotein
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic
PND	Post Natal Day
PR	Partial Remission
R/R	Relapsed/Refractory
RT	Rhabdoid Tumors
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
SLE	Systematic Lupus Erythematosus
SOC	System Organ Class
$t_{1/2}$	Terminal Half-Life
T_{max}	Maximum Concentration
TEAE	Treatment Emergent Adverse Event

TLS	Tumor Lysis Syndrome
Tg HRAS	Wild Type Transgenic Mice
US	United States
VGPR	Very Good Partial Response
WBC	White Blood Cell
WT	Wilms Tumor

Executive Summary

AbbVie and Genentech/Roche (the sponsors) have jointly initiated early development planning to evaluate venetoclax for the treatment of pediatric patients with relapsed/refractory cancers. The sponsors have been invited to this meeting of the oncologic drug advisory committee (ODAC), pediatric subcommittee, to present the proposed venetoclax pediatric oncology program.

Over-expression of anti-apoptotic B-cell lymphoma-2 (BCL-2) family proteins, such as BCL-2, BCL-X_L or MCL-1, enables cancer cell survival and is associated with tumor initiation, disease progression, and increased resistance to chemotherapy. Antagonism of these proteins may enhance response to chemotherapeutic agents or trigger apoptosis directly in certain tumor cells, and thus, these proteins are targets for anti-tumor therapy. Venetoclax (ABT-199/GDC-0199) is a selective, orally bioavailable, small-molecule inhibitor of BCL-2. Venetoclax received accelerated approval in the United States (US) for use in patients who have chronic lymphocytic leukemia (CLL) in the presence of 17p deletion, as detected by an FDA approved test, who have received one prior therapeutic regimen. Venetoclax is also being developed for patients with acute myelogenous leukemia (AML), non-hodgkin lymphoma (NHL), and multiple myeloma (MM).

The Sponsors have used a mechanistic approach to identify pediatric tumors that have high levels of BCL-2 expression, and hence, also have the highest potential to respond to venetoclax. This was followed by evaluation in pre-clinical murine xenograft models. Finally, data from venetoclax studies in adult malignancies that occur in children were considered. This approach resulted in selection of AML, acute lymphocytic leukemia (ALL), NHL, and neuroblastoma as the tumor types proposed for the initial pediatric program.

Overall survival of newly diagnosed patients who have these four tumor types is very high. However, in the relapsed and refractory settings, prognosis remains quite poor and the lack of effective treatment options results in continued high unmet medical need. Data

for venetoclax in pediatric patients are not available. The current safety profile in adults is favorable. The anti-tumor activity observed in adult clinical trials supports initiating evaluation of venetoclax in a pediatric population.

The proposed pediatric clinical study (n ~150 patients) is a global Phase 1 study of venetoclax monotherapy in pediatric patients aged 1 – 18 years with the following relapsed or refractory cancers: AML, ALL, NHL and neuroblastoma. The objectives of this study include assessments of safety, pharmacokinetics and preliminary efficacy of venetoclax. Dose selection for venetoclax in pediatric patients is based on the assumption that exposures (AUC steady state values) similar to adult patients will provide similar safety and efficacy profiles in pediatrics. The currently approved oral tablets will be used for children who are able to tolerate pills, and a venetoclax suspension formulation that is suitable for pediatric patients is currently under development for patients who cannot swallow the oral tablet. The findings of this Phase 1 study will inform the future development of venetoclax in pediatric patients with malignancies

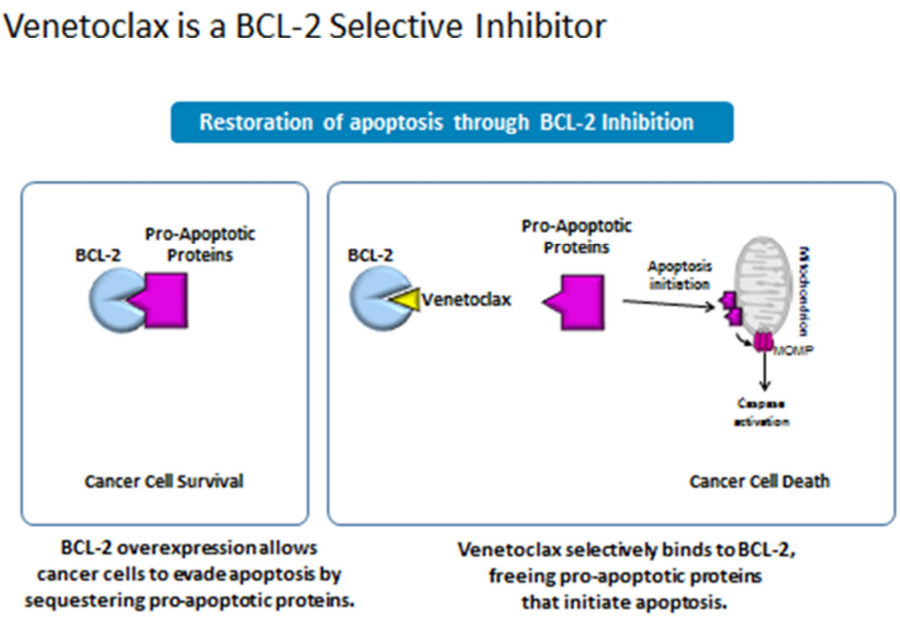
1.0 Mechanism of Action

BCL-2 family proteins are important regulators of the intrinsic apoptosis pathway and were first identified in follicular lymphoma, where the t(14;18) chromosomal translocation results in significant over-expression of BCL-2 in B-cells. The BCL-2 family of genes encodes closely related proteins that possess either pro-apoptotic or anti-apoptotic activity, the latter mediated by BCL-2, BCL-X_L, BCL-W, A-1, and MCL-1.[1] The ratio of pro-apoptotic to anti-apoptotic proteins is associated with the outcome of cell survival or programmed cell death.[1] In contrast to other known oncoproteins, BCL-2 does not stimulate cellular proliferation, but rather inhibits programmed cell death by protecting cells from a wide variety of pro-apoptotic stimuli, including cytotoxic drugs, cytokine withdrawal, irradiation, heat, and deregulated oncogenes.[1-3]

Venetoclax is a potent, selective and orally bioavailable, small-molecule inhibitor of BCL-2, binding with high affinity (K_i < 0.010 nM) to BCL-2 and with lower affinity to BCL-X_L and BCL-W (> 4,000-fold and > 2,000 fold lower affinity). Venetoclax helps

restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM (BCL-2-interacting mediator of cell death), triggering mitochondrial outer membrane permeabilization, and the activation of caspases (Figure 1). In non-clinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.[1]

Figure 1. Venetoclax Mechanism of Action



2.0 Regulatory History

An investigational new drug (IND) application for venetoclax (ABT-199/GDC-0199) for the treatment of hematologic malignancies went into effect in November 2010. Hematologic malignancies under investigation in adult patients include: AML, CLL, MM, NHL and small lymphocytic leukemia (SLL). Over 20 clinical trials in adults have

been initiated in the US, European Union (EU), and other countries worldwide. Five of these trials have been completed.

Venetoclax has been granted Breakthrough Therapy Designation (BTD) for three adult indications:

- for patients with CLL with 17p deletion (granted April 27, 2015)
- in combination with rituximab for patients with relapsed or refractory CLL (granted December 21, 2015)
- in combination with hypomethylating agents (azacitidine or decitabine) for treatment-naïve AML patients who are ≥ 65 years of age and who are not eligible for standard induction therapy (granted January 25, 2016)

On April 11, 2016, venetoclax was granted accelerated approval in the US for the treatment of adult patients with CLL with 17p deletion, as detected by an FDA approved test, who had received at least one prior therapy.

The Sponsors (AbbVie and Genentech/Roche) received orphan drug designations for venetoclax in the US for CLL on September 20, 2012 (#12-3756), DLBCL on March 25, 2014 (#14-4238) and AML on February 04, 2016 (#15-5068). In the EU, orphan status was granted for CLL on December 06, 2012 (EU/3/12/1080) and for AML on February 17, 2016 (EU/3/16/1617).

The Sponsors are actively evaluating clinical study designs, screening, and recruitment strategies that would allow execution of a pediatric study in the US and EU. A Pediatric Investigational Plan (PIP) is in development for submission to the European Medicines Agency (EMA) in the future. The proposed US pediatric study plans will align closely with the EU PIP.

Venetoclax is not currently approved for marketing in any other country worldwide besides the US. The first EU Marketing Authorization Application for the treatment of adult patients with CLL in the presence of 17p deletion or *TP53* mutations was submitted

to the EMA. Additionally, marketing authorization applications have been submitted in a number of other countries.

3.0 Nonclinical Data Supporting Clinical Studies

Toxicology findings are generally consistent with the pharmacologic mechanism of action of selective BCL-2 inhibition.

Animal Toxicology and/or Pharmacology

The primary toxicities associated with repeat-dose administration of venetoclax were effects on the hematologic system (decreased lymphocytes and red blood cell mass) in mice, rats, and dogs, the male reproductive system (testicular germ cell depletion in dogs), and embryo-fetal toxicity in mice. Other noteworthy, but non-adverse findings were minimal to mild single cell necrosis in epithelial tissues (gallbladder, exocrine pancreas, epididymides, prostate, and stomach) of dogs, and hair coat color changes in dogs as the result of loss of melanin pigment in the hair. No evidence was found from in vitro and in vivo studies for mutations or damage to chromosomes with venetoclax, nor was there evidence for phototoxicity.

Results from the toxicology studies of venetoclax are generally consistent with the mechanism of action of selective BCL-2 inhibition by venetoclax. The findings of decreased lymphocytes and red blood cell mass may occur in pediatric patients, but the animal data suggest that they would be dose-related and reversible upon cessation of dosing. The risk of testicular toxicity in pediatric patients is unknown but cannot be excluded. This risk should be considered in the context of potential therapeutic benefits of venetoclax. The translatability of the single cell necrosis (which is a likely effect of venetoclax induced apoptosis) and loss of melanin pigment in the hair is unknown, but the animal data suggest that similar effects in pediatric patients would be mild and non-adverse.

Carcinogenicity studies have not been conducted with venetoclax at this time.

3.1 Nonclinical Toxicity and Development Plan

To support oncology indications for which there are suitable pediatric populations, non GLP dose range-finding studies were conducted in juvenile mice. Venetoclax was administered as a single oral dose of 0 or 100 mg/kg/day to male juvenile mice on Post-Natal Day (PND) 7 and 30 in a toxicokinetics and tolerability study.[4] Venetoclax exposure to the brain was approximately 10-fold higher on PND 7, which is prior to the estimated age at which the blood brain barrier is fully functional, than on PND 30, when the blood brain barrier is expected to be mature. PND 30 in a mouse corresponds to a childhood age of approximately 2 years, at which point the blood brain barrier would be expected to be fully developed. However, there were no clinical signs of central nervous system toxicity at either PND 7 or 30. In a subsequent repeat-dose study, venetoclax was administered orally to male and female juvenile mice at 0, 3, 30, 100, 300 mg/kg/day from PND 7 through 21.[5] All dosages were tolerated. Minor effects of venetoclax were observed, such as reduced body weights or body weight gain. A definitive, GLP-compliant toxicity study in juvenile mice is ongoing.

The overall nonclinical safety profile of venetoclax supports its use in oncology indications.

3.2 Nonclinical Pharmacology

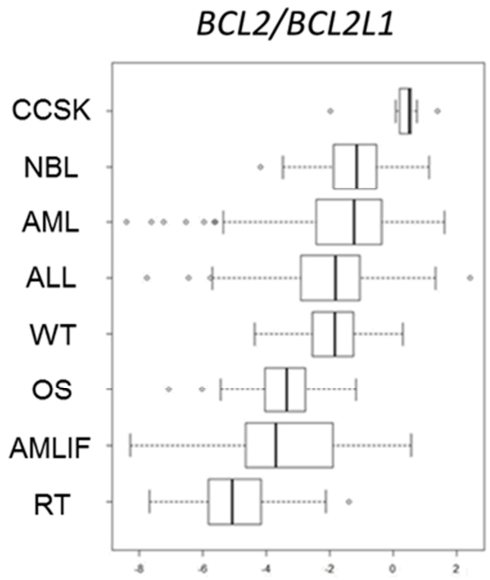
Available preclinical data in support of the mechanistic-based approach of tumor selection is summarized below.

3.2.1 Rationale for Selection of Pediatric Tumor Types

The Sponsors identified pediatric tumor types with the potential to respond to venetoclax through a combination of *in silico* data mining, in vitro and in vivo testing of adult and pediatric tumor models, and analyses of venetoclax clinical data generated to date in corresponding adult tumors. Our *in silico* analyses sought to identify pediatric tumor types expressing high levels of BCL-2 mRNA and/or exhibiting a high ratio of BCL-2 expression relative to BCL-2L1, the gene encoding for BCL-X_L, which is a likely

resistance factor for venetoclax. Figure 2 is an example of one such analysis and highlights pediatric tumor types that express high levels of BCL-2 relative to BCL-2L1 (BCL-X_L): clear cell sarcoma of the kidney (CCSK), neuroblastoma (NBL), AML, ALL, and Wilms tumor (WT). Tumor types with low BCL-2/BCL-2L1 expression ratios include osteosarcoma (OS), AML induction failure (AMLIF), and rhabdoid tumor (RT).

Figure 2. BCL-2/BCL-X_L Expression Ratio Among Pediatric Tumor Types



CCSK = clear cell sarcoma of the kidney; NBL = neuroblastoma; AML = acute myeloid leukemia; ALL = acute lymphocytic leukemia; WT = Wilms tumor; OS = osteosarcoma; AMLIF = AML induction failure; RT = rhabdoid tumor

The ratio of BCL-2 mRNA expression relative to BCL-2L1 is plotted for pediatric tumor samples.

BCL-2 expression alone may not predict sensitivity to venetoclax. Therefore, functional evidence of BCL-2 dependence was also assessed when possible. In pre-clinical studies conducted by the Sponsors and others, venetoclax has been shown to be a potent inducer of apoptosis (cell killing EC_{50} < 1 µM) in a variety of human tumor cell lines and primary tumor samples, including subsets of AML, ALL, NHL and neuroblastoma.[6-13] However, venetoclax showed no activity in other pediatric solid tumor cell lines including Ewing sarcoma, osteosarcoma, rhabdomyosarcoma and medulloblastoma (Reynolds et al

unpublished Pediatric Preclinical Testing Program [PPTP] data). There are currently no data available for venetoclax in clear cell sarcoma of the kidney or Wilms tumor, but the Sponsors have contacted investigators to initiate cell line and murine studies. The Sponsors considered in vivo efficacy in murine models of cancer as the most compelling evidence of the possible efficacy of venetoclax. Pediatric tumor types for which positive murine data exist are summarized below.

AML

Venetoclax has shown potent (IC_{50} < 0.1 µM) killing activity against AML cell lines[10] and primary patient samples, as well as efficacy in both systemic and patient-derived xenograft (PDX) models of AML.[3] Venetoclax slowed tumor growth, reduced tumor burden in liver, spleen and bone marrow, and prolonged survival relative to untreated controls.

ALL

Venetoclax has demonstrated efficacy in a variety of murine tumor models of ALL, including flank xenograft, systemic, and PDX models.[1,6,14] ALL models bearing the t(4;11) translocation are especially sensitive to venetoclax, perhaps due to direct transcriptional upregulation of BCL-2 expression by the MLL-AF4 fusion protein.[6] The Pediatric Preclinical Testing Program (PPTP) has assessed venetoclax in 21 pediatric PDX models of ALL. Three of 6 MLL-ALLs showed strong response to venetoclax (one maintained complete response, one complete response and one partial response) while 3 of 9 B-cell precursor-ALL PDX models showed objective responses (two complete responses and one partial response). BCL-2 expression is also upregulated by TCF3-HLF, the product of the t(17;19)(q22;p13) translocation that is associated with extremely poor prognosis.[15] TCF3-HLF-positive ALL samples are sensitive to venetoclax both ex vivo and in vivo[16] (and PPTP results).

NHL

Venetoclax has shown cell killing activity against NHL cell lines in vitro, especially in cells with BCL-2 amplification or the t(14;18) BCL-2 translocation,[1] and in both DLBCL xenografts such as the Toledo model and genetically engineered mouse models of NHL, including so-called "double hit" lymphoma.[17,18] However, venetoclax did not show activity in Burkitt's lymphoma cell lines (n = 12; AbbVie unpublished data) and therefore patients with Burkitt's lymphoma will not be included in the clinical pediatric study.

Neuroblastoma

Neuroblastoma patient samples show very high levels of BCL-2 relative to other pediatric tumors and normal tissues and have a high ratio of BCL-2/BCL-2L1 (Figure 2). Some neuroblastoma cell lines express high levels of BCL-2 and are sensitive to venetoclax-mediated killing in vitro.[13] Murine testing showed that venetoclax monotherapy delayed and reduced tumor growth, leading to long-term survival in 20% of mice.[12] Combination therapy with cyclophosphamide significantly increased survival to 60%.

4.0 Clinical Trial Experience in Adults

4.1 Overview

The venetoclax clinical oncology program was initiated in June 2011. Multiple ongoing Phase 1/2 AbbVie and Phase 1/2/3 Genentech/Roche clinical studies are evaluating venetoclax as monotherapy or in combination with other therapies in patients with hematologic malignancies, including CLL/SLL, MM, AML and NHL.

Venetoclax is currently being assessed in over 20 ongoing studies in adult oncology patients. Details of ongoing studies are presented in Appendix A.

Five clinical studies in adults have been completed. The completed trials were primarily small Phase 1 studies to assess oral bioavailability and food effect in healthy participants.

4.2 Summary of Pharmacokinetics, Safety and Efficacy

4.2.1 Pharmacokinetics

Venetoclax pharmacokinetics in humans are characterized by a bi-exponential disposition, with a terminal half-life ($t_{1/2}$) of approximately 26 hours. Following multiple-dose administration, the time to reach maximum concentration (T_{max}) of venetoclax was attained by 5 to 8 hours. In patients with CLL, venetoclax showed minimal accumulation, and steady-state area under the plasma concentration-time curve (AUC_{ss}) increased proportionally from 150 mg to 800 mg. Food (low- to high-fat meals) increased the bioavailability of venetoclax by approximately 3- to 5-fold compared to fasting. In adults, venetoclax is administered with a meal and water.

Venetoclax is primarily metabolized by CYP3A4 and was eliminated as metabolites primarily in feces with negligible renal elimination (< 0.1% of the dose). M27 was identified as a major metabolite with an inhibitory activity against BCL-2 that is at least 58-fold lower than venetoclax in vitro. Co-administration of venetoclax with 400 mg once daily ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, in NHL patients increased venetoclax C_{max} by 2.3-fold and AUC_{∞} by 6.4-fold. Co-administration of venetoclax with a 600 mg single dose of rifampin, an OATP1B1/1B3 and P-gp inhibitor, in healthy patients increased venetoclax C_{max} by 2.06-fold and AUC_{∞} by 1.78-fold. Co-administration of 600 mg once daily rifampin, a strong CYP3A inducer, for 13 days in healthy patients decreased venetoclax C_{max} by 42% and AUC_{∞} by 71%. Co-administration of a single 400 mg dose of venetoclax with 5 mg warfarin resulted in 1.18-fold to 1.28-fold increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin.

At multiple doses of venetoclax up to 1200 mg once daily, there was no large effect on QTc interval (i.e., > 20 ms) and no relationship between venetoclax exposure and change in QTc interval. Based on adult population PK analyses, age, race, sex and weight do not have an effect on venetoclax clearance. In addition, patients with mild renal impairment (creatinine clearance 60 to 89 mL/min) or moderate impairment (30 to 59 mL/min) have similar venetoclax exposures to those with normal renal function, and patients with mild

hepatic impairment (< 1 mg/dL bilirubin and > 40 IU/L AST, or > 1.0 and < 1.5 mg/dL bilirubin) or moderate impairment (> 1.5 and < 3.0 mg/dL bilirubin) have venetoclax exposures similar to those with normal hepatic function.

4.2.2 Overview of Safety

Venetoclax has not been evaluated in a pediatric population to date.

As of November 28, 2015, on the basis of data available in the AbbVie and Genentech/Roche clinical databases, a total of 1493 patients have been exposed to at least 1 dose of venetoclax in oncology studies. Of these, 935 patients had CLL/SLL, 346 patients had NHL, 110 patients had MM, and 102 had AML. A total of 560 patients received venetoclax as monotherapy and 933 patients as part of combination with other therapies.

Based on the mechanism of action and nonclinical and clinical data available to date, the safety profile of venetoclax is understood. Common treatment-emergent adverse events across all indications (monotherapy and combination therapy) include grade 1 – 2 gastrointestinal toxicities (nausea and diarrhea) and grade 3 – 4 hematological toxicities (neutropenia/febrile neutropenia, thrombocytopenia and anemia). Grade 1 – 2 upper respiratory tract infections are among the most common infections, but the majority of these events were observed in the CLL population of elderly patients.

Tumor lysis syndrome (TLS) is an important identified risk, particularly in patients with CLL who have high disease burden. The risk has been largely mitigated by a gradual ramp-up dosing regimen and TLS prophylaxis measures. TLS is an oncologic emergency and is manageable by following standard treatment guidelines.

Neutropenia is also an important identified risk in adult patients with CLL. Monitoring of complete blood counts is recommended throughout the treatment period. Dosing adjustments may be needed. Supportive measures should include antimicrobials for signs of infection and use of growth factors (e.g., G-CSF) as clinically indicated.

There are currently no data on the use of venetoclax with vaccination. Hence, patients using venetoclax should not be administered live vaccines prior to, during, or after treatment.

An overview of the most common adverse events (AE) of all grades (Table 1) and grade 3 – 4 AEs (Table 2) of venetoclax monotherapy (doses ranging from 20 – 1200 mg) across various indications is presented below.

Table 1. Treatment Emergent Adverse Events All Grades) in ≥ 10% of Patients Across Monotherapy Studies

MedDra Preferred Term	Overall AE Frequency N=560 n (%)
Nausea	232 (41)
Diarrhea	227 (41)
Fatigue	165 (30)
Neutropenia	161 (29)
Anemia	124 (22)
Upper respiratory tract infection	112 (20)
Vomiting	99 (18)
Cough	95 (17)
Headache	94 (17)
Thrombocytopenia	86 (15)
Constipation	82 (15)
Pyrexia	82 (15)
Hypokalemia	76 (14)
Hyperphosphatemia	57 (10)

Table 2. Grade 3/4 Adverse Events in ≥ 2% of Patients Across Monotherapy Studies

MedDra Preferred Term	Overall AE Frequency N=560 n (%)
Neutropenia	143 (26)
Anemia	77 (14)
Thrombocytopenia	62 (11)
Febrile Neutropenia	33 (6)
Neutrophil count decrease	30 (5)
Pneumonia	29 (5)
Hypokalemia	24 (4)
Platelet count decreased	22 (4)
Tumor lysis syndrome	21 (4)
Fatigue	16 (3)
Diarrhea	14 (3)
Hypocalcemia	9 (2)
Nausea	9 (2)
Urinary tract infection	9 (2)

Venetoclax has been evaluated with several combination regimens. The safety profile of venetoclax in combination with other agents has been largely similar to the venetoclax monotherapy profile, the background disease and/or backbone combination regimen and support continuous development.

4.2.3 Overview of Efficacy

An overview of clinical data from adults in the approved indication (CLL) and indications being included in the proposed pediatric plan (AML and NHL) is presented below.

Clinical Studies in CLL

Venetoclax is currently indicated for treatment of patients who have CLL in the presence of 17p deletion, as detected by an FDA approved test, who have received one prior therapeutic regimen. 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.

The efficacy of venetoclax was established in an open-label, single-arm, multicenter clinical trial of 106 adult patients with CLL with 17p deletion who had received at least one prior therapy. In the study, 17p deletion was confirmed in peripheral blood specimens from patients using the Vysis CLL FISH Probe Kit, which is FDA approved for selection of patients for venetoclax treatment. Patients received venetoclax following a weekly ramp-up schedule starting at 20 mg, increasing to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive 400 mg of venetoclax orally once daily until disease progression or unacceptable toxicity.

The efficacy of venetoclax was evaluated by overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines.[19]

Baseline demographics (n = 106) showed a predominantly white (97.1%) and male (65.1%) study population with a median age of 67 years (range 37 – 83).[20] The median number of prior therapies was 2.5 (range 1 – 10) and the median time since diagnosis was 79.4 months (range 1.2 – 385.6). ECOG performance status was 0 (39.6%), 1 (51.9%), and 2 (8.5%). Baseline disease characteristics showed high tumor burden with 50.0% of patients having an absolute lymphocyte count $\geq 25 \times 10^9$/L and 52.8% have one or more lymph nodes ≥ 5 cm. The median time on venetoclax was 12.1 months (range: 0 – 21.5). Efficacy results are shown in Table 3.

Table 3. Efficacy Results for Patients with Previously Treated CLL with 17p Deletion by IRC

	Venetoclax (N = 106)
ORR, n (%)	85 (80.2)
(95% CI)	(71.3, 87.3)
CR + CRi, n (%)	8 (7.5)
CR, n (%)	6 (5.7)
CRi, n (%)	2 (1.9)
nPR, n (%)	3 (2.8)
PR, n (%)	74 (69.8)

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission

The median time to first response was 0.8 months (range 0.1 – 8.1). The median duration of response (DOR) has not been reached with approximately 12 months median follow-up. The DOR ranged from 2.9 to 19.0+ months.

Clinical Activity in AML

Single agent venetoclax demonstrated tolerability and preliminary activity in a Phase 2 study of 32 adult patients with relapsed or refractory AML or newly diagnosed patients who were unfit for intensive therapy.[21] The median age was 71 years and included one 19-year old patient. Venetoclax monotherapy at 800 mg demonstrated a tolerable safety profile, that was consistent with expectations in this AML patient population, and that was also consistent with the safety profile of venetoclax observed across all indications. The median time on venetoclax was 63 days (range 13 – 246). The primary reason for study discontinuation was progressive disease in 91% of patients. In addition, one patient discontinued due to toxicity, one withdrew consent, and one proceeded to allogeneic hematopoietic stem cell transplant.

Nineteen percent of patients on monotherapy achieved an objective response by International Working Group (IWG) criteria for AML, 6% (2 patients) with complete

response (CR) and 13% (4 patients) with complete response with incomplete marrow recovery (CRi).[20] The median duration of CR/CRi was 48 days. Data from this study prompted evaluation of venetoclax in combination with other agents for the treatment of AML.

An ongoing Phase 1/2 study evaluated venetoclax (600 mg and 800 mg) in combination with low-dose cytarabine in patients ≥ 65 years of age with treatment-naïve AML. The combination demonstrated a tolerable safety profile across both venetoclax doses, with the most common adverse events being nausea (77.8%), anemia (55.6%), and febrile neutropenia, neutropenia, and fatigue (each 38.9%). Febrile neutropenia was the most common serious adverse event occurring in 33.3% of patients. The overall response rate was 44% (8/18, 4 CR and 4 CRi).

Clinical Activity in Non Hodgkin Lymphoma

Venetoclax has shown early signals of anti-tumor activity in NHL, including follicular lymphoma (FL), mantle cell lymphoma (MCL) and DLBCL.[22] Of 106 patients enrolled in a Phase 1 first-in-human study, the median age was 66 years and, included one 25 year old. Adverse events observed were similar to those seen in other studies and indications with venetoclax, summarized in the previous section (Section 4.2.2).

Patients with multiple subtypes of relapsed or refractory NHL were enrolled but only the activity in DLBCL is summarized because the other subtypes occur only rarely in pediatric patients. Thirty-four patients with DLBCL were enrolled. The median age was 68 years (range 25 – 86). Patients were highly pre-treated having received a median of 3 prior therapies (range 1 – 8). The median time on venetoclax was 5 months (range 0.4 – 9). The maximum tolerated dose (MTD) was not reached and patients received up to 1200 mg of venetoclax. For patients with DLBCL (n = 34), the ORR was 18% and the CR rate was 12%. The median duration of response was 3.3 months (range 2 – 4) with no responses ongoing. One patient who achieved CR proceeded to transplant.

Venetoclax in combination with bendamustine and rituximab is also being studied in a Phase 1 study of 48 patients with relapsed or refractory NHL. Multiple subtypes were eligible. The overall safety profile was similar to that seen in other venetoclax studies and in other indications, summarized previously (Section 4.2.2). Sixteen patients had DLBCL and of 15 evaluable patients the ORR was 38% with a CR rate of 25%.[23]

A Phase 3 study (NCT02055820) is testing venetoclax with either rituximab or obinutuzumab and standard doses of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in patients who have never received prior rituximab-CHOP therapy. The cohort expansion portion will only enroll treatment-naïve patients with DLBCL.

5.0 Other Clinical Trials that are Ongoing or Completed

At the time of this report, there are no venetoclax clinical trials in pediatric patients sponsored by AbbVie or conducted in collaboration with partners that are ongoing or have been completed.

6.0 Current Drug Development Plan for Other Indications in Adults

See Section 4.0 (Clinical Trial Experience in Adults) for other indications under investigation in adults.

7.0 Proposed Pediatric Plan

AML, ALL, NHL and neuroblastoma are the proposed indications to be evaluated in pediatric patients. The mechanism-based and functional-assessment approach utilized for selection of these malignancies included expression analysis, preclinical evaluation, and clinical study data in adults. As summarized above, venetoclax has been evaluated in adult patients with AML and NHL. Venetoclax has shown a tolerable safety profile and demonstrated activity in these patients, supporting evaluation in pediatric patients with these malignancies.

7.1 Epidemiology of Pediatric Cancers Included in the Pediatric Plan

AML is the most common acute leukemia in adults and the second most common childhood leukemia. In children, 5-year event free survival is approximately 50%.[24] For relapsed patients, aggressive treatment with chemotherapy with or without stem cell transplant is associated with high morbidity and mortality. Standard of care in these patients ranges from intensive re-induction followed by transplant to the use of experimental agents. Complete remission can be substantial, but 2-year event free survival is only 25%.[25]

For patients with ALL, treatment advances have been remarkable and cure rates are currently almost 85% in newly diagnosed patients. However, 15 – 20% of patients will relapse and prognosis for these patients is extremely poor with less than 30% long-term survival.[26] Treatment of relapsed high-risk patients is with multi drug chemotherapy followed by stem cell transplant. Non-high-risk patients receive 2 years of chemotherapy. In the relapsed setting, studies examining the addition of experimental agents to a chemotherapy backbone, or experimental agents alone, are ongoing.

The predominant non-Hodgkin lymphoma in adolescents and young adults is DLBCL.[27] Long-term event free survival reaches 90%, but overall survival in the relapsed setting is low, defining another patient population with high unmet medical need. Combination chemotherapy using ifosfamide, carboplatin and etoposide, with or without rituximab, is used commonly with the intent of proceeding to transplant. Subsequent relapses are treated with allogeneic stem cell transplant if possible, or experimental agents. The small number of patients at risk, combined with the low rate of relapse, has made it difficult to perform large trials for relapsed patients.

Neuroblastoma is the most common extracranial solid tumor in children with approximately 700 cases diagnosed each year in the US.[28] Outcomes for patients with neuroblastoma have improved with 5-year survival rates of approximately 75%, predominantly due to higher cure rates among low-risk patients. But long-term survival is

only 50% for those with high-risk disease.[28] Recurrence remains a significant obstacle to cure in these patients.

7.1.1 Differences Between Adult and Pediatric Malignancies

Acute Myelogenous Leukemia (AML)

Age has an important impact on AML prognosis, with overall survival varying from 57% in infants, 62% in children, and 42% in young adults, mostly due to differences in initial features and risk factors.[29] Overall survival decreases incrementally with older age to < 10% in those diagnosed over the age of 75.[30] The inability of older patients to tolerate chemotherapy is one important factor contributing to the poorer prognosis of older patients. Another difference between adult and childhood AML is the rate of various cytogenetic abnormalities. For example, *FLT3-ITD* are rare in infants, but present in 10% of children, 20% of young adult patients, and more than 35% of patients older than 55 years of age.[31] Patients with *FLT3-ITD* generally have higher disease burden and poor prognosis.

Acute Lymphocytic Leukemia (ALL)

ALL is heterogeneous and prognosis varies per subtype. Treatment of adults using pediatric ALL protocols has resulted in CR rates similar to those observed in children.[32] However, although 5-year survival rates in children with ALL are greater than 70%, 5-year survival rates in adults range from 19% to 33%.[33] Some of this poor prognosis can be attributable to the higher occurrence of the BCR-ABL gene rearrangement in adults (25% in adults versus 3% in children).[33] Even within the pediatric population, the subtype of ALL has a marked impact on survival. Infants have a very poor outcome, particularly those with MLL gene rearrangement (80% of infant ALL patients) and t(4;11)(q21;q23) translocation (60% of infants). For infants with MLL gene rearrangement, event-free survival rates range between 30% and 40%.[31] Hypodiploidy (< 44 chromosomes), t(17;19)(q22;p13.3) [*TCF3-HLF*] translocation and early T-cell precursor ALL are other subtypes associated with dismal outcome[31]

Diffuse Large B-cell lymphoma (DLBCL)

DLBCL is a subtype of NHL that occurs in both adults and children. Several distinctions exist between pediatric and adult DLBCL, most notably prognosis. DLBCL is a heterogeneous disorder in adults, with the germinal center B-cell (GCB) subtype having a favorable prognosis and the activated B-cell like (ABC) subtype having a poor prognosis. At the molecular level, a large number of adult DLBCL patients harbor a t(14:18) translocation, and these are almost exclusively seen in the GCB subtype.[35] This translocation involves the immunoglobulin heavy chain enhancer and the BCL-2 gene, resulting in BCL-2 overexpression. The majority of pediatric cases are of the GCB subtype,[36] and despite the predominance of the GCB subtype in pediatrics, the t(14;18) translocation is absent. Thus, in contrast to adults, DLBCL in children is primarily of the GCB subtype, lacking translocation, with a better prognosis.

Neuroblastoma

Neuroblastoma occurs almost exclusively in infants and young children. The median age of diagnosis is 19 months, with 37% of patients diagnosed before 1 year of age.[37] The incidence decreases with age. Established treatment guidelines are not available for adult patients with neuroblastoma, and comparisons are difficult due to the rarity of this tumor in adults.

Summary

Based on the mechanism of action in adult hematopoietic and lymphoid malignancies, there are pediatric malignancies that have also demonstrated dependence on the BCL-2 pathway for survival, underlying the rationale that BCL-2 inhibition by venetoclax might demonstrate therapeutic utility in select patient populations. In recent years, treatment of pediatric malignancies using multi-modal therapy has resulted in high cure rates in patients with many tumor types that were once fatal. Unfortunately, patients with relapsed and refractory diseases continue to do poorly, and effective novel therapies to address this unmet medical need are needed. The rationale provided previously has thus

led the Sponsors to pursue AML, ALL, NHL and neuroblastoma as target indications for venetoclax in the pediatric population.

7.2 Pediatric Formulation

A dual approach is planned to enable dosing of all age and dose groups of pediatric patients. For children who can swallow tablets, the adult 10 mg, 50 mg and 100 mg tablets recently approved for relapsed or refractory CLL will be provided. For children who need liquid dosing, a rapidly disintegrating pediatric tablet has been developed that can be used to quickly make a suspension at the time of dosing. The disintegrating tablet strengths are expected to be in the 2.5 to 25 mg range. Depending on the actual dose, one or more of the disintegrating tablets will be dropped into a fixed volume of liquid to make a suspension, and the dosing volumes of the resulting suspension will be targeted in the 10 to 50 mL range.

A Phase 1 adult bioavailability study is planned to determine the food effect and relative bioavailability of the pediatric tablets relative to the adult tablets. Palatability assessment is currently ongoing in expert human taste panels to assess the taste and aroma of the active suspension made from pediatric tablets. Dosing vehicles and foods are also being assessed by this panel to provide mitigation options for potential taste and aroma issues. All development studies and formulation readiness are planned in alignment with the Phase 1 clinical protocol timelines.

7.3 Pediatric Clinical Study

The proposed clinical study is a global Phase 1 study of venetoclax monotherapy in pediatric patients aged 1 – 18 years with select relapsed or refractory cancers. Objectives include safety, pharmacokinetics and preliminary efficacy of venetoclax.

A mechanism-based approach was utilized to identify malignancies with expected dependence on the BCL-2 pathway based on a high ratio of BCL-2/BCL-2L1 and murine xenograft response data. Patients with the following malignancies will be eligible after

meeting specific inclusion/exclusion criteria: AML, ALL, NHL and neuroblastoma, as highlighted in Table 4.

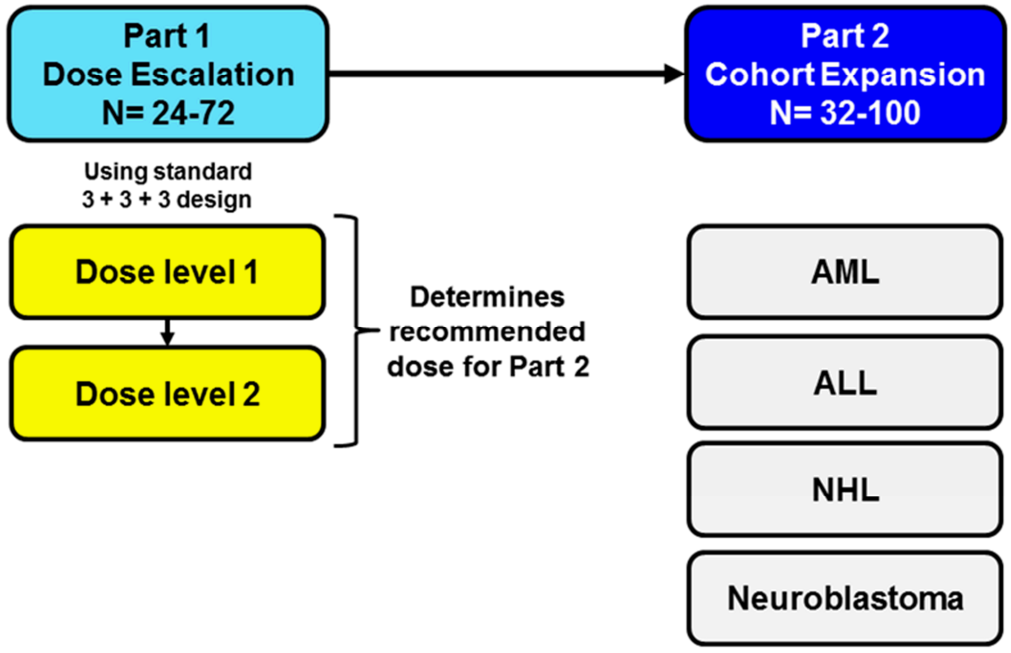
Table 4. Overview of Selection of Tumor Types

Pediatric Cancer	BCL-2 Overexpression	Murine Xenograft Response	Clinical Activity in Adults
AML	Yes	Yes	Yes
ALL	Yes	Yes	not tested
NHL	Yes	Yes	Yes
Neuroblastoma	Yes	Yes	not tested

Proposed Study Design

The Phase 1 study will consist of dose escalation and cohort expansion and enroll approximately 150 patients with AML, ALL, NHL and neuroblastoma (Figure 3).

Figure 3. Proposed Phase 1 Study Design: Two Part Study Design

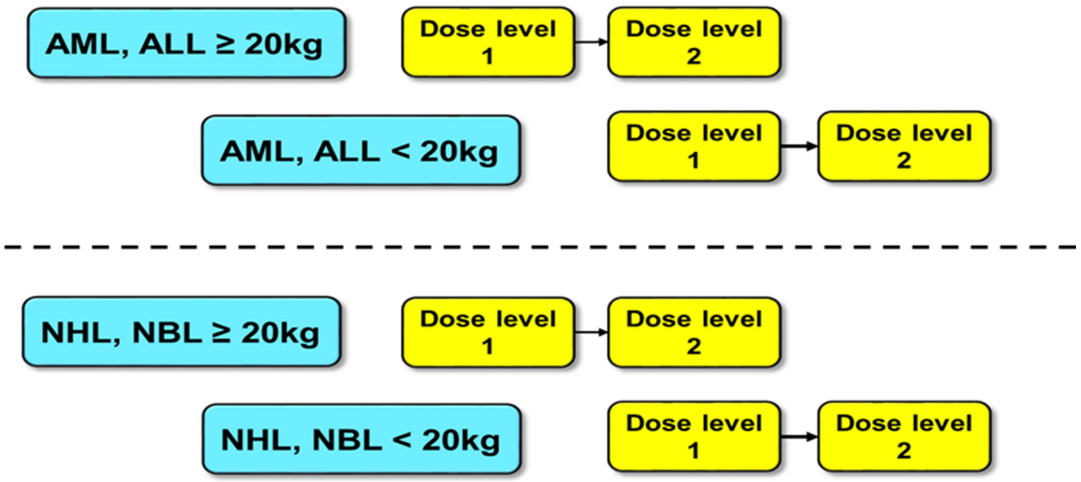


Dose Escalation Portion

Dose escalation will enroll 24 – 72 patients into two target dose levels using a 3 + 3 + 3 design. Individual doses will be age or weight-adjusted to match adult equivalent target doses of 400 mg (dose level 1) and 800 mg (dose level 2).

The dose escalation part is shown in Figure 4.

Figure 4. Part 1: Dose Escalation Scheme



Patients with AML and ALL will be enrolled in distinct dose escalation groups and utilize different criteria for determination of DLTs due to bone marrow involvement. Patients with NHL and neuroblastoma who have extensive bone marrow involvement will use the DLT criteria designed for AML and ALL patients.

Enrollment will be sequential, based on weight and will begin with patients who weigh ≥ 20 kg to evaluate whether dosing modifications for patients who weigh < 20 kg may be required.

There are four distinct dose escalation groups for the purposes of evaluating DLTs:

1. patients who have AML or ALL and weigh ≥ 20 kg,

2. patients who have AML or ALL and weigh < 20 kg,
3. patients who have NHL or neuroblastoma (NBL) and weigh ≥ 20 kg,
4. patients who have NHL or neuroblastoma (NBL) and weigh < 20 kg.

DLTs will be assessed during the first 21 days of venetoclax monotherapy. Safety data will be analyzed by an independent data safety monitor board (DSMB) prior to enrollment in expansion cohorts.

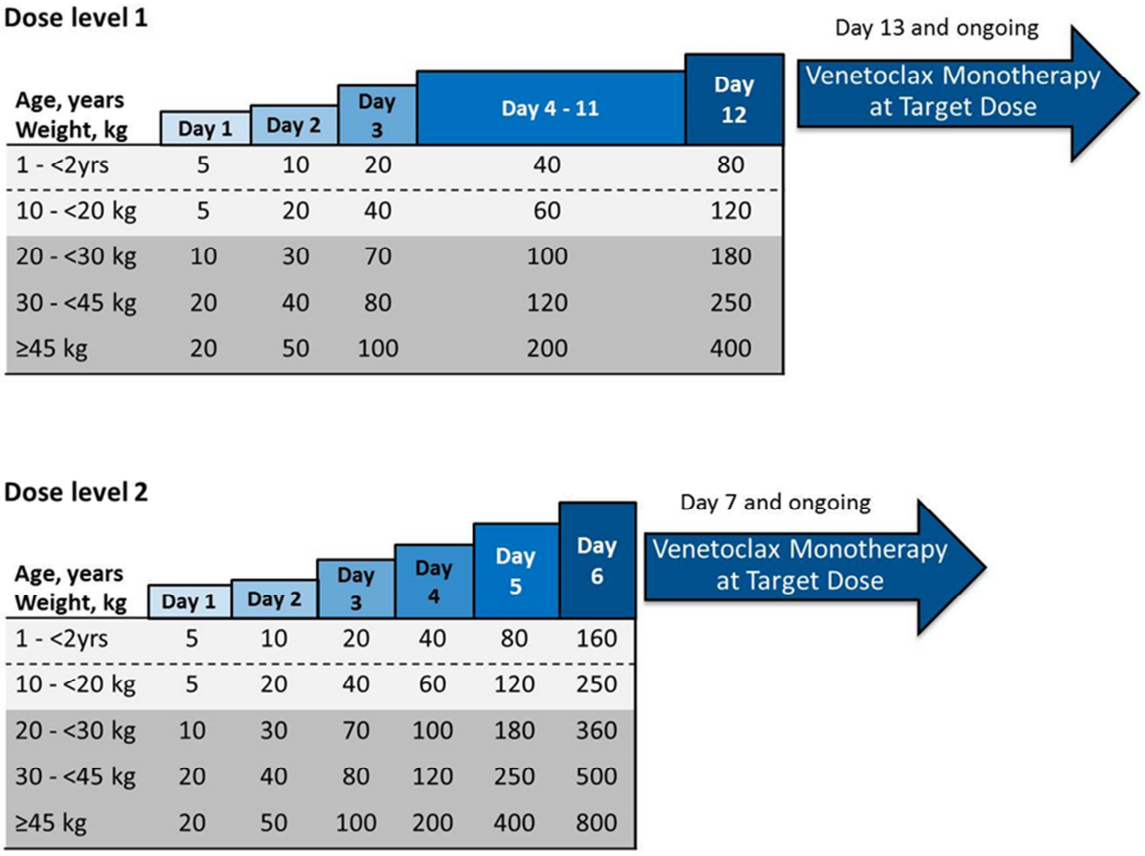
Age-appropriate intensive pharmacokinetics will be evaluated. Blood draws for pharmacokinetic analysis will be within designated institutional limits by weight. If necessary, additional patients may be enrolled to cover uniform age distribution for appropriate collection of PK data.

To monitor for TLS, all patients will be hospitalized for 4 – 6 days during the ramp-up period and receive intravenous hydration, allopurinol, and laboratory monitoring pre-dose and at 4 and 8 hours post-dose, daily during the ramp-up period. Rasburicase may be required for patients with elevated uric acid levels.

Figure 5 shows the dosing scheme for patients in Dose Level 1. Individual doses are age or weight-adjusted to match the adult equivalent target dose of 400 mg. The first row of Figure 5 shows the actual dose that patients who are between 1 and < 2 years of age will receive. For patients aged 2 and older, dosing will be based on weight. Ramp-up dosing will be utilized to mitigate the risk of TLS. Patients will receive the same dose on Days 4 to 11 in order to assess PK at a dose that is less than the target dose. Patients will then ramp-up again on Day 12 and remain at the target dose throughout.

Patients in Dose Level 2 will receive doses to match the adult equivalent target dose of 800 mg. Ramp-up dosing will occur until the target dose is reached on Day 6 and patients will remain at the target dose throughout.

Figure 5. Dosing Schedule



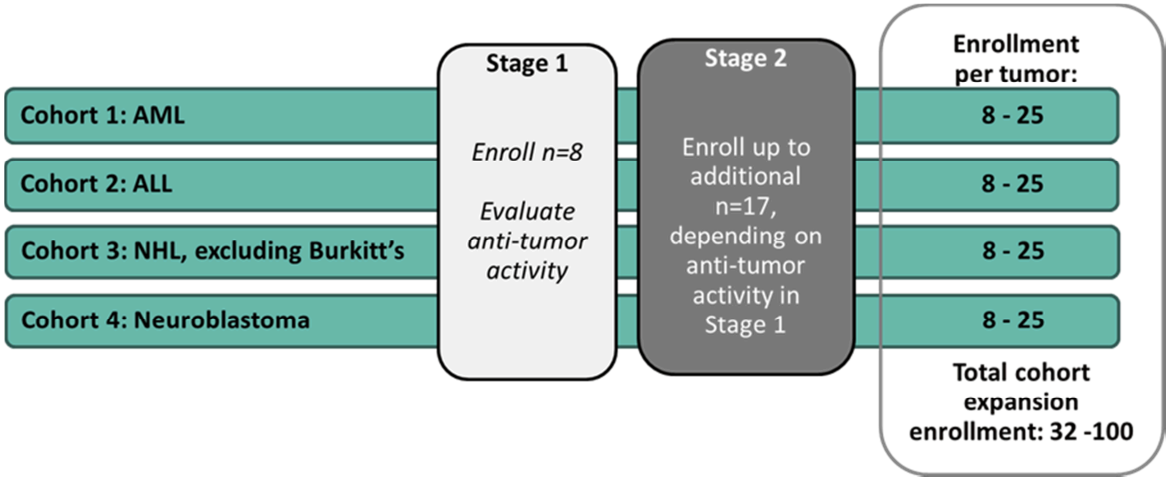
Dose level 1					
Age, years Weight, kg	Day 1	Day 2	Day 3	Day 4 - 11	Day 12
1 - <2yrs	5	10	20	40	80
10 - <20 kg	5	20	40	60	120
20 - <30 kg	10	30	70	100	180
30 - <45 kg	20	40	80	120	250
≥45 kg	20	50	100	200	400

Dose level 2						
Age, years Weight, kg	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1 - <2yrs	5	10	20	40	80	160
10 - <20 kg	5	20	40	60	120	250
20 - <30 kg	10	30	70	100	180	360
30 - <45 kg	20	40	80	120	250	500
≥45 kg	20	50	100	200	400	800

The recommended dose for cohort expansion will be chosen based on evaluation of the two dose levels during dose escalation. If the higher dose is chosen for cohort expansion, patients who were enrolled in Dose Level 1 may increase their dose.

After completion of dose escalation, cohort expansion will proceed. Enrollment of patients in cohort expansion who weigh ≥ 20 kg may begin prior to those who weigh < 20 kg, if that group clears dose escalation first. Similarly, patients with AML or ALL may begin prior to those with NHL or neuroblastoma, if that group clears dose escalation first. Patients will enroll into 4 tumor cohorts (8 – 25 patients per tumor type; Figure 6). The four tumor types are AML, ALL, NHL, and neuroblastoma.

Figure 6. Part 2: Cohort Expansion Using a Gehan 2-Stage Design



The threshold for success for each of the cohorts is 20%. Enrollment in cohort expansion will utilize a Gehan 2-stage design to minimize unnecessary exposure to pediatric patients during the assessment of anti-tumor activity. In the first stage, 8 patients will be enrolled in each of the four tumor cohorts and preliminary anti-tumor activity will be evaluated. If none of the 8 patients has a response, enrollment will halt to that particular cohort, since it will be unlikely that the threshold of 20% will be met. Conversely, the second stage will enroll up to 17 additional patients, depending on the anti-tumor activity observed in the first stage (Table 4). The sample size was determined using a Gehan 2-Stage design with type 1 error of 0.10, type II error of 20%, and a minimum proportion for acceptance at 20%.

Additional patients may be added if required, particularly in the ALL cohort due to disease heterogeneity, to pursue potential signals in different subtypes. Patients with myelodysplastic syndrome (MDS) will be allowed to enroll in the AML cohort during cohort expansion but will not be included in the statistical analysis for this cohort.

Table 5. Number of Patients for Each Tumor Type to be Enrolled in Cohort Expansion

Stage 1 Enrollment	Stage 1, Number of Responses (out of 8)	Stage 2, Enrollment	Total Enrolled
8 *per tumor type*	0	STOP	8
	1	14	22
	2	17	25
	3	17	25
	≥ 4	15	23

Addition of Chemotherapy

Beginning at Week 4 (Day 22 of monotherapy; after completion of the DLT period), the following patients will be eligible to receive venetoclax in combination with chemotherapy:

- Patients with complete remission (CR) and cannot proceed to stem cell transplant (these patients will be documented as CR to venetoclax monotherapy),
- Patients with partial remission (PR) and no evidence of further response at the second response assessment (these patients will be documented as PR to venetoclax monotherapy),
- Patients with stable disease (SD) after 3 stable assessments in the AML and ALL cohorts or after 2 stable assessments in the NHL and neuroblastoma cohorts (these patients will be documented as non-responders to venetoclax monotherapy),
- Patients with progressive disease (PD) (these patients will be documented as PD to venetoclax monotherapy).

For these patients, the tolerability of venetoclax in combination with the following agents will be assessed:

- AML: low-dose cytarabine

- ALL: dexamethasone and vincristine (imatinib if Philadelphia chromosome-positive)
- NHL: rituximab
- Neuroblastoma: cyclophosphamide

Rationale for Combination Therapy in Pediatric Malignancies

Pre-clinically, venetoclax has demonstrated synergistic cancer cell killing in combination with a number of chemotherapeutic agents that are used commonly for pediatric tumors. For example, venetoclax combinations with cytarabine, doxorubicin, or vincristine showed synergistic killing of ~50% of NHL cell lines (n = 23) tested in vitro, when assessed using the Bliss additivity algorithm (data not shown). Venetoclax has also shown synergistic killing of neuroblastoma cells when combined with cyclophosphamide,[12] T-cell acute lymphocytic leukemia and NHL cells when combined with cytarabine[38,39] and multiple myeloma cells when combined with dexamethasone.[40]

Clinically, trials are underway testing venetoclax in combination with low dose cytarabine for AML, and also with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone for NHL.

7.3.1 Investigators/Institutions

Investigators and institutions who will be involved in this study are still to be determined.

7.3.2 Study Population

Patients aged 1 – 18 years with select relapsed or refractory malignancies.

7.3.3 Main Inclusion and Exclusion Criteria

7.3.3.1 Inclusion Criteria

1. The parent or guardian must voluntarily sign and date an informed consent approved (in addition to pediatric assent, if required) by an Independent Ethics

Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures.

2. Patient must be 1 – 18 years of age.
3. Patient must have one of the following relapsed or refractory cancers:
   - acute myelogenous leukemia (AML);
   - acute lymphocytic leukemia (ALL);
   - non-Hodgkin's lymphoma (NHL), excluding Burkitt's lymphoma;
   - Neuroblastoma.
4. Patient must have:
   - Karnofsky of ≥ 50 for patients > 16 years of age;
   - Lansky ≥ 50 for patients ≤ 16 years of age;
   - Patients who are unable to walk because of paralysis but who are up in a wheelchair will be considered ambulatory for the purpose of assessing the performance score.
5. Patient must have adequate bone marrow, hepatic and renal function, as defined specifically per subtype in the protocol.
6. Calculated creatinine clearance ≥ 30 mL/min/1.73 m^2.
7. Patients of childbearing potential must utilize a method of contraception as described in the protocol and sperm banking is recommended.
8. Tumor-specific criteria will be described in the protocol.

7.3.3.2 Main Exclusion Criteria

1. Patient has overt CNS involvement (CNS 3 status) as defined by CSF WBC > 5/hpf with blasts on cytospin or any cranial nerve palsy regardless of cell count.
2. Patient has received a biologic agent (i.e., monoclonal antibodies) for anti-neoplastic intent within 30 days prior to the first dose of study drug.

3. Patient has received any of the following within 5 half-lives or 14 days, whichever is shorter, prior to the first dose of study drug, or has not recovered to less than Common Terminology Criteria for Adverse Events (CTCAE) grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
    - Any anti-cancer therapy including chemotherapy or radiotherapy;
    - Investigational therapy, including targeted small molecule agents.
4. Patient has received the following within 7 days prior to the first dose of study drug:
    - Steroid therapy for anti-neoplastic intent;
    - Strong and moderate CYP3A inhibitors;
    - Strong and moderate CYP3A inducers.
5. Patient has malabsorption syndrome or other condition that precludes enteral administration.
6. Tumor-specific criteria will be described in the protocol.

7.3.4 Pediatric Dose Selection

Dose selection for venetoclax in pediatric patients is based on the assumption that safe and efficacious exposures (AUC steady state values) in adult patients will provide similar safety and efficacy profiles in pediatrics. This assumption is based on safe and efficacious doses of venetoclax in adults for a variety of hematological malignancies (including AML, NHL, and MM) and range from 400 to 1200 mg once daily (QD). Since higher venetoclax exposures in monotherapy were not associated with an increase in adverse events rates, there is no need to test what may be sub-therapeutic doses in pediatrics.

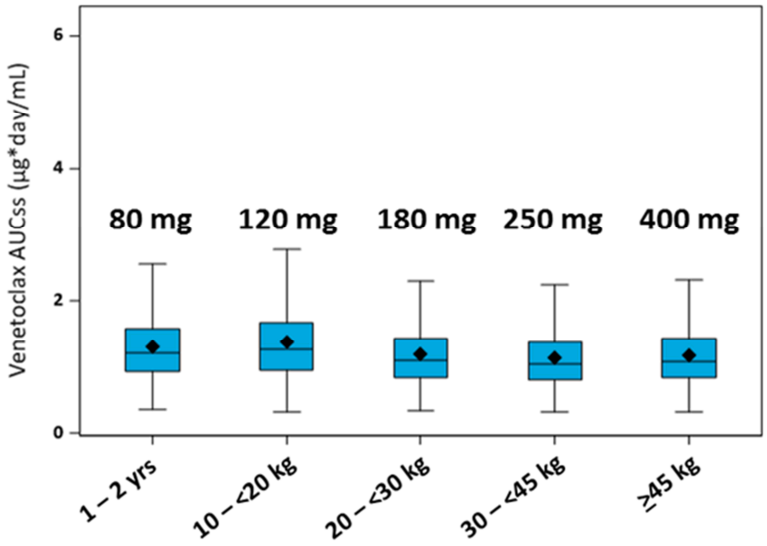
As described in Section 7.3, doses will ramp-up daily as tolerated over a 6 to 12 day period, depending on target dose level. Target dose levels match adult exposure-equivalent doses of 400 mg and 800 mg based on age and weight groups. Dosing will be based on age for children who are between 1 to < 2 years old because of immature

development in CYP3A, which is expected to impact bioavailability. Dosing for patients who are 2 years of age and older will be based on weight (Figure 5).

Venetoclax is predominantly metabolized by CYP3A4 based on in vitro data and clinical drug interaction study results with ketoconazole and rifampin. It is known that CYP3A4/3A5 expression is minimal in early life after birth and CYP3A7 is the major CYP isoform detected in embryonic, fetal, and newborn liver and intestine. Also substrate sharing between CYP3A7 and CYP3A4/5 is minimal.[41,42] It is not known if venetoclax is metabolized by CYP3A7. Therefore, CYP3A4 ontogeny may play a role in venetoclax clearance and bioavailability among the selected pediatric age groups. Ontogeny was simulated using an age-based maturation function (to account for developmental changes in hepatic CYP3A4 metabolism of venetoclax.[42] In addition to age effect, allometric scaling of venetoclax clearance from adults to children based on body weight was applied to project pediatric doses. In adult patient trials, body weight ranged from ~40 – 140 kg, therefore, 45 kg was used as a cutoff for the pediatric dosing scheme, and lower weight bands were selected to project pediatric doses that provide exposure-equivalent to adult target doses (Figure 7).

For children who are between 1 to < 2 years old, dosing is based on age due to incomplete maturation of CYP3A4 as described above. Children who are 2 years of age and older will be dosed based on their body weight as described in Section 7.3 (Figure 5). Pharmacokinetics simulations of venetoclax exposures for each age and weigh band based on the projected pediatric doses are shown in Figure 7 (exposure-equivalent doses that match the adult dose of 400 mg is shown as an example).

Figure 7. Pharmacokinetics Simulations of Venetoclax Exposures for Each Age and Weight Band Based on Projected Pediatric Doses



Population PK modeling and simulation approaches will be utilized to update the doses if necessary based on the PK data in pediatric patients observed earlier in the study. In brief, during dose escalation, patients who are ≥ 20 kg will be enrolled first and PK data from these patients will be evaluated to determine if dose modifications are needed. Clinical trial simulations using the updated population PK model will be performed. The main objective for the simulations will be to estimate mean and range of exposure (AUC_{ss}) across the projected doses for each age and weight band using the PK data from patients who are ≥ 20 kg. In order to ensure appropriate collection of PK data in pediatrics, additional patients may be enrolled once a dose level is cleared to cover a uniform distribution of age groups among pediatric patients.

Food has a significant impact on venetoclax bioavailibity in adults as described in Section 4.2.1. As the effect of food may be different between the adult and pediatric formulation, a relative bioavailability and food effect study in adults is planned with the pediatric formulation prior to initiation of the Phase 1 study.

Exposure-response analyses and population PK modeling approaches may be used to select the recommended Phase 2 dose.

7.3.5 Safety Assessment

Adverse events, ECG and laboratory profiles will be assessed throughout the study. DLTs will be assessed during the first 21 days of venetoclax monotherapy. Safety data will be analyzed by an independent data safety monitor board (DSMB) prior to enrollment in expansion cohorts and as needed.

7.3.6 Pharmacokinetic Assessment

Plasma pharmacokinetic samples will be collected for venetoclax at steady state and at the designated time points throughout the study. Intensive PK samples will be collected and analyzed during dose escalation and sparse PK samples will be collected throughout cohort expansion. In addition, cerebrospinal fluid may be collected if a lumbar puncture is performed for diagnostic purposes, or if performed to administer intrathecal chemotherapy.

7.3.7 Efficacy Assessment

Response will be assessed by the investigator based on standard established response criteria for each tumor type. All measurable disease must be documented at Screening by laboratory testing, CT scan/PET, bone marrow, and lumbar puncture, as appropriate. For patients with AML or ALL, efficacy assessments will occur at Week 4 (Day 22 after initiation), Week 8, Week 12, and then every 12 weeks thereafter, and at any other time point if clinically indicated, including earlier at Day 8. Patients with NHL and neuroblastoma will undergo efficacy assessments at Week 12, and every 12 weeks thereafter, and at any other time point if clinically indicated. Minimal residual disease (MRD) in peripheral blood and/or bone marrow will be assessed by flow cytometry as an exploratory objective when relevant.

7.3.8 Criteria for Evaluation/Statistical Method

7.3.8.1 Safety

The worst grade of each adverse event item will be identified for each patient. Frequencies and percentages (whenever possible given the small number of patients) of each Common Terminology Criteria for Adverse Events term will be tabulated, grouped by system organ class. The worst value of each hematological or biochemical category will be identified and graded for each patient. Frequencies and percentages of each category will be tabulated.

7.3.8.2 Efficacy

The following efficacy analyses will be completed for patients who receive at least one dose of venetoclax: ORR (CR + CRi + PR for ALL and AML; CR + PR for NHL and neuroblastoma), CR rate, PR rate, and MRD status. Efficacy measures may be reported descriptively for each patient and summarized with descriptive statistics (median, range, confidence intervals).

7.3.8.3 Pharmacokinetic Analysis

Individual patient plasma concentrations of venetoclax (and possible metabolite[s]) will be listed and descriptively summarized as appropriate. Pharmacokinetic parameters, including maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), and area under the plasma concentration-time curve over a 24-hour dose interval (AUC_{0-24}), will be determined as applicable and descriptively summarized as appropriate, using non-compartmental methods. Additional parameters may be calculated if useful for data interpretation. Population PK modeling approaches using observed PK data may be used to update the doses for the different age groups. Additional analyses may be performed if useful for the interpretation of the data.

8.0 Current or Potential Challenges that Have Been Identified Regarding Clinical Trials in Children

Development of Age Appropriate Pediatric Formulation

Venetoclax is a poorly soluble compound that is not amenable to conventional formulation technologies. In order to ensure adequate absorption the compound is formulated as an amorphous solid dispersion (ASD). A ready to use multiple dose suspension is not feasible since the ASD does not have sufficient physical stability in an aqueous medium and is eventually converted to crystalline active. Conversion of the active from amorphous to crystalline form will result in a decrease in bioavailability. Hence the ASD utilized in the adult CLL formulation is being used as the basis for formulation of tablets for dispersion. These tablets disintegrate rapidly in an aqueous medium and can be used to conveniently make fixed dose suspensions at the time of dosing. This approach also avoids the use of preservatives.

Palatability is also a potential challenge when developing an oral liquid formulation for pediatric use. AbbVie is currently conducting an adult expert panel taste assessment of prototype suspension formulations in order to determine the taste masking strategy, if needed, for the final pediatric formulation.

At the high body weight and dose bands the total pill burden could be a challenge, and in those cases a combination of the smaller 50 mg tablets and liquid dosing may be an option.

Effect of Food on Pediatric Formulation

Food has a significant impact on venetoclax bioavailability in adults as described in Section 4.2.1. As the effect of food may be different between the adult and pediatric formulation, a relative bioavailability and food effect study is planned with the pediatric formulation, prior to initiation of the Phase 1 study.

Recruitment Challenges

In addition, there may be challenges is recruiting sufficient numbers of pediatric patients with NHL due to the rarity of the disease in the relapsed setting. The Sponsors will conduct outreach to help identify appropriate pediatric patients with this tumor type who are relapsed or refractory. However, there may be a smaller data set available to evaluate the potential to conduct further studies in this tumor type.

9.0 Summary

Venetoclax has recently received accelerated approval for the treatment of patients with CLL with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. Clinical trials are also ongoing in CLL and other adult indications with high unmet need including AML, NHL, and multiple myeloma. The safety profile of venetoclax in the context of treatment of hematologic malignancies in adults has been tolerable and supports the continued use of venetoclax in adult populations.

A mechanism-based and functional-assessment approach was used to identify pediatric malignancies with the highest likelihood of response based on pre-clinical evidence of BCL-2 dependence. The Phase 1 pediatric study will enroll relapsed or refractory patients with AML, ALL, NHL and neuroblastoma, all of whom have poor prognosis. Activity observed in this study will inform future development in pediatric malignancies. The proposed pediatric plan demonstrates the Sponsor's commitment to develop venetoclax for the treatment of pediatric patients.

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11.0 Appendices

Appendix A. Ongoing Oncology Clinical Trials Investigating Venetoclax

Protocol	Countries	Study Title	Dosing Regimen	Study Population	Estimated Enrollment
Indication: AML					
M14-212	US	A Phase 2 study of ABT-199 in subjects with AML	Venetoclax	Adults with relapsed or refractory AML or frontline unfit for intensive therapy	32
M14-358	AU, DE, FR, US	A Phase 1b study of ABT-199 (GDC-0199) + azacitidine or decitabine in treatment-naïve subjects with AML ≥ 65 years of age and who are not eligible for standard induction therapy	Venetoclax + azacitidine or venetoclax + decitabine	Treatment naïve adults with AML (≥ 65 years old) who are not eligible for standard induction therapy	160
M14-387	AU, DE, IT; US	A Phase 1/2 study of ABT-199 + low-dose cytarabine in treatment-naïve subjects with AML ≥ 65 years of age who are not eligible for standard anthracycline-based induction therapy	Venetoclax + cytarabine	Treatment-naïve adults with AML ≥ 65 years of age not eligible for standard anthracycline-based induction therapy	65
GH29914[a]	CA, IT, US	A Phase IB/II Multi-Arm Study With Venetoclax in Combination With Cobimetinib and Venetoclax in Combination With Idasanutlin in Patients Aged >/= 60 Years With Relapsed or Refractory AML	Venetoclax + cobimetinib or Venetoclax + idasanutlin	Adults with AML ≥ 65 years of age	170

Protocol	Countries	Study Title	Dosing Regimen	Study Population	Estimated Enrollment
Indication: NHL					
M12-175	AU, US	A Phase 1 study evaluating the safety and PK study of ABT-199 in relapsed or refractory CLL and NHL	Venetoclax (ABT-199)	Adults with relapsed or refractory CLL/SLL and NHL	211
M13-835	US	An extension study of ABT-199 in subjects with advanced NHL	Venetoclax	Adults with advanced NHL who completed a prior ABT-199 clinical trial	28
M12-630	US	A Phase 1 study evaluating the safety and PK of venetoclax in combination with bendamustine + rituximab (BR) in relapsed or refractory NHL	Venetoclax + BR	Adults with relapsed or refractory NHL	60
GO27878[a]	AT, AU, CA, CZ, ES, FR, HU, IT, NL, US	A Phase 1b/2 safety and PK study of ABT-199 + rituximab (R) or obinutuzumab (G) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in subjects with B-cell NHL and DLBCL	Venetoclax + either R-CHOP or G-CHOP	Adults with B-cell NHL (R-CHOP-naïve), excluding MCL or SLL. Plus adults with previously untreated DLBCL	248
BO29337[a]	AU, BE, CA, DE, FR, IT, UK, US	A Phase 2 study of safety and efficacy of GDC-0199 (ABT-199) plus BR versus BR alone or ABT-199 plus rituximab in subjects with relapsed or refractory follicular lymphoma	Venetoclax + BR versus BR alone or versus venetoclax + rituximab	Adults with relapsed or refractory follicular lymphoma	165
GO29833[a]	US	A Phase Ib/II Study Evaluating the Safety and Efficacy of Obinutuzumab in Combination With Polatuzumab Vedotin and Venetoclax in Patients With Relapsed or Refractory Follicular or Diffuse Large B-Cell Lymphoma	Obinutuzumab + Polatuzumab Vedotin + Venetoclax	Adults with relapsed or refractory follicular or diffuse large B-cell lymphoma	116

Protocol	Countries	Study Title	Dosing Regimen	Study Population	Estimated Enrollment
Indication: CLL					
GP28331[a]	US, UK	A Phase 1b dose-finding and safety study of venetoclax and obinutuzumab in relapsed/refractory or previously untreated CLL	Venetoclax + obinutuzumab	Adults with relapsed, refractory, or previously untreated CLL	90
M13-365	AU, US	A Phase 1b study evaluating the safety and tolerability of ABT-199 with rituximab in relapsed CLL and SLL	Venetoclax + rituximab	Adults with relapsed CLL and SLL	50
M14-032	US	A Phase 2 study of the efficacy and safety of ABT-199 in CLL subjects with relapse or refractory to B-cell receptor (BCR) signaling pathway inhibitor therapy	Venetoclax	Adults with relapsed or refractory CLL after BCR signaling pathway inhibitor therapy	120
M13-982	AU, CA, FR, DE, PL, US, UK	A Phase 2 open-label study of the efficacy of ABT-199 (GDC-0199) in subjects with relapsed/refractory or previously untreated CLL harboring the 17p del	Venetoclax	Adults with relapsed or refractory or Previously Untreated CLL with 17p del	150
GO28440[a]	FR, DE, US	A Phase 1b safety and PK study of ABT-199 with BR or bendamustine plus Obinutuzumab (BO) in relapsed/refractory or previously untreated CLL	Venetoclax + BR	Adults with relapsed, refractory, or previously untreated CLL	100
GO28667[a]	AU, AT, BE, CA, CZ, DK, FR, DE, HU, IT, KR, NL, NZ, PL, ES, SE, CH, RU, TW, US, UK	A Multicenter, Phase III, Open-Label, Randomized Study In Relapsed/Refractory Patients With Chronic Lymphocytic Leukemia To Evaluate The Benefit Of Gdc-0199 (ABT-199) Plus Rituximab Compared With Bendamustine Plus Rituximab	Venetoclax + R versus BR	Adults with relapsed/refractory CLL	392

Protocol	Countries	Study Title	Dosing Regimen	Study Population	Estimated Enrollment
Indication: CLL (Continued)					
BO25323[a]	AR, AT, AU, BG, CA, CH, DE, DK, ES, EE, FR, HR, IT, MX, NZ, PL, RO, RU, UK, US	A Phase 3 randomized study to compare efficacy and safety of ABT-199 + obinutuzumab versus obinutuzumab and chlorambucil in subjects with previously untreated CLL and coexisting medical conditions	Venetoclax + obinutuzumab versus obinutuzumab + chlorambucil	Adults with previously untreated CLL with coexisting medical conditions	432
Indication: MM					
M13-367	FR, US	A Phase 1 safety and PK study of ABT-199 in relapsed or refractory MM	Venetoclax	Adults with relapsed or refractory MM	84
M12-901/	AU, FR, US	A Phase 1b safety and PK study of ABT-199 with bortezomib/dexamethasone in relapsed/refractory MM	Venetoclax + bortezomib + dexamethasone	Adults with relapsed or refractory MM	66
M13-834	Japan	A Phase 1 study evaluating the safety and PK of venetoclax in Japanese subjects with hematological malignancies	Venetoclax	Japanese adults with hematological malignancies	30
M15-330	US	A Phase 1b/2 Study of Duvelisib and Venetoclax in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, or Indolent or Aggressive Non-Hodgkin Lymphoma, Who Have Not Previously Received a Bcl-2 or PI3K Inhibitor	Venetoclax + duvelisib	Adults with relapsed or refractory CLL, SLL, or indolent or aggressive NHL, who have not previously received a Bcl-2 or PI3K inhibitor	174

17p del = deletion of the p13 locus on chromosome 17; AML = acute myeloid leukemia; BR = bendamustine + rituximab; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; MAD = multiple ascending dose; MM = multiple myeloma; NHL = non-Hodgkin lymphoma; PK = pharmacokinetics; SAD = single ascending dose; SLE = systemic lupus erythmatosus; SLL = small lymphocytic lymphoma
Countries: AR = Argentina; AU = Australia; AT = Austria; BE = Belgium; BG = Bulgaria; CA = Canada; CH = Switzerland; CZ = Czech Republic; DE = Germany; DK = Denmark; ES = Spain; EE = Estonia; FR = France; HR = Croatia; HU = Hungary; IT = Italy; KR = South Korea; MX = Mexico; NL = Netherlands; NZ = New Zealand; PL = Poland; RO = Romania; RU = Russia; SE = Sweden; TW = Taiwan; UK = United Kingdom; US = United States

These studies are conducted in collaboration with Genentech/Roche. All other studies shown in table above are conducted by AbbVie (however still in collaboration with Genentech/Roche).
Source: clinicaltrials.gov, accessed on: May 13, 2016.