CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208573Orig1s009

Trade Name:	VENCLEXTA
Generic or Proper Name:	(venetoclax)
Sponsor:	AbbVie Inc.
Approval Date:	November 21, 2018
Indication:	VENCLEXTA® (venetoclax) in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

208573Orig1s009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s009

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208573/S-009

ACCELERATED APPROVAL

AbbVie, Inc.
Attention: John Tiesch, PharmD
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72, Bldg. AP30-4
North Chicago, IL 60064

Dear Dr. Tiesch:

Please refer to your Supplemental New Drug Application (sNDA) dated June 25, 2018, received June 25, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VENCLEXTA® (venetoclax); 10, 50, and 100 mg tablets.

This "Prior Approval" supplemental new drug application provides for the new indication: VENCLEXTA® (venetoclax) in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. This supplement also provides for a new bottle packaging configuration for the 100 mg strength of a 180-tablet bottle.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the Prescribing Information and Medication Guide, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on June 25, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 208573/S-009**." Approval of this submission by FDA is not required before the labeling is used.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated November 20, 2018. This requirement, along with required completion dates, is listed below.

PMR 3545-1 Submit the complete final study report and data that verifies and isolates the clinical efficacy and safety from trial M16-043, a randomized, double-blind, placebo-controlled Phase 3 study of venetoclax co-administered with low-dose cytarabine versus low-dose cytarabine in treatment naïve patients with acute myeloid leukemia who are precluded from receiving standard chemotherapy due to age $\geq$ 75 years or comorbidities. The primary endpoint will be overall survival. An interim analysis of overall survival will be performed and included in the interim analysis submission or the final study report.

Trial Completion: 10/2019
Final Report Submission: 01/2020

PMR 3545-2 Submit the complete final study report and data that verifies and isolates the clinical efficacy and safety from trial M15-656, a randomized, double-blind, placebo-controlled Phase 3 study of venetoclax in combination with azacitidine versus azacitidine in treatment naïve patients with acute myeloid leukemia who are precluded from receiving standard chemotherapy due to age $\geq$ 75 years or comorbidities. The primary endpoint will be overall survival. Interim analysis of response rates and overall survival will be performed and included in the interim analysis submission or the final study report.

Trial Completion: 10/2020
Final Report Submission: 01/2021

Submit clinical protocols to your IND 110159 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirements**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at 301-796-9304**.**

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Prescribing Information
Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALBERT B DEISSEROTH
11/21/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s009

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VENCLEXTA safely and effectively. See full prescribing information for VENCLEXTA.

VENCLEXTA® (venetoclax tablets) for oral use
Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

Indications and Usage (1.1)	06/2018
Indications and Usage (1.2)	11/2018
Dosage and Administration (2.1, 2.2, 2.3, 2.4)	11/2018
Warnings and Precautions (5.2)	11/2018

INDICATIONS AND USAGE

VENCLEXTA is a BCL-2 inhibitor indicated:

- For the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy. (1.1)
- In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
  This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.2)

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for recommended VENCLEXTA starting and ramp-up dosages. (2.1)
- VENCLEXTA tablets should be taken orally once daily with a meal and water. Do not chew, crush, or break tablets. (2.1)
- Perform prophylaxis for tumor lysis syndrome. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, 50 mg, 100 mg (3)

CONTRAINDICATIONS

Concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase in patients with CLL/SLL is contraindicated. (2.4, 4, 7.1)

WARNINGS AND PRECAUTIONS

- Tumor Lysis Syndrome (TLS): Anticipate TLS; assess risk in all patients. Premedicate with anti-hyperuricemics and ensure adequate hydration. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases. (2.2, 5.1)
- Neutropenia: Monitor blood counts and for signs of infection; manage as medically appropriate. (2.3, 5.2)
- Immunization: Do not administer live attenuated vaccines prior to, during, or after VENCLEXTA treatment. (5.3)
- Embryo-Fetal Toxicity: May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment. (5.4)

ADVERSE REACTIONS

In CLL, the most common adverse reactions (≥20%) in combination with rituximab were neutropenia, diarrhea, upper respiratory tract infection, fatigue, cough, and nausea. (6.1)

The most common adverse reactions (≥20%) in the CLL/SLL monotherapy studies were neutropenia, diarrhea, nausea, upper respiratory tract infection, anemia, fatigue, thrombocytopenia, musculoskeletal pain, edema, and cough. (6.1)

In AML, the most common adverse reactions (≥30%) in combination with azacitidine or decitabine or low-dose cytarabine were nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, peripheral edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, back pain, myalgia, dizziness, cough, oropharyngeal pain, and hypotension (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong or moderate CYP3A inhibitors or P-gp inhibitors: Adjust dosage of VENCLEXTA. (2.4, 7.1)
- Strong or moderate CYP3A inducers: Avoid co-administration. (7.1)
- P-gp substrates: Take at least 6 hours before VENCLEXTA. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.

1.2 Acute Myeloid Leukemia

VENCLEXTA is indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

This indication is approved under accelerated approval based on response rates *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Assess patient-specific factors for level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Instruct patients to take VENCLEXTA tablets with a meal and water at approximately the same time each day. VENCLEXTA tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

All VENCLEXTA dose regimens begin with a 5-week ramp-up.

VENCLEXTA 5-week Dose Ramp-Up Schedule

Administer the VENCLEXTA dose according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of 400 mg as shown in Table 1. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS.

Table 1. Dosing Schedule for Ramp-Up Phase in Patients with CLL/SLL

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

The CLL/SLL Starting Pack provides the first 4 weeks of VENCLEXTA according to the ramp-up schedule. The 400 mg dose is achieved using 100 mg tablets supplied in bottles *[see How Supplied/Storage and Handling (16)]*.

VENCLEXTA in Combination with Rituximab

Start rituximab administration after the patient has completed the 5-week dose ramp-up schedule with VENCLEXTA (see Table 1) and has received the 400 mg dose of VENCLEXTA for 7 days. Administer rituximab on Day 1 of each 28-day cycle for 6 cycles, with rituximab dosed at 375 mg/m^2 intravenously for Cycle 1 and 500 mg/m^2 intravenously for Cycles 2-6.

Patients should continue VENCLEXTA 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab.

VENCLEXTA as Monotherapy

The recommended dose of VENCLEXTA is 400 mg once daily after the patient has completed the 5-week dose ramp-up schedule. VENCLEXTA should be taken orally once daily until disease progression or unacceptable toxicity is observed.

Acute Myeloid Leukemia

The dose of VENCLEXTA depends upon the combination agent.

The VENCLEXTA dosing schedule (including ramp-up) is shown in Table 2. Initiate the azacitidine or decitabine or low-dose cytarabine on Day 1.

Table 2. Dosing Schedule for Ramp-up Phase in Patients with AML

	VENCLEXTA Daily Dose	
Day 1	100 mg	
Day 2	200 mg	
Day 3	400 mg	
Days 4 and beyond	400 mg when dosing in combination with **azacitidine or decitabine**	600 mg when dosing in combination with **low-dose cytarabine**

Continue VENCLEXTA, in combination with azacitidine or decitabine or low-dose cytarabine, until disease progression or unacceptable toxicity is observed.

2.2 Risk Assessment and Prophylaxis for Tumor Lysis Syndrome

Patients treated with VENCLEXTA may develop tumor lysis syndrome. Refer to the appropriate section below for specific details on management. Assess patient-specific factors for level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function (creatinine clearance [CLcr] <80 mL/min) further increases the risk. Perform tumor burden assessments, including radiographic evaluation (e.g., CT scan), assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA. The risk may decrease as tumor burden decreases *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

Table 3 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumor burden determination from clinical trial data. Consider all patient comorbidities before final determination of prophylaxis and monitoring schedule.

Table 3. Recommended TLS Prophylaxis Based on Tumor Burden in Patients with CLL/SLL

Tumor Burden		**Prophylaxis**		**Blood Chemistry Monitoring[c,d]**
		Hydration[a]	**Anti-hyperuricemics**	**Setting and Frequency of Assessments**
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent

				ramp-up doses: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with CLcr <80ml/min; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient • For subsequent ramp-up doses: Pre-dose, 6 to 8 hours, 24 hours
ALC = absolute lymphocyte count; CLcr = creatinine clearance; LN = lymph node. [a]Administer intravenous hydration for any patient who cannot tolerate oral hydration. [b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA. [c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time. [d]For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.				

Acute Myeloid Leukemia

- All patients should have white blood cell count less than 25 × 10^9/L prior to initiation of VENCLEXTA. Cytoreduction prior to treatment may be required.
- Prior to first VENCLEXTA dose, provide all patients with prophylactic measures including adequate hydration and anti-hyperuricemic agents and continue during ramp-up phase.
- Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.
- Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up and 24 hours after reaching final dose.
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase (LDH) levels,

or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing VENCLEXTA starting dose.

2.3 Dose Modifications Based on Toxicities

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Interrupt dosing or reduce dose for toxicities. See Table 4 and Table 5 for recommended dose modifications for toxicities related to VENCLEXTA. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary (e.g., all or some levels of the dose ramp-up schedule) *[see Dosage and Administration (2.1, 2.2)]*.

Table 4. Recommended VENCLEXTA Dose Modifications for Toxicities[a] in CLL/SLL

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 5) *[see Dosage and Administration (2.2)]*.
		For any events of clinical TLS,[b] resume at a reduced dose following resolution (see Table 5) *[see Dosage and Administration (2.2)]*.
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt VENCLEXTA. Once the toxicity has resolved to Grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt VENCLEXTA. Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		

Grade 3 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia) *[see Warnings and Precautions (5.2)]*	1st occurrence	Interrupt VENCLEXTA. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with VENCLEXTA if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose.
	2nd and subsequent occurrences	Interrupt VENCLEXTA. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks. [a]Adverse reactions were graded using NCI CTCAE version 4.0. [b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures *[see Adverse Reactions (6.1)]*.		

Table 5. Dose Reduction for Toxicity During VENCLEXTA Treatment in CLL/SLL

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10
[a]During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.	

Acute Myeloid Leukemia

Monitor blood counts frequently through resolution of cytopenias. Management of some adverse reactions *[see Warnings and Precautions (5.2)* and *Adverse Reactions (6.2)]* may require dose interruptions or permanent discontinuation of VENCLEXTA. Table 6 shows the dose modification guidelines for hematologic toxicities.

Table 6. Recommended Dose Modifications for Toxicities[a] in AML

Event	Occurrence	Action
Hematologic Toxicities		

Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia *[see Warnings and Precautions (5.2)]*	Occurrence prior to achieving remission	Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated. In most instances, VENCLEXTA and azacitidine, decitabine, or low-dose cytarabine cycles should not be interrupted due to cytopenias prior to achieving remission.
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent treatment cycle of VENCLEXTA and azacitidine, decitabine, or low-dose cytarabine and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume VENCLEXTA therapy at the same dose in combination with azacitidine or decitabine or low-dose cytarabine.
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent treatment cycle of VENCLEXTA and azacitidine, or decitabine, or low-dose cytarabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume VENCLEXTA therapy at the same dose and the duration reduced by 7 days for each subsequent cycle.

[a] Adverse reactions were graded using NCI CTCAE version 4.0.

2.4 Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors or P-gp Inhibitors

Table 7 describes VENCLEXTA contraindication or dosage modification based on concomitant use with a strong or moderate CYP3A inhibitor or P-gp inhibitor *[see Drug Interactions (7.1)]* at initiation, during, or after the ramp-up phase.

Resume the VENCLEXTA dosage that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*.

Table 7. Management of Potential VENCLEXTA Interactions with CYP3A and P-gp Inhibitors

Coadministered drug	Initiation and Ramp-Up Phase		Steady Daily Dose (After Ramp-Up Phase)[a]
	CLL/SLL	Contraindicated	Reduce VENCLEXTA dose to 70 mg.

Posaconazole	AML	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	
Other strong CYP3A inhibitor	CLL/SLL	Contraindicated	Reduce VENCLEXTA dose to 100 mg.
	AML	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	
Moderate CYP3A inhibitor	Reduce the VENCLEXTA dose by at least 50%.		
P-gp inhibitor			
[a]In patients with CLL/SLL, consider alternative medications or reduce the VENCLEXTA dose as described in Table 7.			

2.5 Missed Dose

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

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

3 DOSAGE FORMS AND STRENGTHS

Table 8. VENCLEXTA Tablet Strength and Description

Tablet Strength	Description of Tablet
10 mg	Round, biconvex shaped, pale yellow film-coated tablet debossed with “V” on one side and “10” on the other side
50 mg	Oblong, biconvex shaped, beige film-coated tablet debossed with “V” on one side and “50” on the other side
100 mg	Oblong, biconvex shaped, pale yellow film-coated tablet debossed with “V” on one side and “100” on the other side

4 CONTRAINDICATIONS

Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during the ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome *[see Dosage and Administration (2.4) and Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA *[see Adverse Reactions (6.1, 6.2)]*.

In patients with CLL, the current (5 week) dose ramp-up, TLS prophylaxis and monitoring, the rate of TLS was 2% in the VENCLEXTA CLL monotherapy studies. The rate of TLS remained consistent with VENCLEXTA in combination with rituximab. With a 2 to 3 week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure *[see Adverse Reactions (6.1)]*.

VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases *[see Dosage and Administration (2.2, 2.3) and Use in Specific Populations (8.6)]*.

Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, may increase the risk of TLS at initiation and during ramp-up phase and requires VENCLEXTA dose adjustment *[see Dosage and Administration (2.4) and Drug Interactions (7.1)]*.

5.2 Neutropenia

In patients with CLL, Grade 3 or 4 neutropenia developed in 64% of patients and Grade 4 neutropenia developed in 31% of patients treated with VENCLEXTA in combination with rituximab (see Table 10). Grade 3 or 4 neutropenia developed in 63% of patients and Grade 4 neutropenia developed in 33% of patients treated with VENCLEXTA monotherapy (see Table 12). Febrile neutropenia occurred in 4% of patients treated with VENCLEXTA in combination with rituximab and in 6% of patients treated with VENCLEXTA monotherapy *[see Adverse Reactions (6.1)]*.

Baseline neutrophil counts worsened in 97% to 100% of patients treated with VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine. Neutropenia can recur with subsequent cycles of therapy.

Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF) *[see Dosage and Administration (2.3)]*.

5.3 Immunization

Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. Advise patients that vaccinations may be less effective.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at the recommended dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant women using VENCLEXTA. Advise females of reproductive potential to avoid pregnancy during treatment. If VENCLEXTA is used during pregnancy or if the patient becomes pregnant while taking VENCLEXTA, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse events are discussed in greater detail in other sections of the labeling:

- Tumor Lysis Syndrome *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trial Experience with CLL/SLL

MURANO

The safety of VENCLEXTA in combination with rituximab (VEN+R) versus bendamustine in combination with rituximab (B+R), was evaluated in an open-label randomized study, in patients with CLL who had received at least one prior therapy.

Patients randomized to VEN+R completed the scheduled ramp-up (5 weeks) and received VENCLEXTA 400 mg once daily in combination with rituximab for 6 cycles followed by single agent VENCLEXTA for a total of 24 months after ramp-up. Patients randomized to B+R received 6 cycles (28 days per cycle) for a total of 6 months. Details of the study treatment are described in Section 14 *[see Clinical Studies (14.1)]*.

At the time of analysis, the median duration of exposure was 22 months in the VEN+R arm compared with 6 months in the B+R arm.

In the VEN+R arm, fatal adverse reactions that occurred in the absence of disease progression and within 30 days of the last VENCLEXTA treatment and/or 90 days of last rituximab were

reported in 2% (4/194) of patients. Serious adverse reactions were reported in 46% of patients in the VEN+R arm, with most frequent (≥5%) being pneumonia (9%).

In the VEN+R arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 15%, and dose interruption in 71%. In the B+R arm, adverse reactions led to treatment discontinuation in 10% of patients, dose reduction in 15%, and dose interruption in 40%. In the VEN+R arm, neutropenia led to dose interruption of VENCLEXTA in 46% of patients and discontinuation in 3%, and thrombocytopenia led to discontinuation in 3% of patients.

Table 9 and Table 10 present adverse reactions and laboratory abnormalities, respectively, identified in the MURANO trial. The MURANO trial was not designed to demonstrate a statistically significant difference in adverse reaction rates for VEN+R as compared with B+R, for any specific adverse reaction or laboratory abnormality.

Table 9. Common (≥10%) Adverse Reactions Reported with ≥5% Higher All-Grade or ≥2% Higher Grade ≥3 Incidence in Patients Treated with VEN+R Compared with B+R

Adverse Reaction by Body System	VENCLEXTA + Rituximab Followed by Single Agent VENCLEXTA (N = 194)		Bendamustine + Rituximab (N = 188)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood & lymphatic system disorders				
Neutropenia[a]	65	62	50	44
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Infections & infestations				
Upper respiratory tract infection[a]	39	2	23	2
Lower respiratory tract infection[a]	18	2	10	2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a]	19	1	13	0
Metabolism and nutrition disorders				
Tumor lysis syndrome	3	3	1	1

[a]Includes multiple adverse reaction terms.

Other adverse reactions (all Grades) reported in ≥10% of patients in the VEN+R arm in MURANO, and other important adverse reactions are presented below:

Blood & lymphatic system disorders: anemia (16%), thrombocytopenia (15%), febrile neutropenia (4%)

Gastrointestinal disorders: nausea (21%), constipation (14%), abdominal pain (13%), mucositis (10%), vomiting (8%)

Respiratory disorders: cough (22%)

General disorders and administration site conditions: fatigue (22%), pyrexia (15%)

Skin disorders: rash (13%)

Nervous system and psychiatric disorders: headache (11%), insomnia (11%)

Infections & infestations: pneumonia (10%)

During treatment with single agent VENCLEXTA after completion of VEN+R combination treatment, the most common all grade adverse reactions (≥10% patients) reported were upper respiratory tract infection (21%), diarrhea (19%), neutropenia (16%), and lower respiratory tract infections (11%).The most common grade 3 or 4 adverse reaction (≥2% patients) were neutropenia (12%) and anemia (3%).

Laboratory Abnormalities

Table 10 describes common treatment-emergent laboratory abnormalities identified in the MURANO trial.

Table 10. Common (≥10%) New or Worsening Laboratory Abnormalities Occurring at ≥5% (Any Grade) or ≥2% (Grade 3 or 4) Higher Incidence with VEN+R Compared with B+R

	VENCLEXTA + Rituximab N = 194		Bendamustine + Rituximab N = 188	
Laboratory Abnormality	**All Grades[a] (%)**	**Grade 3 or 4 (%)**	**All Grades[a] (%)**	**Grade 3 or 4 (%)**
Hematology				
Leukopenia	89	46	81	35
Lymphopenia	87	56	79	55
Neutropenia	86	64	84	59
Chemistry				
Hypocalcemia	62	5	51	2
Hypophosphatemia	57	14	35	4
AST/SGOT increased	46	2	31	3
Hyperuricemia	36	36	33	33
Alkaline phosphatase increased	35	1	20	1
Hyperbilirubinemia	33	4	26	3
Hyponatremia	30	6	20	3
Hypokalemia	29	6	18	3

Hyperkalemia	24	3	19	2
Hypernatremia	24	1	13	0
Hypoglycemia	16	2	7	0

[a]Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.

New Grade 4 laboratory abnormalities reported in ≥2% of patients treated with VEN+R included neutropenia (31%), lymphopenia (16%), leukopenia (6%), thrombocytopenia (6%), hyperuricemia (4%), hypocalcemia (2%), hypoglycemia (2%), and hypermagnesemia (2%).

Monotherapy Studies (M13-982, M14-032, and M12-175)

The safety of single agent VENCLEXTA at the 400 mg recommended daily dose following a dose ramp-up schedule is based on pooled data from three single-arm trials (M13-982, M14-032, and M12-175). In the pooled dataset, consisting of 352 patients with previously treated CLL or SLL, the median age was 66 years (range: 28 to 85 years), 93% were white, and 68% were male. The median number of prior therapies was 3 (range: 0 to 15). The median duration of treatment with VENCLEXTA at the time of data analysis was 14.5 months (range: 0 to 50 months). Fifty-two percent of patients received VENCLEXTA for more than 60 weeks.

Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of venetoclax treatment were reported in 2% of patients in the VENCLEXTA monotherapy studies, most commonly (2 patients) from septic shock. Serious adverse reactions were reported in 52% of patients, with the most frequent (≥5%) being pneumonia (9%), febrile neutropenia (5%), and sepsis (5%).

Adverse reactions led to treatment discontinuation in 9% of patients, dose reduction in 13%, and dose interruption in 36%. The most frequent adverse reactions leading to drug discontinuation were thrombocytopenia and autoimmune hemolytic anemia. The most frequent adverse reaction (≥5%) leading to dose reductions or interruptions was neutropenia (8%).

Adverse reactions identified in these trials of single-agent VENCLEXTA are presented in Table 11.

Table 11. Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade ≥3) of Patients with Previously Treated CLL/SLL (VENCLEXTA Monotherapy)

Body System	Adverse Reaction	Any Grade (%) N = 352	Grade ≥3 (%) N = 352
Blood and lymphatic system disorders	Neutropenia[a]	50	45
	Anemia[a]	33	18
	Thrombocytopenia[a]	29	20
	Lymphopenia[a]	11	7
	Febrile neutropenia	6	6
Gastrointestinal disorders	Diarrhea	43	3
	Nausea	42	1

	Abdominal pain[a]	18	3
	Vomiting	16	1
	Constipation	16	<1
	Mucositis[a]	13	<1
General disorders and administration site conditions	Fatigue[a]	32	4
	Edema[a]	22	2
	Pyrexia	18	<1
Infections and infestations	Upper respiratory tract infection[a]	36	1
	Pneumonia[a]	14	8
	Lower respiratory tract infection[a]	11	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[a]	29	2
	Arthralgia	12	<1
Nervous system disorders	Headache	18	<1
	Dizziness[a]	14	0
Respiratory, thoracic, and mediastinal disorders	Cough[a]	22	0
	Dyspnea[a]	13	1
Skin and subcutaneous tissue disorders	Rash[a]	18	<1
Adverse Reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0. [a]Includes multiple adverse reaction terms.			

Laboratory Abnormalities

Table 12 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline. The most common (>5%) Grade 4 laboratory abnormalities observed with VENCLEXTA monotherapy were hematologic laboratory abnormalities, including neutropenia (33%), leukopenia (11%), thrombocytopenia (15%), and lymphopenia (9%).

Table 12. New or Worsening Laboratory Abnormalities with VENCLEXTA Monotherapy (≥40% Any Grade or ≥10% Grade 3 or 4)

Laboratory Abnormality	**All Grades[a] (%) N = 352**	**Grade 3 or 4 (%) N = 352**
Hematology		
Leukopenia	89	42
Neutropenia	87	63
Lymphopenia	74	40

Anemia	71	26
Thrombocytopenia	64	31
Chemistry		
Hypocalcemia	87	12
Hyperglycemia	67	7
Hyperkalemia	59	5
AST increased	53	3
Hypoalbuminemia	49	2
Hypophosphatemia	45	11
Hyponatremia	40	9
[a]Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown.		

Important Adverse Reactions

Tumor Lysis Syndrome

Tumor lysis syndrome is an important identified risk when initiating VENCLEXTA.

MURANO

In the open-label randomized phase 3 study, the incidence of TLS was 3% (6/194) in patients treated with VEN+R. After 77/389 patients were enrolled in the study, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures described in sections 2.1 and 2.2 *[see Dosage and Administration (2.1, 2.2)]*. All events of TLS occurred during the VENCLEXTA ramp-up period and were resolved within two days. All six patients completed the ramp-up and reached the recommended daily dose of 400 mg of VENCLEXTA. No clinical TLS was observed in patients who followed the current 5-week ramp-up schedule and TLS prophylaxis and monitoring measures described in sections 2.1 and 2.2 *[see Dosage and Administration (2.1, 2.2)]*. Rates of laboratory abnormalities relevant to TLS for patients treated with VEN+R are presented in Table 10.

Monotherapy Studies (M13-982 and M14-032)

In 168 patients with CLL treated according to recommendations described in sections 2.1 and 2.2, the rate of TLS was 2% *[see Dosage and Administration (2.1, 2.2)]*. All events either met laboratory TLS criteria (laboratory abnormalities that met ≥2 of the following within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L); or were reported as TLS events. The events occurred in patients who had a lymph node(s) ≥5 cm and/or ALC ≥25 x 10^9/L. All events resolved within 5 days. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CLcr ≥50 mL/min. Laboratory abnormalities relevant to TLS were hyperkalemia (17% all Grades, 1% Grade ≥3), hyperphosphatemia (14%

all Grades, 2% Grade ≥3), hypocalcemia (16% all Grades, 2% Grade ≥3), and hyperuricemia (10% all Grades, <1% Grade ≥3).

In the initial Phase 1 dose-finding trials, which had shorter (2-3 week) ramp-up phase and higher starting doses, the incidence of TLS was 13% (10/77; 5 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis. After this experience, TLS risk assessment, dosing regimen, TLS prophylaxis and monitoring measures were revised *[see Dosage and Administration (2.1, 2.2)]*.

6.2 Clinical Trial Experience with AML

The safety of VENCLEXTA (400 mg daily dose) in combination with azacitidine (n=67) or decitabine (n= 13) and VENCLEXTA (600 mg daily dose) in combination with low-dose cytarabine (n= 61) is based on two non-randomized trials of patients with newly-diagnosed AML *[see Clinical Studies (14.3)]*. The median duration of exposure for patients taking VENCLEXTA in combination with azacitidine and decitabine was 6.5 months (range: 0.1 to 31.9 months) and 8.4 months (range: 0.5 to 22.3 months), respectively. The median duration of exposure for patients taking VENCLEXTA in combination with low dose cytarabine was 3.9 months (range: 0.2 to 29.2 months).

VENCLEXTA in Combination with Azacitidine or Decitabine

Azacitidine

The most common adverse reactions (≥30%) of any grade were nausea, diarrhea, constipation, neutropenia, thrombocytopenia, hemorrhage, peripheral edema, vomiting, fatigue, febrile neutropenia, rash, and anemia.

Serious adverse reactions were reported in 75% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, pneumonia (excluding fungal), sepsis (excluding fungal), respiratory failure, and multiple organ dysfunction syndrome.

The incidence of fatal adverse drug reactions was 1.5% within 30 days of starting treatment. No reaction had an incidence of ≥2%.

Discontinuations due to adverse reactions occurred in 21% of patients. The most frequent adverse reactions leading to drug discontinuation (≥2%) were febrile neutropenia and pneumonia (excluding fungal).

Dosage interruptions due to adverse reactions occurred in 61% of patients. The most frequent adverse reactions leading to dose interruption (≥5%) were neutropenia, febrile neutropenia, and pneumonia (excluding fungal).

Dosage reductions due to adverse reactions occurred in 12% of patients. The most frequent adverse reaction leading to dose reduction (≥5%) was neutropenia.

Decitabine

The most common adverse reactions (≥30%) of any grade were febrile neutropenia, constipation, fatigue, thrombocytopenia, abdominal pain, dizziness, hemorrhage, nausea, pneumonia

(excluding fungal), sepsis (excluding fungal), cough, diarrhea, neutropenia, back pain, hypotension, myalgia, oropharyngeal pain, peripheral edema, pyrexia, and rash.

Serious adverse reactions were reported in 85% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, sepsis (excluding fungal), pneumonia (excluding fungal), diarrhea, fatigue, cellulitis, and localized infection.

One (8%) fatal adverse drug reaction of bacteremia occurred within 30 days of starting treatment.

Discontinuations due to adverse reactions occurred in 38% of patients. The most frequent adverse reaction leading to drug discontinuation (≥5%) was pneumonia (excluding fungal).

Dosage interruptions due to adverse reactions occurred in 62% of patients. The most frequent adverse reactions leading to dose interruption (≥5%) were febrile neutropenia, neutropenia, and pneumonia (excluding fungal).

Dosage reductions due to adverse reactions occurred in 15% of patients. The most frequent adverse reaction leading to dose reduction (≥5%) was neutropenia.

Adverse reactions reported in patients with newly-diagnosed AML using VENCLEXTA in combination with azacitidine or decitabine are presented in Table 13.

Table 13. Adverse Reactions Reported in ≥30% (Any Grade) or ≥5% (Grade ≥3) of Patients with AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Body System	Adverse Reaction	VENCLEXTA in Combination with Azacitidine		VENCLEXTA in Combination with Decitabine	
		Any Grade (%) N = 67	Grade ≥3 (%) N = 67	Any Grade (%) N = 13	Grade ≥3 (%) N = 13
Blood and lymphatic system disorders	Thrombocytopenia[a]	49	45	54	54
	Neutropenia[a]	49	49	38	38
	Febrile neutropenia	36	36	69	69
	Anemia[a]	30	30	15	15
Gastrointestinal disorders	Nausea	58	1	46	0
	Diarrhea	54	3	38	8
	Constipation	49	3	62	0
	Vomiting[a]	40	0	23	0
	Abdominal pain[a]	22	4	46	0
General disorders and administration site conditions	Peripheral edema[a]	46	1	31	0
	Fatigue[a]	36	7	62	15
	Pyrexia	21	3	31	0
	Cachexia	0	0	8	8
	Multiple organ	6	6	0	0

	dysfunction syndrome				
Infections and infestations	Pneumonia (excluding fungal)[a]	27	25	46	31
	Sepsis (excluding fungal)[a]	13	13	46	46
	Urinary tract infection	16	6	23	0
	Cellulitis	6	0	15	8
	Localized infection	0	0	8	8
Musculoskeletal and connective tissue disorders	Back pain	15	0	31	0
	Myalgia[a]	10	0	31	0
Nervous system disorders	Dizziness[a]	28	1	46	0
Skin and subcutaneous tissue disorders	Rash[a]	33	1	31	0
Respiratory, thoracic and mediastinal disorders	Cough[a]	25	0	38	0
	Hypoxia	18	6	15	0
	Oropharyngeal pain	9	0	31	0
Vascular disorders	Hemorrhage[a]	46	7	46	0
	Hypotension[a]	21	6	31	0
	Hypertension	12	7	15	8

Adverse Reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0.
[a]Includes multiple adverse reaction terms.

Laboratory Abnormalities

Table 14 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

Table 14. New or Worsening Laboratory Abnormalities with VENCLEXTA Reported in ≥40% (Any Grade) or ≥10% (Grade 3 or 4) of Patients with AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Laboratory Abnormality	VENCLEXTA in Combination with Azacitidine		VENCLEXTA in Combination with Decitabine	
	Any Grade[a] (%) N = 67	Grade 3 or 4[a] (%) N = 67	Any Grade[a](%) N = 13	Grade 3 or 4[a] (%) N = 13

Hematology				
Neutropenia	100	100	100	100
Leukopenia	100	98	100	100
Thrombocytopenia	91	78	83	83
Lymphopenia	88	73	100	92
Anemia	57	57	69	69
Chemistry				
Hyperglycemia	75	12	69	0
Hypocalcemia	58	7	85	0
Hypoalbuminemia	52	4	38	8
Hypokalemia	49	7	46	0
Hyponatremia	49	4	38	0
Hypophosphatemia	46	15	23	8
Hyperbilirubinemia	45	9	46	15
Hypomagnesemia	21	0	54	8
[a]Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown.				

VENCLEXTA in Combination with Low-Dose Cytarabine

The most common adverse reactions (≥30%) of any grade were nausea, thrombocytopenia, hemorrhage, febrile neutropenia, neutropenia, diarrhea, fatigue, constipation, and dyspnea.

Serious adverse reactions were reported in 95% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, sepsis (excluding fungal), hemorrhage, pneumonia (excluding fungal), and device-related infection.

The incidence of fatal adverse drug reactions was 4.9% within 30 days of starting treatment with no reaction having an incidence of ≥2%.

Discontinuations due to adverse reactions occurred in 33% of patients. The most frequent adverse reactions leading to drug discontinuation (≥2%) were hemorrhage and sepsis (excluding fungal).

Dosage interruptions due to adverse reactions occurred in 52% of patients. The most frequent adverse reactions leading to dose interruption (≥5%) were thrombocytopenia, neutropenia, and febrile neutropenia.

Dosage reductions due to adverse reactions occurred in 8% of patients. The most frequent adverse reaction leading to dose reduction (≥2%) was thrombocytopenia.

Adverse reactions reported in patients with newly-diagnosed AML receiving VENCLEXTA in combination with low-dose cytarabine are presented in Table 15.

Table 15. Adverse Reactions Reported in ≥30% (Any Grade) or ≥5% (Grade ≥3) of Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Body System	Adverse Reaction	Any Grade (%) N = 61	Grade ≥3 (%) N = 61
Blood and lymphatic system disorders	Thrombocytopenia[a]	59	59
	Neutropenia[a]	46	46
	Febrile neutropenia	46	44
	Anemia[a]	26	26
Gastrointestinal disorders	Nausea	64	2
	Diarrhea	44	3
	Constipation	33	0
General disorders and administration site conditions	Fatigue[a]	44	10
Infections and infestations	Sepsis[a]	20	18
	Pneumonia[a]	18	16
	Device related infection	13	11
	Urinary tract infection	8	7
Metabolic and nutritional disorders	Decreased appetite[a]	28	7
Respiratory disorders	Dyspnea[a]	31	3
Vascular disorders	Hemorrhage[a]	49	15
	Hypotension[a]	21	7
	Hypertension	15	8

Adverse Reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0.
[a]Includes multiple adverse reaction terms.

Laboratory Abnormalities

Table 16 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

Table 16. New or Worsening Laboratory Abnormalities with VENCLEXTA Reported in ≥40% (Any Grade) or ≥10% (Grade 3 or 4) of Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Laboratory Abnormality	All Grades[a] (%) N = 61	Grade 3 or 4[a] (%) N = 61
Hematology		
Thrombocytopenia	100	96

Neutropenia	96	96
Leukopenia	96	96
Lymphopenia	93	66
Anemia	61	59
Chemistry		
Hyperglycemia	85	8
Hypocalcemia	79	16
Hyponatremia	62	11
Hyperbilirubinemia	57	3
Hypoalbuminemia	59	5
Hypokalemia	56	20
Hypophosphatemia	51	21
Hypomagnesemia	46	0
Blood creatinine increased	46	3
Blood bicarbonate decreased	41	0
[a]Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown.		

Tumor Lysis Syndrome

Tumor lysis syndrome is an important risk when initiating treatment in patients with AML. The incidence of TLS was 3% (2/61) with VENCLEXTA in combination with low-dose cytarabine with implementation of dose ramp-up schedule in addition to standard prophylaxis and monitoring measures. All events were laboratory TLS, and all patients were able to reach the target dose.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on VENCLEXTA

Strong or Moderate CYP3A Inhibitors or P-gp Inhibitors

Concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax C_{max} and AUC_{inf} *[see Clinical Pharmacology (12.3)]*, which may increase VENCLEXTA toxicities, including the risk of TLS *[see Warnings and Precautions (5)]*.

Concomitant use with a strong CYP3A inhibitor at initiation and during the ramp-up phase in patients with CLL/SLL is contraindicated *[see Contraindications (4)]*.

In patients with CLL/SLL taking a steady daily dosage (after ramp-up phase), consider alternative medications or adjust VENCLEXTA dosage and closely monitor for signs of VENCLEXTA toxicities *[see Dosage and Administration (2.3, 2.4)]*.

In patients with AML, adjust VENCLEXTA dosage and closely monitor for signs of VENCLEXTA toxicities *[see Dosage and Administration (2.3, 2.4)]*.

Resume the VENCLEXTA dosage that was used prior to concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor *[see Dosage and Administration (2.3, 2.4)]*.

Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A.

Strong or Moderate CYP3A Inducers

Concomitant use with a strong CYP3A inducer decreases venetoclax C_{max} and AUC_{inf} *[see Clinical Pharmacology (12.3)]*, which may decrease VENCLEXTA efficacy. Avoid concomitant use of VENCLEXTA with strong CYP3A inducers or moderate CYP3A inducers.

7.2 Effect of VENCLEXTA on Other Drugs

Warfarin

Concomitant use of VENCLEXTA increases warfarin C_{max} and AUC_{inf} *[see Clinical Pharmacology (12.3)]*, which may increase the risk of bleeding. Closely monitor international normalized ratio (INR) in patients using warfarin concomitantly with VENCLEXTA.

P-gp Substrates

Concomitant use of VENCLEXTA increases C_{max} and AUC_{inf} of P-gp substrates *[see Clinical Pharmacology (12.3)]*, which may increase toxicities of these substrates. Avoid concomitant use of VENCLEXTA with a P-gp substrate. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on VENCLEXTA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Based on toxicity observed in mice, VENCLEXTA may cause fetal harm when administered to pregnant women. In mice, venetoclax was fetotoxic at exposures 1.2 times the human clinical exposure based on AUC at the recommended human dose of 400 mg daily. If VENCLEXTA is used during pregnancy or if the patient becomes pregnant while taking VENCLEXTA, the patient should be apprised of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other

adverse outcomes. The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal data

In embryo-fetal development studies, venetoclax was administered to pregnant mice and rabbits during the period of organogenesis. In mice, venetoclax was associated with increased post-implantation loss and decreased fetal body weight at 150 mg/kg/day (maternal exposures approximately 1.2 times the human AUC exposure at the recommended dose of 400 mg daily). No teratogenicity was observed in either the mouse or the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of VENCLEXTA in human milk, the effects of VENCLEXTA on the breastfed child, or the effects of VENCLEXTA on milk production. Venetoclax was present in the milk when administered to lactating rats *(see Data).*

Because many drugs are excreted in human milk and because the potential for serious adverse reactions in a breastfed child from VENCLEXTA is unknown, advise nursing women to discontinue breastfeeding during treatment with VENCLEXTA.

Data

Animal Data

Venetoclax was administered (single dose; 150 mg/kg oral) to lactating rats 8 to 10 days parturition. Venetoclax in milk was 1.6 times lower than in plasma. Parent drug (venetoclax) represented the majority of the total drug-related material in milk, with trace levels of three metabolites.

8.3 Females and Males of Reproductive Potential

VENCLEXTA may cause fetal harm *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]*.

Pregnancy Testing

Conduct pregnancy testing in females of reproductive potential before initiation of VENCLEXTA *[see Use in Specific Populations (8.1)]*.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose *[see Use in Specific Populations (8.1)]*.

Infertility

Based on findings in animals, male fertility may be compromised by treatment with VENCLEXTA *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

In a juvenile toxicology study, mice were administered venetoclax at 10, 30, or 100 mg/kg/day by oral gavage from 7 to 60 days of age. Clinical signs of toxicity included decreased activity, dehydration, skin pallor, and hunched posture at ≥30 mg/kg/day. In addition, mortality and body weight effects occurred at 100 mg/kg/day. Other venetoclax-related effects were reversible decreases in lymphocytes at ≥10 mg/kg/day; a dose of 10 mg/kg/day is approximately 0.06 times the clinical dose of 400 mg on a mg/m^2 basis for a 20 kg child.

8.5 Geriatric Use

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Of the 352 patients with previously treated CLL/SLL evaluated for safety from 3 open-label trials of VENCLEXTA monotherapy, 57% (201/352) were ≥65 years of age and 18% (62/352) were ≥75 years of age.

No overall differences in safety and effectiveness were observed between older and younger patients in MURANO and the monotherapy studies.

Acute Myeloid Leukemia

Of the 67 patients treated with VENCLEXTA in combination with azacitidine in the clinical trial, 96% were ≥65 years of age and 50% were ≥ 75 years of age. Of the 13 patients treated with VENCLEXTA in combination with decitabine in the clinical trial, 100% were ≥65 years of age and 26% were ≥ 75 years of age. Of the 61 patients treated with VENCLEXTA in combination with low-dose cytarabine, 97% were ≥65 years of age and 66% were ≥75 years of age.

The efficacy and safety data presented in the Adverse Reactions and Clinical Studies sections were obtained from these patients *[see Adverse Reactions (6.2) and Clinical Studies (14.2)]*. There are insufficient patient numbers to show differences in safety and effectiveness between geriatric and younger patients.

8.6 Renal Impairment

Due to the increased risk of TLS, patients with reduced renal function (CLcr <80 mL/min, calculated by Cockcroft-Gault formula) require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.1)]*.

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr ≥ 30 mL/min *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been determined for patients with severe renal impairment (CLcr < 30 mL/min) or patients on dialysis.

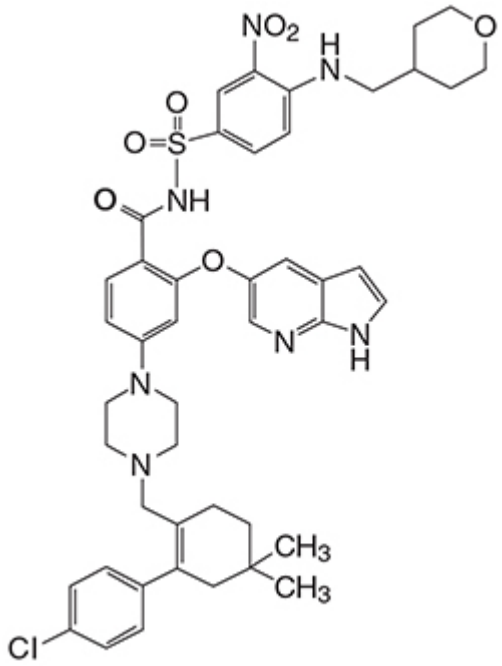
10 OVERDOSAGE

There is no specific antidote for VENCLEXTA. For patients who experience overdose, closely monitor and provide appropriate supportive treatment; during ramp-up phase interrupt

VENCLEXTA and monitor carefully for signs and symptoms of TLS along with other toxicities *[see Dosage and Administration (2.2, 2.3)]*. Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.

11 DESCRIPTION

Venetoclax is a selective inhibitor of BCL-2 protein. It is a light yellow to dark yellow solid with the empirical formula $C_{45}H_{50}ClN_7O_7S$ and a molecular weight of 868.44. Venetoclax has very low aqueous solubility. Venetoclax is described chemically as 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide) and has the following chemical structure:



VENCLEXTA tablets for oral administration are supplied as pale yellow or beige tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient. Each tablet also contains the following inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. In addition, the 10 mg and 100 mg coated tablets include the following: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. The 50 mg coated tablets also include the following: iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, talc, polyethylene glycol and titanium dioxide. Each tablet is debossed with “V” on one side and “10”, “50” or “100” corresponding to the tablet strength on the other side.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 CLL and AML cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. 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 tumor cells that overexpress BCL-2.

12.2 Pharmacodynamics

Based on the exposure response analyses for efficacy, a relationship between drug exposure and a greater likelihood of response was observed in clinical studies in patients with CLL/SLL, and in patients with AML. Based on the exposure response analyses for safety, a relationship between drug exposure and a greater likelihood of some safety events was observed in clinical studies in patients with AML. No exposure-safety relationship was observed in patients with CLL/SLL at doses up to 1200 mg given as monotherapy and up to 600 mg given in combination with rituximab.

Cardiac Electrophysiology

The effect of multiple doses of VENCLEXTA up to 1200 mg once daily (2 times the maximum approved recommended dosage) on the QTc interval was evaluated in an open-label, single-arm study in 176 patients with previously treated hematologic malignancies. VENCLEXTA had no large effect on QTc interval (i.e., > 20 ms) and there was no relationship between venetoclax exposure and change in QTc interval.

12.3 Pharmacokinetics

Venetoclax mean (± standard deviation) steady state C_{max} was 2.1 ± 1.1 mcg/mL and AUC_{0-24} was 32.8 ± 16.9 mcg•h/mL following administration of 400 mg once daily with a low-fat meal. Venetoclax steady state AUC increased proportionally over the dose range of 150 to 800 mg (0.25 to 1.33 times the maximum approved recommended dosage). The pharmacokinetics of venetoclax does not change over time.

Absorption

Maximum plasma concentration of venetoclax was reached 5 to 8 hours following multiple oral administration under fed conditions.

Effect of Food

Administration with a low-fat meal (approximately 512 kilocalories, 25% fat calories, 60% carbohydrate calories, and 15% protein calories) increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal (approximately 753 kilocalories, 55% fat calories, 28% carbohydrate calories, and 17% protein calories) increased venetoclax exposure by 5.1- to 5.3-fold compared with fasting conditions.

Distribution

Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 micromolar (0.87-26 mcg/mL). The mean blood-to-plasma ratio was 0.57. The apparent volume of distribution (Vd_{ss}/F) of venetoclax ranged from 256-321 L in patients.

Elimination

The terminal elimination half-life of venetoclax was approximately 26 hours.

Metabolism

Venetoclax is predominantly metabolized by CYP3A *in vitro*. The major metabolite identified in plasma, M27, has an inhibitory activity against BCL-2 that is at least 58-fold lower than venetoclax *in vitro* and its AUC represented 80% of the parent AUC.

Excretion

After single oral dose of radiolabeled [^{14}C]-venetoclax 200 mg to healthy subjects, > 99.9% of the dose was recovered in feces (20.8% as unchanged) and < 0.1% in urine within 9 days.

Specific Populations

No clinically significant differences in the pharmacokinetics of venetoclax were observed based on age (19 to 90 years), sex, race (White, Black, Asians, and Others), weight, mild to moderate renal impairment (CLcr 30 to 89 mL/min, calculated by Cockcroft-Gault), or mild to moderate hepatic impairment (normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin 1 to 3 times ULN). The effect of severe renal impairment (CLcr < 30 mL/min), dialysis, or severe hepatic impairment (total bilirubin > 3 times ULN) on venetoclax pharmacokinetics is unknown.

Drug Interactions Studies

Clinical Studies

No clinically significant differences in venetoclax pharmacokinetics were observed when co-administered with azacitidine, azithromycin, cytarabine, decitabine, gastric acid reducing agents, or rituximab.

Ketoconazole

Concomitant use of ketoconazole (a strong CYP3A, P-gp and BCRP inhibitor) 400 mg once daily for 7 days increased venetoclax C_{max} by 130% and AUC_{inf} by 540% *[see Drug Interactions (7.1)]*.

Ritonavir

Concomitant use of ritonavir (a strong CYP3A, P-gp and OATP1B1/B3 inhibitor) 50 mg once daily for 14 days increased venetoclax C_{max} by 140% and AUC by 690% *[see Drug Interactions (7.1)]*.

Posaconazole

Concomitant use of posaconazole (a strong CYP3A and P-gp inhibitor) 300 mg with venetoclax 50 mg and 100 mg for 7 days resulted in 61% and 86% higher venetoclax C_{max}, respectively, compared with venetoclax 400 mg administered alone. The venetoclax AUC_{24} was 90% and 144% higher, respectively.

Rifampin

Concomitant use of a single dose of rifampin (an OATP1B1/1B3 and P-gp inhibitor) 600 mg increased venetoclax C_{max} by 106% and AUC_{inf} by 78%. Concomitant use of multiple doses of rifampin (as a strong CYP3A inducer) 600 mg once daily for 13 days decreased venetoclax C_{max} by 42% and AUC_{inf} by 71% *[see Drug Interactions (7.1)]*.

Warfarin

Concomitant use of a single 400 mg dose of venetoclax with 5 mg warfarin resulted in 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin *[see Drug Interactions (7.2)]*.

Digoxin

Concomitant use of a single dose of venetoclax 100 mg with digoxin (a P-gp substrate) 0.5 mg increased digoxin C_{max} by 35% and AUC_{inf} by 9% *[see Drug Interactions (7.2)]*.

In Vitro Studies

Venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19 CYP2D6 or CYP3A4. Venetoclax is a weak inhibitor of CYP2C8, CYP2C9, and UGT1A1.

Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

Venetoclax is an inhibitor and substrate of P-gp and BCRP and weak inhibitor of OATP1B1.

Venetoclax is not an inhibitor of OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with venetoclax.

Venetoclax was not mutagenic in an *in vitro* bacterial mutagenicity (Ames) assay, did not induce numerical or structural aberrations in an *in vitro* chromosome aberration assay using human peripheral blood lymphocytes, and was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay at doses up to 835 mg/kg. The M27 metabolite was negative for genotoxic activity in *in vitro* Ames and chromosome aberration assays.

Fertility and early embryonic development studies were conducted in male and female mice. These studies evaluate mating, fertilization, and embryonic development through implantation. There were no effects of venetoclax on estrous cycles, mating, fertility, corpora lutea, uterine implants or live embryos per litter at dosages up to 600 mg/kg/day. However, a risk to human male fertility exists based on testicular toxicity (germ cell loss) observed in dogs at exposures as low as 0.5 times the human AUC exposure at the recommend dose.

13.2 Animal Toxicology and/or Pharmacology

In dogs, venetoclax caused single-cell necrosis in various tissues, including the gallbladder, exocrine pancreas, and stomach with no evidence of disruption of tissue integrity or organ dysfunction; these findings were minimal to mild in magnitude. Following a 4-week dosing period and subsequent 4-week recovery period, minimal single-cell necrosis was still present in some tissues and reversibility has not been assessed following longer periods of dosing or recovery.

In addition, after approximately 3 months of daily dosing in dogs, venetoclax caused progressive white discoloration of the hair coat, due to loss of melanin pigment.

14 CLINICAL STUDIES

14.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Combination Therapy

MURANO

MURANO was a randomized (1:1), multicenter, open label study (NCT02005471) that evaluated the efficacy and safety of VENCLEXTA in combination with rituximab (VEN+R) versus bendamustine in combination with rituximab (B+R) in patients with CLL who had received at least one line of prior therapy. Patients in the VEN+R arm completed the 5-week ramp-up schedule *[see Dosage and Administration (2.1, 2.2)]* and received VENCLEXTA 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. Rituximab was initiated intravenously after the 5-week dose ramp-up at 375 mg/m^2 on Day 1 of Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2-6. Each cycle was 28 days. Patients randomized to B+R received bendamustine at 70 mg/m^2 on Days 1 and 2 for 6 cycles (28-day cycle) and rituximab at the above described dose and schedule.

A total of 389 patients were randomized: 194 to the VEN+R arm and 195 to the B+R arm. Baseline demographic and disease characteristics were similar between the VEN+R and B+R arms. The median age was 65 years (range: 22-85 years), 97% were white, 74% were male, and 99% had ECOG performance status <2. Median prior lines of therapy was 1 (range: 1-5); 59% had received 1 prior therapy, 26% had received 2 prior therapies, and 16% had received 3 or more prior therapies. Prior therapies included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%), and prior purine analogs (81%, including fludarabine/cyclophosphamide/rituximab in 55%). A 17p deletion was detected in 24% of patients, *TP53* mutations in 25%, 11q deletion in 32%, and unmutated *IgVH* in 63%.

Efficacy was based on progression-free survival (PFS) as assessed by an Independent Review Committee (IRC). The median follow-up for PFS was 23.4 months (range: 0 to 37.4+ months).

Efficacy results for MURANO are shown in Table 17. The Kaplan-Meier curve for PFS is shown in Figure 1.

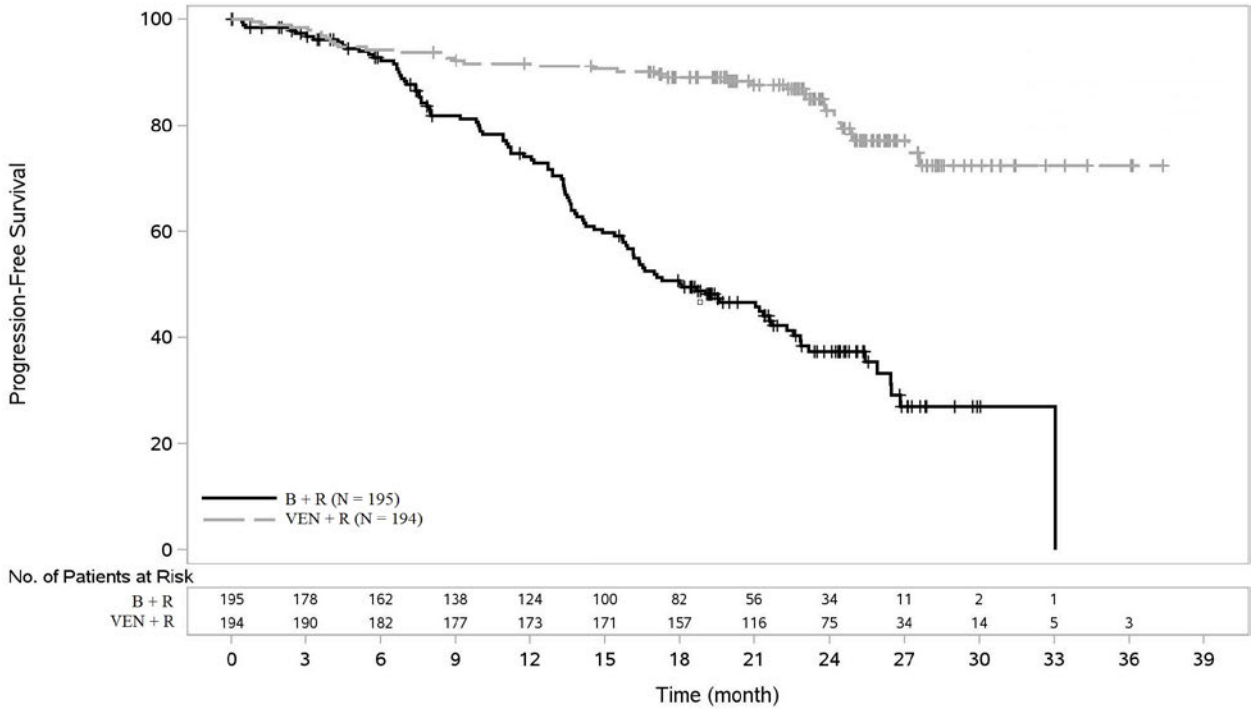
Table 17. IRC-Assessed Efficacy Results in MURANO

Endpoint	VENCLEXTA + Rituximab	Bendamustine + Rituximab

	(N = 194)	(N = 195)
Progression-free survival[a]		
Number of events, n (%)	35 (18)	106 (54)
Disease progression, n	26	91
Death events, n	9	15
Median, months (95% CI)	Not Reached	18.1 (15.8, 22.3)
HR (95% CI)[b]	0.19 (0.13, 0.28)	
p-value[b]	<0.0001	
Response rate[c], n (%)		
ORR	179 (92)	141 (72)
95% CI	(88, 96)	(65, 78)
CR+CRi	16 (8)	7 (4)
nPR	3 (2)	1 (1)
PR	160 (82)	133 (68)

CI = confidence interval; HR = hazard ratio; CR = complete remission; CRi = complete remission with incomplete marrow recovery; nPR = nodular partial remission; PR = partial remission; ORR = overall response rate (CR + CRi + nPR + PR).
[a]Kaplan-Meier estimate.
[b]HR estimate is based on Cox-proportional hazards model stratified by 17p deletion, risk status, and geographic region; p-value based on log-rank test stratified by the same factors.
[c]Per 2008 International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines.

Figure 1. Kaplan-Meier Curve of IRC-Assessed Progression-free Survival in MURANO



At the time of analysis, median overall survival had not been reached in either arm after a median follow-up of 22.9 months.

Minimal residual disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The definition of negative status was less than one CLL cell per 10^4 leukocytes. At 3 months after the last dose of rituximab, the MRD negativity rate in peripheral blood in patients who achieved PR or better was 53% (103/194) in the VEN+R arm and 12% (23/195) in the B+R arm. The MRD-negative CR/CRi rate at this timepoint was 3% (6/194) in the VEN+R arm and 2% (3/195) in the B+R arm.

Monotherapy

The efficacy of VENCLEXTA monotherapy in previously-treated CLL or SLL is based on three single-arm studies.

Study M13-982

The efficacy of VENCLEXTA was established in study M13-982 (NCT01889186), an open-label, single-arm, multicenter clinical trial of 106 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 Vysis CLL FISH Probe Kit, which is FDA approved for selection of patients for VENCLEXTA treatment. Patients received VENCLEXTA via a weekly ramp-up schedule starting at 20 mg and ramping to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive 400 mg of VENCLEXTA orally once daily until disease progression or unacceptable toxicity.

Efficacy was based on overall response rate (ORR) as assessed by an Independent Review Committee (IRC).

Table 18 summarizes the baseline demographic and disease characteristics of the study population.

Table 18. Baseline Patient Characteristics in Study M13-982

Characteristic	N = 106
Age, years; median (range)	67 (37-83)
White; %	97
Male; %	65
ECOG performance status; % 0 1 2	 40 52 8
Tumor burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 50 53
Number of prior therapies; median (range)	2.5 (1-10)
Time since diagnosis, years; median (range)[a]	6.6 (0.1-32.1)
[a]N=105.	

The median time on treatment at the time of evaluation was 12.1 months (range: 0 to 21.5 months). Efficacy results are shown in Table 19.

Table 19. Efficacy Results per IRC for Patients with Previously Treated CLL with 17p Deletion in Study M13-982

Endpoint	VENCLEXTA N = 106
ORR, n (%)[a]	85 (80)
(95% CI)	(71, 87)
CR + CRi, n (%)	8 (8)
CR, n (%)	6 (6)
CRi, n (%)	2 (2)
nPR, n (%)	3 (3)
PR, n (%)	74 (70)

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.

[a]Per 2008 IWCLL guidelines.

The median time to first response was 0.8 months (range: 0.1 to 8.1 months).

Based on a later data cutoff date and investigator-assessed efficacy, the duration of response (DOR) ranged from 2.9 to 32.8+ months. The median DOR has not been reached with median follow-up of 22 months.

MRD was evaluated in peripheral blood and bone marrow for patients who achieved CR or CRi, following treatment with VENCLEXTA. Three percent (3/106) achieved MRD negativity in the peripheral blood and bone marrow (less than one CLL cell per 10^4 leukocytes).

Study M12-175

Study M12-175 (NCT01328626) was a multicenter, open-label trial that enrolled previously treated patients with CLL or SLL, including those with 17p deletion. Efficacy was evaluated in 67 patients (59 with CLL, 8 with SLL) who had received a 400 mg daily dose of VENCLEXTA. Patients continued this dose until disease progression or unacceptable toxicity. The median duration of treatment at the time of evaluation was 22.1 months (range: 0.5 to 50.1 months).

The median age was 66 years (range: 42 to 84 years), 78% were male and 87% were white. The median number of prior treatments was 3 (range: 1 to 11). At baseline, 67% of patients had one or more nodes ≥5 cm, 30% of patients had ALC ≥25 x 10^9/L, 33% had documented unmutated *IgVH*, and 21% had documented 17p deletion.

Efficacy in CLL was evaluated according to 2008 IWCLL guidelines. As assessed by an IRC, the ORR was 71% (95% CI: 58%, 82%), CR + CRi rate was 7%, and PR rate was 64%.

Based on investigator assessments, the ORR in patients with CLL was 80% (14% CR+ CRi, 66% PR + nPR). With an estimated median follow-up of 25.2 months, the DOR ranged from 2.3+ to 48.6+ months. Of the 47 responders, 83% had a DOR of at least 12 months.

For the 8 patients with SLL, the investigator-assessed ORR was 100%.

Study M14-032

Study M14-032 (NCT02141282) was an open-label, multicenter, study that evaluated the efficacy of VENCLEXTA in patients with CLL who had been previously treated with and progressed on or after ibrutinib or idelalisib. Patients received a daily dose of 400 mg of VENCLEXTA following the ramp-up schedule. Patients continued to receive VENCLEXTA 400 mg once daily until disease progression or unacceptable toxicity. At the time of analysis, the median duration of treatment was 14.3 months (range: 0.1 to 31.4 months).

Of the 127 patients treated (91 with prior ibrutinib, 36 with prior idelalisib), the median age was 66 years (range: 28 to 85 years), 70% were male and 92% were white. The median number of prior treatments was 4 (range: 1 to 15). At baseline, 41% of patients had one or more nodes ≥5 cm, 31% had an absolute lymphocyte count ≥25 x 10^9/L, 57% had documented unmutated *IgVH*, and 39% had documented 17p deletion.

Efficacy was based on 2008 IWCLL guidelines. Based on IRC assessment, the ORR was 70% (95% CI: 61%, 78%), with a CR + CRi rate of 1%, and PR rate of 69%.
Based on investigator assessment, the ORR was 65% (95% CI: 56%, 74%). The median DOR per investigator has not been reached with an estimated median follow-up of 14.6 months.

14.2 Acute Myeloid Leukemia

VENCLEXTA was studied in two open-label non-randomized trials in patients with newly-diagnosed AML who were ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, or CLcr <45 mL/min or other comorbidity. Efficacy was established based on the rate of complete remission (CR) and the duration of CR.

Study M14-358

VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02203773) of VENCLEXTA in combination with azacitidine (N=84) or decitabine (N=31) in patients with newly-diagnosed AML. Of those patients, 67 who received azacitidine combination and 13 who received decitabine combination were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy.

Patients received VENCLEXTA via a daily ramp-up to a final 400 mg once daily dose *[see Dosage and Administration (2.1)]*. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Azacitidine at 75 mg/m^2 was administered either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. Decitabine at 20 mg/m^2 was administered intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity, see azacitidine full prescribing information. Dose reductions for decitabine were not implemented in the clinical trial.

Table 20 summarizes the baseline demographic and disease characteristics of the study population.

Table 20. Baseline Patient Characteristics for Patients with AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Characteristic	VENCLEXTA in Combination with Azacitidine N = 67	VENCLEXTA in Combination with Decitabine N = 13
Age, years; median (range)	76 (61-90)	75 (68-86)
Race		
White; %	87	77
Black or African American; %	4.5	0
Asian; %	1.5	0
Native Hawaiian or Pacific Islander; %	1.5	15
American Indian/Alaskan Native; %	0	7.7
Unreported/Other; %	6.0	0
Male; %	60	38
ECOG performance status; % 0-1 2 3	 64 33 3	 92 8 0
Disease history; % *De Novo* AML Secondary AML	 73 27	 85 15
Mutation analyses detected[a]; %		
TP53	21	31
IDH1 or IDH2	27	0
FLT-3	16	23
NPM1	19	15
Cytogenetic risk detected[b,c]; %		
Intermediate	64	38
Poor	34	62
Baseline comorbidities[d], %		
Severe cardiac disease	4.5	7.7
Severe pulmonary disease	1.5	0
Moderate hepatic impairment	9	0
Creatinine clearance <45 mL/min	13	7.7

[a]Includes 6 patients with insufficient sample for analysis in the azacitidine group and 4 in the decitabine group.

[b]As defined by the National Comprehensive Cancer Network (NCCN) risk categorization v2014.
[c]No mitosis in 1 patient in azacitidine group (excluded favorable risk by Fluorescence in situ Hybridization [FISH] analysis).
[d]Patients may have had more than one comorbidity.

The efficacy results are shown in Table 21.

Table 21. Efficacy Results for Patients with Newly-Diagnosed AML Treated with VENCLEXTA in Combination with Azacitidine or Decitabine

Efficacy Outcomes	VENCLEXTA in Combination with Azacitidine N = 67	VENCLEXTA in Combination with Decitabine N = 13
CR, n (%) (95% CI)	25 (37) (26, 50)	7 (54) (25, 81)
CRh, n (%) (95% CI)	16 (24) (14, 36)	1 (7.7) (0.2, 36)

CI = confidence interval; NR = not reached.
CR (complete remission) was defined as absolute neutrophil count >1,000/microliter, platelets >100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh (complete remission with partial hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

The median follow-up was 7.9 months (range: 0.4 to 36 months) for VENCLEXTA in combination with azacitidine. At the time of analysis, for patients who achieved a CR, the median observed time in remission was 5.5 months (range: 0.4 to 30 months). The observed time in remission is the time from the start of CR to the time of data cut-off date or relapse from CR.

The median follow-up was 11 months (range: 0.7 to 21 months) for VENCLEXTA in combination with decitabine. At the time of analysis, for patients who achieved a CR, the median observed time in remission was 4.7 months (range: 1.0 to 18 months). The observed time in remission is the time from the start of CR to the time of data cut-off date or relapse from CR.

Median time to first CR or CRh for patients treated with VENCLEXTA in combination with azacitidine was 1.0 month (range: 0.7 to 8.9 months).

Median time to first CR or CRh for patients treated with VENCLEXTA in combination with decitabine was 1.9 months (range: 0.8 to 4.2 months).

Of patients treated with VENCLEXTA in combination with azacitidine, 7.5% (5/67) subsequently received stem cell transplant.

The study enrolled 35 additional patients (age range: 65 to 74 years) who did not have known comorbidities that preclude the use of intensive induction chemotherapy and were treated with VENCLEXTA in combination with azacitidine (N=17) or decitabine (N=18).

For the 17 patients treated with VENCLEXTA in combination with azacitidine, the CR rate was 35% (95% CI: 14%, 62%). The CRh rate was 41% (95% CI: 18%, 67%). Seven (41%) patients subsequently received stem cell transplant.

For the 18 patients treated with VENCLEXTA in combination with decitabine, the CR rate was 56% (95% CI: 31%, 79%). The CRh rate was 22% (95% CI: 6.4%, 48%). Three (17%) patients subsequently received stem cell transplant.

Study M14-387

VENCLEXTA was studied in a non-randomized, open-label clinical trial (NCT02287233) of VENCLEXTA in combination with low dose cytarabine (N=82) in patients with newly-diagnosed AML, including patients with previous exposure to a hypomethylating agent for an antecedent hematologic disorder. Of those patients, 61 were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the criterion: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, or CLcr ⩾30 to <45 mL/min or other comorbidity.

Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose *[see Dosage and Administration (2.1)]*. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Cytarabine at a dose of 20 mg/m^2 was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trial.

Table 22 summarizes the baseline demographic and disease characteristics of the study population.

Table 22. Baseline Patient Characteristics for Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Characteristic	VENCLEXTA in Combination with Low-Dose Cytarabine N = 61
Age, years; median (range)	76 (63-90)
Race	
White; %	92
Black or African American; %	1.6
Asian; %	1.6
Unreported; %	4.9
Male; %	74
ECOG performance status; % 0-1 2 3	 66 33 1.6
Disease history, %	

De novo AML Secondary AML	54 46
Mutation analyses detected[a]; %	
TP53	8
IDH1 or IDH2	23
FLT-3	21
NPM1	9.8
Cytogenetic risk detected[b]; %	
Intermediate	59
Poor	34
No mitoses	6.6
Baseline comorbidities[c], %	
Severe cardiac disease	9.8
Moderate hepatic impairment	4.9
Creatinine clearance ⩾30 or <45 mL/min	3.3

[a]Includes 7 patients with insufficient sample for analysis.
[b]As defined by the National Comprehensive Cancer Network (NCCN) risk categorization v2014
[c]Patients may have had more than one comorbidity.

Efficacy results are shown in Table 23.

Table 23. Efficacy Results for Patients with Newly-Diagnosed AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Efficacy Outcomes	**VENCLEXTA in Combination with Low-Dose Cytarabine N = 61**
CR, n (%) (95% CI)	13 (21) (12, 34)
CRh, n (%) (95% CI)	13 (21) (12, 34)

CI = confidence interval; NR = not reached.
CR (complete remission) was defined as absolute neutrophil count >1,000/microliter, platelets >100,000/microliter, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRh (complete remission with partial hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts

(platelets >50,000/microliter and ANC >500/microliter).

The median follow-up was 6.5 months (range: 0.3 to 34 months). At the time of analysis, for patients who achieved a CR, the median observed time in remission was 6.0 months (range: 0.03 to 25 months). The observed time in remission is the time from the start of CR to the time of data cut-off date or relapse from CR.

Median time to first CR or CRh for patients treated with VENCLEXTA in combination with low-dose cytarabine was 1.0 month (range: 0.8 to 9.4 months).

The study enrolled 21 additional patients (age range: 67 to 74 years) who did not have known comorbidities that preclude the use of intensive induction chemotherapy and were treated with VENCLEXTA in combination with low-dose cytarabine. The CR rate was 33% (95% CI:15%, 57%). The CRh rate was 24% (95% CI: 8.2%, 47%). One patient (4.8%) subsequently received stem cell transplant.

16 HOW SUPPLIED/STORAGE AND HANDLING

VENCLEXTA is dispensed as follows:

Packaging Presentation	Number of Tablets	National Drug Code (NDC)
CLL/SLL Starting Pack	Each pack contains four weekly wallet blister packs: • Week 1 (14 x 10 mg tablets) • Week 2 (7 x 50 mg tablets) • Week 3 (7 x 100 mg tablets) • Week 4 (14 x 100 mg tablets)	0074-0579-28
Wallet containing 10 mg tablets	14 x 10 mg tablets	0074-0561-14
Wallet containing 50 mg tablets	7 x 50 mg tablets	0074-0566-07
Unit dose blister containing 10 mg tablets	2 x 10 mg tablets	0074-0561-11
Unit dose blister containing 50 mg tablet	1 x 50 mg tablet	0074-0566-11
Unit dose blister containing 100 mg tablet	1 x 100 mg tablet	0074-0576-11
Bottle containing 100 mg tablets	120 x 100 mg tablets	0074-0576-22
Bottle containing 100 mg tablets	180 x 100 mg tablets	0074-0576-34

VENCLEXTA 10 mg film-coated tablets are round, biconvex shaped, pale yellow debossed with “V” on one side and “10” on the other side.

VENCLEXTA 50 mg film-coated tablets are oblong, biconvex shaped, beige debossed with “V” on one side and “50” on the other side.

VENCLEXTA 100 mg film-coated tablets are oblong, biconvex shaped, pale yellow debossed with “V” on one side and “100” on the other side.

Store at or below 86°F (30°C).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- **Tumor Lysis Syndrome**
  Advise patients of the potential risk of TLS, particularly at treatment initiation and during ramp-up phase, and to immediately report any signs and symptoms associated with this event (fever, chills, nausea, vomiting, confusion, shortness of breath, seizure, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle pain, and/or joint discomfort) to their health care provider (HCP) for evaluation *[see Warnings and Precautions (5.1)]*.

  Advise patients to be adequately hydrated every day when taking VENCLEXTA to reduce the risk of TLS. The recommended volume is 6 to 8 glasses (approximately 56 ounces total) of water each day. Patients should drink water starting 2 days before and on the day of the first dose, and every time the dose is increased *[see Dosage and Administration (2.2)]*.

  Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Dosage and Administration (2.2)]*.

  Advise patients that it may be necessary to take VENCLEXTA in the hospital or medical office setting to allow monitoring for TLS.
- **Neutropenia**
  Advise patients to contact their HCP immediately if they develop a fever or any signs of infection. Advise patients of the need for periodic monitoring of blood counts *[see Warnings and Precautions (5.2)]*.
- **Drug Interactions**
  Advise patients to avoid consuming grapefruit products, Seville oranges, or starfruit during treatment with VENCLEXTA. Advise patients that VENCLEXTA may interact with some drugs; therefore, advise patients to inform their health care provider of the use of any prescription medication, over-the-counter drugs, vitamins and herbal products *[see Contraindications (4) and Drug Interactions (7.1)]*.
- **Immunizations**
  Advise patients to avoid vaccination with live vaccines because they may not be safe or effective during treatment with VENCLEXTA *[see Warnings and Precautions (5.3)]*.
- **Pregnancy and Lactation**
  Advise women of the potential risk to the fetus and to avoid pregnancy during treatment with VENCLEXTA. Advise female patients of reproductive potential to use effective contraception during therapy and for at least 30 days after completing of therapy. Advise females to contact their HCP if they become pregnant, or if pregnancy is suspected, during treatment with VENCLEXTA. Also advise patients not to breastfeed while taking

VENCLEXTA *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.1, 8.2, and 8.3)]*.

- **Male Infertility**
  Advise patients of the possibility of infertility and possible use of sperm banking for males of reproductive potential *[see Use in Specific Populations (8.3)]*.

Instructions for Taking VENCLEXTA

Advise patients to take VENCLEXTA exactly as prescribed and not to change their dose or to stop taking VENCLEXTA unless they are told to do so by their HCP. Advise patients to take VENCLEXTA orally once daily, at approximately the same time each day, according to their HCP's instructions and that the tablets should be swallowed whole with a meal and water without being chewed, crushed, or broken *[see Dosage and Administration (2.1)]*.

Advise patients with CLL/SLL to keep VENCLEXTA in the original packaging during the first 4 weeks of treatment, and not to transfer the tablets to a different container.

Advise patients that if a dose of VENCLEXTA is missed by less than 8 hours, to take the missed dose right away and take the next dose as usual. If a dose of VENCLEXTA is missed by more than 8 hours, advise patients to wait and take the next dose at the usual time *[see Dosage and Administration (2.5)]*.

Advise patients not to take any additional dose that day if they vomit after taking VENCLEXTA, and to take the next dose at the usual time the following day.

Manufactured and Marketed by:
AbbVie Inc.
North Chicago, IL 60064

and

Marketed by:
Genentech USA, Inc.
A Member of the Roche Group
South San Francisco, CA 94080-4990

03-B700 November 2018

MEDICATION GUIDE
VENCLEXTA® (ven-KLEKS-tuh)
(venetoclax tablets)

What is the most important information I should know about VENCLEXTA?
VENCLEXTA can cause serious side effects, including:
Tumor lysis syndrome (TLS). TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure, the need for dialysis treatment, and may lead to death. Your healthcare provider will do tests to check your risk of getting TLS before you start taking VENCLEXTA. You will receive other medicines before starting and during treatment with VENCLEXTA to help reduce your risk of TLS. You may also need to receive intravenous (IV) fluids into your vein. Your healthcare provider will do blood tests to check for TLS when you first start treatment and during treatment with VENCLEXTA. It is important to keep your appointments for blood tests. Tell your healthcare provider right away if you have any symptoms of TLS during treatment with VENCLEXTA, including:

- fever
- chills
- nausea
- vomiting
- confusion
- shortness of breath
- seizures
- irregular heartbeat
- dark or cloudy urine
- unusual tiredness
- muscle or joint pain

Drink plenty of water during treatment with VENCLEXTA to help reduce your risk of getting TLS. Drink 6 to 8 glasses (about 56 ounces total) of water each day, starting 2 days before your first dose, on the day of your first dose of VENCLEXTA, and each time your dose is increased.
Your healthcare provider may delay, decrease your dose, or stop treatment with VENCLEXTA if you have side effects.
See "**What are the possible side effects of VENCLEXTA?**" for more information about side effects.

What is VENCLEXTA?
VENCLEXTA is a prescription medicine used:

- to treat adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with or without 17p deletion, who have received at least 1 prior treatment.
- in combination with azacitidine, or decitabine, or low-dose cytarabine to treat adults with newly-diagnosed acute myeloid leukemia (AML) who:
  - are 75 years of age or older, **or**
  - have other medical conditions that prevent the use of standard chemotherapy.

It is not known if VENCLEXTA is safe and effective in children.

Who should not take VENCLEXTA?
Certain medicines must not be taken when you first start taking VENCLEXTA and while your dose is being slowly increased because of the risk of increased tumor lysis syndrome (TLS).

- **Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. VENCLEXTA and other medicines may affect each other causing serious side effects.
- Do not start new medicines during treatment with VENCLEXTA without first talking with your healthcare provider.

Before taking VENCLEXTA, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems
- have problems with your body salts or electrolytes, such as potassium, phosphorus, or calcium
- have a history of high uric acid levels in your blood or gout
- are scheduled to receive a vaccine. You should not receive a “live vaccine” before, during, or after treatment with VENCLEXTA, until your healthcare provider tells you it is okay. If you are not sure about the type of immunization or vaccine, ask your healthcare provider. These vaccines may not be safe or may not work as well during treatment with VENCLEXTA.
- are pregnant or plan to become pregnant. VENCLEXTA may harm your unborn baby.
  - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with VENCLEXTA.
  - Females who are able to become pregnant should use effective birth control during treatment and

for at least 30 days after the last dose of VENCLEXTA.
- If you become pregnant or think you are pregnant, tell your healthcare provider right away.

- are breastfeeding or plan to breastfeed. It is not known if VENCLEXTA passes into your breast milk. Do not breastfeed during treatment with VENCLEXTA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VENCLEXTA and other medicines may affect each other causing serious side effects. See **"Who should not take VENCLEXTA?"**

How should I take VENCLEXTA?

- Take VENCLEXTA exactly as your healthcare provider tells you to take it. Do not change your dose of VENCLEXTA or stop taking VENCLEXTA unless your healthcare provider tells you to.
- When you first take VENCLEXTA:
  - You may need to take VENCLEXTA at a hospital or clinic to be monitored for TLS.
  - If you are taking VENCLEXTA for CLL or SLL, your healthcare provider will start VENCLEXTA at a low-dose. Your dose will be slowly increased weekly over 5 weeks up to the full dose. Read the **Quick Start Guide** that comes with VENCLEXTA before your first dose.
  - If you are taking VENCLEXTA for AML, your healthcare provider will start VENCLEXTA at a low-dose. Your dose will be slowly increased daily up to the full dose. Follow your healthcare provider's instructions carefully while increasing to the full dose.
- Follow the instructions about drinking water described in the section of this Medication Guide about TLS called **"What is the most important information I should know about VENCLEXTA?"** and also in the **Quick Start Guide**.
- Take VENCLEXTA 1 time a day with a meal and water at about the same time each day.
- Swallow VENCLEXTA tablets whole. Do not chew, crush, or break the tablets.
- If you miss a dose of VENCLEXTA and it has been less than 8 hours, take your dose as soon as possible. If you miss a dose of VENCLEXTA and it has been more than 8 hours, skip the missed dose and take the next dose at your usual time.
- If you vomit after taking VENCLEXTA, do not take an extra dose. Take the next dose at your usual time the next day.

What should I avoid while taking VENCLEXTA?

You should not drink grapefruit juice, eat grapefruit, Seville oranges (often used in marmalades), or starfruit while you are taking VENCLEXTA. These products may increase the amount of VENCLEXTA in your blood.

What are the possible side effects of VENCLEXTA?

VENCLEXTA can cause serious side effects, including:

- **See "What is the most important information I should know about VENCLEXTA?"**

Low white blood cell count (neutropenia). Low white blood cell counts are common with VENCLEXTA, but can also be severe. Your healthcare provider will do blood tests to check your blood counts during treatment with VENCLEXTA. Tell your healthcare provider right away if you have a fever or any signs of an infection during treatment with VENCLEXTA.

The most common side effects of VENCLEXTA when used in combination with rituximab in people with CLL include:

- diarrhea
- upper respiratory tract infection
- cough
- tiredness
- nausea

The most common side effects of VENCLEXTA when used alone in people with CLL/SLL include:

- diarrhea
- nausea
- upper respiratory tract infection
- low red blood cell counts
- tiredness
- low platelet counts
- muscle and joint pain
- swelling of your arm, legs, hands, and feet
- cough

The most common side effects of VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine in people with AML include:

- nausea
- diarrhea
- low platelet counts
- constipation
- fever with low white blood cell counts
- low red blood cell counts
- infection in blood
- rash
- dizziness
- low blood pressure
- fever
- swelling of your arms, legs, hands, and feet
- vomiting
- tiredness
- shortness of breath
- bleeding
- infection in lung
- stomach (abdominal) pain
- pain in muscles or back
- cough
- sore throat

VENCLEXTA may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of VENCLEXTA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VENCLEXTA?

- Store VENCLEXTA at or below 86°F (30°C).
- For people with CLL/SLL, keep VENCLEXTA tablets in the original package during the first 4 weeks of treatment. **Do not** transfer the tablets to a different container.

Keep VENCLEXTA and all medicines out of reach of children.

General information about the safe and effective use of VENCLEXTA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VENCLEXTA for a condition for which it was not prescribed. Do not give VENCLEXTA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about VENCLEXTA that is written for health professionals.

What are the ingredients in VENCLEXTA?

Active ingredient: venetoclax

Inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic.

The 10 mg and 100 mg coated tablets also include: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. The 50 mg coated tablets also include: iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, talc, polyethylene glycol, and titanium dioxide.

Manufactured and Marketed by:
AbbVie Inc.
North Chicago, IL 60064

03-B700

Marketed by:
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South San Francisco, CA 94080-4990

For more information go to www.venclexta.com or call 1-800-633-9110

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 11/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s009

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	208573, S-009
Priority or Standard	Priority
Submit Date(s)	June 25, 2018
Received Date(s)	June 25, 2018
PDUFA Goal Date	December 25, 2018
Division/Office	Division of Hematology Products, OHOP
Review Completion Date	November 20, 2018
Established/Proper Name	Venetoclax
(Proposed) Trade Name	VENCLEXTA
Pharmacologic Class	BCL-2 inhibitor
Code name	Abt-199
Applicant	AbbVie, Inc.
Doseage form	Tablets: 10, 50, and 100 mg
Applicant proposed Dosing Regimen	In combination with azacitidine or decitabine, venetoclax is 100 mg on day 1, 200 mg on day 2, and 400 mg on days 3 and beyond. In combination with low-dose cytarabine, venetoclax is 100 mg on day 1, 200 mg on day 2, 400 mg on day 3, and 600 mg on days 4 and beyond.
Applicant Proposed Indication(s)/Population(s)	VENCLEXTA (venetoclax) in combination with a hypomethylating agent (HMA) or in combination with low dose cytarabine (LDAC) for the treatment of newly diagnosed patients with acute myeloid leukemia (AML) ineligible for intensive chemotherapy
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	91861009 |Acute myeloid leukemia, disease (disorder)|
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s) (if applicable)	VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy
Recommended SNOMED CT Indication Disease Term for each Indication	As above
Recommended Dosing Regimen	As above

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AR	adverse reaction
AST	aspartate aminotransferase
BCL-2	B-cell lymphoma-2
BRF	Benefit Risk Framework
BTD	breakthrough therapy designation
CCR	conventional care regimens
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CLcr or CrCl	creatinine clearance
CLL	chronic lymphocytic leukemia
COA	clinical outcomes assessment
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CSR	clinical study report
DDI	drug-drug interactions
DLCO	diffusing capacity of the lungs for carbon monoxide
DLT	dose-limiting toxicity
DOR	duration of remission
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EFS	event-free survival
EOP2	end-of-phase 2
E-R	exposure-response
FDA	Food and Drug Administration
FEV1	forced expiratory volume in the first second of expiration
GCP	good clinical practice
GO	gemtuzumab ozogamicin
HMA	hypomethylating agent
HR	hematologic response
HSCT	hematopoietic stem cell transplantation
IDMC	independent data review committee
IEC	Independent Ethics Committee

IND	Investigational New Drug
IRB	Institutional Review Board
LDAC	low-dose cytarabine
MAED	MedDRA adverse events diagnostic
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MPN	myeloproliferative neoplasms
MRC	myelodysplasia-related changes
MRD	minimal residual disease
MTD	maximum tolerated dose
NAI	no action indicated
NDA	new drug application
OCP	Office of Clinical Pharmacology
ORR	overall response rate
OS	overall survival
OSI	Office of Scientific Investigation
PFS	progression-free survival
PK	pharmacokinetics
PMR	postmarketing requirement
PND	post-natal day
PR	partial remission
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
R/R	relapsed or refractory
RBC	red blood cell
RD	resistant disease
SAE	serious adverse event
SAP	statistical analysis plan
SLL	small lymphocytic lymphoma
SOC	standard of care
STEAE	serious treatment-emergent adverse events
SWFI	sterile water for injection
TEAE	treatment emergent adverse event
TLS	tumor lysis syndrome
TTP	time to progression
ULN	upper limit of normal
VAI	voluntary action indicated
WBC	white blood cell

1 Executive Summary

1.1. Product Introduction

Trade name:	Venclexta®
Established name:	Venetoclax
Also known as:	ABT-199, GDC-0199
Dosage form:	Tablets: 10, 50, and 100 mg
Therapeutic class:	Antineoplastic
Chemical class:	Small molecule
Pharmacologic class:	B-cell lymphoma-2 (BCL-2) inhibitor
Mechanism of action:	Inhibition of BCL-2 protein, inducing apoptosis of malignant cells

Venetoclax is an orally administered BCL-2 inhibitor, currently approved for chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL), with or without 17p deletion, who have received at least one prior therapy. Venetoclax is approved as a single agent or in combination with rituximab for CLL/SLL.

The present supplement serves to add the indication for treatment of patients with AML in combination with azacitidine, decitabine, or low-dose cytarabine. In combination with azacitidine or decitabine, the recommended dose-schedule is a 3-day ramp-up of venetoclax to 400 mg daily, then 400 mg daily. Azacitidine or decitabine are dosed per standard regimens. Azacitidine dosage was 75 mg/m^2, intravenously or subcutaneously, on Days 1-7 of each 28-day cycle. Decitabine dosage was 20 mg/m^2, intravenously, on Days 1-5 of each 28-day cycle. Venetoclax and azacitidine or decitabine are continued until disease progression or unacceptable toxicity. In combination with low-dose cytarabine (LDAC), the recommended dose-schedule is a 4-day ramp-up of venetoclax to 600 mg daily, then 600 mg daily. LDAC is dosed per standard regimen of 20 mg/m^2, subcutaneously, on Days 1-10 of each 28-day cycle. Venetoclax and low-dose cytarabine is continued until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval (21 CFR 314 Subpart H) of venetoclax "in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy." The recommendation is based on the findings of durable complete remission (CR) and supported by CR with partial hematopoietic recovery (CRh) in Studies M14-358 and M14-387.

Venetoclax was evaluated in two open-label, non-randomized trials in patients with newly diagnosed AML who were greater than or equal to 75 years of age, or had comorbidities that

precluded the use of intensive induction chemotherapy based on at least one of the criterion: poor performance status, severe cardiac or pulmonary comorbidity, moderate hepatic or renal impairment, or any other comorbidity that precluded a patient from receiving intensive induction therapy.

Study M14-358 was an open-label, single-arm, multicenter clinical trial of venetoclax in combination with azacitidine or decitabine for the treatment of patients with newly-diagnosed AML who are not eligible for standard induction chemotherapy. The trial enrolled 84 patients treated at the target dose of venetoclax (400 mg) in combination with azacitidine and 31 patients treated at the target dose of venetoclax (400 mg) in combination with decitabine. The efficacy population consisted of 67 and 13 patients in each combination respectively met pre-specified criteria of age ≥75 year or comorbidities that preclude the use of intensive induction chemotherapy. In combination with azacitidine, the CR rate was 37% (95% CI: 26, 50) with an observed duration of CR of 5.5 months (range: 0.4-30). In combination with decitabine, the CR rate was 54% (95% CI: 25, 81) with an observed duration of CR of 4.7 months (range: 1-18). The CRh rate was 24% and 8% in the venetoclax plus azacitidine and venetoclax plus decitabine groups, respectively.

Study M14-387 was an open-label, single-arm, multicenter clinical trial of venetoclax in combination with low-dose cytarabine (LDAC) for the treatment of patients with newly-diagnosed AML who are not eligible for standard induction chemotherapy. The trial enrolled 82 patients treated at the target dose of venetoclax (600 mg) in combination with LDAC. The efficacy population consisted of 61 patients met pre-specified criteria of age ≥75 year or comorbidities that preclude the use of intensive induction chemotherapy. In combination with LDAC, the CR rate was 21% (95% CI: 12, 34) with an observed duration of CR of 6 months (range: 0.03-25). The CRh rate was 21%.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Venetoclax is an orally administered BCL-2 inhibitor, currently approved for chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL), with or without 17p deletion, who have received at least one prior therapy. Venetoclax is approved for CLL/SLL as a single agent or in combination with rituximab. This supplement NDA serves to add the indication for treatment of patients with acute myeloid leukemia (AML) in combination with azacitidine, decitabine, or low-dose cytarabine. There is biological rationale for the combination of venetoclax and the backbone agents, which cause DNA damage.

AML is an aggressive hematological malignancy with increasing incidence with age. Intensive chemotherapy, the mainstay of treatment, is often not an option for elderly or patients with comorbidities due to toxicities of the therapy and represent a large portion of patients with AML. As such, the limited available effective non-intensive therapies for this approval represent a significant unmet medical need.

The recommendation for accelerated approval is based on the efficacy results from two single arm studies evaluating venetoclax in combination with azacitidine, decitabine and low dose cytarabine. Study M14-358 was an open-label, single-arm, multicenter clinical trial of venetoclax in combination with azacitidine or decitabine for the treatment of patients with newly-diagnosed AML who are not eligible for standard induction chemotherapy. The trial enrolled 84 patients treated at the target dose of venetoclax (400 mg) in combination with azacitidine and 31 patients treated at the target dose of venetoclax (400 mg) in combination with decitabine. The efficacy population consisted of 67 and 13 patients in each combination respectively met pre-specified criteria of age ≥75 year or comorbidities that preclude the use of intensive induction chemotherapy. In combination with azacitidine, the CR rate was 37% (95% CI: 26, 50) with an observed duration of CR of 5.5 months (range: 0-30). In combination with decitabine, the CR rate was 54% (95% CI: 25, 81) with an observed duration of CR of 4.7 months (range: 1-18). The median follow-up was 7.9 months (range: 0.4 to 35.5 months) for venetoclax in combination with azacitidine and the median follow-up was 11 months (range: 0.7 to 20.9 months). The observed time in remission is the time from start of CR to the time of data cut-off date or relapse from CR.

Study M14-387 was an open-label, single-arm, multicenter clinical trial of venetoclax in combination with low-dose cytarabine (LDAC) for the treatment of patients with newly-diagnosed AML who are not eligible for standard induction chemotherapy. The trial enrolled 82 patients treated at the target dose of venetoclax (600 mg) in combination with LDAC. The efficacy population consisted of 61 patients met pre-specified criteria of age ≥75 year or comorbidities that preclude the use of intensive induction chemotherapy. In combination with LDAC, the CR rate was 23% (95% CI: 13, 36) and A median follow-up was 6.5 months (range: 0.3 to 33.9 months). At the time of analysis, for patients who achieved a

CR, the median observed time in remission was 6.05 months (range: 0.03 to 25.4 months). The observed time in remission from start of CR to the time of data cut-off date or relapse from CR.

Safety was demonstrated in the population who should not receive intensive chemotherapy based on age or comorbidities. Common adverse reactions for the combination of venetoclax and azacitidine, decitabine, or low dose cytarabine included (>30%) nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, peripheral edema, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, back pain, neck pain, myalgia, dizziness, cough, oropharyngeal pain, and hypotension. Frequent serious adverse events included febrile neutropenia, pneumonia, sepsis, and hemorrhage and multi-organ dysfunction, diarrhea, fatigue, cellulitis and localized infections. The events were managed by anti-infectives, G-CSF, and transfusions as indicated. TLS was an infrequent event and can be mitigated by dose ramp up, prophylaxis, and monitoring.

In conclusion, the endpoints used to assess efficacy in the presented studies was CR rate and duration of CR, supported by CRh rate. The CR rate was 37% in combination with azacitidine, 54% in combination with decitabine, and 21% in combination with LDAC. The durability of responses support effectiveness in this population. Because the results were based on single arm trials with endpoints of response rates, uncertainty remains regarding the benefit of the addition of venetoclax to the backbone therapy. While it appears the addition of venetoclax to the backbone therapy adds substantial efficacy without excess toxicity, this will be better evaluated in randomized trials. The information submitted supports accelerated approval for this indication. The results will be confirmed by the completion of two randomized studies for venetoclax in combination with azacitidine and venetoclax in combination with LDAC, respectively.

The conclusion for substantial benefit of efficacy is based on complete response and durability of response supported by CRh. The endpoint used to assess efficacy in the presented studies was CR rate and duration of CR, supported by CRh rate. The CR rate was 37% in combination with azacitidine, 54% in combination with decitabine, and 21% in combination with LDAC. The durability of responses support effectiveness in this population.

The recommendation for accelerated approval is based on the nature of the trials designs (single trial design of combination therapy) and the following: difficulty in isolating the treatment effect of venetoclax in single arm trial, lack of stringent historical controls, and inconclusive survival due to singe arm trial designs. While CR can be considered a clinical benefit in some population of patients with AML, there is uncertainty regarding the benefit of addition of venetoclax to the hypomethylating agents or low dose cytarabine given the single arm nature of the trials.

The evaluation of azacitidine, decitabine, and LDAC published response rates is limited due to known or unknown confounders, the comparison with venetoclax in these combinations is useful to establish efficacy. Favorable CR rates with venetoclax in combination with azacitidine, decitabine, and LDAC were seen relative to the historical information. Additionally, LDAC monotherapy is not as commonly used for the treatment of newly-diagnosed AML due to suggestion of lower efficacy in cross-trial comparisons. However, a survival benefit has not been shown for azacitidine or decitabine over LDAC therapy. Similarly, the combination of venetoclax with LDAC appears to have lower response rates, but the durability of responses is similar. The combination of venetoclax with LDAC is therefore a useful treatment option for the treatment of patients with AML.

Accelerated approval also requires demonstration of an improvement over available therapies. In the indicated patient population, the only approved available therapy is gemtuzumab ozogamicin (GO). The CR rate was not reported in the PI, but shown in the review to be 15% (95% CI: 9-23%) with median overall survival of 4.9 mo. The CR rate of venetoclax with LDAC has a higher point estimate, but overlapping confidence with GO; however, the combinations of venetoclax in combination with azacitidine or decitabine show an improvement with non-overlapping confidence intervals. Other standard therapies used in this patient population are azacitidine, decitabine, and LDAC. The addition of venetoclax with any of these backbone therapies appears to show an improvement in CR rates that is not attributable to either agent alone.

The population enrolled on the two clinical trials in support of this application primarily consisted of patients who were over the age of 75 or had comorbidities that precluded the use of intensive chemotherapy. This is a population that represents a significant unmet medical need. The population included in the USPI for this application includes patients who met a pre-defined definition of age greater than or equal to 75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the criterion: poor performance status, severe cardiac or pulmonary comorbidity, moderate hepatic or renal impairment, or any other comorbidity that precluded a patient from receiving intensive induction therapy. There were additional patients in each combination who did not meet the pre-defined criteria and thus could not definitely conclude that these were patients who were not eligible for intensive chemotherapy and thus excluded from the primary analysis by the Division.

The approval of the combinations in single-arm trials is based on the following: unmet medical need in proposed population, biologic rationale for the combination based on the mechanism of action of venetoclax when combined with hypomethylating agents and low dose cytarabine, nonclinical data describing the activity of the combination and individual agents suggestive of synergistic activity, the complete remission rates with the combinations are higher than would be expected for any of the agents as single therapy.

In summary, the addition of venetoclax to the backbone of azacitidine, decitabine and low dose cytarabine appears to improve the complete response rate and durability supported by CRh, however given the limitations with the single arm trials submitted in support of this application to isolate the treatment effect, randomized clinical trials will need to be performed to confirm the clinical benefit of the combination therapy in newly diagnosed patients with AML who have comorbidities that preclude the use of intensive chemotherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AML is a fatal disease • Most elderly patients or those with comorbidities would not tolerate intensive chemotherapy due to toxicities.	AML is a fatal disease Elderly patients or those with comorbidities would not tolerate intensive chemotherapy
Current Treatment Options	• In untreated AML, in patients who cannot receive intensive chemotherapy, the reported complete response rates using current available therapy is 8%-20%. The median OS is approximately 5-10 months. • Gemtuzumab ozogamicin (GO) is approved for patients with AML. The CR rate described in the review is 15% (95% CI: 9-23%) with median overall survival of 4.9 mo.	There is need for effective therapies for treatment of patients with AML that can be tolerated by older patients or those that have comorbidities that do not allow use of intensive chemotherapy
Benefit	• In study M14-387, a single-arm trial, 61 patients with age ≥ 75 or with comorbidities that precluded intensive chemotherapy received venetoclax (600mg) and low-dose cytarabine. Twenty-one percent of patients achieved a complete remission. The observed duration of response was 6 months (range 0, 25). The observed time in remission is the time from start of CR to the time of data cut-off date or relapse from CR.	The endpoint of CR and the durability of responses support effectiveness in patients who are age ≥ 75 or have comorbidities that preclude the use of intensive chemotherapy. The addition of venetoclax with any of these backbone therapies (azacitidine, decitabine, low dose cytarabine) appears to show an

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In Study M14-385, a single-arm trial, venetoclax (400 mg) was administered in combination with azacitidine to 67 patients and in combination with decitabine to 13 patients. The complete remission rate was 37% for patients who received venetoclax and azacitidine and 54% in patients who receive venetoclax and decitabine. The observed duration of response in the azacitidine group was 5.5 months (0, 30) and in the decitabine group was 4.7 (1,18). The observed time in remission is the time from start of CR to the time of data cut-off date or relapse from CR.	improvement in CR rates that is not attributable to either agent alone.
Risk and Risk Management	• Common adverse reactions included (>30%) in combination with azacitidine, decitabine, or low dose cytarabine were nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, peripheral edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, back pain, myalgia, dizziness, cough, oropharyngeal pain, and hypotension. • Frequent serious adverse events included febrile neutropenia, pneumonia, sepsis, and hemorrhage and multi-organ dysfunction, diarrhea, fatigue, cellulitis and localized infections. • TLS was an infrequent event in this population	Adverse reactions can be managed with anti-infectives, G-CSF and transfusions. TLS is an infrequent event and can be mitigated by dose ramp up, prophylaxis and monitoring. Risks of venetoclax in combination therapy with azacitidine, decitabine or low dose cytarabine can be sufficiently addressed through warnings and precautions in the United States Prescribing Information.

1.4. Patient Experience Data

Patient experience data was not submitted as part of the application.

2 Therapeutic Context

2.1. Analysis of Condition

AML is a heterogeneous group of clonal myeloid precursors that include a variety of morphological, immunophenotypic, cytogenetic, and molecular changes[1]. Based on SEER database, AML represents 1.1% of all new cancer cases in the US. An estimated 19,520 cases were reported in 2018 with 10,670 deaths. The 5-year survival rate is 27.4%. AML is more common in men than women and is slightly more common in Whites than other races. AML occurs in all age groups including pediatrics, but is more common in older adults with an overall median age at diagnosis of 68 years[2].

The clinical course of AML varies based on risk stratification by cytogenetics, molecular abnormalities including FLT-3 and MLL, and whether the patient has secondary AML[1]. Of the disease-related factors, cytogenetics is the most important prognostic factor for response and survival, and patients can be stratified into favorable-, intermediate-, or poor-risk categories. In patients with favorable-risk cytogenetics, long-term overall survival approaching 50% can be expected. In contrast, patients with intermediate- or poor-risk cytogenetics have long-term overall survival of approximately 10-20%[3].

In addition to disease-related factors that are prognostic for resistance to current treatment, patient-related factors are strong prognostic indicators in treatment-related early deaths. Patient-related factors include increasing age, comorbidities, and performance status[4]. Patient-related risk factors can prevent the administration of intensive chemotherapy and hematopoietic stem cell transplantation (HSCT) which are potentially curative. Consensus guidelines have been published to define patients who should not receive intensive chemotherapy based on age or fragility[5]. Using an age of ≥75 or younger patients with comorbidities that preclude the use of intensive chemotherapy regimens, this represents approximately half of patients diagnosed with AML[6-8].

Due to infiltration of the bone marrow by leukemic cells, AML is complicated by myelosuppression, and as a result, infection is a major cause of death in patients with AML.

2.2. Analysis of Current Treatment Options

For patients who should not receive intensive chemotherapy regimens based on age or comorbidities, treatment is limited to non-intensive chemotherapy regimens or best supportive care including transfusion support, antibiotics, and cytoreduction. NCCN guidelines suggest lower-intensity therapy with hypomethylating agents (HMA), preferred or low-dose cytarabine. Other potential therapies include gemtuzumab ozogamicin for CD33-positive AML, enasidenib for IDH2-mutated AML, and ivosidenib for IDH1-mutated AML[9]. CD33 expression is near-ubiquitous in AML[10] and for the purposes of available treatment options, will be considered for the general population. IDH1- and IDH2-mutated AML are infrequent[11] and are not

considered available therapy for the general AML population.

The currently available HMAs, azacitidine and decitabine, are approved for use in patients with myelodysplastic syndrome (MDS), but not for the treatment of AML. In published reports, azacitidine and decitabine failed to show a survival advantage over conventional care regimens[12, 13]. Low-dose cytarabine (LDAC) is a reported as a frequent conventional care regimen. See Table 1 for reported efficacy for these treatments.

Gemtuzumab ozogamicin (GO) recently received FDA-approval as monotherapy or in combination with chemotherapy for patients with newly-diagnosed or relapsed or refractory CD33-positive AML. For the treatment of newly-diagnosed CD33-positive AML in patients with comorbidities that preclude the use of intensive chemotherapy regimens, GO was approved based on an overall survival advantage over best supportive care; see Table 1 for reported efficacy results.

As noted, patients who should not receive intensive chemotherapy due to age or comorbidities represent a large portion of patients with AML. As such, the limited available effective non-intensive therapies represent a significant unmet medical need.

Biologic rationale and pre-clinical information supports the use of venetoclax in combination with an HMA or cytarabine, which cause DNA damage. AML cells overexpress both BCL-2 and MCL-1 which are anti-apoptotic proteins that sequester the pro-apoptotic proteins such as BIM and BAX. Venetoclax inhibits BCL-2 and releases the pro-apoptotic proteins. In the absence of additional treatment, BIM can be taken up by the overexpressed MCL-1, decreasing the pro-apoptotic activity. If MCL-1 is inhibited by DNA damaging agents, such as hypomethylating agents or cytarabine, then BIM is also released to promote pro-apoptotic activity. Apoptosis is therefore restored to the malignant AML cells leading to cell death[14, 15].

Table 1: Summary of available therapy for front-line AML who are not candidates for intensive chemotherapy

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Gemtuzumab ozogamicin	For the treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults.	2000	Induction cycle: 6 mg/m^2 as a single agent on Day 1, and 3 mg/m^2 on Day 8. Continuation: 2 mg/m^2 on Day 1 every 4 weeks. 1 cycle of induction followed by up to 8 cycles of continuation	GO vs. BSC: Median OS 4.9 mo vs. 3.6 mo HR 0.69 (95% CI: 0.53-0.90) Response rates not reported in the PI CR+CRi:27% (95% CI: 19-36%) CR: 15% (95% CI: 9-23%)	GO has a boxed warning for hepatoxicity including vaso-occlusive disease. W&P include infusion related reactions, hemorrhage, and embryo-fetal toxicity.	In the frontline setting, GO is approved for use as a single-agent with efficacy results reported in the prescribing information and published in Amadori, et al, 2016[16]. GO is also approved in combination with daunorubicin and cytarabine which would not be appropriate for the proposed population.
Other Treatments						
Azacitidine	n/a	2004	75 mg/m2, SC, days 1-7, every 4 weeks	N=241 CR: 19.5% (95% CI: 15, 25) CR+CRi: 27.8% (95% CI: 22, 34) Duration CR+CRi: 10.4 mo (range 7.2-15.2) Median OS: 10.4 mo	Azacitidine has W&P for anemia, neutropenia, and thrombocytopenia.	Efficacy of azacitidine in frontline AML is based on a phase 3 trial of azacitidine vs. conventional care regimens (CCR) published in Dombret, et al, 2015[12]. CCR included BSC, LDAC, or standard induction chemotherapy. The study was conducted October 2010 to January 2014.

Decitabine	n/a	2006	20 mg/m2, IV, days 1-5, every 4 weeks	N=242 CR: 15.7% (95% CI: 11, 21) CR+CRi: 25.6% (95% CI: 20, 32) Median OS: 7.7 mo	Decitabine has W&P for neutropenia, thrombocytopenia, and embryo-fetal toxicity.	Efficacy of decitabine in frontline AML is based on a phase 3 trial of decitabine vs. treatment choice of best supportive care or LDAC, published in Kantarjian, et al, 2012[13]. The study was conducted January 2006 to April 2009.
Low-dose cytarabine	In combination with other approved anticancer drugs is indicated for remission induction in acute non-lymphocytic leukemia of adults and children	1969	20 mg/m2, SC, days 1-10, every 4 weeks	N=215 CR: 7.9% (95% CI: 5, 12) CR+CRi: 10.7% (95% CI: 7, 16) Median OS: 5.0 mo	Cytarabine causes myelosuppression, liver toxicity, nausea, vomiting.	The approval for cytarabine does not have approval as a single agent or dosing information that would be appropriate for use in the proposed population. Efficacy of LDAC in patients with frontline AML was reported in the Kantarjian, et al, 2012[13] as the control arm of the phase 3 trial of decitabine vs. treatment choice.

Abbreviations: BSC=best supportive care, CCR=conventional care regimens, GO=gemtuzumab ozogamicin, PI=prescribing information, W&P=warnings and precautions

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Venetoclax received accelerated approval on April 11, 2016, 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.

On June 8, 2018, venetoclax received regular approval for CLL with 17p deletion. The indication was expanded to include CLL and small lymphocytic leukemia (SLL) with or without 17p deletion, including use of venetoclax in combination with rituximab.

3.2. Summary of Presubmission/Submission Regulatory Activity

The trials for the treatment of patients with AML were conducted under IND 110159, which was opened in the US on November 28, 2010.

FDA granted Orphan Drug Designation (Designation #15-5068) to AbbVie on February 4, 2016, for venetoclax for the treatment of AML.

On January 25, 2016, FDA granted breakthrough therapy designation (BTD) to venetoclax combination with a HMA in patients with newly diagnosed acute myeloid leukemia (AML) ineligible for intensive chemotherapy.

On May 17, 2016 and December 9, 2016, Type B meetings were held to discuss the initial phase 1/2 results of venetoclax in combination with azacitidine. The Agency recommended that the Sponsor clearly define the patient population who are “ineligible” for intensive chemotherapy based on patient comorbidities. The Agency also provided feedback on the design and endpoints of the phase 3 trial of venetoclax with azacitidine versus azacitidine alone.

On December 9, 2016, a Type B End-of-Phase 2 (EOP2) meeting was held and the Agency agreed with the Sponsor’s proposed definition of the patient population “ineligible” or “unfit” for intensive chemotherapy based on patient comorbidities. The Agency also provided feedback on the design and endpoints of the phase 3 trial of venetoclax with LDAC versus LDAC alone.

On July 21, 2017, FDA granted BTD to venetoclax combination with LDAC in patients with newly diagnosed acute myeloid leukemia (AML) ineligible for intensive chemotherapy.

On November 16, 2017, a Type B meeting was held to discuss the phase 1/2 results of venetoclax in combination with LDAC. The Agency suggested that the Sponsor should consider evaluation of CR and duration of CR as potential basis for efficacy in AML. The Agency also suggested that the Sponsor evaluation rates of CRh, transfusion independence, hospitalization

rates, and infections as supportive evidence of clinical benefit.

Additional meetings were held from February 15, 2018 to April 23, 2018 to discuss the planned submission of this efficacy supplement for the treatment of patients with newly-diagnosed AML.

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

4.1. Office of Scientific Investigations (OSI)

For the venetoclax clinical program for AML, two clinical sites were selected for inspection. Site 50868 (Daniel Pollyea, University of Colorado, Denver, CO) was the highest enrolling site for Study M14-358 with 34 patients enrolled. Site 50863 (Jing-Zhou Hou, University of Pittsburgh, Pittsburgh, PA) was the highest enrolling U.S site for Study M14-387 with 16 patients enrolled.

The regulatory classification for Dr. Pollyea was No Action Indicated (NAI).

The regulatory classification for Dr. Hou was Voluntary Action Indicated (VAI) and a 483 was issued. The main concerns revealed by the OSI inspection that could influence the response rates reported for patients enrolled at that site were errors in reporting bone marrow blast counts in the case report forms (CRFs), errors in reporting neutrophil or platelet counts in the CRFs, and failure to report concomitant medications that affect venetoclax exposure. This lead to errors in assigning response categories.

Eight patients enrolled at Dr. Hou's site had errors that could lead to a change in best response categorization. For 5 cases, the mis-categorization would be detected by review of the provided datasets. For 3 cases, transcription errors would not have been detected by review of the datasets or the case report forms, and those cases are summarized below:

Patient (b) (6): For the (b) (6) response assessment, the pathology report showed bone marrow blasts of 6%, but the investigator reported the bone marrow blasts as <5% (1%) in the CRF. The response category on this date was recorded as MLFS which is not correct with a bone marrow blasts ≥5%. Overall, this patient has a best response of MLFS, so the error did not change the response rate.

Patient (b) (6): For the (b) (6) baseline criteria, the pathology report showed bone marrow blasts of 73.7%, but the investigator reported the bone marrow blasts as <5% in the CRF. On the same date, platelet count was 123,000, but was reported as <100,000 in the CRF. This was the baseline assessment for the patient, so it did not affect response categorization. The patient had a best response of CRi.

Patient (b) (6): For the (b) (6) response assessment, the pathology report showed that the sample was inadequate for interpretation, but the investigator reported and IWG response of CR. The response categorization was incorrect due to unknown marrow morphology, and this was the date of the patient's best response of CR. The investigator's response to the inspection stated that this patient was categorized as CR due to flow cytometry results on the same specimen that reported a CD34+ cell count <0.1%. The investigator also states that the results

from (b) (6), prior to the results in question, showed a bone marrow blast count of 1.3% and a normal neutrophil and platelet count. It is unclear why 5/26/17 was not recorded as the patient's best response of CR if that is accurate.

Reviewer comment: The OSI investigation revealed errors at site 50863 that had a potential to impact the overall response rate and duration of response for Study M14-387. All errors were reviewed, and the response rates for the study were not impacted.

4.2. Product Quality

No changes to the venetoclax drug substance or drug product were submitted with this application.

4.3. Devices and Companion Diagnostic Issues

No device or companion diagnostic is needed for the safe use of venetoclax for the proposed indication.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Pharmacology/Toxicology data for venetoclax supporting the approval and labeling of venetoclax was reviewed under NDA 208573. The venetoclax prescribing information (label) contains the relevant nonclinical data needed for prescribing. For the current supplement to NDA 208573, additional information regarding lactation and pediatric use was added to the venetoclax label. To support the addition of this data to the label, data from placental and lacteal transfer, metabolite profiles of radioactive [^{14}C]-venetoclax in milk and plasma in rats and repeat dose reproductive developmental toxicity study in juvenile mice were reviewed.

Venetoclax demonstrated cell killing against patient-derived tumor cells treated ex vivo, killing AML cells with a median IC_{50} of 10 to 20 nM. Given as a single-agent, venetoclax inhibits subcutaneous xenograft growth of human tumor cell lines derived from AML (MOLM-13).

Lactating and pregnant rats were administered a single oral dose of [^{14}C]-venetoclax at 150 mg/kg. The plasma:milk exposure ratio was 1.6 following single dose administration. The tissue distribution of [^{14}C]-venetoclax-derived radioactivity was distributed fetal liver and fetal gastrointestinal tract in pregnant rats confirming placental transfer. In the metabolite profile of [^{14}C]-venetoclax in lactating rats, venetoclax was the only major component observed in the rat milk and plasma. Trace amounts of minor metabolites including M6, M10 and M14 in milk, and M2, M5 and M6 in plasma were detected.

To evaluate the effects of venetoclax on the development of mice, a repeat dose toxicity study with 12-weeks recovery period was conducted in ICR mice. Venetoclax was administered by daily oral gavage starting from Postnatal Day (PND) 7 to PND 60 at the doses of 0, 10, 30, or 100 mg/kg/day. The toxicities observed in this study were similar to the toxicities observed in the general toxicology studies. The toxicities included reversible decreases in lymphocyte counts at ≥10 mg/kg/day correlating with decreased lymphoid cellularity in the spleen and/or lymph nodes at ≥ 30 mg/kg/day. There were no venetoclax-related effects on food consumption, physical development (vaginal opening or preputial separation) or behavioral assessments.

5.2. Referenced NDAs, BLAs, DMFs

NDA 208573

5.3. Pharmacology

Not applicable.

5.4. ADME/PK

Study Title: Placental Transfer, Lacteal Excretion, and Tissue Distribution of Radioactivity in Pregnant Female Sprague Dawley Rats After Oral Administration of [^{14}C]-ABT-199.

Key Findings:

- When venetoclax was administered to lactating rats (single dose; 150 mg/kg oral), the plasma:milk exposure ratio was 1.6.
- [^{14}C]-venetoclax -derived radioactivity was present in milk for 48 hours postdose following single dose in lactating rats and declined below measurable levels by 72 hours postdose.
- The tissue distribution of [^{14}C]-venetoclax -derived radioactivity was distributed fetal liver and fetal gastrointestinal tract in pregnant rats.
- Maternal exposure (AUC) in plasma was approximately 14 times higher than human exposure at the recommended 400 mg dose.

Methods

Doses:	0 and 150 mg/kg
Frequency of dosing:	Single dose
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Polyethylene glycol 400:Cremophor EL:oleic acid (10:10:80 w:w:w)
Species/Strain:	Female Sprague-Dawley Rats (lactating and pregnant female Sprague Dawley rats)
Number/Sex/Group:	Females: 1 in group 1 control, 27 in group 2 lactating rats at 150 mg/kg and 9 in group 3 pregnant rats

Study design

Group	Number of Female SD Rats	Dose Route	Target Dose Level (mg/kg)	Target Dose Volume (mL/kg)	Samples Collected
1[a]	1	Oral	0	10	Control Blood, Plasma, and Milk
2[b]	27	Oral	150	10	Blood, Plasma, and Milk
3[c]	9	Oral	150	10	Blood, Plasma, and Carcasses for QWBA

[a] Group 1 was a control group and was administered vehicle only at 8 to 12 days after parturition. Samples were collected prior to dosing Groups 2 and 3 and were used for matrix background subtraction.
[b] Group 2 was dosed at 8 to 10 days after parturition.
[c] Group 3 was dosed at Gestation Day 18.

Table 2: Pharmacokinetic parameters for radioactivity in maternal blood, milk, and plasma from lactating rats (Group 2, 150 mg/kg)

Matrix	T_{max} (hours)	C_{max} (ng eq/g)	$t_{½}$ (hours)	AUC_{0-t} (ng eq·hours/g)	$AUC_{0-\infty}$ (ng eq·hours/g)
Blood	8	4890	NC	160000	NC
Milk	12	5420	NC	163000	NC
Plasma	24	7860	NC	259000	NC

eq Equivalents ^{14}C-ABT-199.
NC Not calculated. The $t_{1/2}$ and $AUC_{0-\infty}$ values could not be determined because a definitive elimination phase was not discernible.

Placental Transfer

- Radioactivity was detected in the fetal liver at 12 through 72 hours postdose, the fetal gastrointestinal tract at 48 and 72 hours postdose, and the whole fetus at 48 hours postdose.
- Radioactivity was measurable in the amniotic sac, mammary gland, ovary, and uterus from 8 to 72 hours postdose.
- All other fetal tissues examined, including fetal blood, brain, eye, heart, kidney, lung, muscle and spinal cord were devoid of radioactivity throughout the course of this study.

Table 3: Pharmacokinetic parameters for radioactivity in maternal blood and plasma collected from pregnant female rats (Group 3, 150 mg/kg)

Matrix	T_{max} (hours)	C_{max} (ng eq/g)	$t_{½}$ (hours)	AUC_{0-t} (ng eq·hours/g)	$AUC_{0-\infty}$ (ng eq·hours/g)
Blood	24	8190	NC	294000	NC
Plasma	24	12700	NC	448000	NC

eq Equivalents ^{14}C-ABT-199.
NC Not calculated. The $t_{1/2}$ and $AUC_{0-\infty}$ values could not be determined because a definitive elimination phase was not discernible.

Study Title: Metabolite Profiles of [^{14}C]-A-1195425 ([^{14}C]-ABT-199, [^{14}C]-venetoclax) in Milk and Plasma after a 150 mg/kg Oral Dose in Lactating Female Sprague-Dawley Rats (study number: R&D/16/0673)

Key findings:

- The radiochemical profile demonstrated that [^{14}C]-venetoclax was the only major component observed from the rat milk and plasma.

- Trace amounts of minor metabolites including M6, M10 and M14 in milk, and M2, M5 and M6 in plasma were detected by LC/MS.

Lactating female Sprague-Dawley rats received a single oral dose of [^{14}C]-A-1195425 formulated in polyethylene glycol 400 (PEG-400), Cremophor El and oleic acid at 150 mg/kg and approximately 200 µCi/kg in a dose volume of 10 mL/kg. pooled milk (0-48 hour) and plasma (0-48 hour) samples were analyzed by HPLC-MS/MS and radio analysis.

Figure 1: The representative HPLC-radiochromatograms of pooled milk (0- 48 hour) following a single 150 mg/kg oral dose of [^{14}C]-venetoclax to lactating female rats.

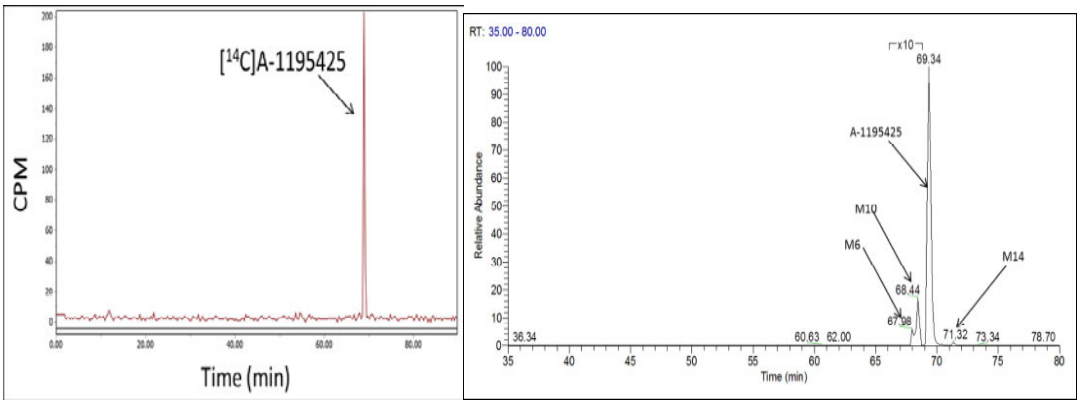
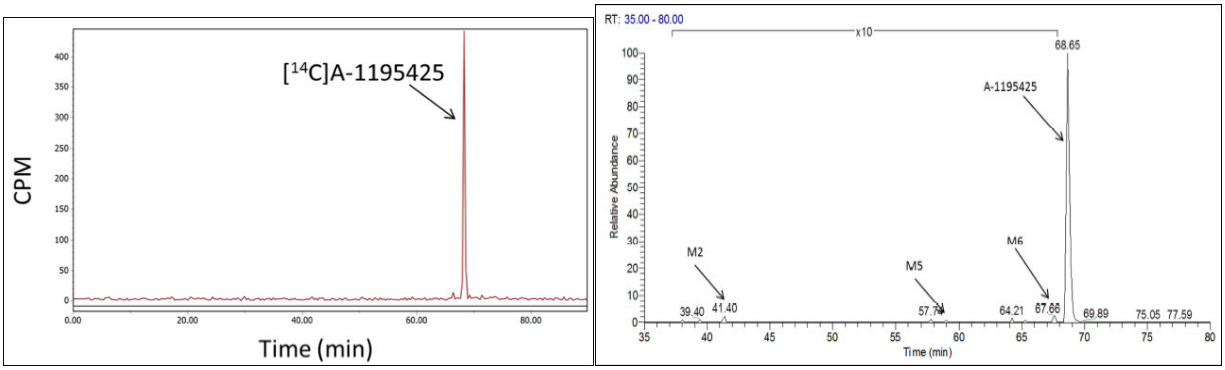


Figure 2: The representative HPLC-radiochromatograms of pooled plasma (0-48 hour) following a single 150 mg/kg oral dose of [^{14}C]-venetoclax to lactating female rats



5.5. Toxicology

5.5.1. General Toxicology

No new studies submitted.

5.5.2. Genetic Toxicology

No new studies submitted.

5.5.3. Carcinogenicity

No studies submitted.

5.5.4. Reproductive and Developmental Toxicology

The objectives of this study were to determine the potential effects of venetoclax (A-1195425) on the development of the juvenile mouse, and to evaluate the potential reversibility of any findings.

Study title: A 8 Week Study of A-1195425 Free Form (b) (4) by Oral Gavage in the Mouse with a 12 Week Recovery Period

Study no.:	R&D/16/0922
Study report location:	4.2.3.5.4.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 13, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ABT-199 (b) (4), ABT-199 or A-1195425.0, lot# 97059-1, purity 117.3 mg A-1195425.0/g (b) (4) (assigned chemical potency)

A correction factor of 8.53 was used in formulations.

Key Study Findings.

- Mortality was observed in reference item and venetoclax groups were euthanized or found dead in the pre-weaning period due to gavage accident. Mortality at high dose (10/134) were attributed to test article related.
- There were no adverse developmental effects
- There were no new toxicities observed in the juvenile mice sacrificed on Postnatal Day 61 compared to adult mice in repeat dose toxicology studies up to 26- weeks duration (toxicities effecting lymphoid organs and red-cell mass).

Methods	
Doses:	0, 10, 30, and 100 mg/kg/day
Frequency of dosing:	Daily from postnatal Day (PND) 7 to 60
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Reference item; Placebo (b) (4) ((b) (4) Copovidone and (b) (4) Polysorbate 80 [w/w]), in sterile water for injection, USP
Species/Strain:	Crl:CD1(ICR) mice
Number/Sex/Group:	15 for main and 10 for recovery

Study design: (See table below)

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	A-1195425 Concentration[a] (mg/mL)	Number of Animals[b]			
					Main Study Subset A		Recovery Study Subset B	
					Males	Females	Males	Females
1	Reference Item	0	10	0	15 (1)	15 (1)	10 (2)	10 (2)
2	A-1195425	10	10	1	15 (1)	15 (1)	10 (2)	10 (2)
3	A-1195425	30	10	3	15 (1)	15 (1)	10 (2)	10 (2)
4	A-1195425	100	10	10	15 (1)	15 (1)	10 (2)	10 (2)

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	A-1195425 Concentration[a] (mg/mL)	Number of Animals[b]			
					Behavior Subset C		Toxicokinetic Study Subsets D and E	
					Males	Females	Males	Females
1	Reference Item	0	10	0	15 (1)	15 (1)	3 (1) + 3(1)	3 (1) + 3(1)
2	A-1195425	10	10	1	15 (1)	15 (1)	9 (1) + 18 (1)	9 (1) + 18 (1)
3	A-1195425	30	10	3	15 (1)	15 (1)	9 (1) + 18 (1)	9 (1) + 18 (1)
4	A-1195425	100	10	10	15 (1)	15 (1)	9 (1) + 18 (1)	9 (1) + 18 (1)

[a] The Test Item A-1195425, suspended in Sterile Water for Injection (SWFI), USP; assigned chemical potency = 117.3 mg A-1195425.0/gram (b) (4).

[b] Numbers listed in parentheses indicate the targeted number of dosed spare animals. Dose spares were used as replacements in any subset where they were required. These animals were retained until weaning, at which time animals were euthanized without further examination.

Observations: clinical signs, body weights, food consumption, physical development, behavioral assessments, clinical pathology, whole blood and brain venetoclax concentrations, peripheral blood lymphocyte immunophenotyping, organ weights, bone measurements and histopathologic examinations.

Mortality

- There were 40 unscheduled deaths in animals at all dose groups during of the study.
- Thirty-two mice were found dead or euthanized in the pre-weaning period (PND7-PND21), and 8 mice were found dead or euthanized post-weaning (≥ PND 22) as summarized in the Table below.
- Most of the deaths or unscheduled euthanasia were attributed to gavage accidents based on the macroscopic results: pale material in the thorax with or without esophagus perforation; and rarely: pale frothy material in the trachea, uncollapsed lungs, or pulmonary mass.
- The incidence of mortality noted at 100 mg/kg/day during the pre-weaning and post weaning (10/134) periods was above the historical data range and was therefore attributed to venetoclax.

Table 4: **Summary mortality/cause of death pre-weaning period**

Cause of Death		
	Gavage accident	**Undetermined**
Group No.	**Animal No.**	**Animal No.**
1/Reference Item	1528, 1563	1577
2/10-mg/kg/day	2513, 2547	2626
3/30-mg/kg/day	3571, 3572, 3573, 3578, 3612, 3615, 3617, 3621, 3627, 3635, 3638, 3641	3513, 3593
4/100-mg/kg/day	4603, 4627, 4632, 4645, 4647	4527, 4562, 4571, 4591, 4594, 4602, 4623

Table 5: Summary mortality/cause of death post-weaning period

Cause of Death		
	Gavage accident	Undetermined/Other
Group No.	Animal No.	Animal No.
1/Reference Item	-	-
2/10-mg/kg/day	-	2514
3/30-mg/kg/day	3038	3017
4/100-mg/kg/day	4029, 4540	4006, 4019, 4541

Most of the deaths or unscheduled euthanasia were attributed to gavage accidents based on the macroscopic results.

Clinical Signs

30 and 100 mg/kg: Clinical signs included decreased activity, skin pallor, increased incidence of abdominal distension, dehydration, hunched posture and brown fur staining.

Table 6: Summary of clinical observations: F1 generation pups

Total Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals (main, behavior, recovery)	**M:40**	**F:40**	**M:40**	**F:40**	**M:40**	**F:40**	**M:40**	**F:40**
Number Died or Euthanized Moribund	1	2	1	2	8	6	8	4
Decreased activity	0/0	0/0	0/0	0/0	3/0	2/1	6/1	10/11
Abdominal distension	3/0	0/1	3/3	1/1	8/5	10/2	21/12	27/17
Dehydration	2/0	4/0	5/0	9/0	16/1	21/1	38/6	39/11
Skin pallor	0/0	0/0	0/0	0/0	18/8	17/6	39/24	40/28
Hunched posture	2/1	3/0	4/3	2/2	7/2	12/1	17/2	22/4
Fur staining brown	0/0	1/0	0/0	0/0	1/0	1/0	17/0	13/0

Body Weight

Table 7: Summary of pup body weights (g): F1 generation pups

Total Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals (main, behavior, recovery)	**M:40**	**F:40**	**M:40**	**F:40**	**M:40**	**F:40**	**M:40**	**F:40**
Body Weight Change (%[a]) – PND 7-21	8.6 g	7.9g	+2	+1	-3	-1	-22***	-19***
Body Weight Change (%[a]) – PND 21-56	24.0 g	16.1 g	-3	-4	0	-5	-2	-2
Body Weight Change (%[a]) - PND 63 to 147	9.2 g	8.8 g	-22	-20	+20	-9	+19	-9

[a]For controls, group means are shown. For treated groups, percent differences from controls are shown.

Food Consumption
Unremarkable

Vaginal opening and preputial separation

Table 8: Summary of vaginal opening: F1 generation adults

Total Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**M:10**	**F:10**	**M:10**	**F:10**	**M:9**	**F:10**	**M:9**	**F:10**
Preputial separation (PND)	26.2	-	26.5	-	26.1	-	27.6	-
Vaginal opening (PND)	-	25.9	-	24.8	-	24.7	-	28.0

Functional Observation Battery
Motor Activity- unremarkable
Auditory Startle Habituation - unremarkable
Biel Water Maze- unremarkable

Hematology

Table 9: Venetoclax-related changes in hematology parameters at the end of dosing*

Total Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**M:8**	**F:8**	**M:8**	**F:8**	**M:7**	**F:7**	**M:6**	**F:8**
Hematology – PND 61								
White blood cell (10^3/µL)	5.303	3.943	-38	-33	-54	-59*	-49	59
RBC (10^6/µL)	8.989	8.825	-1	-1	-6	-4	-1	-3
HGB (g/dL)	14.2	14.06	-4	-1	-8	-5	-9	11
HCT (%)	45.38	45.3	-1	-3	-5	-5	-7	10
MCV (fL)	50.49	51.6	0	-2	+1	-2	-6	-7
MCH (pg)	15.83	15.94	-3	0	-3	-2	-8	-7
RDW	12.4	13.13	+2	0	+9	+7	+14	+11
PLT (10^3/µL)	1222.1	958.6	-2	+5	+1	+6	-15	+20

* Unremarkable on PND151
Dash (-) indicates absence of change in group.
Numerical values indicate percent difference of mean Day 61 values relative to mean respective control value.
Values in bold are statistically significant from control group mean.

Clinical Chemistry

Table 10: Venetoclax-related changes in clinical chemistry parameters

Total Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**M:7**	**F:7**	**M:7**	**F:6**	**M:7**	**F:7**	**M:7**	**F:7**
PND 61								
Glucose (mg/dL)	188.9	169.0	+1	+35	+8	+24	+25	+24
Number of Animals	M:5	F:5	M:4	F:5	M:4	F:5	M:4	F:5
PND 151								
Glucose (mg/dL)	209.4	174.0	-13	+19	-2	+7	0	+14

Immunophenotyping

Table 11: Summary of phenotyping in blood values: F1 generation adults

Total Daily Dose (mg/kg/day)	0 (Control)		10		30		100	
Number of Animals	M:14	F:15	M:15	F:15	M:13	F:13	M:10	F:14
PND 61[a]								

Total T Lymphocytes (cells/µl)	2152	2430	796**	842**	751**	795**	557**	567**
Helper T Lymphocytes (cells/µl)	1491	1733	629**	667**	599**	650**	454**	471**
Cytotoxic T Lymphocytes (cells/µl)	635	651	162**	172**	137**	137**	92**	86**
B Lymphocytes (cells/µl)	3240	3025	1510***	990**	1253**	1000**	815**	652**
PND 151[a]								
Total T Lymphocytes (cells/µl)	970	1328	1088	1423	1101	1092	886	993
Helper T Lymphocytes (cells/µl)	673	953	754	1099.9	724	750	688	736
Cytotoxic T Lymphocytes (cells/µl)	270	323	314	281	357	300	181	236
B Lymphocytes (cells/µl)	934	1581	2190	1585	1436	1544	1704	1646

[a]. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
* $p \leq 0.05$; ** $p \leq 0.001$; *** $p \leq 0.01$

Organ Weights
Unremarkable-PND61/PND151

Bone Measurements
Unremarkable-PND61/PND151

Gross Pathology
Unremarkable-PND61/PND151

Histopathology

Table 12: Summary of microscopic findings – scheduled euthanasia (PND 61)

Total Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**100**	
Number of Animals	**M:15**	**F:15**	**M:15**	**F:14**	**M:14**	**F:15**	**M:13**	**F:15**
PND 61								
Spleen								
Minimal decreased cellularity; lymphoid	0	0	0	0	3	3	4	7
Minimal increased hematopoiesis	0	5	3	6	4	6	4	8
Mild increased hematopoiesis	0	0	0	0	1	1	0	2
Lymph Node, Mesenteric								
Minimal decreased cellularity, lymphoid	0	0	0	0	0	0	3	5
PND151	-	-	-	-	-	-	-	-

Toxicokinetics

- The exposure (whole blood AUCs) on PND 7 nd PND 60 (4.17, 13.0 and 25.2 µg•hr/mL in the low, mid and high dose groups, respectively) were approximately proportional to dose.
- On PND 7, brain AUC exposure to venetoclax was approximately proportional to dose. There were no measurable levels of venetoclax in the brain on PND 60.
- There were no sex-related differences in venetoclax exposure on PND 7 or PND 60.

Table 13: Toxicokinetic profile of venetoclax in juvenile mice

Total Daily Dose (mg/kg/day)	0 (Control)		10		30		100	
Toxicokinetics								
Whole Blood PND 7								
Number of Animals	M:3	F:3	M:18	F:18	M:18	F:18	M:18	F:18
C_{max} (µg/mL)	ND	ND	3.52	3.26	11.5	7.18	11.4	12.0
$AUC_{0\text{-}24hr}$ (µg•hr/mL)	ND	ND	46.9	45.7	124	111	169	178
Whole Blood PND 60								
Number of Animals	M:3	F:3	M:9	F:9	M:9	F:9	M:9	F:9
C_{max} (µg/mL)	ND	ND	0.801	0.619	1.71	1.75	4.32	2.97
AUC (µg•hr/mL)	ND	ND	4.88	3.47	14.4	11.6	26.6	23.1
Brain PND 7								
Number of Animals	M:3	F:3	M:18	F:18	M:18	F:18	M:18	F:18
C_{max} (µg/gram brain tissue)	ND	ND	1.17	1.65	3.61	4.30	8.74	10.6
$AUC_{0\text{-}24hr}$ (µg•hr/gram brain tissue)	ND	ND	19.6	23.1	67.0	72.1	169	181
Brain PND 60								
Number of Animals	M:3	F:3	M:9	F:9	M:9	F:9	M:9	F:8
C_{max} (µg/gram brain tissue)	ND	ND	ND	ND	ND	ND	ND	ND
$AUC_{0\text{-}24hr}$ (µg•hr/gram brain tissue)	ND	ND	ND	ND	ND	ND	ND	ND

M = Male; F= Female; ND = Not detectable (LLOQ = 0.00495 µg/mL); PND = Postnatal day

5.5.5. Other Toxicology Studies

No new studies submitted

6 Clinical Pharmacology

6.1. Executive Summary

The applicant submitted this efficacy supplement to seek the approval of venetoclax in combination with a hypomethylating agent (HMA) (azacitidine or decitabine) or low-dose cytarabine (LDAC) for the treatment of newly diagnosed patients with AML who are ineligible for intensive chemotherapy.

Clinical pharmacokinetics (PK) analyses indicated that PK exposure of venetoclax as a monotherapy (Study M14-212) or in combination with a HMA (Study M14-358) or LDAC (Study M14-387) in patients with AML were within the range of that observed in patients with CLL/SLL or NHL. There was no significant drug-drug interaction (DDI) between venetoclax and the combination agents azacitidine, decitabine or cytarabine.

In patients who were ineligible for intensive chemotherapy, after the initial venetoclax dose ramp-up, the combination of venetoclax 400 mg daily (QD) and azacitidine or decitabine achieved rates of CR + CRi of 70.2% and 74.2% respectively. The combination of venetoclax 600 mg QD and LDAC achieved rates of CR + CRi of 53.7%. These responses were also associated with increased durable of response (DOR) and overall survival (OS).

Clinical pharmacology exposure-response (E-R) analyses for efficacy and safety further support the recommended dose of venetoclax in combination with a HMA or LDAC in this patient population.

In Study M14-358, exposure-efficacy analyses indicated that venetoclax dose of 400 mg QD maximizes the probability a complete remission (CR) with either azacitidine or decitabine as backbone therapies. No significant relationship between venetoclax exposure and occurrence of Grade ≥3 neutropenia or any Serious Treatment-Emergent Adverse Events (STEAE) were observed. However, treatment-emergent Grade ≥3 infections were statistically significantly related with venetoclax exposure in combination with HMAs.

In Study M14-387, the response rate from venetoclax in combination with LDAC showed a trend of increase with the increase of venetoclax exposure. Although the predicted probability of response increased with increasing exposure based on the above relationship, the venetoclax dose of 600 mg QD in combination with LDAC was determined to be the MTD due to prolonged thrombocytopenia at the 800 mg QD dose level and dose interruption by 4 of the 5 patients at 800 mg who continued to Cycle 2. The probability of occurrence of adverse events including Grade ≥ 3 neutropenia, Grade ≥ 3 infection, and STEAEs did not show a statistically significant association with venetoclax exposure in combination with LDAC. Therefore, the 600 mg QD dose of venetoclax was recommended for the combination with LDAC in patients with AML.

No events of TLS were reported during the use of venetoclax with HMAs. Only 2 events of laboratory TLS occurred out of 82 patients who received venetoclax 600 mg QD in combination with LDAC. As one of the current TLS risk minimization measures, the venetoclax daily ramp-up to target dose of 400 mg or 600 mg over 3 to 4 days appears acceptable.

There is a significant DDI between venetoclax and posaconazole based on results from Arm C of the Study M14-358. The magnitude of DDI with posaconazole is even higher than that from the another strong CYP3A inhibitor ketoconazole. Therefore, dose reduction of venetoclax during the ramp-up, as well as after the ramp-up to 70 mg QD and 100 mg QD is recommended for concomitant use of posaconazole and ketoconazole, respectively.

Finally, population PK analysis supports the recommendation of no dose adjustment for intrinsic factors including age, sex, race, weight, mild to moderate renal impairment, or mild to moderate hepatic impairment.

In summary, clinical pharmacology analyses support the recommended venetoclax dose regimens in combination with a HMA or LDAC in patients with AML.

Recommendations

The Office of Clinical Pharmacology's Divisions of Clinical Pharmacology V and Pharmacometrics have reviewed the information contained in this supplement of NDA 208573. The NDA Supplement 009 is approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The PK, pharmacodynamics, and E-R relationship for venetoclax were previously reviewed under original NDA 208573 (DARRTS ID 3836843) and efficacy supplements 004 and 005 (DARRTS ID 4274661 & 4274676) for the treatment of patients with CLL/SLL.

The following is a summary of the clinical PK and pharmacology of venetoclax alone and in combination with HMAs or LDAC in patients with AML based on data from Studies M14-212, M14-358 and M14-387 submitted in this efficacy supplement.

- Concentrations of venetoclax alone and in combination with HMAs or LDAC in patients with AML were within the range of that observed in patients with CLL/SLL and NHL
- Steady-state exposure (AUC) of venetoclax in combination were dose-proportional across dose range of 400 to 1200 mg.
- Concomitant administration of HMA (azacitidine or decitabine) or LDAC had no significant effect on venetoclax exposure, and vice versa.
- Concomitant administration of posaconazole 300 mg with venetoclax resulted in significant drug-drug interaction that requires a dose reduction of venetoclax.

- The population PK analysis for venetoclax built upon the a previously developed model showed that:
    - the key parameter estimates and intrinsic or extrinsic covariate effects were comparable to the estimates from the previously developed model, suggesting the similarity of PK between patients with AML and the other patient populations.
    - Intrinsic factors did not have an effect on the venetoclax apparent clearance (CL/F).
    - Administration of strong CYP3A inhibitors resulted in approximately 84% decrease of CL/F, which requires a dose reduction of venetoclax.
    - Coadministration with combination drugs azacitidine, decitabine or LDAC had no significant effect on venetoclax CL/F.
- The E-R analyses for both efficacy and safety support the recommended dosing regimens for venetoclax in combination with HMAs or LDAC.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Venetoclax in combination with a hypomethylating agent: Initiate therapy with VENCLEXTA at 100 mg on Day 1, followed by a daily ramp-up dosing schedule (see Table 14) to the recommended daily dose of 400 mg.

Venetoclax in combination with low dose cytarabine: Initiate therapy with VENCLEXTA at 100 mg on Day 1, followed by a daily ramp-up dosing schedule (see Table 14) to the recommended daily dose of 600 mg.

Table 14: Dosing Schedule for Ramp-up Phase in Patients with AML

	VENCLEXTA Daily Dose	
Day 1	100 mg	
Day 2	200 mg	
Day 3	400 mg	
Days 4 and beyond	400 mg when dosing in combination with a **hypomethylating agent**	600 mg when dosing in combination with **low dose cytarabine**

Therapeutic Individualization

None.

Outstanding Issues

None.

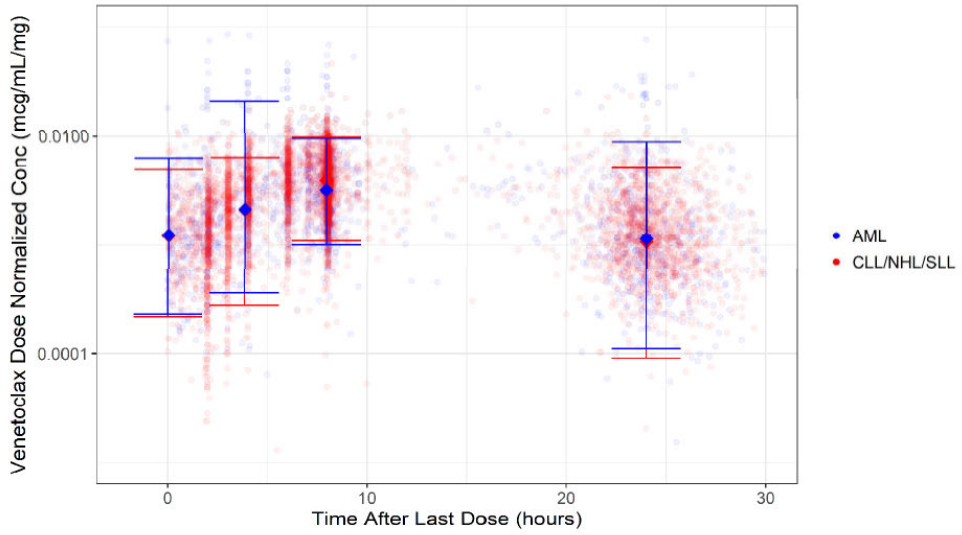
6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Following multiple-dose administrations of 800 mg QD venetoclax monotherapy in 13 patients with AML in Study M14-212, the median Tmax was 6 hours, and the mean Cmax and AUC0-24 were 3.74 µg/mL and 61.6 µg•h/mL, respectively.

Pharmacokinetic data from 314 patients receiving venetoclax doses ranging from 10 mg to 1200 mg QD from the 3 AML studies M14-212, M14-358 and M14-387 were compared to those in other patient populations. As shown in **Figure 3**, after dose-normalization, observed venetoclax concentrations in patients with AML were within the range of those from patients with CLL/SLL or NHL.

Figure 3: Observed Dose-Normalized Venetoclax Concentrations Versus Binned Time After Last Dose



Blue circles represent observed data from AML Trials M14-212, M14-358 and M14-387. Red circles represent observed data from CLL, SLL, NHL subjects from 5 studies included in the legacy population PK model (R&D/15/0256). Closed diamonds and error bars represent median and 5th and 95th percentiles for the binned observed data.

Source: popPK and ER report R&D/18/0339, Table 6

Noncompartmental analyses indicated that exposure of venetoclax was not significantly affected by the coadministration of HMA (azacitidine and decitabine) or LDAC compared to that from venetoclax monotherapy in patients with AML. In contrast, the concomitant use of posaconazole (a strong CYP3A and P-gp inhibitor) 300 mg with venetoclax 50 mg and 100 mg for 7 days resulted in 61% and 86% higher venetoclax Cmax, respectively, compared to

venetoclax 400 mg administered alone. The venetoclax AUC0-24 was 90% and 144% higher, respectively.

Azacitidine and cytarabine mean Cmax and AUCinf were not significantly different after coadministration with multiple doses of venetoclax. Decitabine mean Cmax was not statistically significantly different (P > 0.05) after coadministration with multiple doses of venetoclax. The mean AUCinf of decitabine showed nominally significant differences after coadministration with venetoclax. However, the dose-normalized AUC exposures of decitabine observed in this study are comparable to those reported in literature (Cashen AF et al, Cancer Chemother Pharmacol. 2008;61(5):759-66 2008).

The PK parameter estimates and intrinsic or extrinsic covariate effects from the final population PK model analysis based on data from patients with AML are shown in Table 15.

Table 15: Parameter Estimates and Variability for Venetoclax Pharmacokinetics: Final Model

Parameter	Estimate	%RSE[a]	95% Confidence Interval[b]	Population Estimate in the Legacy Model
	Population Value (θ)			
CL/F (L/day)	456	3.16	428, 484	447
$\theta_{CL/F,\ moderate\ CYP3A\ inhibitor}$	0.911	2.67	0.863, 0.959	0.842
$\theta_{CL/F,\ strong\ CYP3A\ inhibitor}$	0.163	5.07	0.147, 0.179	0.184
$\theta_{CL/F,\ OATP1B3\ inhibitor}$	0.853 (fixed)	--	--	0.853
$\theta_{CL/F,\ RTX}$	1.20	2.93	1.13, 1.27	1.22
V_2/F (L)	115	12.9	86.0, 144	118
$\theta_{V2/F,\ Sex}$[c]	0.728	5.19	0.654, 0.802	0.680
$\theta_{V2/F,\ AML}$[d]	1.84	11.2	1.44, 2.24	1.71
K_a (1/day)	3.75	3.55	3.49, 4.01	3.72
Q/F (L/day)	96.7	5.31	86.6, 107	97.2
V_3/F (L)	120	3.97	111, 129	119
F1[e]	1 (fixed)	--	--	1
Dose nonlinearity[f]	–0.219	1.98	–0.227, –0.211	-0.180
$\theta_{F1,\ fasting}$	0.332	0.952	0.326, 0.338	0.335
$\theta_{F1,\ fed}$[g]	1.13	3.58	1.05, 1.21	1.23
$\theta_{F1,\ moderate\text{-}fat}$	1.24	8.15	1.04, 1.44	1.31
$\theta_{F1,\ high\text{-}fat}$	1.42	1.27	1.38, 1.46	1.43
	Inter-Individual Variability (ω^2)			
CL/F (L/day) (Variance and %CV[h])	0.177 (44.0%)	7.46	0.151, 0.203	0.153 (40.7%)
V_2/F (L) (Variance and %CV[h])	0.209 (48.2%)	5.93	0.185, 0.233	0.205 (47.7%)
F1 (L) (Variance and %CV[h])	0.105 (33.3%)	10.9	0.0827, 0.127	0.0972 (32.0%)
	Residual Variability (σ^2)			
σ_1^2 (Proportional)	0.224	1.47	0.218, 0.230	0.223
σ_2^2 (Additive)	2.95×10^{-7}	39.3	6.76×10^{-8}, 5.22×10^{-7}	3.07×10^{-7}

CL/F = Apparent clearance; V_2/F = Apparent volume of distribution of the central compartment; K_a = First-order absorption rate constant; Q/F = Apparent inter-compartmental clearance; V_3/F = Apparent volume of distribution of the peripheral compartment; F1 = relative bioavailability

a. % Relative Standard Error (RSE) was estimated as the standard error of estimate (SEE) divided by the population estimate multiplied by 100.
b. 95% confidence interval (CI) was approximated as the point estimate ± 1.96 × SEE.
c. Reference Male.
d. Reference healthy volunteers (in the prior).
e. Reference low-fat meal.
f. Reference 400 mg.
g. Relative bioavailability under fed conditions without specification of fat-content.
h. Percent coefficient of variation (%CV) was approximated as $\sqrt{e^{\omega^2}-1} \times 100\%$.

Source: popPK and ER report R&D/18/0339, Table 6

The key parameter estimates and covariate effects from the final model based on data from patients with AML (see **Table 15**) were comparable to the results from the previously developed model of venetoclax in patients with relapsed or refractory CLL/SLL, NHL and healthy patients as shown in **Table 16**, This supports the conclusion that venetoclax PK are similar in healthy subjects, and patients with AML or CLL/SLL/NHL.

Table 16: Difference in parameter estimates between the legacy model and current final model

Parameter	Estimate Prev.	Estimate Final	Diff. Percentage
CL/F (L/day)	447	456	2.013
V2/F (L)	118	115	-2.542
Q/F (L/day)	97.2	96.7	-0.514
V3/F (L/day)	119	120	0.840
KA (1/day)	3.72	3.75	0.806
Fasting on F	0.335	0.332	-0.896
Moderate fat on F	1.31	1.24	-5.344
High fat on F	1.43	1.42	-0.699
Any meal on F	1.23	1.13	-8.130
Dose on F	-0.180	-0.219	21.667
Moderate CYP3A inhibitor on CL/F	0.842	0.911	8.195
Strong CYP3A inhibitor on CL/F	0.184	0.163	-11.413
SEX on V2/F	0.680	0.728	7.059
CLL/NHL/SLL/AML on V2/F	1.71	1.84	7.602
RTX on CL/F	1.22	1.20	-1.639
OATP1B3 inhibitor on CL/F	0.853	0.853	0.000
Inter-Individual Variability on CL/F	0.153	0.177	15.686
Inter-Individual Variability on V2/F	0.205	0.209	1.951
Inter-Individual Variability on F	0.0972	0.105	8.025
Proportional Error	0.223	0.224	0.448
Additive Error	3.07E-07	2.95E-07	-3.909

Source: popPK and ER report R&D/18/0339, Table 13.2_8

Consistent with the previous population PK analysis, the current analysis results indicated that intrinsic covariates of age (19-84 years), body weight (47-126 kg), race (78% White, 13% Black, 9% Asian), sex, hepatic impairment (mild and moderate) and renal impairment (mild and moderate) did not have a clinically significant effect on the venetoclax apparent clearance (CL/F).

Consistent with the noncompartmental analysis results, the population PK results also indicated that coadministration with azacitidine, decitabine or LDAC had no significant effect on the CL/F

of venetoclax. However, coadministration of strong CYP3A inhibitors resulted in approximately 84% decrease of CL/F.

6.3.2. Clinical Pharmacology Questions

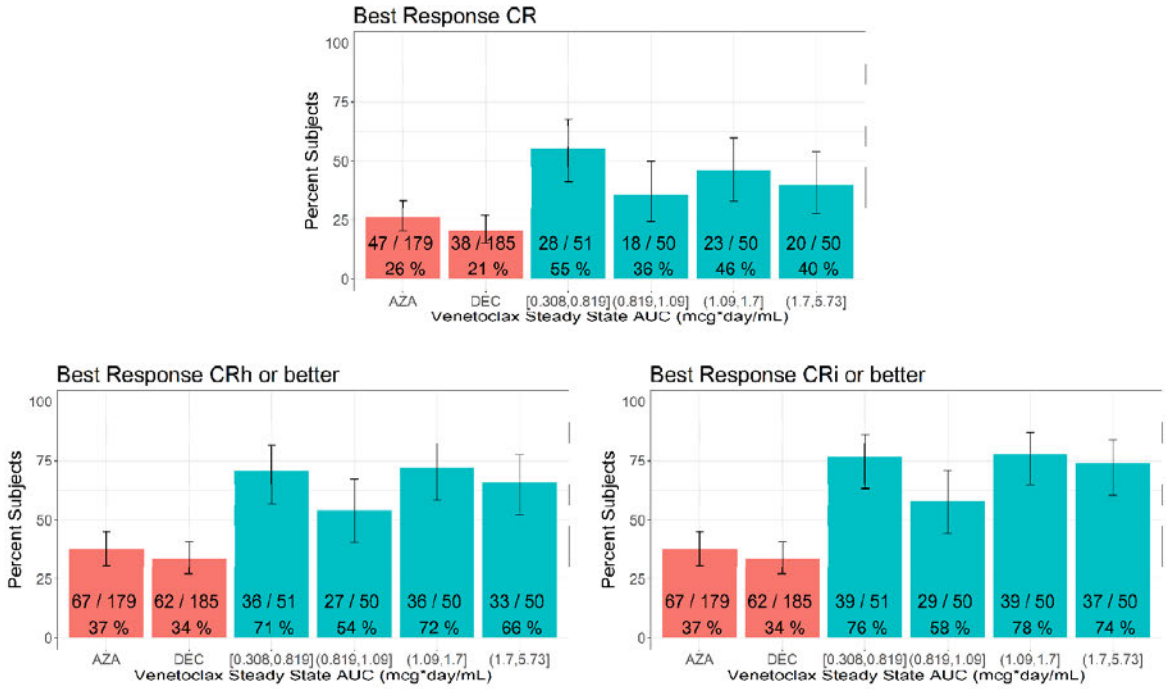
Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The recommended doses of venetoclax to be used in combination with HMAs or LDAC are supported by the following dose-efficacy and exposure-efficacy analyses results.

Venetoclax in Combination with HMAs

In Study M14-358, a total of 201 patients were included in the E-R analysis with venetoclax QD doses of 400 mg (N=121), 800 mg (N=71) and 1200 mg (N=9) in combination with azacitidine or decitabine. As shown in **Figure 4**, the response rates (CR, CR+CRh, or CR+CRh+CRi) of the combination therapy were higher than that of the historical controls with azacitidine or decitabine monotherapy. In addition, there is no trend of increase in the response rate with the increase of venetoclax PK exposure (AUC at steady state, AUCss) stratified by quartiles, suggesting that the maximum efficacy has been achieved at 400 mg QD dose of venetoclax.

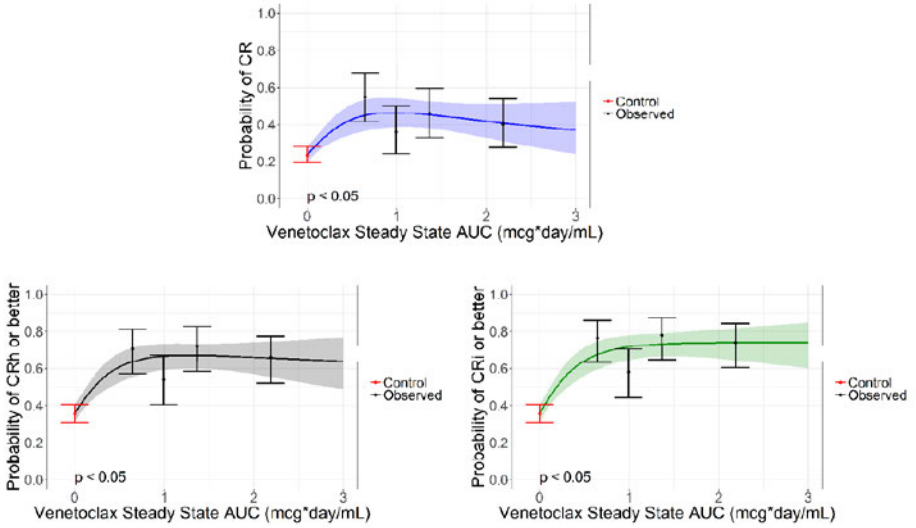
Figure 4: Observed Response Rates and 95% CI for Historical Azacitidine and Decitabine Monotherapy and in Combination with Venetoclax by AUCss Exposure Quartiles



Source: popPK and ER report R&D/18/0339, Figure 12

In line with the observed data, the cumulative logistic regression analysis indicated that the response rate at the recommended venetoclax 400 mg QD (median AUCss = 1.0 µg•day/mL) in combination with HMAs is in the flat region of the E-R curve (**Figure 5**). The effect of azacitidine vs decitabine was tested as a covariate on the slope of the E-R relationship but it did not reach statistical significance (*P > 0.05*). Based on the exposure-response relationships, the predicted probabilities of achieving a CR, CRh or better, CRi or better at venetoclax exposures at 400 mg were not different for either HMA backbone therapies and no remarkable gain in efficacy at higher dose levels of venetoclax in combination with HMAs is expected (see **Table 17**).

Figure 5: Probability of Achieving CR, CRh or Better, CRi or Better Versus AUCss for Patients Receiving Venetoclax in Combination with HMA (Results of Cumulative Logistic Regression Model)



Shaded regions indicate the predicted 95% CI and points with vertical bars indicate the observed proportions with 95% binomial CI at the observed concentration quartile. Points and vertical bars at venetoclax AUC_{ss} = 0 are combined historical rates for azacitidine and decitabine monotherapy.

Source: popPK and ER report R&D/18/0339, Figure 12

Table 17: Predicted Probability of Response for Patients Receiving Venetoclax in Combination with HMA by Venetoclax Dose

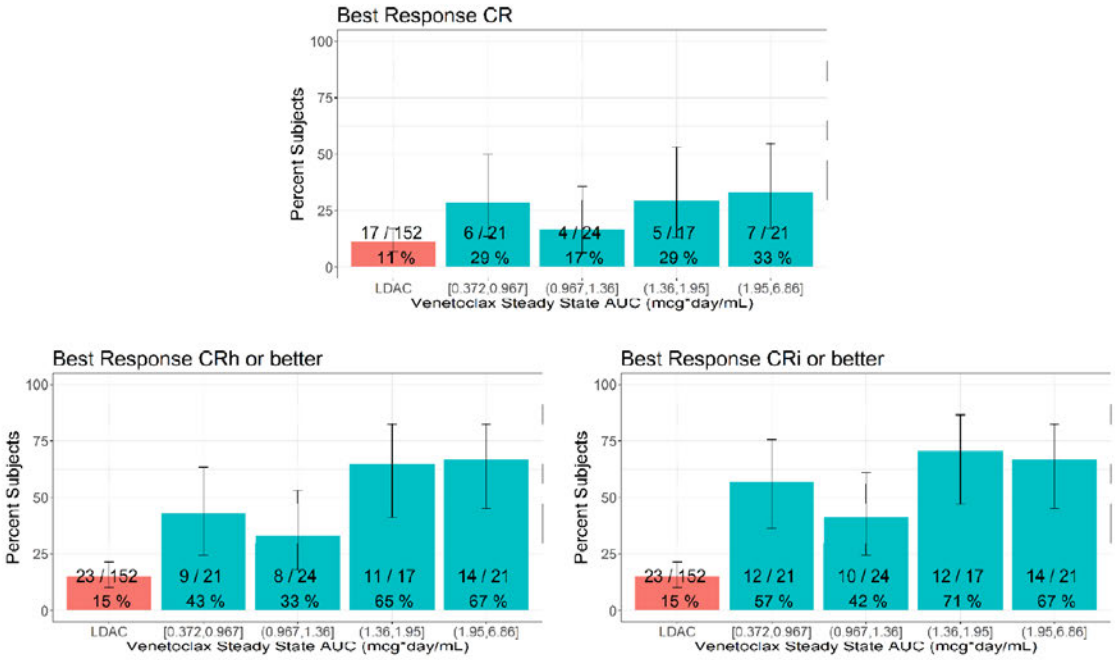
Response	Dose Group	Prediction	95% Confidence Interval
CRi or better (CRi + CRh + CR)	400 mg	0.717	0.644, 0.779
	800 mg	0.737	0.663, 0.800
	1200 mg	0.740	0.636, 0.823
CRh or better (CRh + CR)	400 mg	0.666	0.590, 0.734
	800 mg	0.666	0.588, 0.736
	1200 mg	0.652	0.541, 0.749
CR	400 mg	0.462	0.386, 0.541
	800 mg	0.433	0.356, 0.514
	1200 mg	0.400	0.296, 0.513

Source: popPK and ER report R&D/18/0339, Table 9

Venetoclax in Combination with LDAC

In Study M14-387, the response rate from combination therapy showed a trend of increase with the increase of venetoclax AUCss quartiles (**Figure 6**). The cumulative logistic regression analysis also indicated a significant association between venetoclax exposure AUCss and the response rates (**Figure 7**).

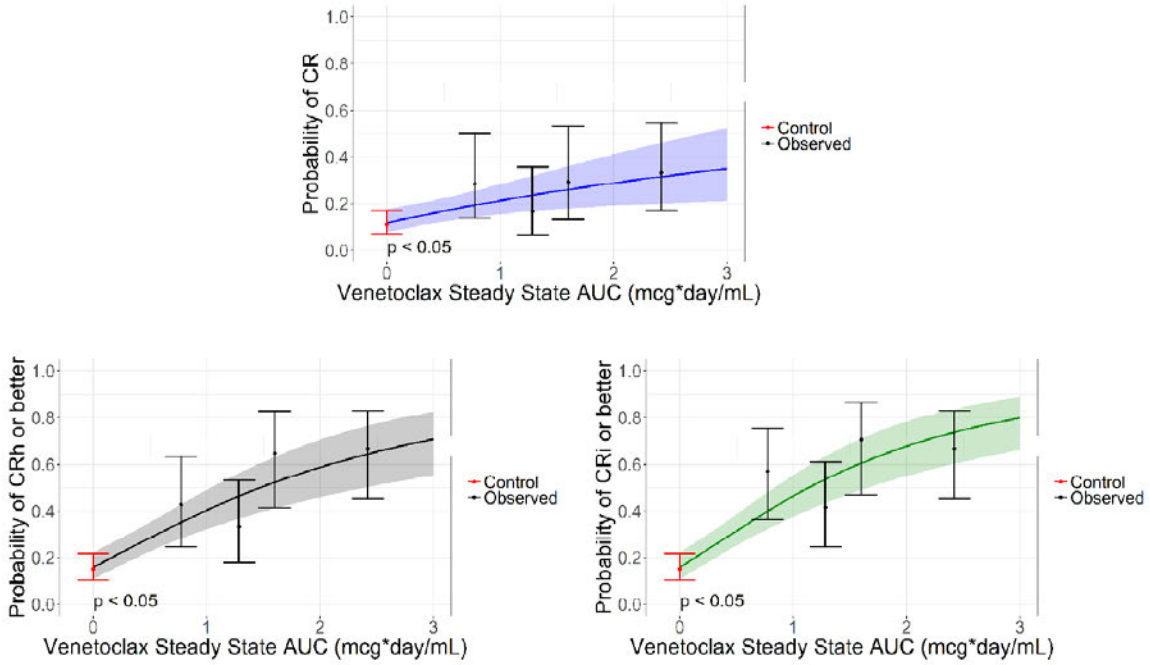
Figure 6: Observed Response Rates and 95% Binomial CI for Historical Low-Dose Cytarabine Monotherapy and in Combination with Venetoclax by AUCss Exposure Quartiles



Vertical bars indicate the observed proportions with 95% binomial CI at the observed concentration quartile. Historical response rates for LDAC were adjusted to exclude subjects who were not evaluable. CRh rate for LDAC monotherapy were assumed to be same as CRi using a conservative approach.

Source: popPK and ER report R&D/18/0339, Figure 21

Figure 7: Probability of Achieving CR, CRh or Better CRi or Better and Overall Responses Versus AUCss for Patients Receiving Venetoclax in Combination with LDAC (Results from Cumulative Logistic Regression Model)



Shaded regions indicate the predicted 95% CI and points with vertical bars indicate the observed proportions with 95% binomial CI at the observed concentration quartile. Points and vertical bars at venetoclax $AUC_{ss} = 0$ are historical rates for LDAC monotherapy.

Source: popPK and ER report R&D/18/0339, Figure 22

The predicted probability of achieving CRi or better (CRi+CRh+CR) was approximately 46% [95% CI: 37% – 55%] and 55% [95% CI: 45% – 66%] at exposures associated with the 400 mg and 600 mg dosage regimen given once daily, respectively. Although the predicted probability of response increased with increasing exposures based on the above relationship, the venetoclax dose of 600 mg QD in combination with LDAC was determined to be the MTD and selected as the recommended dose due to prolonged thrombocytopenia at the 800 mg QD dose level and dose interruption by 4 of the 5 patients at 800 mg who continued to Cycle 2 in Study M14-387. Therefore, the 600 mg QD dose of venetoclax is recommended for the combination with LDAC in patients with AML.

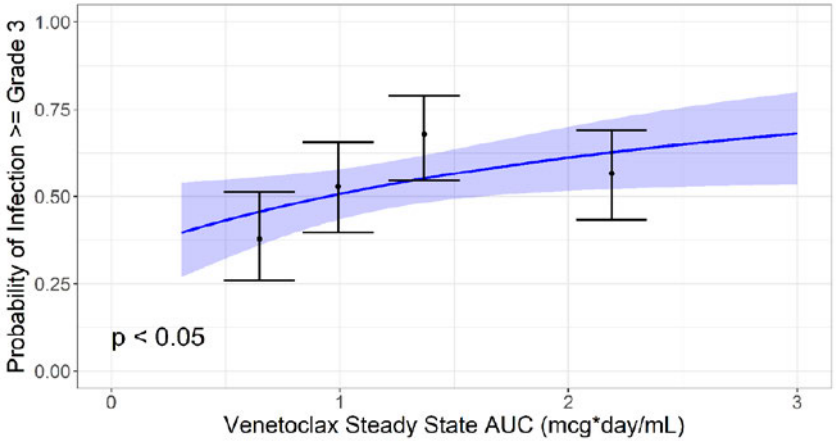
Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimens are supported by the observed dose/exposure-response relationships for both efficacy (detailed above) and safety in the newly diagnosed patients with AML who are ineligible for intensive chemotherapy.

Venetoclax in Combination with HMAs

In the exposure-safety analyses based on data from Study M14-358, there was no significant relationship between venetoclax exposure and occurrence of Grade ≥3 neutropenia or any Serious Treatment-Emergent Adverse Events (STEAE). Only treatment-emergent Grade ≥ 3 infections showed a statistically significant relationship with venetoclax exposures over the tested venetoclax dose range (400 – 1200 mg QD) (**Figure 8**).

Figure 8: Probability of Infections (Grade ≥ 3) Versus AUCss for Patients Receiving Venetoclax in Combination with HMAs



Source: popPK and ER report R&D/18/0339, Figure 17

Additionally, there were observations of prolonged neutropenia lasting for at least 2 weeks after the completion of a 28-day cycle at the 800 mg and higher dose levels in Study M14-358, suggesting that doses higher than 400 mg may not be well tolerated. Therefore, based on the results of exposure-response analyses above and the observed tolerability data, the 400 mg dose of venetoclax is considered appropriate to be used in combination with either azacitidine or decitabine.

Venetoclax in Combination with Low-Dose Cytarabine

The recommended dose of 600 mg QD for venetoclax in combination with LDAC is appropriate for the general population. The probability of occurrence of adverse events including Grade ≥ 3 neutropenia, Grade ≥ 3 infection, and STEAEs did not show a statistically significant increase with venetoclax exposure over the venetoclax dose range of 600 – 800 mg QD. The venetoclax dose of 600 mg QD was determined to be the maximum tolerated dose (MTD) due to prolonged thrombocytopenia at the 800 mg dose level and high rate of dose interruption, suggesting poor tolerability.

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

No. The population PK analysis indicated that intrinsic factors including age, sex, race, weight, mild to moderate renal impairment (CLcr 30 to 89 mL/min, calculated by Cockcroft-Gault), or mild to moderate hepatic impairment (normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin 1 to 3 times ULN) had no clinically significant effect on exposure of venetoclax. Therefore, no dose adjustments are required for intrinsic factors.

In addition, the overall incidence of AEs, grade ≥ 3 AEs, and SAEs was similar between male and female patients, patients with age < 75 years and ≥ 75 years, and patients with weight < 75 kg and ≥ 75 kg. The safety profile was not affected by mild and moderate renal impairment or mild and moderate hepatic impairment. No patients with severe renal or hepatic impairment were enrolled for safety assessment.

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

Yes. There is a significant food effect on PK of venetoclax based on the population PK analysis. Compared to that from low fat meal, the relative oral bioavailability was 0.33 under fasting condition, 1.42 with high-fat meal, and 1.13 with any meal (without specification of fat-content). As shown in **Table 16**, the food-drug interaction findings in patients with AML are similar to that identified in other patient populations. Because the significant food effect compared to that under fasting condition, venetoclax should be taken with food in the combination therapy with HMAs or LDAC.

There is also a significant DDI between venetoclax and a strong CYP3A inhibitor posaconazole based on results from Arm C (N=12) of the Study M14-358. Compared to venetoclax 400 mg administered alone, co-administration of posaconazole with venetoclax 50 mg and 100 mg resulted in 61% and 86% higher venetoclax Cmax, respectively. The venetoclax AUC24 was 90% and 144% higher, respectively (**Table 18**).

Table 18: Ratio of Central Values and 90% Confidence Intervals for Venetoclax (Study M14-358)

Regimens Test vs. Reference	Pharmacokinetic Parameter (units)	Central Value		Ratio of Central Values[a]	
		Test	Reference	Point Estimate	90% Confidence Interval
Venetoclax 100 mg w/Posaconazole (Cycle 1 Day 28) vs Venetoclax 400 mg Alone (Cycle 1 Day 20)	C_{max} (µg/mL)	3.699	1.989	1.859	(1.214 – 2.847)
	AUC_{24} (µg•h/mL)	75.137	30.793	2.440	(1.535 – 3.879)
Venetoclax 50 mg w/Posaconazole (Cycle 1 Day 28) vs Venetoclax 400 mg Alone (Cycle 1 Day 20)	C_{max} (µg/mL)	2.321	1.445	1.606	(0.915 – 2.818)
	AUC_{24} (µg•h/mL)	41.888	22.023	1.902	(0.929 – 3.894)

a. Cycle 1 Day 28 (Venetoclax w/Posaconazole)/Cycle 1 Day 20 (Venetoclax Alone).

Source: 2.7.2 Summary of Clinical Pharmacology, Table 4

The effects of coadministration of strong CYP3A inhibitors on venetoclax CL/F were also evaluated in the population pharmacokinetic analysis (R&D/18/0339). The final model indicated that administration of strong CYP3A inhibitors resulted in approximately 84% (6.3-fold) decrease of CL/F.

Based on the magnitude of DDI with posaconazole and other strong CYP3A inhibitor, the dose of venetoclax should be reduced as described in **Table 19**.

Table 19: Management of Potential VENCLEXTA Interactions with strong CYP3A Inhibitors

Coadministered drug	Initiation and Ramp-Up Phase	Steady Daily Dose (After Ramp-Up Phase)
Posaconazole	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	Reduce VENCLEXTA dose to 70 mg.
Other strong CYP3A inhibitor	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	Reduce VENCLEXTA dose to 100 mg.

Question on clinically relevant specifications (TBD)?

None.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Two major studies were used as sources of clinical data to support the efficacy and safety of venetoclax with azacitidine, decitabine, or LDAC, and they are listed below. One additional supportive study was submitted for the efficacy of venetoclax monotherapy for the treatment of patients with R/R AML.

Table 20: Summary of trials used to support review

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety of Combination Therapy								
M14-358	NCT02203773	Phase 1b, single-arm, dose escalation and dose expansion	Venetoclax: 400 mg, 800 mg, or 1200 mg PO daily, 28-day cycles Azacitidine: 75 mg/m^2, SC or IV, Days 1-7 for each cycle Decitabine: 20 mg/m^2, IV, Days 1-5 for each cycle	Safety, PK Efficacy: CR + CRh rate, CR + CRi rate, CR rate, CRh rate, and CRi rate; duration of CR + CRh, duration of CR + CRi, duration of CR, duration of CRh, duration of CRi; overall survival; transfusion independence rate MRD negativity	Treatment until disease progression or intolerance Venetoclax + azacitidine = 5.5 months (median) Venetoclax + decitabine = 6.7 months (median) DDI sub-study = 2.2 months (median)	212 (127 in Ven+Aza, 73 in Ven+Dec, 12 in DDI sub-study)	Newly-diagnosed AML who are elderly (≥60 years) and who are not eligible for standard induction therapy	18 sites; 4 countries

M14-387	NCT02287233	Phase 1/2, single-arm, dose escalation and dose-expansion	Venetoclax: 600 mg or 800 mg PO daily, 28-day cycles Cytarabine: 20 mg/m^2, SC, Days 1-10 for each cycle	Safety, PK Efficacy: ORR (CR + CRi + PR), CR rate, CRi rate, CRh rate, CR + CRi rate, CR + CRh rate, DOR, EFS, OS MRD negativity, transfusion independence rates	Treatment until disease progression or intolerance Median treatment duration 4.4 months	92 (82 at 600 mg Ven, 10 at 800 mg Ven)	Newly-diagnosed AML who are elderly (≥60 years) and who are not eligible for standard induction therapy	9 sites; 4 countries
Study to Support Efficacy and Safety of Monotherapy								
M14-212	NCT01994837	Phase 2, single-arm, dose-ranging, single-agent	Venetoclax: 800 mg or 1200 mg, PO, daily	Safety, PK Efficacy: ORR (CR + CRi + PR), CR rate, CRi rate, CR + CRi rate, DOR, TTP, PFS, OS MRD negativity	Treatment until disease progression or intolerance Median treatment duration 62 days	32 (30 R/R, 2 frontline)	R/R AML or untreated AML unfit for intensive therapy	5 sites; 1 country

7.2. Review Strategy

The key materials used for the review of efficacy and safety include:

- NDA 208573
- IND 110159
- Relevant published literature
- Relevant information in the public domain

The review of efficacy was primarily based on analysis of patients treated on Study M14-358 for venetoclax in combination with azacitidine or decitabine and on Study M14-387 for venetoclax in combination with LDAC. Data from both trials was used to support dose selection for each combination. All efficacy results were verified by independent analysis, except where indicated. Efficacy evaluations were conducted using the following efficacy populations (summarized in Table 21):

- All patients treated at the proposed labeled dose of venetoclax in each combination
- Patients in each treatment combination who met the modified Ferrara criteria to identify patients whose age or comorbidities preclude the use of intensive induction chemotherapy. See Trial Designs for details on these criteria.
- Additional patients enrolled who did not have known comorbidities that preclude the use of intensive therapy but were enrolled prior to defining the criteria.

Table 21: Patient enrollment in each efficacy population by treatment combination

	Venetoclax (400 mg) + Azacitidine	Venetoclax (400 mg) + Decitabine	Venetoclax (600 mg) + LDAC
Overall	84	31	82
Modified Ferrara Yes	67	13	61
Modified Ferrara No	17	18	21

The description of the treatment combination in the indication proposed by the Applicant was for venetoclax in combination with hypomethylating agents or low-dose cytarabine. For the purposes of this review, the two HMAs, azacitidine and decitabine, are considered two independent combination and not HMAs as a class. While the HMAs have a similar mechanism of action, the efficacy and safety profiles of each differ.

Efficacy of venetoclax monotherapy for treatment of relapsed/refractory AML was reviewed from Study M14-212. Because an indication for the treatment of patients with r/r AML was not sought, independent analyses were not verified for this study. Only summary results are provided for Study M14-212.

Safety analyses were conducted in Studies M14-358 and M14-387 for venetoclax in combination with each therapy. Because the backbone therapy was different for each study, pooled analyses were not performed. A pooling of common adverse events in Study M14-358 was performed for the azacitidine and decitabine combinations to aid in signal detection for less common adverse reactions.

Summaries of data and statistical analysis by the clinical reviewer were performed using JMP 11.1.1 (SAS Institute, Inc., Cary, NC). MedDRA Adverse Events Diagnostic 1.8 (MAED) (FDA, Silver Spring, MD) was also used to look for safety signals. For the results of the efficacy analysis by the statistical reviewer were performed using SAS and R.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

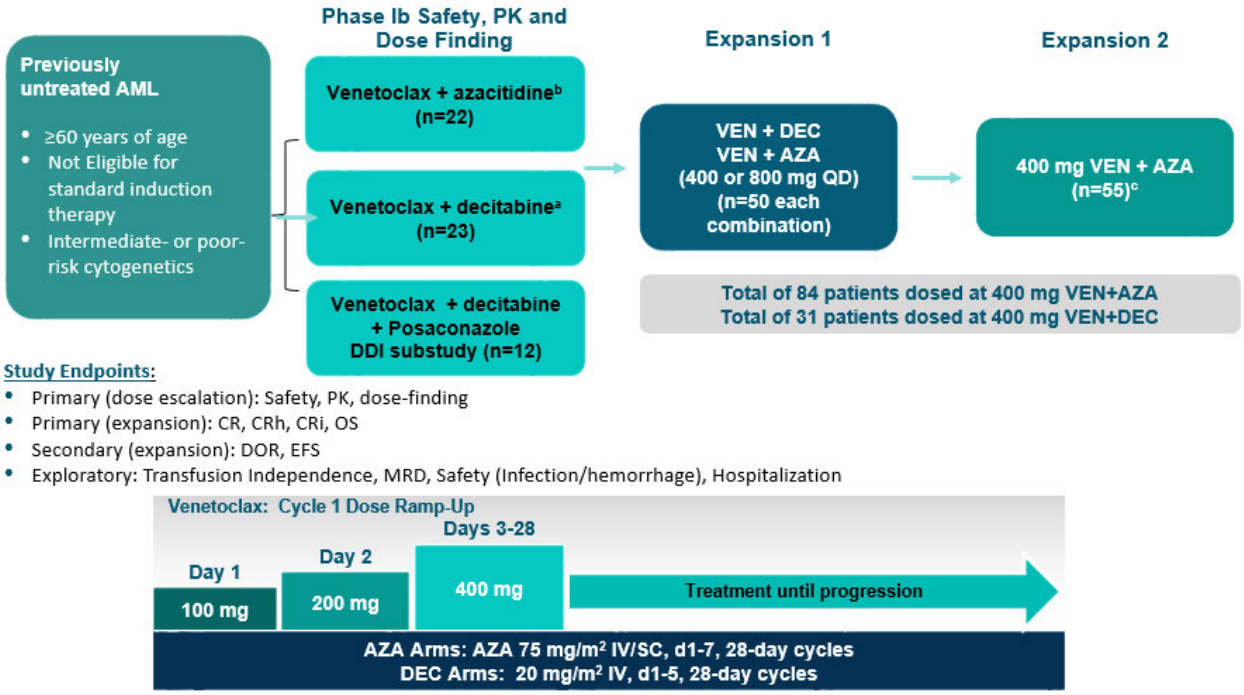
8.1.1. M14-358

Title: A Phase 1b Study of ABT-199 (GDC-0199) in Combination with Azacitidine or Decitabine in Treatment-Naïve Subjects with Acute Myelogenous Leukemia Who Are ≥ 60 Years of Age and Who Are Not Eligible for Standard Induction Therapy

Trial Design

Study M14-358 is a Phase1b, open-label, non-randomized, multicenter study evaluating the safety and preliminary efficacy of orally administered venetoclax combined with decitabine or azacitidine in newly diagnosed patients with AML ≥ 60 years old and who are not eligible for standard induction therapy due to co-morbidities. Patients were enrolled into 2 stages: a Dose Escalation stage (N = 45) with a drug-drug interaction substudy (N = 12); and an Expansion Stage (N = 155), comprised of Expansion 1 (n = 100) and of Expansion 2 (n = 55). Figure 9 shows study M14-358 design schema.

Figure 9: Study M14-358 Design Schema



a:=20 mg/m² IV, d1-5, 28-day cycles; b=75 mg/m² IV/SC, d1-7, 28-day cycles; c=The 55 subjects in expansion 2 were ≥60 years old and fulfilled the modified Ferrara criteria' AZA=azacitidine; DEC=decitabine; VEN=venetoclax; CRi=complete remission with incomplete blood count recovery;

[Source: Applicant's Orientation Meeting]

All patients enrolled into the dose escalation stage, Expansion 1, and the DDI substudy were ≥ 65 years of age, while patients enrolled into Expansion 2 were ≥ 60 years of age. The dose escalation stage of the trial consisted of two separate dose escalation arms. Arm A was venetoclax in escalating doses plus decitabine. Arm B was venetoclax in escalating doses plus azacitidine. The escalation stage for each combination was projected to consist of approximately 4 cohorts of up to 6 patients each, with the objective of evaluating safety and pharmacokinetics of the regimen. During the escalation stage of the study an additional arm, Arm C (posaconazole cohort in the DDI substudy), was enrolled at a single site, MD Anderson Cancer Center, Houston, Texas, United States, to assess the safety and pharmacokinetics of venetoclax when co-administered with posaconazole. These patients were treated with 400 mg venetoclax combined with decitabine and co-administration of posaconazole; patients at MDACC were assigned only to the DDI substudy until enrollment in Arm C was complete.

None of the patients who received venetoclax at doses up to 1200 mg in combination with either azacitidine or decitabine in the dose escalation stage experienced a dose limiting toxicity (DLT). Subsequently, in the expansion stage two doses of venetoclax, 400 mg daily and 800 mg with intermittent administration, in combination with both HMAs were evaluated to confirm anti-leukemia effects and the safety of both combinations and to determine the regimen to be evaluated in a Phase 2/3 trial. The first expansion (Expansion 1) consisted of 100 patients, with 25 patients in each dose level, treated with azacitidine (Arm E1 and E2) or decitabine (D1 and D2). For patients who were enrolled into Arms E2 and D2 with the venetoclax 800 mg dose, duration of venetoclax was to be reduced to 21 days during each cycle upon clearance of leukemia with < 5% bone marrow blasts. If there was delay in initiation of subsequent cycles for recovery of recurrent neutropenia, further reduction to 14 days, and then 10 days during each of the subsequent 28-day cycles was implemented.

Based on the efficacy, safety and response exposure data from Expansion 1, venetoclax 400 mg was determined to be the proposed Phase 2 dose. Consequently, Expansion 2 was designed to confirm the efficacy of venetoclax 400 mg in combination with HMAs in a newly diagnosed AML population with objectively-defined comorbidities (defined by these modified Ferrara criteria) who were ineligible to receive standard induction therapy. Previously excluded CYP3A inhibitors were permitted with appropriate dose reductions of venetoclax as identified from the DDI substudy. Expansion 2 consisted of 55 additional patients enrolled to the 400 mg daily dose of venetoclax in combination with azacitidine (Arm G). Twenty-three sites were activated; 19 sites enrolled patients in the United States, France, Germany, and Australia. Each center prospectively chose their preferred hypomethylating agent prior to the dose escalation stage of the trial and agreed to use the combination previously chosen at their center in both escalation and expansion stages of the trial. In Expansion 2, sites that had chosen decitabine as their preferred hypomethylating agent could enroll to the azacitidine arm.

To mitigate the potential risk of tumor lysis syndrome (TLS), patients received TLS prophylaxis prior to venetoclax dose escalation in combination with azacitidine or decitabine. Patients were

hospitalized during the venetoclax dose ramp-up, e.g., Days –1 through the ramp-up, to Day 6 or 7 of Cycle 1, and for at least 24 hours after reaching the designated cohort dose (based on the ramp-up steps specific for the cohort). TLS prophylaxis was initiated with uric acid reducing agents in all patients, starting at least 48 hours prior to the first dose of venetoclax; patients received hydration and were monitored with chemistry labs before and 6 - 8 hours after each daily dose of the ramp-up. As no laboratory abnormalities indicative of potential TLS were observed in the patients enrolled into escalation stage, prophylactic measures in the protocol were simplified for the expansion stage. Patients enrolled into the expansion stage could be hospitalized beginning on Day –1 or Day 1 and during the ramp-up of venetoclax dose and for at least 24 hours after reaching the target dose. TLS prophylaxis measures were implemented by the investigators per their institutional standards, with daily chemistry lab monitoring.

Based on safety and efficacy data from the escalation stage, 2 venetoclax dosing schedules were evaluated in the expansion stage; these dosing schedules consisted of 400 mg venetoclax daily or 800 mg venetoclax daily during Cycle 1 followed by reduced duration to 21 days, 14 days, and 10 days during each subsequent cycle, in combination with either azacitidine or decitabine. Venetoclax dosing began on Cycle 1 Day 2 for all patients enrolled in the escalation stage to enable sample collections for pharmacokinetics assessments for the hypomethylating agents. Venetoclax dosing began on Cycle 1 Day 1 for all patients enrolled into the expansion stage.

During the dose escalation, DDI substudy, and Expansion 1 portions of the study, patients enrolled were ≥ 65 years of age, had histological confirmation of AML, and were ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidities. Patients did not receive prior treatment for AML, with the exception of hydroxyurea, and had a projected life expectancy of at least 12 weeks. Patients with prior HMA or chemotherapy for MDS, AML with favorable risk cytogenetics as categorized by the NCCN Guidelines Version 2, 2014 for Acute Myeloid Leukemia,11 or known central nervous system involvement with AML were excluded. During the Expansion 2 portion of the study, patients could be enrolled if they were ≥ 60 years of age and fulfilled the modified Ferrara criteria to define ineligibility for intensive therapy, as described below. In addition, patients in the Expansion 2 cohort were allowed moderate or strong CYP3A inhibitors, which were previously excluded as concomitant medications, with appropriate venetoclax dose reduction per protocol if medically necessary.

Modified Ferrara Criteria

The following are the objective criteria to support evaluation of ineligibility for intensive therapy that is referred to in this Review as modified Ferrara Criteria.

≥ 75 years of age;

OR

60 to 74 years of age with at least one of the following comorbidities:

- Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3
- cardiac history of congestive heart failure requiring treatment or ejection fraction ≤ 50% or chronic stable angina
- diffusing capacity of the lungs for carbon monoxide (DLCO) ≤ 65% or forced expiratory volume in the first second of expiration (FEV1) ≤ 65%
- creatinine clearance ≥ 30 mL/minute to < 45 mL/minute
- moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × upper limit of normal
- any other comorbidity that the physician judges to be incompatible with intensive chemotherapy must be reviewed and approved by the AbbVie Therapeutic Area Medical Director (TA MD) before screening and study enrollment

Clinical reviewer comment: *Both clinical studies M14-358 and M14-387 were initiated with inclusion criteria that stated, "Subject must have histological confirmation of AML and be ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidity or other factors". However, patients were required to have age ≥65 years, ECOG PS 0-2, adequate renal function (CrCl ≥50 mL/min), and adequate liver function (AST/ALT ≤2.5x ULN, bilirubin ≤1.5x ULN) which likely identified patients who did not have comorbidities that would preclude the use of an intensive chemotherapy regimen. In May 2016, the Agency indicated that the Sponsor should more clearly define the inclusion criteria to identify a patient population by specific patient comorbidities that would preclude the use of intensive induction chemotherapy. The Agency indicated that the consensus criteria published by Ferrara, et al[5], may be acceptable. The Sponsor proposed modification to the criteria based on the venetoclax development (i.e. uncertainty around effects of renal and hepatic impairment at the time). In late 2016, the Agency agreed that the "modified Ferrara criteria" may suitably define the population of interest. Of note, patients enrolled on the study who were age ≥75 had to have ECOG PS 0-2, and patients with ECOG PS of 3 were excluded in this age group. Notable differences from the consensus criteria published by Ferrara, et al, are that patients were eligible for study with chronic stable angina, creatine clearance <45 without being on dialysis, moderate hepatic impairment, or ECOG performance status of 2 or more.*

Both studies M14-358 and M14-387 enrolled expansion cohorts using the modified Ferrara criteria. In study M14-358, the expansion cohort using the modified Ferrara criteria (Expansion 2, Arm G) was treated with venetoclax with azacitidine. There was no expansion cohort for

patients who met the modified Ferrara criteria who were treated with venetoclax with decitabine. The Applicant retrospectively analyzed the patients who had been enrolled prior to amending the protocol to include the current enrollment criteria to determine which patients may have already met the modified Ferrara criteria. This resulted in a final enrollment of 67 patients treated with the target dose of venetoclax (400 mg) in combination with azacitidine and 13 patients treated with venetoclax (400 mg) in combination with decitabine who met the modified Ferrara criteria.

Of note, only patients with intermediate- or poor-risk cytogenetics were enrolled in M14-358. For inclusion criteria, the cytogenetics were based on the NCCN guidelines, version 2, 2014.

Study Endpoints

Complete Remission

Complete Remission (CR) is a response based on investigator report using modified IWG criteria for AML: absolute neutrophil count (ANC) > 10^3/µL, platelet counts > 10^5/µL, RBC transfusion independence, and bone marrow with < 5% blasts.

Complete Remission rate is defined as the proportion of patients who achieve a complete remission at any time point during the study per the modified IWG criteria for AML[1]. Patients who never achieve CR or have no IWG disease assessment are considered non-responders in the calculation of CR rate.

Complete Remission with Partial Hematologic Recovery

Complete remission with partial hematologic recovery (CRh) is a derived response based on bone marrow blast and hematology lab values.

CRh criteria:

- Bone marrow with < 5% blasts and
- Peripheral blood neutrophil count of > 0.5 × 10^3/µL and
- Peripheral blood platelet count of > 0.5 × 10^5/µL and
- A 1 week (≥ 7 days) platelet transfusion-free period prior to the hematology lab collection.

For a bone marrow sample collected before the last cycle of study treatment, the hematology lab results collected from the date of the bone marrow sample collection up to the Day 1 of a subsequent cycle of study treatment will be used for CRh analysis. For a bone marrow sample collected during or after the last cycle of study treatment, the hematology lab results collected within 14 days after bone marrow sample collection date are used for CRh analysis.

CRh rate is defined as the proportion of patients who achieve CRh as the best response at any

time point during the study. Patients who never achieve CRh or have not had disease assessment or hematology data are considered non-responders in the calculation of CRh rate.

Complete Remission with Incomplete Blood Count Recovery

Complete Remission with Incomplete Blood Count Recovery (CRi) is defined as the lack of morphologic evidence of leukemia (blasts < 5%), platelet counts > 50,000/µL, and ANC > 500/µL without recovery of platelets > 100,000/µL and ANC > 1,000/µL, which would define CR.

Duration of Response

Duration of response (DOR) is defined as number of days from date that patient achieved remission to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest. If a patient is still responding at the data cutoff date, then the patient's data are censored. The disease assessment data after the onset of any post-treatment therapy are not be included in the duration of response analysis.

Clinical Reviewer comment: *The definition of complete remission with partial hematologic recovery (CRh) is not part of either the 2003 Cheson modified IWG criteria[1] or the 2017 ELN AML response criteria[17]. However, the FDA has used this response criteria in AML to help identify patients that may be receiving objective clinical benefit from the therapy.*

Notably, the 2003 Cheson criteria define CR as requiring platelets >100,000/uL and neutrophils >1000/uL in the Table of the publication, but platelets ≥100,000/uL in the text. The Sponsor used platelets ≥100,000/uL and neutrophils ≥1000/uL in their analyses. The definition accepted by the Agency is platelets >100,000/uL and neutrophils >1000/uL. The response analyses were updated with the current CR definition.

Statistical Analysis Plan

Analysis Populations

Full Analysis Set: the full analysis set includes all patients who received at least one dose of venetoclax.

Safety Analysis Set: the safety analysis set includes all patients who received at least one dose of venetoclax.

Sample Size Determination

No formal statistical hypotheses testing was planned.

Study M14-358 is a 2-stage study where the first stage is a dose escalation study and the second stage is a dose expansion study. The number of patients required for dose escalation

portion depends upon the toxicities observed as the trial progresses. Within the dose expansion study, there are two expansion stages: Expansion 1 and Expansion 2.

Expansion 1 was planned to consist of up to 100 additional patients, with 25 patients in each dose level, treated with the each of the combinations (venetoclax and decitabine or venetoclax and azacitidine) to confirm safety and to evaluate anti-tumor effects. For Expansion 1, with 25 patients the observed response rate (CR + CRi + PR) would be within 21% of the true response rate (maximum distance from the center to the outer bounds of the 95% confidence interval).

For Expansion 2, assuming a control CR + CRi rate of 27.8% for azacitidine monotherapy and a target CR + CRi rate 50%, a sample size of 55 patients for venetoclax 400 mg combined with azacitidine would yield 91% power to achieve statistical significance at a 1-sided alpha of 0.025.

For the DDI sub-study, sample size is based on feasibility, however some justification is provided as follows: complete data from 12 patients would provide 90% power for the test on the dose-normalized pharmacokinetic parameters if the true ratio of the central values is 1.7 (70% increase). Complete data from 10 patients would provide at least 89% power for the test on the dose-normalized pharmacokinetic parameters if the true ratio of the central values is 1.8 (80% increase). The power calculations were performed using logarithmic transformation and assumed an error term variance of 0.1328. This value is based on the observed error term variance for log-transformed AUCt from Study M13-364 (DDI study with ketoconazole in NHL patients).

Analysis of the Endpoints

Calculation of the remission rates and the corresponding 95% confidence intervals are based on the binomial distribution (Clopper-Pearson exact method). The disease assessment collected after the post-treatment therapy is excluded for analyses.

The distribution of duration of response was planned to be estimated using Kaplan-Meier methodology. Median duration of response with the corresponding 95% CI was planned to be provided from Kaplan-Meier estimation.

Protocol Amendments

Key protocol changes relevant to design and analysis of the Study M14-358 are summarized below.

Amendment 1 (22 April 2015)

- Update throughout the document to allow for bone marrow assessments to be performed prior to the start of the appropriate treatment cycle to allow for results to be known prior to starting treatment.
- Update throughout the document to clarify that patients with AML have

- recurrent or relapse disease instead of progressive disease in alignment with IWG criteria for AML.
- Update Section 5.3.3 Efficacy Variables as follows:
    - To add resistant disease (RD) as criteria for evaluation to have a category
    - for those patients who are not responding to treatment.
    - To clarify the need for collecting transfusion history for up to 8 weeks
    - prior to treatment as the information is needed to assess response.
    - Added a definition for aplasia and morphologic relapse for clarity.
    - Modified the reporting of result categories.

Amendment 2 (20 August 2015)

- Update throughout the document to modify dosing schema for Cohort 4. ABT-199 will be given Days 2 – 21 of a 28-day cycle during Cycle 1. Beginning with Cycle 2, ABT-199 will be given Days 1 – 21 of a 28-day cycle. Rationale: Due to the neutropenia observed in patients from the first 3 Cohorts, an interrupted dosing schedule for Cohort 4 will be implemented, which escalates from a 100 mg dose (beginning on C1D2) to 1200 mg. The modified dosing schema for Cohort 4 Arms A and Arm B will be to provide ABT-199 on Days 2 – 21 in Cycle 1 and Days 1 – 21 in all subsequent Cycles as opposed to continuous dosing.

Amendment 3 (11 December 2015)

- Update Section 4.0, Study Objectives, to incorporate two dosing schemas to be evaluated during the expansion stage, to include language that both hypomethylating agents will move into expansion, and update the protocol accordingly including considerations regarding sample size and changes of visit and evaluation schedule. Rationale: To allow for both hypomethylating agents to move into expansion stage at two different venetoclax dosing levels.
- Update Section 1.2, Synopsis, to increase the number of patients to be enrolled from approximately 100 to approximately 160. Rationale: To address unmet need in targeted patient population.

Amendment 4 (04 March 2016)

- Update Section 5.2.2, Exclusion Criteria, to update inclusion and exclusion criteria. Modifications made to Inclusion Criterion 8. Rationale: To further clarify enrollment criteria for patients entered into the study.
- Update Table 4, Treatment Schedule for Arms A and B – Escalation Stage, to change procedures for patients enrolled into the Expansion stage. Rationale: To further clarify study procedures in the expansion stage.

Amendment 5 (14 November 2016)

- Update Section 1.0, Title, updated to include patients ≥ 60 years of age. Rationale: Lowering age limit to be consistent with the NCCN guidelines for treatment of AML.
- Update Section 1.2, Synopsis, to update objectives, inclusion and exclusion criteria,

number of patients to be enrolled, background, methodology, doses at expansion 2, Pharmacodynamic and predictive biomarker analysis, criteria for evaluation. Rationale: Updated to reflect addition of Expansion 2 stage of the study.

- Update Section 5.1, Overall Study Design and Plan: Description, to include new age limits, to clarify arms that are no longer enrolling and to add overall design for Expansion 2 addition. Rationale: Updated to explain the addition of 100 additional patients and the dosing schema for these patients. Update Section 5.2.1, Inclusion Criteria, inclusion criteria have been updated to define patients that will be enrolled. Rationale: To define patients who are unfit for standard induction.
- Update Section 5.2.2, Exclusion Criteria, exclusion criteria have been updated to define patients that will be enrolled. Rationale: To define patients who are unfit for standard induction.
- Section 8.1.3.1.2, Duration of Response, removed Time to Progression. Rationale: Removed as Duration of Response will be assessed.
- Section 8.1.3.1.3, Event-Free Survival, added. Rationale: Updated to add Event Free survival as an endpoint.
- Section 8.1.3.1.4, Progression Free Survival, removed. Rationale: Removed as Event free survival will be assessed.
- Section 8.2, Determination of Sample Size, updated, added language to support determination of sample size in Expansion 2. Rationale: To add language to support the addition of Expansion 2.

Amendment 6 (07 February 2018)

- Update to remove reference to Arm F. Rationale: Sponsor decision to advance enrollment into the Expansion 2 with Azacitidine combination instead of combination with both hypomethylating agents to support the planned randomized trial.
- Update Section 8.1.3. Rationale: CRh rates and transfusion independence endpoints were added for efficacy summary.

Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with Good Clinical Practices including review of the clinical protocol, the informed consent, and patient information and/or advertising by an Independent Ethics Committee or Institutional Review Board (IEC/IRB).

Financial Disclosure

A summary of financial disclosures for the studies included in the submission is provided in Appendix 15.2. The Applicant submitted financial disclosure information from all investigators and sub-investigators from M14-358. One investigator had disclosable financial interests. Fourteen patients were enrolled at that site with only seven patients included in the efficacy evaluable population at the target dose of venetoclax. The CR rate at this site was similar to the overall CR rate in the trial. No bias is expected in the study outcome.

Patient Disposition

Nineteen study sites in the US, Australia, Germany, and France screened 278 patients. As of the efficacy data cutoff date (22 December 2017), 212 participants were enrolled and treated with the study drug. Table 22 and Table 23 show patient disposition for venetoclax (400mg) in combination with azacitidine (n=84) and decitabine (n=31), respectively.

The following is a summary for patients meeting the modified Ferrara criteria (n=67) in venetoclax in combination with azacitidine group (n=84). The most common reason for study discontinuation was progressive disease (27%). Most common reasons for venetoclax discontinuation were adverse event (21%) and progressive disease (19%). Most common reasons for azacitidine discontinuation were investigator decision (18%), adverse event (16%), progressive disease (15%).

Table 22: Study M14-358 Patient Disposition: Venetoclax + Azacitidine

	Modified Ferrara No N=17 n (%)	Modified Ferrara Yes N=67 n (%)	Overall N=84 n (%)
Discontinued Study	12 (71)	39 (58)	51 (61)
Adverse Event	3 (18)	10 (15)	13 (15)
Investigator Judgment and/or Request	0 (0)	2 (3)	2 (2)
Other[1]	3 (18)	6 (9)	9 (11)
Progressive Disease	6 (35)	18 (27)	24 (29)
with Death	0 (0)	2 (3)	2 (2)
without Death	6 (35)	16 (24)	22 (26)
Withdrawal by Patient	0 (0)	3 (4)	3 (4)
Discontinued Venetoclax	15 (88)	44 (66)	59 (70)
Adverse Event	3 (18)	14 (21)	17 (20)
Investigator Judgment and/or Request	1 (6)	0 (0)	1 (1)
Other[1]	7 (41)	15 (22)	22 (26)
Progressive Disease	4 (24)	13 (19)	17 (20)
Withdrawal by Patient	0 (0)	2 (3)	2 (2)
Discontinued Azacitidine	15 (88)	48 (72)	63 (75)
Adverse Event	2 (12)	11 (16)	13 (15)
Investigator Judgment and/or Request	2 (12)	12 (18)	14 (17)
Other[1]	8 (47)	13 (19)	21 (25)
Death	1 (6)	1 (1)	2 (2)
Progressive Disease	3 (18)	10 (15)	13 (15)
Withdrawal by Patient	0 (0)	2 (3)	2 (2)

[Source: FDA Statistical Reviewer's Analysis; CSR, Table 14.1, pages 647-656]
[1] Most common reasons under Other category included patient refusal for study participation, bone marrow transplant, and stem cell transplant.

Reviewer's Comments: *Patient disposition results were derived from SDTM data by the Statistical Reviewer.*

The following is a summary for patients meeting the modified Ferrara criteria (n=13) in venetoclax in combination with decitabine group (n=31). The most common reason for study discontinuation was progressive disease (62%).

Table 23: Study M14-358 Patient Disposition: Venetoclax + Decitabine

	Modified Ferrara No N=18 n (%)	Modified Ferrara Yes N=13 n (%)	Overall N=31 n (%)
Discontinued Study	13 (72)	11 (85)	24 (77)
Adverse Event	1 (6)	1 (8)	2 (6)
Other	6 (33)	1 (8)	7 (23)
Death	2 (11)	0 (0)	2 (6)
Progressive Disease	5 (28)	8 (62)	13 (42)
Withdrawal by Patient	1 (6)	1 (8)	2 (6)
Discontinued Venetoclax	13 (72)	11 (85)	24 (77)
Adverse Event	2 (11)	2 (15)	4 (13)
Investigator Judgment and/or Request	1 (6)	0 (0)	1 (3)
Other	7 (39)	1 (8)	8 (26)
Progressive Disease	3 (17)	7 (54)	10 (32)
Withdrawal by Patient	0 (0)	1 (8)	1 (3)
Discontinued Decitabine	14 (78)	11 (85)	25 (81)
Adverse Event	1 (6)	1 (8)	2 (6)
Investigator Judgment and/or Request	1 (6)	0 (0)	1 (3)
Other	9 (50)	2 (15)	11 (35)
Death	2 (11)	0 (0)	2 (6)
Progressive Disease	3 (17)	7 (54)	10 (32)
Withdrawal by Patient	0 (0)	1 (8)	1 (3)

[Source: FDA Statistical Reviewer's Analysis; CSR, Table 14.1, pages 647-656]

Protocol Violations/Deviations

Protocol deviations were defined in accordance with the ICH guidelines and included, but were not limited to: inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications.

Inclusion/Exclusion Criteria Violation
Two patients enrolled into the study upon fulfilling the study entry criteria. Both patients were enrolled under Amendment 4, however they met Exclusion Criteria 17 for early discontinuation for stem cell transplant, which indicated that "Subject is a candidate for a bone marrow or stem cell transplant within 16 weeks after study enrollment."

Receipt of Wrong Treatment or Incorrect Dose
Five patients received study treatment at the wrong time or at the incorrect dose level and one patient did not comply with dosing requirements.

Use of Prohibited Concomitant Medication
Eighteen patients took prohibited concomitant medications: ciprofloxacin, posaconazole, fluconazole, diflucan, clotrimazole, voriconazole, and cardizem.

Reviewer's Comments: *The small number and the nature of the violations/deviations, as described above, are unlikely to have any substantial impact on the final efficacy results of the Study M14-358.*

Demographic Characteristics

Table 24 and Table 25 summarize demographic characteristics of patients treated with venetoclax in combination with azacitidine and decitabine, respectively.

Table 24: Demographic Characteristics: Venetoclax + Azacitidine

	Modified Ferrara No n (%)	Modified Ferrara Yes n (%)	Total n (%)
N	17 (100)	67 (100)	84 (100)
Age: Median (Range)	70 (65-74)	76 (61-90)	74 (61-90)
Age Group			
<75	17 (100)	25 (37)	42 (50)
>=75	0 (0)	42 (63)	42 (50)
Sex			
Female	6 (35)	27 (40)	33 (39)
Male	11 (65)	40 (60)	51 (61)
Race			
Asian	0 (0)	1 (1)	1 (1)
Black	1 (6)	3 (4)	4 (5)
Missing	3 (18)	3 (4)	6 (7)
Multi Race	0 (0)	1 (1)	1 (1)
Native Hawaiian or Pacific Islander	0 (0)	1 (1)	1 (1)
White	13 (76)	58 (87)	71 (85)
Country			
Australia	1 (6)	6 (9)	7 (8)
France	2 (12)	3 (4)	5 (6)
Germany	0 (0)	2 (3)	2 (2)
United States	14 (82)	56 (84)	70 (83)

[Source: FDA Statistical Reviewer's Analysis]

Table 25: Demographic Characteristics: Venetoclax + Decitabine

	Modified Ferrara No n (%)	Modified Ferrara Yes n (%)	Overall n (%)
N	18 (100)	13 (100)	31 (100)
Age: Median (Range)	70 (65-74)	75 (68-86)	72 (65-86)
Age Group			
<75	18 (100)	5 (38)	23 (74)
>=75	0 (0)	8 (62)	8 (26)
Sex			
Female	8 (44)	8 (62)	16 (52)
Male	10 (56)	5 (38)	15 (48)
Race			
American Indian/Alaska Native	0 (0)	1 (8)	1 (3)
Black	1 (6)	0 (0)	1 (3)
Native Hawaiian or Pacific Islander	0 (0)	2 (15)	2 (6)
White	17 (94)	10 (77)	27 (87)
Country			
Australia	1 (6)	1 (8)	2 (6)
United States	17 (94)	12 (92)	29 (94)

[Source: FDA Statistical Reviewer's Analysis]

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

Table 26 and Table 27 summarize baseline characteristics of patients treated with venetoclax in combination with azacitidine and decitabine, respectively.

Table 26: Baseline Characteristics: Venetoclax + Azacitidine

	Modified Ferrara No n (%)	Modified Ferrara Yes n (%)	Overall n (%)
N	17 (100)	67 (100)	84 (100)
Cytogenetics			
Intermediate	7 (41)	43 (64)	50 (60)
Poor	10 (59)	23 (34)	33 (39)
No Mitoses[1]	0 (0)	1 (1)	1 (1)
AML Type			
Primary	14 (82)	49 (73)	63 (75)
Secondary	3 (18)	18 (27)	21 (25)
AML w/MRC			
No	10 (59)	52 (78)	62 (74)
Yes	7 (41)	15 (22)	22 (26)
ECOG			
0	4 (24)	10 (15)	14 (17)
1	11 (65)	33 (49)	44 (52)
2	2 (12)	22 (33)	24 (29)
3	0 (0)	2 (3)	2 (2)
Blasts			
< 30%	5 (29)	19 (28)	24 (29)
≥30%-<50%	6 (35)	22 (33)	28 (33)
≥ 50%	6 (35)	25 (37)	31 (37)
Missing	0 (0)	1 (1)	1 (1)

[1] As defined by the National Comprehensive Cancer Network (NCCN) risk categorization v2014
[Source: FDA Statistical Reviewer's Analysis]

Clinical Reviewer comment: *One patient did not have adequate mitoses to perform standard cytogenetics, however, favorable risk cytogenetics was ruled out based on Fluorescence in situ Hybridization [FISH] analysis.*

Table 27: Baseline Characteristics: Venetoclax + Decitabine

	Modified Ferrara No n (%)	Modified Ferrara Yes n (%)	Overall n (%)
N	18 (100)	13 (100)	31 (100)
Cytogenetics			
Intermediate	11 (61)	5 (38)	16 (52)
Poor	7 (39)	8 (62)	15 (48)
AML Type			
Primary	11 (61)	11 (85)	22 (71)
Secondary	7 (39)	2 (15)	9 (29)
AML w/MRC			
No	10 (56)	8 (62)	18 (58)
Yes	8 (44)	5 (38)	13 (42)
ECOG			
0	5 (28)	2 (15)	7 (23)
1	10 (56)	10 (77)	20 (65)
2	3 (17)	1 (8)	4 (13)
Blasts			
< 30%	4 (22)	3 (23)	7 (23)
≥30%-<50%	10 (56)	4 (31)	14 (45)
≥ 50%	4 (22)	6 (46)	10 (32)

[Source: FDA Statistical Reviewer's Analysis]

Clinical Reviewer comment: *As noted in the trial design, patients could be enrolled under the modified Ferrara criteria based on age ≥75 years or comorbidities of ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, or creatinine clearance of <45 mL/min or other comorbidity. Patients could have more than one comorbidity. Based on the Applicant's responses to an information request, 29 (43%) patients in the azacitidine group and 5 (39%) patients in the decitabine group qualified based on ECOG 2-3. The ECOG statuses were based on the screening visit. The percentage of patients with ECOG 2-3 reported in the tables above and the prescribing information is lower because these were derived from the patients' baseline visit (at cycle 1, day 1). In some cases, the ECOG performance status changed between screening and baseline.*

For 4 patients in the azacitidine group and 2 patients in the decitabine group, patients qualified for the modified Ferrara group based on a ECOG 2-3 at screening without any additional known comorbidities, but then had an ECOG of 0-1 at baseline. Arguably, with a baseline ECOG score

of 0-1 and no other known comorbidities, these patients could have been excluded from the modified Ferrara group. However, the clinical decision for the appropriate treatment for these patients was made at screening which was acceptable for enrollment on the study. These patients remained in the modified Ferrara groups, and their baseline ECOG (not at screening) was reflected in the demographics tables here and in the prescribing information.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

See Section 8.2.2 for review of overall exposure. The Applicant completed an analysis of dose intensity. Among patients receiving 400 mg venetoclax with azacitidine, the median dose intensity, accounting for planned dose reductions with concomitant CYP3A inhibitors and interruptions between cycles, was 83.3% (range, 18.9% to 256.4%). Among patients receiving 400 mg venetoclax with decitabine, median dose intensity for all patients, accounting for planned dose reductions with concomitant CYP3A inhibitors and interruptions between cycles, was 80.5% (range, 45.3% to 217.8%).

Hydroxyurea use was permitted to meet eligibility criterion of WBC count ≤25 $x10^9$/L. In patients treated at any dose of venetoclax in combination with azacitidine or decitabine, 20% and 18% used hydroxyurea, respectively.

For TLS prophylaxis, patients were required to received anti-hyperuricemics (allopurinol or rasburicase). Allopurinol was used in 78% of patients treated with venetoclax with azacitidine and 81% of patients treated with venetoclax with decitabine.

Filgrastim was used in 41% of patients with venetoclax with azacitidine and 53% of patients treated with venetoclax with decitabine.

The most frequent concomitant medications taken by ≥40% of patients in either treatment combination were: acyclovir, cefepime, cefpodoxime, diphenhydramine, docusate, filgrastim, furosemide, levofloxacin, lorazepam, magnesium sulfate, micafungin, ondansetron, oxycodone, pantoprazole, paracetamol, potassium, prochlorperazine, sodium chloride, valaciclovir, and vancomycin.

Moderate and strong CYP3A inhibitors were permitted with a 2-fold or 8-fold reduction in venetoclax, respectively, starting in Amendment 5. The following moderate or strong CYP3A inhibitors were used in patients treated with 400 mg venetoclax in combination with azacitidine: ciprofloxacin (14.3%), diltiazem (6%), isavuconazonium (21.4 %), posaconazole (21.4 %) and voriconazole (9.5%). Patients with decitabine were enrolled prior to Amendment 5, so moderate and strong CYP3A inhibitors were allowed only venetoclax interruption.

Efficacy Results – Primary Endpoint

Table 28 and Table 29 summarize efficacy results on key endpoints of Study M14-358. Comparison of study remission rates with historical controls are shown in Figure 10 and Figure 11.

Table 28: Study M14-358 Remission Rates and Duration: Venetoclax + Azacitidine

Response	Modified Ferrara No N=17	Modified Ferrara Yes N=67	Overall N=84
CR [Responders/N, % (95% CI)]	6/17, 35 (14, 62)	25/67, 37 (26, 50)	31/84, 37 (27, 48)
DOR [Median (Range), months][1]	9.3 (0, 18)	5.5 (0, 30)	5.5 (0, 30)
CRh [Responders/N, % (95% CI)]	7/17, 41 (18, 67)	16/67, 24 (14, 36)	23/84, 27 (18, 38)

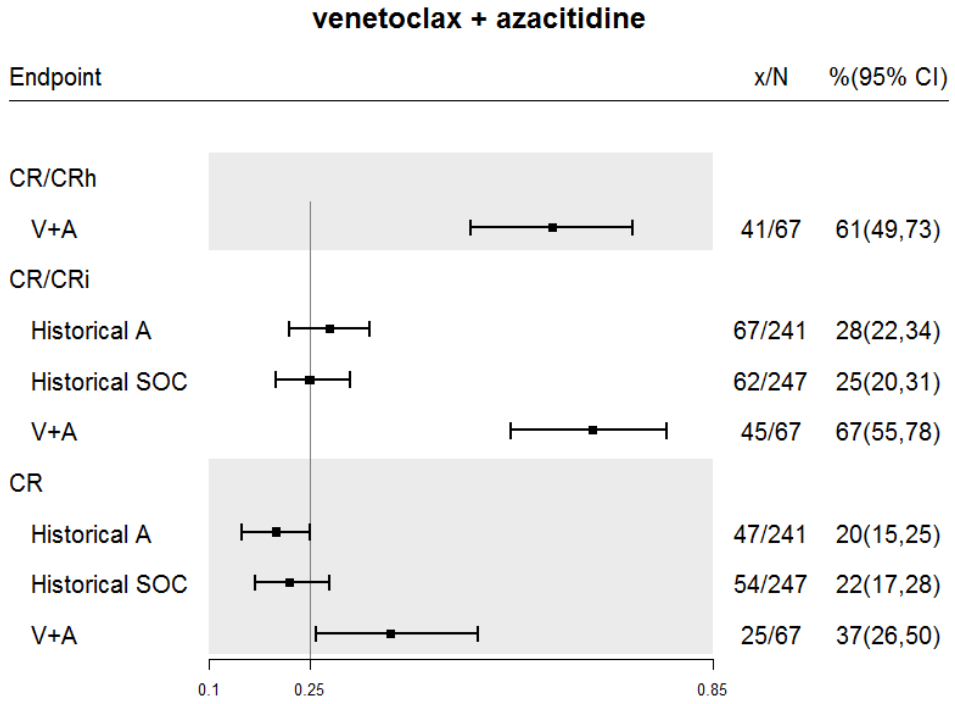
[Source: FDA Statistical Reviewer's Analysis]
[1] Observed DOR

Table 29: Study M14-358 Remission Rates and Duration: Venetoclax + Decitabine

Response	Modified Ferrara No N=18	Modified Ferrara Yes N=13	Overall N=31
CR [Responders/N, % (95% CI)]	10/18, 56 (31, 78)	7/13, 54 (25, 81)	17/31, 55 (36, 73)
DOR [Median (Range), months][1]	6.9 (0, 21)	4.7 (1, 18)	6.3 (0, 21)
CRh [Responders/N, % (95% CI)]	4/18, 22 (6, 48)	1/13, 8 (0, 36)	5/31, 16 (5, 34)

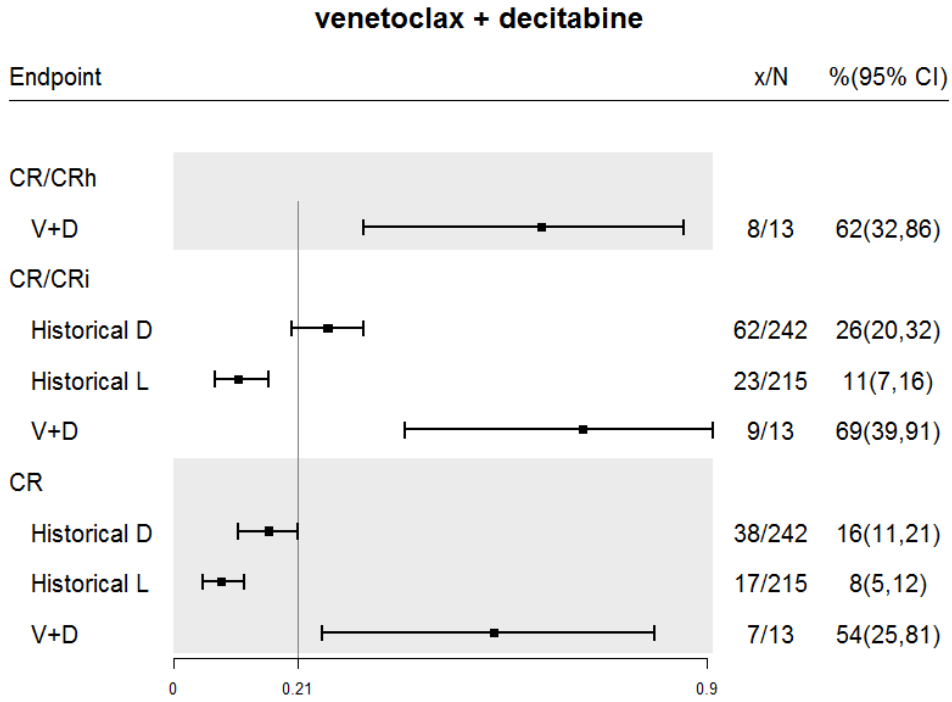
[Source: FDA Statistical Reviewer's Analysis]
[1] Observed DOR

Figure 10: Study M14-358 Remission Rates: Venetoclax + Azacitidine



V=venetoclax; A=azacitidine; V+A=venetoclax in combination with azacitidine; SOC=Standard of Care (standard induction chemotherapy, low-dose cytarabine, or supportive care only); Historical A and Historical SOC CR rates are based on Dombret et. al (2015); x=number of responders; N=sample size; CI=confidence interval.
[Source: FDA Statistical Reviewer's Analysis]

Figure 11: Study M14-358 Remission Rates: Venetoclax + Decitabine



V=venetoclax; D=decitabine; L=LDAC; V+D=venetoclax in combination with decitabine; Historical D and Historical L CR rates are based on Kantarjian et. al (2012); x=number of responders; N=sample size; CI=confidence interval.
[Source: FDA Statistical Reviewer's Analysis]

Data Quality and Integrity

Data from the Study M14-358 were provided electronically. The data quality of the submission was acceptable to perform the review.

Efficacy Results – Secondary and other relevant endpoints

Time to response

Time to response is the time from the first dose of study drug to the day of the first response. Table 30 and Table 31 summarize time to CR and time to CR or CRh.

Table 30: Study M14-358 Time to Response: Venetoclax + Azacitidine

Time to Response	Venetoclax + Azacitidine Median Days (Range)
Time to CR	
Modified Ferrara Yes (n=25)	28 (22-151)
Modified Ferrara No (n=6)	28 (27-100)
Time to CR or CRh	
Modified Ferrara Yes (n=41)	29 (22-271)
Modified Ferrara No (n=13)	30 (26-100)

[Source: FDA Statistical Reviewer's Analysis]

Table 31: M14-358 Time to Response: Venetoclax + Decitabine

Time to Response	Venetoclax + Decitabine Median Days (Range)
Time to CR	
Modified Ferrara Yes (n=7)	58 (27-128)
Modified Ferrara No (n=10)	40 (24-108)
Time to CR or CRh	
Modified Ferrara Yes (n=8)	58 (25-128)
Modified Ferrara No (n=14)	54 (24-421)

[Source: FDA Statistical Reviewer's Analysis]

MRD

Minimal residual disease (MRD) was evaluated in Study M14-358 by multicolor flow cytometry from bone marrow aspirate samples using a MRD threshold of <0.1% (10^{-3}). MRD was collected at the end of cycle 1 and cycle 3 then every 3 cycles thereafter and at the final visit or time of relapse. The frequency of MRD <0.1% reported in patients who achieved a best response of CR or CRh are shown in Table 32.

Table 32: MRD results for patient who had a best response of CR or CRh

	Venetoclax 400 mg + Azacitidine N=54	Venetoclax 400 mg + Decitabine N=22
	n (%)	n (%)
MRD <0.1%	27 (50%)	8 (36%)
MRD ≥0.1% to 1.0%	21 (39%)	10 (46%)
MRD ≥1.0%	4 (7%)	1 (5%)
Missing	2 (4%)	3 (14%)

Source: Clinical CSR

Of the patients who had a best response of CR or CRh, 4 patients in the azacitidine combination and 2 in the decitabine combination had MRD <0.01%. Based on the total patients treated in those combination, this represents 5% in the azacitidine arm and 6% in the decitabine arm who had MRD <0.01%.

Reviewer comment: *AML is a heterogenous disease, and it can be difficult to distinguish leukemia cells from underlying clonal hematopoiesis. For this reason, the false-positive and false-negative rate for MRD assays in AML can be variable. While MRD is a continuum, the appropriate threshold that correlates to an improvement in survival has not been validated. While this information is suggestive of efficacy of venetoclax in combination with azacitidine or decitabine, insufficient evidence is provided to include this information in the prescribing information.*

Transfusion independence
Transfusion independence was evaluated in patients who were transfusion dependent at baseline defined as those who required a red blood cells (RBC) or platelet transfusion in 8 weeks prior to starting study treatment. Transfusion independence was defined as any 56-day window without a transfusion.

In the azacitidine group, 50 patients were RBC transfusion dependent and 26 patients were platelet transfusion dependent. For RBCs, 25/50 (50%) became RBC transfusion independent with 20 of those patients with response of CR or CRh. For platelets, 15/26 (58%) became platelet transfusion independent, with 11 patients of those patients with a response of CR or CRh.

In the decitabine group, 23 patients were RBC transfusion dependent and 5 patients were platelet transfusion dependent. For RBCs, 12/23 (52%) became RBC transfusion independent, with 11 of those patients with response of CR or CRh. For platelets, 3/5 (60%) became platelet transfusion independent, with 1 of those patients with a response of CR or CRh.

Reviewer comment: *Rates of transfusion independence have been reported in the prescribing information for low-intensity therapies for AML that are generally considered non-curative where transfusion independence can be considered a measure of clinical benefit. While transfusion independence may be considered of benefit in the trials of venetoclax in combination, the transfusion independence is driven largely by the responses where a platelet count of >50,000/uL precludes the need for platelet transfusion. Hemoglobin is not in the response criteria for AML, but most patients with response also have an improvement in hemoglobin which also precludes the need for RBC transfusion.*

Other endpoints
Secondary endpoints of TTP, PFS, and OS were presented by the Applicant, but were not evaluated for purposes of this review.

Dose/Dose Response

See Section 6.3 of the review.

Durability of Response

See Table 28 and Table 29 for duration of response data for venetoclax in combination with azacitidine or decitabine

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient experience data have not been submitted in this application.

Additional Analyses Conducted on the Individual Trial

Table 33 and Table 34 show CR rates by subgroup in venetoclax in combination with azacitidine (N=84) and decitabine groups (N=31), respectively.

Table 33: Study M14-358 Subgroup Analyses: Venetoclax + Azacitidine

		Responders/N	% (95% CI)
Age	<75	16/42	38(24,54)
	>=75	15/42	36(22,52)
Sex	Female	10/33	30(16,49)
	Male	21/51	41(28,56)
Race	Missing	3/6	50(12,88)
	Non-White	3/7	43(10,82)
	White	25/71	35(24,47)
Cytogenetics	Intermediate	22/50	44(30,59)
	No Mitosis	0/1	NA
	Poor	9/33	27(13,46)
AML	Primary	27/63	43(30,56)
	Secondary	4/21	19(5,42)
ECOG	2-3	11/26	42(23,63)
	0-1	20/58	34(22,48)
Mutations	FLT3	6/11	55(23,83)
	IDH1 or IDH2	8/20	40(19,64)
	NPM1	7/14	50(23,77)
	TP53	6/20	30(12,54)

[Source: FDA Statistical and Clinical Reviewer's Analysis]

Table 34: Study M14-358 Subgroup Analyses: Venetoclax + Decitabine

		Responders/N	% (95% CI)
Age	<75	13/23	57(34,77)
	>=75	4/8	50(16,84)
Sex	Female	9/16	56(30,80)
	Male	8/15	53(27,79)
Race	Non-White	1/4	25(1,81)
	White	16/27	59(39,78)
Cytogenetics	Intermediate	10/16	62(35,85)
	Poor	7/15	47(21,73)
AML	Primary	11/22	50(28,72)
	Secondary	6/9	67(30,93)
ECOG	2-3	1/4	25(1,81)
	0-1	16/27	59(39,78)
Mutations	FLT3	1/3	33(1,91)
	IDH1 or IDH2	5/5	100(48,100)
	NPM1	3/3	100(29,100)
	TP53	4/7	57(18,90)

[Source: FDA Statistical and Clinical Reviewer's Analysis]

***Reviewer's Comments**: The subgroups analyses generally support the efficacy of venetoclax in combination with azacitidine or decitabine. No outlier subgroups were observed.*

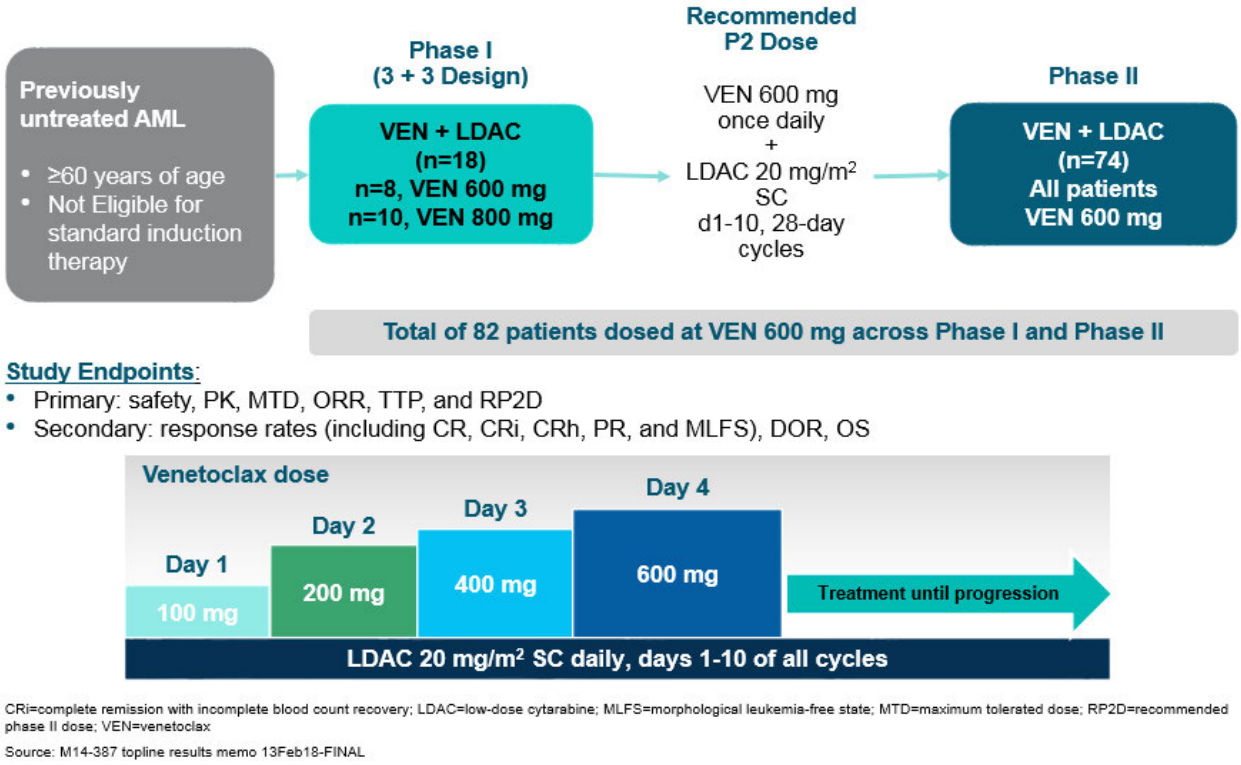
8.1.2. M14-387

Title: A Phase 1/2 Study of Venetoclax in Combination with Low-Dose Cytarabine in Treatment-Naïve Subjects with Acute Myelogenous Leukemia Who Are ≥ 60 Years of Age and Who Are Not Eligible for Standard Anthracycline-Based Induction Therapy

Trial Design

Study M14-387 was a Phase 1/2, nonrandomized, multicenter study that evaluated the PK, safety, and preliminary efficacy of venetoclax in combination with LDAC in newly diagnosed patients with AML ≥ 60 years old and who were not eligible for standard induction therapy because of age, co-morbidity, or other factors. Figure 12 shows Study M14-387 design schema.

Figure 12: Study M14-387 Design Schema



CRi=complete remission with incomplete blood count recovery; LDAC=low-dose cytarabine; MLFS=morphological leukemia-free state; MTD=maximum tolerated dose; RP2D=recommended phase II dose; VEN=venetoclax

Source: M14-387 topline results memo 13Feb18-FINAL

[Source: Applicant's Orientation Meeting]

This study consisted of 3 distinct portions. The first portion of the study was a Phase 1, or dose-escalation portion, that evaluated the safety and PK profile of venetoclax administered with LDAC with the objectives of defining the MTD and generating data to support a RPTD. A subsequent initial Phase 2 portion evaluated whether the RPTD had sufficient efficacy and acceptable toxicity to warrant further development of the combination therapy. Subsequently, a Phase 2, Cohort C was enrolled to evaluate the ORR for patients who were allowed additional supportive medications (e.g., strong CYP3A inhibitors), if medically indicated, because new PK data emerged from external studies demonstrating that these previously excluded concomitant medications may be tolerable with an appropriate venetoclax dose adjustment during co-administration.

The study was designed to enroll up to approximately 42 patients (actual enrollment: 18 patients) in Phase 1, approximately 50 patients (actual enrollment: 53 patients) in the initial Phase 2 portion at the RPTD, and approximately 20 patients (actual enrollment: 23 patients [only 21/23 patients received study drug]) in Phase 2, Cohort C.

Clinical reviewer comment: *See comment under trial design for Study M14-358 regarding identifying patients who should not receive intensive induction chemotherapy by age or patient comorbidities. Patients were enrolled under the modified Ferrara criteria starting in*

Amendment 2. Additional patients were identified retrospectively who met the modified Ferrara criteria prior to the change in inclusion criteria. This resulted in 61 patients who were treated with the target dose of 600 mg of venetoclax in combination with LDAC in this study. Of note, patients with any cytogenetics could be enrolled in this study, and patients could have been treated with prior hypomethylating agents for preceding myelodysplastic syndrome.

Study Endpoints

Study M14-387 used the same endpoints as Study M14-358 (see Study Endpoints in Section 8.1.1).

Statistical Analysis Plan

Study M14-387 used the same analysis populations and analysis methods as Study M14-358 (see Study Endpoints in Section 8.1.1).

Sample Size Determination

M14-387 was a Phase 1/2 study where the Phase 1 portion is a dose escalation study and the Phase 2 portion is a dose expansion study. For the Phase 1 portion of the study, the sample size is dependent upon the dose levels utilized and whether toxicities require and allow enrollment of 3 or 6 patients to dose levels. For the initial Phase 2 portion, approximately 50 patients were planned to be enrolled. With 50 patients, the 95% confidence intervals for estimation of ORR would have a margin of error not exceeding 15%. Clopper and Pearson 95% confidence intervals for expected observed rates for a sample size of 50 patients were calculated. With 50 patients, an ORR rate of approximately 15% lower than the observed rate would be ruled out.

For Cohort C, approximately 20 patients were planned to be enrolled to assess the experience of dosing venetoclax with LDC to evaluate if the efficacy of the combination is still consistent with that observed in previously treated patients. These factors include more objectively defined criteria with a lower age limit, modification to the venetoclax dose to account for strong CYP3A inhibitors, and potential reduction in liver/kidney function allowed for enrollment.

Protocol Amendments

Amendment 1 (11 November 2015)

- Update Section 5.1, Overall Study Design and Plan: Description; Section 8.2, Determination of Sample Size; Table 10, 95% Confidence Intervals for Assumed Observed Rates Based on Sample Size of 50 Patients; and throughout the protocol, to increase the number of patients to be enrolled in Phase 2 to approximately 50. Rationale: To improve accuracy of estimation of the Overall Response Rate (ORR) rate.

- Replace Week 12 with Cycle 3 throughout the protocol. Rationale: For consistency throughout the protocol and to account for the possibility that delays may happen in earlier cycles which would uncouple the number of weeks and the number of cycles on study.
- Change every 12 weeks to every 3 Cycles. Rationale: For consistency throughout the protocol.
- Update Section 5.3.3, Efficacy Variables, Efficacy Assessments, Reporting of Results. Rationale: To clarify results to be reported: "The secondary objectives of the Phase 2 portion are to evaluate leukemia response (rates of CR, CRi, PR, RD, and HR, including transfusion support needs) and duration of response (DOR)."

Amendment 2 (28 November 2016)

- Updated the primary objective and in turn added Cohort C to the study which increases the sample size by 20 patients. Rationale: To evaluate the ORR and safety when allowing patients who potentially require co-treatment with a strong CYP3A inhibitors.
- Added the Cohort C study population. Rationale: To add additional objective criteria to help define patients with AML who are not eligible for anthracycline-based induction therapy.
- Updated Section 5.1, Overall Study Design and Plan: Description; Section 5.3.1, Safety and Efficacy Measurement; Section 5.4.1, Discontinuation of Individual Patients, with Post-treatment follow-up visit and Survival Assessment language. Rationale: To carefully evaluate the disease course and survival of patients after study treatment has concluded.

Amendment 3 (31 May 2017)

- Efficacy endpoint was modified to remove Time to Progression (TTP) and Progression Free Survival (PFS) and add Event Free Survival (EFS) throughout the protocol. Rationale: To be consistent with AML indication.
- Leukemia response rate was updated to include MLFS. Rationale: The leukemia response should include CR, CRi, PR, and MLFS only.

Amendment 4 (24 January 2018)

To update Section 8.1.3. Rationale: CRh rates and transfusion independence endpoints were added for efficacy summary.

Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with Good Clinical Practices including review of the clinical protocol, the informed consent, and patient information and/or advertising by an Independent Ethics Committee or Institutional

Review Board (IEC/IRB).

Financial Disclosure

A summary of financial disclosures for the studies included in the submission is provided in Appendix 15.2. The Applicant submitted financial disclosure information from all investigators and sub-investigators from M14-387. No investigators had disclosable financial interests. No bias is expected in the study outcome.

Patient Disposition

Nine study sites in the US, Australia, Germany, and Italy screened 115 patients. As of the efficacy data cutoff date (8 November 2017), 94 participants were enrolled. Ninety-two participants received at least one dose of study drug and two participants did not receive study drug. **Table 35** shows patient disposition for venetoclax (600mg) in combination with low-dose cytarabine (n=82).

The following is a summary for patients meeting the modified Ferrara criteria (n=61) in venetoclax in combination with low-dose cytarabine. The most common reason for study discontinuation was progressive disease (41%). Most common reasons for venetoclax discontinuation were adverse event (26%) and progressive disease (39%). Most common reasons for low-dose cytarabine discontinuation were investigator decision (20%), adverse event (28%), progressive disease (31%).

Table 35: Study M14-387 Patient Disposition: Venetoclax + LDAC

	Modified Ferrara No N=21 n (%)	Modified Ferrara Yes N=61 n (%)	Overall N=82 n (%)
Discontinued Study	21 (100)	54 (89)	75 (91)
Adverse Event	5 (24)	14 (23)	19 (23)
Investigator Request	2 (10)	4 (7)	6 (7)
Other	4 (19)	6 (10)	10 (12)
Death	0 (0)	1 (2)	1 (1)
Progressive Disease	7 (33)	25 (41)	32 (39)
With Death	1 (5)	10 (16)	11 (13)
Without Death	6 (29)	15 (25)	21 (26)
Withdrawal by Patient	3 (14)	5 (8)	8 (10)
Discontinued Venetoclax	21 (100)	54 (89)	75 (91)
Adverse Event	6 (29)	16 (26)	22 (27)
Investigator Judgment and/or Request	2 (10)	6 (10)	8 (10)
Other	4 (19)	4 (7)	8 (10)
Death	0 (0)	1 (2)	1 (1)
Progressive Disease	6 (29)	24 (39)	30 (37)
Withdrawal by Patient	3 (14)	4 (7)	7 (9)
Low-dose Cytarabine	21 (100)	54 (89)	75 (91)
Adverse Event	7 (33)	17 (28)	24 (29)
Investigator Judgment and/or Request	3 (14)	12 (20)	15 (18)
Other	3 (14)	2 (3)	5 (6)
Progressive Disease	5 (24)	19 (31)	24 (29)
Withdrawal by Patient	3 (14)	4 (7)	7 (9)

[Source: FDA Statistical Reviewer's Analysis]

Protocol Violations/Deviations

Protocol deviations were defined in accordance with the ICH guidelines and included but were not limited to: inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications.

Inclusion/Exclusion Criteria Violation
Three patients received study treatment but did not fulfill the study entry criteria (Exclusion Criteria 6). Per CSR, patient (b) (6) was incorrectly listed as also meeting Exclusion Criteria 5, this error has been subsequently corrected in the live database. In all 3 instances, patients received a CYP3A inhibitor which was an exclusion at the time of enrollment.

Receipt of Wrong Treatment or Incorrect Dose
Five patients received study treatment at the wrong time or at the incorrect dose level.

Use of Prohibited Concomitant Medication
Nineteen patients took concomitant medication that was prohibited at the time of receipt: ciprofloxacin, clarithromycin, diltiazem, fluconazole, and voriconazole. Subsequently, protocol amendments allowed each of these medications with an appropriate reduction in venetoclax dose.

Demographic Characteristics

Table 36 summarizes demographic characteristics of patients treated with venetoclax in combination with LDAC.

Table 36: Demographic Characteristics: Venetoclax + LDAC

	Modified Ferrara No n (%)	Modified Ferrara Yes n (%)	Overall n (%)
N	21	61	82
Age: Median (Range)	72 (67-74)	76 (63-90)	74 (63-90)
Age Group			
<75	21 (100)	21 (34)	42 (51)
>=75	0 (0)	40 (66)	40 (49)
Sex			
Female	13 (62)	16 (26)	29 (35)
Male	8 (38)	45 (74)	53 (65)
Race			
Asian	1 (5)	1 (2)	2 (2)
Black	1 (5)	1 (2)	2 (2)
Missing	0 (0)	3 (5)	3 (4)
White	19 (90)	56 (92)	75 (91)
Country			
Australia	11 (52)	10 (16)	21 (26)
Germany	2 (10)	5 (8)	7 (9)
Italy	1 (5)	2 (3)	3 (4)
United States	7 (33)	44 (72)	51 (62)

[Source: FDA Statistical Reviewer's Analysis]

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

Table 37 summarizes baseline characteristics of patients treated with venetoclax in combination with LDAC.

Table 37: Baseline Characteristics: Venetoclax + LDAC

	Modified Ferrara No n (%)	Modified Ferrara Yes n (%)	Overall n (%)
N	21 (100)	61 (100)	82 (100)
Cytogenetics			
Intermediate	13 (62)	36 (59)	49 (60)
Poor	5 (24)	21 (34)	26 (32)
No Mitoses	3 (14)	4 (7)	7 (9)
AML Type			
Primary	9 (43)	33 (54)	42 (51)
Secondary	12 (57)	28 (46)	40 (49)
AML w/MRC			
No	9 (43)	33 (54)	42 (51)
Yes	12 (57)	28 (46)	40 (49)
ECOG			
0	6 (29)	6 (10)	12 (15)
1	12 (57)	34 (56)	46 (56)
2	3 (14)	20 (33)	23 (28)
3	0 (0)	1 (2)	1 (1)
Blasts			
< 30%	5 (24)	22 (36)	27 (33)
≥30%-<50%	6 (29)	12 (20)	18 (22)
≥ 50%	10 (48)	26 (43)	36 (44)
Missing	0 (0)	1 (2)	1 (1)
Prior HMA use			
Yes	8 (38)	16 (26)	24 (29)
No	13 (62)	45 (74)	58 (71)

[Source: FDA Statistical and Clinical Reviewer's Analysis]

Clinical Reviewer comment: *In 4 patients with secondary AML from prior myeloproliferative neoplasms (MPN), no responses were observed. After enrollment of these 4 patients, patients with prior MPN were excluded from both studies. The Applicant suggests that pre-clinical data indicate the MPN is more dependent on BCL-XL than BCL-2. Patients with prior MPN were not excluded from the efficacy evaluable population. However, the data on the treatment of patients with prior MPN is limited by their exclusion from the studies.*

See comment under baseline characteristics for M14-385 regarding ECOG performance status for enrollment in the modified Ferrara criteria treatment group. There was one patient in the LDAC group who qualified for the modified Ferrara group based on a ECOG 2-3 at screening without any additional known comorbidities, but then had an ECOG of 0-1 at baseline. This patient was retained in the modified Ferrara group for the reasons outlined under M14-385.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

See Section 8.2.2 for review of overall exposure. The Applicant completed an analysis of dose intensity. The median dose intensity of venetoclax accounting for the planned dose reductions when taking concomitant CYP3A inhibitors and interruptions was 96.5% (range: 33.4% to 191.5%) for all patients.

Hydroxyurea use was permitted to meet eligibility criterion of WBC count ≤25 x109/L. In patients treated at any dose of venetoclax in combination with LDAC, 7% used hydroxyurea.

For TLS prophylaxis, patients were required to received anti-hyperuricemics (allopurinol or rasburicase). Allopurinol was used in 90% of patients treated with venetoclax with LDAC.

Filgrastim was used in 25% of patients with venetoclax with LDAC.

The most frequent concomitant medications taken by ≥40% of patients were: acyclovir, furosemide, levofloxacin, lidocaine, magnesium sulfate, ondansetron, oxycodone, pantoprazole, paracetamol, piperacillin/tazobactam, potassium, valaciclovir, and vancomycin.

Moderate and strong CYP3A inhibitors were permitted with a 2-fold or 8-fold reduction in venetoclax, respectively, starting in Amendment 2. Thirty-seven patients (40.2%) took moderate inhibitors with venetoclax for a period of at least 7 days and 6 patients (6.5%) took strong inhibitors.

Efficacy Results – Primary Endpoint

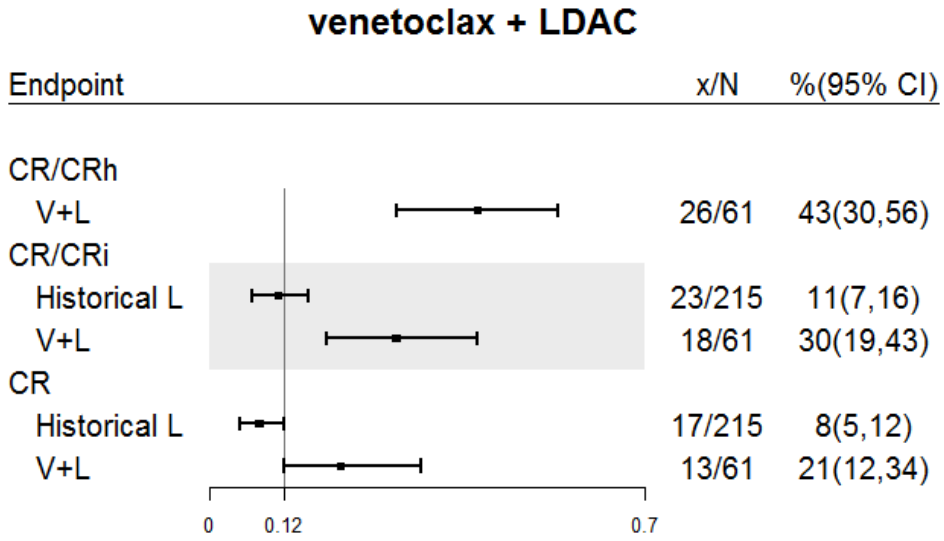
Table 38 summarizes efficacy results on key endpoints of Study M14-387. Comparison of study remission rates with historical controls are shown in Figure 13.

Table 38: Study M14-387 Remission Rates and Duration: Venetoclax and LDAC

Response	Modified Ferrara No N=21	Modified Ferrara Yes N=61	Overall N=82
CR [Responders/N, % (95% CI)]	7/21, 33 (15, 57)	13/61, 21 (12, 34)	20/82, 24 (16, 35)
DOR [Median (Range), months][1]	7.2 (1.6, 17)	6.0 (0, 25)	6.6 (0, 25)
CRh [Responders/N, % (95% CI)]	5/21, 24 (8, 47)	13/61, 21 (12, 34)	18/82, 22 (14, 32)

[Source: FDA Statistical Reviewer's Analysis]
[1] Observed DOR

Figure 13: Study M14-387 Remission Rates: Venetoclax + LDAC



V=venetoclax; L=LDAC; V+L=venetoclax in combination with LDAC; Historical L CR rates are based on Kantarjian et. al (2012); x=number of responders; N=sample size; CI=confidence interval.
[Source: FDA Statistical Reviewer's Analysis]

Data Quality and Integrity

Data from the Study M14-387 were provided electronically. The data quality of the submission was acceptable to perform the review.

Efficacy Results – Secondary and other relevant endpoints

Time to Response

Time to response is the time from the first dose of study drug to the day of the first response. Table 39 summarizes time to CR and time to CR or CRh.

Table 39: Study M14-387 Time to Response: Venetoclax + LDAC

Time to Response	Venetoclax + LDAC Median Days (Range)
Time to CR	
Modified Ferrara Yes (n=13)	30 (24-90)
Modified Ferrara No (n=7)	57 (23-139)
Time to CR or CRh	
Modified Ferrara Yes (n=26)	30 (23-285)
Modified Ferrara No (n=12)	47 (23-139)

[Source: FDA Statistical Reviewer's Analysis]

MRD

MRD was evaluated in Study M14-387 by multicolor flow cytometry from bone marrow aspirate samples using a MRD threshold of <0.1% (10^{-3}). MRD was collected at the end of cycle 1 and cycle 3 then every 3 cycles thereafter and at the final visit or time of relapse. The frequency of MRD <0.1% reported in patients who achieved a best response of CR or CRh are shown in Table 40.

Table 40: MRD results for patient who had a best response of CR or CRh

	Venetoclax 400 mg + LDAC N=38
	n (%)
MRD <0.1%	13 (34%)
MRD ≥0.1% to 1.0%	21 (55%)
MRD ≥1.0%	4 (11%)
Missing	0

Source: Clinical CSR

Of the patients who had a best response of CR or CRh, 1 patient in the LDAC combination had MRD <0.01%. Based on the total patients treated in this combination, this represents 1% in the LDAC arm who had MRD <0.01%.

Reviewer comment: *See results of Study M14-358 for a discussion of the inclusion of MRD information in the in the prescribing information.*

Transfusion independence
Transfusion independence was evaluated in patients who were transfusion dependent at baseline defined as those who required a red blood cells (RBC) or platelet transfusion in 8 weeks prior to starting study treatment. Transfusion independence was defined as any 56-day window without a transfusion.

In the LDAC group, 53 patients were RBC transfusion dependent and 23 patients were platelet transfusion dependent. For RBCs, 23/53 (43%) became RBC transfusion independent with 18 of those patients with response of CR or CRh. For platelets, 15/23 (65%) became platelet transfusion independent, with 12 patients of those patients with a response of CR or CRh.

Reviewer comment: *See results of Study M14-358 for a discussion of the inclusion of transfusion independence information in the in the prescribing information.*

Other endpoints
Secondary endpoints of TTP, PFS, and OS were presented by the Applicant, but were not evaluated for purposes of this review.

Dose/Dose Response

See Section 6.3 of the review.

Durability of Response

See Table 38 for duration of response data for venetoclax in combination with LDAC.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient experience data have not been submitted in this application.

Additional Analyses Conducted on the Individual Trial

Table 41 shows subgroup analysis for venetoclax in combination with LDAC group (N=82).

Table 41: Study M14-387 Subgroup Analyses: Venetoclax + LDAC

		Responders/N	% (95% CI)
Age	<75	10/42	24(12,39)
	>=75	10/40	25(13,41)
Sex	Female	8/29	28(13,47)
	Male	12/53	23(12,36)
Race	Missing	1/3	33(1,91)
	Non-White	1/4	25(1,81)
	White	18/75	24(15,35)
Cytogenetics	Intermediate	16/49	33(20,48)
	No Mitosis	0/7	0(0,41)
	Poor	4/26	15(4,35)
AML	Primary	18/42	43(28,59)
	Secondary	2/40	5(1,17)
ECOG	2-3	3/24	12(3,32)
	0-1	17/58	29(18,43)
Mutations	FLT3	2/16	13(2,38)
	IDH1 or IDH2	6/18	33(13,59)
	NPM1	6/9	67(30,93)
	TP53	0/10	0(0,31)

[Source: FDA Statistical and Clinical Reviewer's Analysis]

Reviewer's Comments*: The subgroups analyses generally support the efficacy of venetoclax in combination with azacitidine or decitabine. No outlier subgroups were observed.*

8.1.3. M14-212

Title: A Phase 2 Study of ABT-199 in Subjects with Acute Myelogenous Leukemia (AML)

Trial Design

M14-212 was a Phase 2 study of preliminary efficacy and safety of single-agent venetoclax that was conducted primarily in patients with relapsed or refractory AML. There was a small cohort of newly-diagnosed patients who declined standard induction chemotherapy.

Patient inclusion criteria (summary) included:

- ≥ 18 years of age.
- Histological or cytological confirmation of R/R AML (by WHO classification) OR untreated AML in patients who were unfit for intensive therapy.
- Eastern Cooperative Oncology Group (ECOG) Performance score of 0 to 2.
- Adequate renal function, adequate liver function
- Patient *excluded* if a white blood cell (WBC) count > 25×10^9/L. Hydroxyurea was

permitted to meet this criterion.

Dosing began with a dose of 20 mg of venetoclax on Day 1, 50 mg on Day 2, 100 mg on Day 3, 200 mg on Day 4, 400 mg on Day 5, and 800 mg on Day 6 and daily thereafter.

Tumor lysis prophylaxis was administered in all patients including hospitalization for the first week, allopurinol administration, oral and IV hydration, and frequent chemistry assessments during dose ramp up.

Study Endpoints

Primary objective: to evaluate the preliminary efficacy of venetoclax administered orally in patients with R/R AML or frontline in patients with AML who were unfit for intensive therapy.

Secondary objective: to evaluate the preliminary safety of venetoclax administered orally in patients with AML

Statistical Analysis Plan

The study used a Simon 2-stage optimal design to evaluate preliminary efficacy.
The first portion of the study was to enroll 19 patients. If ≥5 of 19 patients achieved an overall response (CR+CRi+PR), then an additional 35 patients may be enrolled. The criterion for success would have been met if ≥16 of 54 patients achieved remission.

Study Results

Compliance with Good Clinical Practices

The independent ethics committee (IEC)/institutional review board (IRB) reviewed the relevant clinical documents as required by Good Clinical Practice (GCP).

Financial Disclosure

A summary of financial disclosures for the studies included in the submission is provided in Appendix 15.2. The Applicant submitted financial disclosure information from all investigators and sub-investigators from M14-212. One sub-investigator had disclosable financial interests. Fifteen patients were enrolled at that site. The CR rate at this site was similar to the overall CR rate in the trial. No bias is expected in the study outcome.

Patient Disposition

Overall, 32 patients were enrolled. All patients have now discontinued therapy. 72% discontinued due to progressive disease, 9% due to an AE related to progressive disease, and 3% due to an AE not related to disease progression.

Table of Demographic Characteristics and Baseline Disease Characteristics

Demographic characteristics and baseline disease characteristics were summarized by the Applicant and provided in the Table below.

Table 42: M14-212 Demographics and baseline disease characteristics

Characteristic		All Subjects N = 32
Sex, n (%)	Female	16 (50.0)
	Male	16 (50.0)
Race, n (%)	White	25 (78.1)
	Black	4 (12.5)
	Asian	3 (9.4)
Ethnicity	Hispanic or Latino	2 (6.3)
	No ethnicity	30 (93.8)
Age (years)	Mean (Std Dev)	65.9 (14.81)
	Median	70.5
	Min – Max	19.0 – 84.0
Age, n (%)	< 65 years	13 (40.6)
	≥ 65 years	19 (59.4)
Weight (kg)	Mean (Std Dev)	77.0 (18.25)
	Median	72.9
	Min – Max	46.8 – 125.8

Characteristic		All Subjects N = 32
Any prior hematologic illness		32 (100)
	AML	11 (34.4)
	AML and myelodysplastic syndromes	11 (34.4)
	AML with maturation	1 (3.1)
	AML with multilineage dysplasia	1 (3.1)
	AML with recurrent genetic abnormalities	4 (12.5)
	AML, minimally differentiated	2 (6.3)
	Acute myelomonocytic leukemia	1 (3.1)
	AML with IDH-1 mutation	1 (3.1)
Number of prior anti-tumor agents, n (%)	0	1 (3.1)
	1	8 (25.0)[a]
	2	10 (31.3)
	3	5 (15.6)
	4	4 (12.5)
	5	1 (3.1)
	≥ 6	3 (9.4)
Prior anti-tumor therapies, n (%)[b]	Standard induction (7 + 3) therapy	17 (53.1)
	Hypomethylating agents	26 (81.3)
	Allogenic stem cell transplant	4 (12.5)
	None (treatment naïve)	2 (6.3)[a,c]
Bone marrow blast count, %[d]	Mean (Std Dev)	48.2 (26.24)
	Median	50
	Min – Max	5.0 – 97.0
ECOG performance status, n (%)	Grade 0	3 (9.7)
	Grade 1	14 (45.2)
	Grade 2	14 (45.2)
	Missing	1
LDH, U/L[e]	Mean (Std Dev)	695.9 (877.69)
	Median	514.0
	Min – Max	138.0 – 4800.0

Source: CSR

Efficacy Results – Primary Endpoint

At interim analysis, 19 patients had been enrolled, and 4 patients achieved a CR/CRi. Based on the Simon 2-stage optimal design, this did not meet the threshold of ≥5 CR/CRi events to enroll into the second stage. During the time of the interim analysis, several patients were in the screening and were allowed to initiate treatment during the analysis. Therefore, 32 patients were enrolled overall. Table 43 shows the efficacy results from all enrolled patients. Two

patients were newly-diagnosed and had a best response of stable disease and progressive disease.

Table 43: Response rate in patients treated with venetoclax monotherapy

	All Patients N=32
CR	2 (6.3%) 95% CI: 0.8-20.8
CRi	4 (12.5%)
PR	-
SD	17 (53.1%)
PD	8 (25%)
Incomplete data	1 (3.1%)

Source: Clinical CSR

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints of TTP, PFS, OS, and MRD negativity were presented by the Applicant, but were not evaluated for purposes of this review.

Dose/Dose Response

Patients were treated with a short ramp up to a daily dose of 800 mg venetoclax, see Trial Design above. Patients could escalate to 1200 mg venetoclax at disease relapse or for lack of response. Four patients escalated for disease relapse and 11 patients for lack of response. No patients showed additional anti-leukemic activity after escalation to 1200 mg.

Durability of Response

Duration of response was not assessed due to the low remission rate. In the two patients who achieved a CR, the duration was 71 days and 207 days, respectively. In the patients who achieved a CRi, the duration was 28+ days, 50+ days, 56 days, and 77 days.

8.1.4. Assessment of Efficacy Across Trials

Due to the different backbone therapy for each combination, no formal comparison of efficacy was made across the two studies for the treatment of newly-diagnosed AML.

8.1.5. Integrated Assessment of Effectiveness

In this reviewer's assessment, the submitted evidence has provided substantial evidence of effectiveness for venetoclax in combination with azacitidine, decitabine, or LDAC for the treatment of patients with newly-diagnosed AML who are ≥75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy. The endpoint used to assess efficacy in the presented studies was CR rate and duration of CR, supported by CRh rate. The CR rate was 37% in combination with azacitidine, 54% in combination with decitabine, and 21% in combination with LDAC. The durability of responses support effectiveness in this population.

Reviewer comment: *An improvement in overall survival is generally the endpoint used for approval for the treatment of newly-diagnosed AML. However, for the patient population whose age or comorbidities preclude the use of intensive chemotherapy, the lack of approved available therapies that show long-term survival result in a high unmet medical need in this population. The CR rate and duration of CR represents a clinical benefit in this population.*

The studies presented use venetoclax in combination with other agents that are routinely used to treat this patient population without isolation of the treatment effect of either agent in the combination. There is no single-agent monotherapy data for the treatment of patients with newly-diagnosed AML. In the R/R AML setting, the efficacy of venetoclax monotherapy was unacceptably low for further development. In addition, the mechanism of action of venetoclax in combination with agents that cause DNA damage indicate that the combination therapy may show benefit over either venetoclax monotherapy or the backbone therapy alone.

While evaluation of azacitidine, decitabine, and LDAC published response rates is limited due to known or unknown confounders, the comparison with venetoclax in these combinations is useful to establish efficacy. Favorable CR rates with venetoclax in combination with azacitidine, decitabine, and LDAC were seen relative to the historical information.

Because the expansion cohort for the modified Ferrara group was for the treatment of patients with venetoclax in combination with azacitidine and no equivalent expansion cohort was enrolled for the treatment of patients with venetoclax in combination with decitabine, the enrollment in the decitabine group (any dose) overall was less. When only patients who were ≥75 years or with comorbidity were evaluated, only 13 patients treated with venetoclax in combination with decitabine were included. While these numbers are quite small for evaluation, the efficacy in the non-modified Ferrara criteria group were supportive of efficacy. In the modified Ferrara group, the response rates with decitabine may be higher than with azacitidine, though the 95% CI in the decitabine group is wide due to small patient numbers. The combination of venetoclax with decitabine represents an important treatment combination for these patients.

LDAC monotherapy is not as commonly used for the treatment of newly-diagnosed AML due to

suggestion of lower efficacy in cross-trial comparisons. However, a survival benefit has not been shown for azacitidine or decitabine over LDAC therapy. Similarly, the combination of venetoclax with LDAC appears to have lower response rates, but the durability of responses is similar. The combination of venetoclax with LDAC is therefore a useful treatment option for the treatment of patients with AML.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety for the combination of venetoclax in combination with azacitidine or decitabine was analyzed in study M14-358, and safety for the combination of venetoclax in combination with LDAC was analyzed in study M14-387. The studies were not designed to demonstrate statistically significant differences in adverse reaction rates or laboratory abnormalities for each combination, and observed differences could be attributed to both the difference in backbone therapy as well as differences in venetoclax dosing. Safety analyses were not pooled due to the differences in each combination backbone.

Any patient who received at least one dose of venetoclax was included in the safety evaluation. Review of deaths on study was performed for the whole safety population. Review of serious adverse reactions (ARs), severe ARs, and common ARs was limited to the adverse events at the planned labeled dose, however, an evaluation of dose-dependent ARs was performed if possible.

The proposed indication for use for venetoclax in combination with azacitidine, decitabine, or LDAC is limited to patients who should not receive intensive chemotherapy due to age or comorbidities. To ensure an adequate representation of the safety of venetoclax in this potentially frail population, additional analyses were performed for patients who met those criteria referred to as the modified Ferrara criteria in this review. See Section 8.1 for full details.

In M14-358, 212 patients received venetoclax at all doses with 127 in combination with azacitidine and 85 in combination with decitabine. Of those, 115 patients received venetoclax at the proposed labeled dose of 400 mg daily (84 with azacitidine and 31 with decitabine). In M14-387, 92 patients received venetoclax with LDAC at all doses of venetoclax with 82 patients at the proposed labeled dose of 600 mg daily.

MedDRA preferred terms were grouped when biologically reasonable to be considered the same event. See Appendix 15.6 for FDA grouped preferred terms. The grouping of preferred terms allowed for signal detection of relevant adverse events.

Reviewer comment: *The Sponsor agreed with the proposed grouping of preferred terms for the safety analysis. The grouped terms will be used for the safety evaluation in the prescribing information.*

8.2.2. Review of the Safety Database

Overall Exposure

See Section 8.1 for details of the treatment regimen for each combination. In these single arm trials, all patients received at least one dose of study drug. The median treatment duration for each combination is shown in Table 44.

Table 44: Median treatment duration in months

	Venetoclax + Azacitidine	Venetoclax + Decitabine	Venetoclax + LDAC
At all doses			
N	127	73*	92
Median	5.5 mo	6.7 mo	4.0 mo
Range	0.1-31.9	0.1-35.9	0.2-29.2
At proposed labeled dose			
N	84	31	82
Median	6.4 mo	5.7 mo	4.2 mo
Range	0.1-31.9	0.5-35.8	0.2-29.2

* Does not include 12 patients on DDI sub-study with venetoclax with decitabine and posaconazole
Source: Clinical CSRs

Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions, and the duration of treatment is adequate to allow assessment of adverse reactions over time.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

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

Categorization of Adverse Events

Adverse events were reported down to the verbatim term. The severity of events was rated

using the NCI CTCAE, version 4.0. A TEAE was defined as any event with onset after the first dose of study treatment and no more than 30 after discontinuation of study drug administration, whichever comes last. AEs were coded using MedDRA dictionary version 20.1, except for the monotherapy study which used version 18.1.

Safety data coding was evaluated by comparing the verbatim term and the MedDRA version 19.1 preferred term. Adverse events were assessed by frequency (i.e., events per patient).

Routine Clinical Tests

The frequency of clinical assessments is adequate to assess the risks of serious safety signals. Refer to the review of efficacy for the relevant trials for the general schedule of assessments.

8.2.4. Safety Results

Deaths

In Study M14-358 for the combination of venetoclax with azacitidine or decitabine, there were 115 overall. In the azacitidine combination, 38 deaths were due to disease progression per investigator assessment and 24 deaths not attributed to disease progression. The causes of deaths were:

Table 45: On treatment deaths in the safety population

	Venetoclax (all doses) + Azacitidine N=127	Venetoclax (all doses) + Decitabine N=85*	Venetoclax (all doses) + LDAC N=92
Total deaths	63 (58%)	52 (48%)	66 (72%)
30-day mortality	3 (2%)	4 (4%)	6 (7%)
60-day mortality	12 (9.4%)	8 (7%)	14 (15%)
Cause			
Primary disease	38 (30%)	34 (31%)	50 (53%)
Non-disease	24 (19%)	18 (17%)	16 (17%)
Missing	1 (1%)	-	-

* Includes DDI sub-study of 12 patients treated with venetoclax with decitabine and posaconazole
Source: Clinical CSR

Of note, the 30- and 60-day mortality rates for patients treated at 400 mg venetoclax were 2.4% and 8.3% for azacitidine and 6.5% and 9.7% for decitabine.

The FDA reviewed individual patient narratives from the 58 patients with deaths due to causes other than disease progression to confirm the cause of on-treatment deaths. Narratives were

not available for deaths due to disease progression or deaths that occurred more than 30 days after the last study treatment.

Reviewer comment: *The prescribing information describes only deaths due to adverse reactions in the first 30 days only. Additional deaths due to adverse events occurred throughout the trial, however, in a non-randomized trial it can be difficult to attribute deaths to underlying disease or to treatment. The deaths within the first 30 days of treatment is a reasonable landmark in AML to describe potential treatment effects.*

Serious Adverse Events

Serious adverse events (SAEs) in patients treated at the labeled dose of venetoclax on study M14-358 and M14-387 are shown in Table 46 and Table 47, respectively. The most frequent SAE in any combination was febrile neutropenia. See Sections 8.2.5.2 and 8.2.5.3 for discussion of neutropenia and infections. Sepsis appears to occur more frequently in the decitabine combination with caution due to the small sample size in that arm.

Table 46: SAEs occurring at >5% for venetoclax with azacitidine or decitabine

	Venetoclax 400 mg + Azacitidine N=84		**Venetoclax 400 mg + Decitabine N=31**	
	n	%	n	%
Febrile neutropenia	25	29.8	14	45.2
Pneumonia	18	21.4	8	25.8
Sepsis	8	9.5	10	32.3
Medical observation	7	8.3	0	0.0
Respiratory failure	5	6.0	2	6.5
Multiple organ dysfunction syndrome	4	4.8	0	0.0

Source: FDA analysis

Table 47: SAEs occurring at >5% for venetoclax with LDAC

	Venetoclax 600 mg + LDAC N=82	
	n	%
Febrile neutropenia	22	26.8
Sepsis	14	17.1
Pneumonia	12	14.6
Hemorrhage	10	12.2
Device related infection	4	4.9
Pyrexia	4	4.9

Source: FDA analysis

In patients who met the modified Ferrara criteria, the most frequent SAEs were:

- With venetoclax 400 mg + azacitidine (N=67)
  - Febrile neutropenia = 18 (26.9%)
  - Pneumonia = 14 (20.9%)
  - Medical observation = 7 (10.4%)
  - Sepsis = 6 (9.0%)
  - Respiratory failure = 5 (7.5%)
  - Multiple organ dysfunction syndrome = 4 (6.0%)
- With venetoclax 400 mg + decitabine (N=13)
  - Febrile neutropenia = 6 (46.2%)
  - Sepsis = 6 (46.2%)
  - Pneumonia = 3 (23.1%)
  - 1 (7.7%) SAE each of Respiratory failure, Acute coronary syndrome, Diarrhea, Fatigue, Leukocytosis, Cellulitis, Embolic stroke, 3rd nerve disorder, Localized infection, Lung infection, Respiratory arrest
- With venetoclax 600 mg + LDAC (N=61)
  - Febrile neutropenia = 19 (31.1%)
  - Sepsis = 10 (16.4%)
  - Hemorrhage = 8 (13.1%)
  - Pneumonia = 8 (13.1%)
  - Device related infection = 4 (6.6%)
  - Malignant neoplasm progression = 4 (6.6%)
  - Pyrexia = 3 (4.9%)

Dropouts and/or Discontinuations Due to Adverse Effects

In study M14-358, AEs that led to discontinuation of venetoclax occurred in 25 patients (20%)

treated with venetoclax plus azacitidine, for 15 patients (21%) treated with venetoclax plus decitabine, and for 3 patients (25%) treated with venetoclax plus decitabine in the DDI sub-study. AEs occurring in 2 or more patients were: pneumonia (3 with azacitidine, 3 with decitabine, 1 in DDI sub-study), sepsis (4 with azacitidine, 2 with decitabine), febrile neutropenia (2 with azacitidine), respiratory failure (3 with azacitidine, 1 with decitabine).

In study M14-387, AEs that lead to discontinuation of venetoclax occurred in 32 patients (35%) treated with venetoclax plus LDAC. AEs occurring in 2 or more patients were hemorrhage (4), sepsis (3), leukopenia (2), neutropenia (2), and thrombocytopenia (2).

Significant Adverse Events

Grade ≥3 adverse events defined by NCI-CTCAE in patients are shown in Table 48 for Study M14-358 and Table 49 for Study M14-387. Grade ≥3 adverse events for patients who met the modified Ferrara criteria are shown in Table 50 and Table 51.

The frequency of cytopenias is more accurately reflected in the analysis of the laboratory values. See the Laboratory Findings section below. The most common grade 3 or higher AEs were a result of cytopenias, including febrile neutropenia, pneumonia, sepsis, and hemorrhage. See relevant sections below for further discussion into these AEs.

Table 48: Grade ≥3 TEAEs occurring at >5% for venetoclax with azacitidine or decitabine

	Venetoclax 400 mg + Azacitidine N=84		**Venetoclax 400 mg + Decitabine N=31**	
	n	%	n	%
Febrile neutropenia	31	36.9	20	64.5
Pneumonia*	24	28.6	9	29.0
Sepsis	12	14.3	12	38.7
Hypertension	7	8.3	2	6.5
Fatigue	6	7.1	3	9.7
Hemorrhage	6	7.1	0	0.0
Hypotension	6	7.1	0	0.0
Diarrhea	2	2.4	2	6.5
Hypoxia	5	6.0	0	0.0
Pneumonia (fungal)	5	6.0	1	3.2
Respiratory failure	3	3.6	4	12.9

*Excludes fungal pneumonia
Source: FDA analysis

Table 49: Grade ≥3 TEAEs occurring at >5% for venetoclax with LDAC

	Venetoclax 600 mg + LDAC N=82	
	n	%
Febrile neutropenia	34	41.5
Hemorrhage	11	13.4
Sepsis	16	19.5
Pneumonia	14	17.1
Hypertension	9	11.0
Fatigue	8	9.8
Hypotension	6	7.3
Decreased appetite	5	6.1

Source: FDA analysis

Table 50: Grade ≥3 TEAEs occurring at >5% for venetoclax with azacitidine or decitabine for patients who met the modified Ferrara criteria

	Venetoclax 400 mg + Azacitidine N=67		Venetoclax 400 mg + Decitabine N=13	
	n	%	n	%
Febrile neutropenia	24	35.8	9	69.2
Pneumonia	18	25.4	3	23.1
Sepsis	10	14.9	6	46.2
Fatigue	5	7.5	2	15.4
Hemorrhage	5	7.5	-	-
Hypertension	5	7.5	1	7.7
Hypotension	4	6.0	-	-
Hypoxia	4	6.0		-
Multiple organ dysfunction syndrome	4	6.0	-	-
Urinary tract infection	4	6.0	-	-
Diarrhea	2	3.0	1	7.7

Source: FDA analysis

Table 51: Grade ≥3 TEAEs occurring at >5% for venetoclax with LDAC for patients who met the modified Ferrara criteria

	Venetoclax 600 mg + LDAC N=61	
	n	%
Febrile neutropenia	27	44.3
Sepsis	12	19.7
Pneumonia	10	16.4
Hemorrhage	9	14.8
Device related infection	7	11.5
Fatigue	6	9.8
Hypertension	5	8.2
Decreased appetite	4	6.6
Hypotension	4	6.6
Urinary tract infection	4	6.6

Source: FDA analysis

Treatment Emergent Adverse Events and Adverse Reactions

All grade treatment-emergent adverse events (TEAE) in patients treated at the labeled dose of venetoclax on study M14-358 and M14-387 are shown in Table 52 and Table 53, respectively. All grade TEAEs for patients who met the modified Ferrara criteria are shown in Table 54 and Table 55.

All patients experienced at least one TEAE (100%). Gastrointestinal AEs (diarrhea, nausea, constipation, vomiting were frequent events and is described in venetoclax monotherapy (for the treatment of CLL) and for the backbone therapy. AEs related to cytopenias such as hemorrhage and febrile neutropenia were common. Cytopenias can occur with the backbone therapy, and neutropenia is a known adverse reaction related to venetoclax. See Section 8.2.5.2 for further discussion.

Febrile neutropenia and sepsis appear to occur more frequently with venetoclax in combination with decitabine, though the small patient numbers in the decitabine group make the rates less reliable and a formal comparison between treatment arms should not be made.

The LDAC combination appears to have a similar profile to the combination with azacitidine or decitabine. The rate of febrile neutropenia is also similar to the other combinations, but the rate of pneumonia (18.3%) and sepsis (20.7%) appear to be slightly less frequent and did not meet the threshold to be included in the table of common events. This is likely reflective of the general lower toxicity profile of LDAC including shorter duration and depth of neutropenia.

Table 52: Common TEAEs occurring at >30% for venetoclax with azacitidine or decitabine

	Venetoclax 400 mg + Azacitidine N=84		Venetoclax 400 mg + Decitabine N=31	
	n	%	n	%
Any event	84	100	31	100
Nausea	51	60.7	19	61.3
Diarrhea	47	56.0	13	41.9
Constipation	41	48.8	15	48.4
Hemorrhage	41	48.8	14	45.2
Peripheral edema	36	42.9	12	38.7
Febrile neutropenia	31	36.9	20	64.5
Fatigue	33	39.3	15	48.4
Vomiting	31	36.9	11	35.5
Dyspnea	27	32.1	7	22.6
Arrhythmias	26	31.0	7	22.6
Sepsis	13	15.5	12	38.7
Myalgia	9	10.7	12	38.7
Cough	21	25	11	35.5
Pneumonia	25	29.8	11	35.5
Abdominal pain	18	21.4	11	35.5
Decreased appetite	23	27.4	10	32.3
Dizziness	22	26.2	10	32.3
Headache	18	21.4	10	32.3
Hypotension	16	19.1	10	32.3

Source: FDA analysis

Table 53: All grade TEAE occurring at >30% for venetoclax with LDAC

	Venetoclax 600 mg + LDAC N=82	
	n	%
Any event	82	100
Nausea	57	69.5
Hemorrhage	43	52.4
Diarrhea	40	48.8
Fatigue	38	46.3
Febrile neutropenia	35	42.7
Constipation	30	36.6
Decreased appetite	29	35.4
Dyspnea	26	31.7
Vomiting	26	31.7

Source: FDA analysis

Table 54: All grade TEAEs occurring at >30% for venetoclax with azacitidine or decitabine for patients who met the modified Ferrara criteria

	Venetoclax 400 mg + Azacitidine N=67		Venetoclax 400 mg + Decitabine N=13	
	n	%	n	%
Any event	67	100	13	100
Nausea	39	58.2	6	46.2
Diarrhea	36	53.7	5	38.5
Constipation	33	49.3	8	61.5
Hemorrhage	31	46.3	6	46.2
Peripheral edema	31	46.3	4	30.8
Vomiting	27	40.3	3	23.1
Febrile neutropenia	24	35.8	9	69.2
Fatigue	24	35.8	8	61.5
Rash	22	32.8	3	23.1
Pneumonia	19	28.4	5	38.5
Sepsis	10	14.9	6	46.2
Abdominal pain	15	22.4	6	46.2
Dizziness	19	28.4	6	46.2
Cough	17	25.4	5	38.5
Back pain	10	14.9	4	30.8
Hypotension	14	20.9	4	30.8
Myalgia	7	10.5	4	30.8
Pyrexia	14	20.9	4	30.8

Source: FDA analysis

Table 55: All grade TEAEs occurring at >30% for venetoclax with LDAC for patients who met the modified Ferrara criteria

	Venetoclax 600 mg + LDAC N=61	
	n	%
Any event	61	100
Nausea	39	63.9
Febrile neutropenia	28	45.9
Hemorrhage	31	50.8
Diarrhea	27	44.3
Fatigue	27	44.3
Constipation	21	34.4
Dyspnea	19	31.2

Source: FDA analysis

Reviewer comment: *Preferred terms related to laboratory evaluations were excluded from the table of reported TEAEs. Reporting of laboratory abnormalities as adverse reactions tend to underreport the actual frequency of laboratory-related AEs. Evaluation of laboratory findings is in the next section.*

Laboratory Findings

Laboratory shift analyses were performed by the Applicant for the clinical studies to evaluate the frequency of laboratory abnormalities that worsened from baseline or from baseline unknown.

Reviewer comment: *Lymphopenia is a known direct effect of venetoclax based on its mechanism of action. Myelosuppression resulting in leukopenia, anemia, and thrombocytopenia are known direct effects of the backbone therapies (azacitidine, decitabine, and LDAC). See Section 8.2.5 for review of the consequences of cytopenias including infections and hemorrhage.*

Table 56: Laboratory assessments in M14-358, new or worsening from baseline

	Venetoclax 400 mg + Azacitidine N=84		**Venetoclax 400 mg + Decitabine N=31**	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Hematology				
Neutropenia	100	98	100	100
Leukopenia	100	99	97	97
Thrombocytopenia	64	57	86	76
Anemia	56	56	68	65
Chemistry				
Hyperglycemia	75	12	77	0
Hypocalcemia	61	8	87	3
Hypoalbuminemia	55	5	48	6
Hypokalemia	51	7	48	6
Hyponatremia	50	8	52	3
Hypophosphatemia	49	19	26	6
Hyperbilirubinemia	48	8	32	10
Hypomagnesemia	29	0	45	3

Source: Clinical CSR

Table 57: Laboratory assessments in M14-387, new or worsening from baseline

	Venetoclax 600 mg + LDAC N=82	
	Any grade	Grade 3-5
Hematology		
Neutropenia	97	94
Leukopenia	96	95
Thrombocytopenia	98	95
Anemia	63	62
Chemistry		
Hyperglycemia	84	12
Hypocalcemia	82	15
Hyponatremia	63	11
Hyperbilirubinemia	63	9
Hypoalbuminemia	63	9
Hypokalemia	60	20
Hypophosphatemia	55	23
Hypomagnesemia	45	1
Hyperphosphatemia	41	1

Source: Clinical CSR

For patients who had grade 0-2 laboratory abnormalities, the Table 58 shows the percent that worsened to grade 3-4 for select hematology laboratory values.

Table 58: Hematology laboratory values, change from baseline grade 0-2 to on treatment grade 3-4

	Venetoclax (all doses) + Azacitidine N=84	Venetoclax (all doses) + Decitabine N=31	Venetoclax (all doses) + LDAC N=82
Neutrophils	54	38	91
White blood cells	43	33	94
Platelets	50	18	95
Hemoglobin	22	20	96

Source: Clinical CSRs

Vital Signs

Clinically significant elevation in systolic blood pressure defined as >160 mmHg was observed in 25% of patients treated with 400 mg venetoclax in combination with azacitidine, in 32% of patients in combination with decitabine, and in 27% of patients in combination with 600 mg of

venetoclax and LDAC. However, the mean change in systolic blood pressure for any patient visit was not substantial. Hypertension was reported as an AE infrequently in any combination. No clinically significant changes in heart rate, weight, temperature, or BMI were observed.

Electrocardiograms (ECGs)

One patient treated on the DDI sub-study had a clinically significant ECG abnormality of atrial fibrillation. No other clinically significant ECG abnormalities occurred in either study.

QT

A thorough QT study was reviewed under the initial NDA submission for R/R CLL. There were no apparent effects of venetoclax on the QT interval.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is listed as a Warning and Precaution in the current venetoclax prescribing information for CLL/SLL. Due to the potential occurrence of TLS in patients with AML, all patients had prophylaxis and monitoring including cytoreduction if needed to WBC <25 x 109/uL prior to initiation, hydration, anti-hyperuricemics, and laboratory monitoring. In the overall venetoclax clinical development program, the occurrence of severe TLS appeared to be largely limited to CLL/SLL, therefore the ramp-up dosing has been shorted to 3-4 days as noted above.

For any dose of venetoclax in combination with azacitidine or decitabine, no cases of TLS were reported as an AE or by laboratory evaluation. For any dose of venetoclax in combination with LDAC, 4 events of TLS occurred; 3 were laboratory TLS. The other event was reported as clinical TLS that occurred after disease progress and other therapy and is not included in the overall evaluation. 5 additional patients had laboratory abnormalities that met Howard criteria[18] for TLS. Laboratory TLS by Howard criteria were difficult to interpret due to baseline laboratory abnormalities that confounded the analysis and were not included in the analysis.

Across all doses of venetoclax in combination with azacitidine, decitabine, or LDAC, 3/304 (1%) had laboratory TLS.

Reviewer comment: *TLS occurred in 2-6% of patients with CLL (depending on the trial and prophylaxis measure).*

8.2.5.2. Neutropenia

Neutropenia is an expected component of AML due to marrow involvement of malignant cells. Neutropenia is listed as a Warning and Precaution in the current venetoclax prescribing information for CLL/SLL. Grade 3-4 neutropenia was also reported frequently in the published reports of azacitidine[12], decitabine[13], and LDAC[13].

In both clinical studies, grade 3-4 neutropenia that was new or worsening from baseline occurred in 97-100% of patients. See the review of laboratory values above. As with treatment with azacitidine, decitabine, or LDAC alone, treatment was generally not interrupted for neutropenia prior to achieving AML remission, and neutropenia was managed with anti-infectives. After achieving remission, neutropenia was managed by dose interruption and/or dose delay for neutropenia >7 days and G-CSF if indicated. Venetoclax dose was decreased for the second occurrence of neutropenia >7 days after achieving remission.

8.2.5.3. Infections

Infections are a common occurrence in patients with AML due to marrow involvement of malignant cells and resulting neutropenia and lymphopenia. Infection is also a known complication of the backbone therapies given with venetoclax.

Using the MedDRA system organ class (SOC) of Infections and Infestations, 60/84 (71%) patients treated with 400 mg venetoclax with azacitidine, 25/31 (81%) patients treated with 400 mg venetoclax with decitabine, and 60/82 (73%) patients treated with 600 mg venetoclax with LDAC had an AE in that category.

The rate of infections for these combinations cannot be directly compared to the rate in patients with AML treated with the backbone therapy alone. However, the pattern of infections appears to be similar.

8.2.5.4. Hemorrhage

Thrombocytopenia is an expected complication of AML due to marrow involvement of malignant cells. The backbone combination therapies may also case thrombocytopenia due to myelosuppression or direct effects of the drugs.

No single preferred term related to hemorrhage occurred at high frequency. However, grouping of hemorrhage preferred terms (See Appendix 15.6) resulted in reporting of 41/84 (49%) events in the azacitidine arm, 14/31 (45%) events in the decitabine arm, and 43/82 (52%) events in the LDAC arm at the target dose of venetoclax.

The rate of hemorrhage for these combinations cannot be directly compared to the rate in patients with AML treated with the backbone therapy alone.

8.2.5.5. Potential Drug-Induced Liver Toxicity

In Study M14-358, 4 (3%) patients treated with venetoclax in combination with azacitidine had liver enzyme values meeting the criteria for potential drug-induced liver injury (DILI; defined as ALT or AST >3x ULN and total bilirubin >2x ULN); 2 at 400 mg venetoclax and 1 at 800 mg venetoclax). All three had alternative causality for the laboratory values.

One patient treated with 800 mg venetoclax in combination with decitabine and 1 patient treated with venetoclax 400 mg in combination with decitabine and posaconazole in the DDI sub-study met the criteria. Both had alternative causality for the laboratory values

In Study M14-387, 2 (2%) met criteria for potential DILI. One of these patients (patient (b) (6)) died of acute hepatic failure with post-mortem biopsy with nonspecific findings of drug-induced hepatitis. The patient received other medications that could be associated with liver injury, but was assessed as possibly related to venetoclax or LDAC. The other patient (patient (b) (6) met criteria for DILI and died 10 days later of disease progression. The laboratory abnormalities were likely related to underlying disease.

In the Study M14-212, 3 patients had clinical laboratory results that met the criteria for Hy's law (AST or ALT >3x ULN, total bilirubin >2x ULN, without findings of cholestatis (normal alkaline phosphatase). In 2 patients, the laboratory abnormalities were reversibly and venetoclax treatment was continued. In the other patient, the elevated laboratory values occurred in the setting of fatal sepsis.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No safety evaluations were performed using clinical outcome assessments.

8.2.7. Safety Analyses by Demographic Subgroups

The majority of patients enrolled were White in either efficacy study for the treatment of newly-diagnosed AML in combination with azacitidine, decitabine, or LDAC. Similarly, almost all patients enrolled were ≥65 years of age due to the design of the study. Therefore, analyses by race, ethnicity, or age were not conducted.

The Applicant performed an analysis of common AEs between male and female patients. No significant differences in the safety profile was noted.

8.2.8. Specific Safety Studies/Clinical Trials

No studies or trials were conducted to evaluate a specific safety concern.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

A formal human carcinogenicity was not conducted for venetoclax.

Human Reproduction and Pregnancy

No pregnancies have been reported in the AML population treated with venetoclax.

Pediatrics and Assessment of Effects on Growth

No pediatric patients were enrolled.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Venetoclax has been marketed in the US since April 2016. No new safety signals have been identified in the post-market setting.

Expectations on Safety in the Postmarket Setting

Expectations on safety in the postmarket setting remain unchanged from the initial NDA approval. Namely, tumor lysis syndrome is the most significant risk, though the risk in AML is significantly less than for CLL/SLL. The rate of TLS is managed with a 3- to 4-day dose ramp up of venetoclax in combination treatment for AML, TLS prophylaxis, and laboratory monitoring. The prescribing information and medication guide provide details on TLS risk assessment, prophylaxis, and monitoring.

Neutropenia and resulting infections are expected to occur at significant rates in the post-market setting. The prescribing information provides details on management of neutropenia in patients with AML.

The overall safety in the post-market setting is expected to be similar to that observed in the clinical trials in this Application.

8.2.11. Integrated Assessment of Safety

In this reviewer's assessment, the submitted evidence has provided substantial evidence for the safe use of venetoclax in combination with azacitidine, decitabine, or LDAC for the treatment of patients with newly-diagnosed AML who are >75 years old or who have comorbidities that preclude the use of intensive chemotherapy. Evidence of safety was provided from all patients with newly-diagnosed AML treated with venetoclax in combination in Studies M14-358 and M14-387 and for patients with R/R AML treated with venetoclax monotherapy in Study M14-212.

For patients treated at the target doses of venetoclax (400 mg in combination with azacitidine or decitabine, or 600 mg in combination with LDAC), the median duration of exposure was 4.2-6.4 months with a maximum exposure of 36 months. Although all patients had at least one treatment-emergent adverse event, 25-35% of patients discontinued therapy due to an AE, and some of these AEs could be attributed to underlying disease in patients who did not achieve remission.

The most common TEAEs not related to a laboratory evaluation that occurred in >40% in any combination were nausea, diarrhea, constipation, hemorrhage, peripheral edema, febrile neutropenia, and fatigue. The most common grade ≥3 TEAEs (>10%) were febrile neutropenia, pneumonia, sepsis, hemorrhage, and device-related infection. The most common serious AEs (>10%) were febrile neutropenia, pneumonia, sepsis, and hemorrhage.

Generally, the rate and pattern of treatment emergent AEs, grade ≥3 AEs, and serious AEs were similar between the overall population and those who met the modified Ferrara criteria. No additional safety signals were identified in the modified Ferrara group who are potentially more fragile. The prescribing information will describe only the modified Ferrara criteria to adequately describe safety in patients who may not tolerate more intensive regimens.

Of note, events of febrile neutropenia, sepsis, and pneumonia appear to occur more frequently with venetoclax in combination with decitabine compared to venetoclax in combination with azacitidine. However, the small patient numbers in the decitabine group make the rates less reliable and a formal comparison between treatment arms should not be made.

The LDAC combination appears to have a similar profile to the combination with azacitidine or decitabine. The rate of febrile neutropenia is also similar to the other combinations, but the rate of pneumonia and sepsis appear to be slightly less frequent. This may reflect the general lower toxicity profile of LDAC including shorter duration and depth of neutropenia. Again, formal comparisons between arms should not be made as none of the studies were powered to show differences between any safety signals in the treatment arms.

The published reports of the backbone therapies alone for the treatment of patients with newly-diagnosed AML do not report granular safety data to make comparisons between the

safety of the combinations compared to the backbone alone. However, broadly speaking, the rate and pattern of events appear similar. The addition of venetoclax to the backbone therapy may add additional gastrointestinal toxicity as this is an oral medication with well described occurrence of gastrointestinal upset, but these events are typically low grade and did not lead to dose interruptions.

Overall, venetoclax in combination was well tolerated for the treatment of AML. Patients who are >75 years or who have comorbidities tend to have very poor survival due to both the aggressiveness of the disease and the difficulty with tolerating therapy. The level of toxicity described with the combination of venetoclax with azacitidine, decitabine, or LDAC is acceptable for the clinical benefit observed.

8.3. Statistical Issues

Treatment Effect Isolation

The treatment effect of venetoclax monotherapy for the treatment of patients with newly-diagnosed AML who are >75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy cannot be isolated based on submitted studies. Efficacy of venetoclax in combination with azacitidine, decitabine, or LDAC was demonstrated by evaluating CR rate and duration in single-arm studies M14-358 and M14-387.

Historical Controls

The efficacy results from studies M14-358 and M14-387 were supported by a favorable CR rate relative to historical estimates from studies of azacitidine, decitabine, or LDAC monotherapies. Historical comparison does not control for unknown or known confounders as randomization would. Efficacy and benefit-risk will be assessed on completion of two ongoing randomized studies for venetoclax in combination with azacitidine and venetoclax in combination with LDAC, respectively.

8.4. Conclusions and Recommendations

Venetoclax in combination with azacitidine, decitabine, or LDAC shows substantial evidence of effectiveness for the treatment of patients with newly-diagnosed AML who are >75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy.

Efficacy was demonstrated by evaluating the rate of CR and duration of CR in two single arm trials of venetoclax in combination for the treatment of patients with newly diagnosed AML. In patients who should not receive intensive chemotherapy based on age or comorbidities, the CR rate for venetoclax was 37% in combination with azacitidine, 54% in combination with

decitabine, and 21% in combination with LDAC. The durability of responses support effectiveness in this population. These durable responses represent a substantial improvement over available therapies.

Safety was demonstrated in the population who should not receive intensive chemotherapy based on age or comorbidities. Frequent serious adverse events included febrile neutropenia, pneumonia, sepsis, and hemorrhage. The events were managed by anti-infectives, G-CSF, and transfusions as indicated. TLS was an infrequent event and can be mitigated by dose ramp up, prophylaxis, and monitoring.

While the patients enrolled in the studies were limited to age ≥60 years, the efficacy and safety is not expected to be significantly different for patients who are <60 years old who have comorbidities that preclude the use of intensive induction chemotherapy. The indication is not limited by a lower limit of age for the treatment of adults with AML.

Because the results were based on single arm trials with endpoints of response rates, uncertainty remains regarding the benefit of the addition of venetoclax to the backbone therapy. While it appears the addition of venetoclax to the backbone therapy adds substantial efficacy without excess toxicity, this will be better evaluated in a randomized trial. The information submitted supports accelerated approval for this indication. The results will be confirmed by the completion of two randomized studies for venetoclax in combination with azacitidine and venetoclax in combination with LDAC, respectively.

Accelerated approval requires demonstration of an improvement over available therapies. In the indicated patient population, the only approved available therapy is gemtuzumab ozogamicin (GO). The CR rate was not reported in the PI, but shown in the published literature to be 15% (95% CI: 9-23%) with median overall survival of 4.9 mo. The CR rate of venetoclax with LDAC has a higher point estimate, but overlapping confidence with GO; however, the combinations of venetoclax in combination with azacitidine or decitabine show an improvement in response rates with non-overlapping confidence intervals. Other standard therapies used in this patient population are azacitidine, decitabine, and LDAC. As discussed previously, the addition of venetoclax with any of these backbone therapies appears to show an improvement in CR rates that is not attributable to either agent alone.

9 Advisory Committee Meeting and Other External Consultations

This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

10 Pediatrics

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

Currently no safety or dosing information is available for the treatment of pediatric patients with AML or any other indication. Therefore, the indication sought in this application could not be extended to the pediatric population. Studies are currently ongoing under a Written Request for the evaluation of venetoclax in pediatric patients including those with relapsed or refractory AML.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

A summary of labeling changes to include the treatment of patients with venetoclax in combination with rituximab is provided in the following table.

Summary of Significant Labeling Changes		
Section	Proposed Labeling	Approved Labeling
1 INDICATIONS AND USAGE	For the treatment of AML in combination with a hypomethylating agent or in combination with low dose cytarabine for newly-diagnosed pts who are ineligible for intensive chemotherapy.	1. Defined patient population by age or comorbidity that would preclude the use of intensive induction chemotherapy. 2. Revised label to consider azacitidine and decitabine as two separate combinations, now with HMAs as a class.
2 DOSAGE AND ADMINISTRATION	1. Venetoclax in combination with HMAs or low-dose cytarabine added, including ramp-up schedule. 2. Added AML-specific recommendations for management of potential TLS. 3. Added dose-modification criteria for AML. 4. Added new information on concomitant medication	Approved inclusion of new regimens and safety measures
5 WARNINGS AND PRECAUTIONS	(b) (4)	Included rates of neutropenia based on laboratory evaluations.
6 ADVERSE REACTIONS	Added safety from the clinical trial experience in AML trials.	Modified the safety to include safety only in the intended indication to accurately describe the safety in a population of patients who should not receive intensive chemotherapy.
7 DRUG INTERACTIONS	Revised to include new information from the DDI substudy.	Consolidated information for clarity.
8 USE IN SPECIFIC POPULATIONS	Added relevant pre-clinical information regarding use in	Revised pre-clinical to reflect risk summary.

	lactation and pediatric patients.	Removed information on hepatic impairment as there were no differences in safety.
12 CLINICAL PHARMACOLOGY	None	Consolidated and revised information for clarity and ease of use.
14 CLINICAL STUDIES	Added efficacy results from M14-358 and M14-387.	1. Revised main efficacy tables to include only patients who met the intended indication to accurately describe efficacy in a patient population who should not receive intensive chemotherapy. 2. Revised efficacy results tables to include only CR rate, duration of CR, and CRh rate as these were the basis of approval. 3. Removed CRi rates and transfusion independence. 4. Added text to include efficacy in patients who were enrolled by did not meet the intended indication to describe efficacy in a larger patient population. 5. Removed time-to-event endpoints as these are difficult to interpret in a single arm study.

11.2. Patient Labeling

The Medication Guide was updated to include information on the new indication in patients with AML including expected adverse reactions in all patients and those expected in patients with AML. The ramp-up dose is 3-4 days in patients with AML, and therefore does not require a Starting Pack or Quick Start Guide. The Starting Pack and Quick Start Guide were modified to indicate that these are for patients with CLL/SLL.

12 Risk Evaluation and Mitigation Strategies (REMS)

The risks of venetoclax including neutropenia and TLS can be adequately managed in the post-market setting through product presentation and labeling. There are no additional risk management strategies required beyond the recommended packaging and labeling.

13 Post-marketing Requirements and Commitment

The applicant seeks accelerated approval which is subject to confirmation and verification of clinical benefit with a confirmatory trial or trials. The planned PMR trials are the confirmatory trials for accelerated approval venetoclax when used in combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of patients with newly-diagnosed AML who are 75 or older or who have comorbidities that preclude the use of intensive induction chemotherapy. PMR#1 will serve to confirm and verify the clinical benefit of venetoclax in combination with both azacitidine and decitabine. PMR#1 will serve to confirm and verify the clinical benefit of venetoclax in combination with low-dose cytarabine.

PMR #1 Description:	Submit the complete final study report and data that verifies and isolates the clinical efficacy and safety from trial M16-043, a randomized, double-blind, placebo-controlled Phase 3 study of venetoclax co-administered with low-dose cytarabine versus low-dose cytarabine in treatment naïve patients with acute myeloid leukemia who are precluded from receiving standard chemotherapy due to age $\geq$ 75 years or comorbidities. The primary endpoint will be overall survival. An interim analysis of overall survival will be performed and included in the interim analysis submission or* the final study report.			
PMR Schedule Milestones:	Study/Trial Completion: Interim Analysis Submission:		10/2019 08/2019 or*	
	Final Report Submission:		01/2020	

*Study M16-043 is a blinded, randomized confirmatory trial that is being monitored by an independent data monitoring committee (IDMC). There is a pre-specified interim analysis when 75% of the anticipated death events have occurred. If the study crosses the efficacy threshold at the interim analysis per the statistical analysis plan (SAP), the study will conclude and the interim CSR will be completed and will be submitted prior to August 2019. If the study does not cross the efficacy threshold at the interim analysis, no formal report will be generated for the ongoing blinded study and the final analysis is anticipated at the time that 100% OS events occur. The CSR is projected to be submitted prior to January 2020.

PMR #2 Description:	Submit the complete final study report and data that verifies and isolates the clinical efficacy and safety from trial M15-656, a randomized, double-blind, placebo-controlled Phase 3 study of venetoclax in combination with azacitidine versus azacitidine in treatment naïve patients with acute myeloid leukemia who are precluded from receiving standard chemotherapy due to age $\geq$ 75 years or comorbidities. The primary endpoint will be overall survival. Interim analysis of response rates and overall survival will be performed and included in the interim analysis submission or* the final study report.			
PMR Schedule Milestones:	Study/Trial Completion: Interim Analysis Submission		10/2020 02/2020 or*	
	Final Report Submission:		01/2021	

*Study M15-656 is a blinded randomized confirmatory trial that is being monitored by an IDMC. There is a pre-specified interim analysis when 75% of the anticipated death events have occurred. If the study crosses the efficacy threshold at the interim analysis per the SAP, the study will conclude and the interim CSR will be completed and will be submitted prior to February 2020. If the study does not cross the efficacy threshold at the interim analysis, no formal report will be generated for the ongoing blinded study and the final analysis is anticipated at the time that 100% OS events occur. The CSR is projected to be submitted prior to January 2021.

Reviewer comment: See the approval letter for final agreed language for the PMRs.

14 Division Director (Clinical) Comments

(This review was based in part on the reviews of Dr. Lori Ehrlich, Dr. Tanya Wroblewski, Dr. Ann Farrell, and Dr. Alexei Ionan.)

Background: On June 25, 2018, FDA NDA 208573 S-009 was submitted to the FDA in which AbbVie, in collaboration with Genentech/Roche, requested accelerated approval of venetoclax (Venclexta) in combination with azacitidine or decitabine, which will be referred to collectively as hypomethylating agents (HMA), or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy.

This request for approval relied upon two single arm Phase 1b trials: 1. Study M14-358 which is a study of 400 mg of venetoclax in combination with azacitidine (67 patients) or decitabine (13 patients) in newly diagnosed elderly subjects with AML who are ineligible for intensive induction therapy by dint of age ≥75 or comorbidities, and 2. Study M14-387, which is a study of 600 mg of venetoclax in combination with LDAC (61 patients) in newly diagnosed elderly subjects with AML who are ineligible for intensive induction therapy by dint of age ≥75 or comorbidities. These trials used the Ferrara criteria to identify subjects with objective evidence of ineligibility for intensive therapy.

Efficacy Results: The rates of complete response (CR) in Study M14-358 for 400 mg venetoclax in combination with azacitidine or decitabine are 37% (95%CI: 26, 50) and 54% (95%CI: 25, 81) respectively. These CR rates for the combination of venetoclax and azacitidine or decitabine were higher than the historical rates of 20% (95% CI: 15, 25) for azacitidine alone or 16% (95% CI: 11, 21) for decitabine alone. The observed CR duration was 5.5 months (range: 0.4-30) for the combination of venetoclax with azacitidine and 4.7 months (range: 1-18) for the combination of venetoclax with decitabine. The observed CR rate for single agent venetoclax in patients with newly diagnosed AML or relapsed disease was 6.3% in Study M14-212. Of note, in patients with no prior treatment (newly diagnosed), no complete responses were observed (0% complete response rate).

The CR rate in Study M14-387 for 600mg of venetoclax in combination with LDAC is 21% (95%CI: 12, 34). This CR rate for the combination of venetoclax and LDAC was higher than the historical CR rate of 8% (95% CI: 5, 12) for LDAC alone. The observed CR duration was 6 months (range: 0-25) for the combination of venetoclax with LDAC.

Safety Results: The percent of patients with treatment emergent adverse events (TEAEs) leading to death for the combination of venetoclax with azacitidine, decitabine or LDAC was: 13%, 19.4% and 22.0% respectively. Frequent serious adverse events (SAEs) included febrile neutropenia, pneumonia, sepsis, and hemorrhage and multi-organ dysfunction, diarrhea, fatigue, cellulitis and localized infections.

Common adverse reactions for the combination of venetoclax and azacitidine, decitabine, or low dose cytarabine included (> 30%) nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, peripheral edema, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, back pain, neck pain, myalgia, dizziness, cough, oropharyngeal pain, and hypotension.

The Grade 3 or 4 adverse events (AEs) experienced by >10% of subjects treated with venetoclax and decitabine was: anemia, bacteremia, febrile neutropenia, neutropenia, pneumonia and thrombocytopenia. The Grade 3 or 4 AEs experienced by >10% of subjects treated with venetoclax and LDAC was: febrile neutropenia, neutropenia, pneumonia and hypotension.

Benefit Risk Discussion: The CDTL (Dr. Wroblewski) stated in her review: "The addition of venetoclax to any of the backbone therapies (azacitidine, decitabine or LDAC) appears to show an improvement in CR rates that is not attributable to either agent alone. Accelerated approval requires demonstration of an improvement over available therapies. In the indicated population, the only approved available therapy is gemtuzumab ozogamicin (GO). The CR rate for GO was shown to be 15% (95% CI: 9, 23) with a median overall survival of 4.9 months." No new safety signals were seen above and beyond that expected based on the patient population and the component therapies. Thus, the benefit risk profile appears favorable but will have to be confirmed with randomized trials.

Benefit Risk Discussion:
Typically, the Agency does not approve combinations of drugs based on a trial design that is unlikely to provide information on the contributions of the individual components of the combination. The Agency's Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination provides framework and support for the approval of the proposed indication for combination treatment based on the compelling phase 1b clinical trial data. The Guidance suggests that codevelopment should be reserved for situations where:

- The combination is intended to treat a serious disease or condition.
- There is a strong biological rationale for use of the combination (e.g., the agents inhibit distinct targets in the same molecular pathway or steps in disease pathogenesis, provide inhibition of both a primary and compensatory pathway, or inhibit the same target at different binding sites to decrease resistance or allow use of lower doses to minimize toxicity).
- A full nonclinical characterization of the activity of both the combination and the individual new investigational drugs, or a short-term clinical study on an established biomarker, suggests that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents. A nonclinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), or a better toxicity profile than the individual agents.

- There is a compelling reason why the new investigational drugs cannot be developed independently (e.g., monotherapy for the disease of interest leads to resistance, one or both of the agents would be expected to have very limited activity when used as monotherapy).

In this application all 4 scenarios are met.

AML is a serious disease or condition.

The strong biologic rationale for the combination is provided through the mechanistic understanding of apoptotic pathway and interaction of BIM, BAX and MCL-1 (see Dr. Ehrlich's review for full discussion). All products have been approved for as single agents with well-characterized safety profiles and have had extensive non-clinical development.

Although clinical trial data exists for all these agents as monotherapy, and some for many years, none of the monotherapies are approved as single agents based on currently available complete response rate data for the treatment of newly diagnosed AML. The observed complete response rates with the combinations are much higher than would be expected for any of the agents as monotherapies suggesting an additive interaction.

Mylotarg (GO) is approved in this newly diagnosed AML setting. However, as noted in Dr. Wroblewski's review, the observed complete response rates with the combinations are better than those achieved with GO therapy. Thus, the combination therapies are better than available therapy and therefore eligible for accelerated approval. Due to the uncertainty about clinical benefit (i.e. survival) for patients with newly diagnosed AML, the application will receive an accelerated approval with the requirement for post-marketing trials to confirm benefit.

Recommended Regulatory Action: This Supervisory Associate Division Director reviewer agrees with the recommendation of the review teams that the NDA 208573 S-009 be given accelerated approval for the following indication: venetoclax in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy.

15 Appendices

15.1. References

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15.2. Financial Disclosure

This supplement includes 3 covered studies, M14-212, M14-358 and M14-387.

Covered Clinical Study (Name and/or Number): M14-212

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5 investigators, 61 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A**	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): M14-358

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 18 investigators, 286 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A**	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): M14-387

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9 investigators, 106 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: **N/A**	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A**	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Not applicable

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable

15.5. Additional Clinical Outcome Assessment Analyses

No clinical outcome assessment analyses were performed.

15.6. Grouping of MedDRA Preferred Terms

Group	Preferred terms
Abdominal pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain
Acute coronary syndrome	Acute myocardial infarction, Angina unstable, Myocardial infarction
Angioedema	Face oedema, Mouth swelling, Swelling face, Tongue oedema
Anxiety	Adjustment disorder with anxiety, Anxiety
Arrhythmias	Arrhythmia, Atrial fibrillation, Atrial flutter, Bradycardia, Cardiac flutter, Extrasystoles, Sinus bradycardia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular tachycardia
Confusional state	Confusional state, Disorientation
Cough	Cough, Productive cough, Upper-airway cough syndrome
Decreased appetite	Decreased appetite, Hypophagia
Dizziness	Dizziness, Dizziness postural, Vertigo
Dry mouth	Dry mouth, Lip dry
Dyspepsia	Dyspepsia, Oesophageal pain
Dyspnea	Dyspnoea, Dyspnoea exertional, Dyspnoea paroxysmal nocturnal, Orthopnoea, Respiratory distress, Tachypnoea
Erythema	Erythema, Palmar erythema, Scrotal erythema
Fatigue	Asthenia, Fatigue
Hemorrhage	Anal haemorrhage, Blood blister, Blood urine present, Cerebral haematoma, Conjunctival haemorrhage, Contusion, Diverticulum intestinal haemorrhagic, Ecchymosis, Epistaxis, Eye haemorrhage, Eyelid contusion, Eyelid haematoma, Gastric

	haemorrhage, Gastrointestinal haemorrhage, Gingival bleeding, Haemarthrosis, Haematemesis, Haematochezia, Haematoma, Haematuria, Haemoptysis, Haemorrhage intracranial, Haemorrhoidal haemorrhage, Melaena, Mouth haemorrhage, Oral contusion, Penile haemorrhage, Periorbital haematoma, Petechiae, Pulmonary alveolar haemorrhage, Purpura, Rectal haemorrhage, Retinal haemorrhage, Retroperitoneal haematoma, Scleral haemorrhage, Subarachnoid haemorrhage
Hypotension	Hypotension, Orthostatic hypotension
Leukopenia	Leukopenia, White blood cell count decreased
Myalgia	Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Myalgia
Myocardial infarction	Acute myocardial infarction, Myocardial infarction
Myocardial ischaemia	Angina pectoris, Angina unstable
Neutropenia	Neutropenia, Neutrophil count decreased
Paraesthesia	Burning sensation, Hypoaesthesia, Paraesthesia
Peripheral edema	Generalised oedema, Oedema, Oedema peripheral, Peripheral swelling
Pneumonia (excluding fungal)	Lung consolidation, Lung infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia bacterial, Pneumonia klebsiella, Pneumonia staphylococcal
Pruritus	Anal pruritus, Eye pruritus, Pruritus, Pruritus generalized, Rash pruritic, Vulvovaginal pruritus
Rash	Blister, Catheter site dermatitis, Catheter site rash, Erythema multiforme, Nodular rash, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash vesicular
Sepsis (excluding fungal)	Bacillus bacteraemia, Bacteraemia, Bacterial sepsis, Clostridium bacteraemia, Corynebacterium bacteraemia, Corynebacterium sepsis, Enterobacter bacteraemia, Enterococcal bacteraemia, Escherichia bacteraemia, Escherichia sepsis, Klebsiella bacteraemia, Klebsiella sepsis, Neutropenic sepsis, Pulmonary sepsis, Pseudomonal sepsis, Sepsis, Septic shock, Serratia sepsis, Staphylococcal bacteraemia, Streptococcal bacteraemia
Somnolence	Hypersomnia, Lethargy, Somnolence
Tachycardia	Sinus tachycardia, Supraventricular tachycardia, Tachycardia
Thrombocytopenia	Platelet count decreased, Thrombocytopenia
Tremor	Asterixis, Tremor
Vomiting	Haematemesis, Retching, Vomiting

Note: Groupings in bold occurred at a high enough frequency to be included in the safety table for common or grade ≥3 adverse reactions.

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s009

OTHER REVIEW(S)

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 16, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208573/S-009
Product Name and Strength:	Venclexta (venetoclax) Tablets 10 mg, 50 mg, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AbbVie Inc.
FDA Received Date:	June 25, 2018, September 19, 2018, and November 13, 2018
OSE RCM #:	2018-2481
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BS Pharm
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Hematology Products (DHP) to evaluate the container label and carton labeling for Venclexta (NDA 208573) for areas of vulnerability that could lead to medication errors. Efficacy Supplement S-009 proposes to add the indication for the treatment of newly-diagnosed acute myeloid leukemia (AML) in combination with a hypomethylating agent or in combination with low dose cytarabine. In addition, the Applicant is proposing to add a new packaging configuration for the 100 mg strength, in bottles of 180 tablets.

2 REGULATORY HISTORY

Venclexta (venetoclax) tablets was originally approved on April 11, 2016 for the treatment of chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy. On June 8, 2018 Venclexta received approval for small lymphocytic lymphoma (SLL).

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – n/a
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – n/a
Other	F – n/a
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Venclexta is currently available in 10 mg, 50 mg, and 100 mg tablets. The lower strengths (10 mg and 50 mg) are used during the first week(s) of therapy. For the approved indication of CLL/SLL the 100 mg strength is used for the recommended maintenance dose of 400 mg daily (4 tablets x 100 mg). Therefore, the applicant currently offers the 100 mg tablets in bottles of 120 units for 30 days of treatment.

The recommended maintenance dose for the proposed indication of AML in combination with a hypomethylating agent is 400 mg daily (4 tablets x 100 mg), while the recommended maintenance dose for the proposed indication of AML in combination with low dose cytarabine is 600 mg (6 tablets x 100 mg). Therefore, the currently marketed 100 mg tablets in bottles of 120 units provides for 30 days of treatment for AML in combination with a hypomethylating agent. AbbVie is proposing to market the 100 mg tablets in bottles of 180 units to provide for 30 days of treatment for AML in combination with low dose cytarabine.

We reviewed the revised Prescribing Information (PI), carton labeling and container labels for the 180-tablet bottle. We note that the proposed container label and carton labeling for the 180-tablet bottle follows the same format and content as the currently approved labels for the 120-tablet bottle, including all of our previous recommendations.

5 CONCLUSION & RECOMMENDATIONS

DMEPA finds the Applicant's proposal to add a packaging configuration for the 100 mg strength of 180-tablet bottles acceptable. In addition, we find the revised PI, proposed container label and carton labeling acceptable. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Venclexta received on November 13, 2018 from AbbVie Inc..

Table 2. Relevant Product Information for Venclexta

Initial Approval Date	April 11, 2016
Active Ingredient	venetoclax
Indication	*Approved*: Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy *Proposed*: In combination with azacytidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
Route of Administration	Oral
Dosage Form	Tablets
Strength	10 mg, 50 mg, 100 mg
Dose and Frequency	*Approved*: • CLL: Initiate therapy with VENCLEXTA at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg. • CLL: For VENCLEXTA in combination with rituximab, administer rituximab after the 5-week ramp-up schedule with VENCLEXTA. Continue VENCLEXTA for 24 months from Cycle 1 Day 1 of rituximab. *Proposed*: • AML in combination with a hypomethylating agent: Initiate therapy with VENCLEXTA at 100 mg on Day 1, followed by a daily ramp-up dosing schedule to the recommended daily dose of 400 mg. • AML in combination with low dose cytarabine: Initiate therapy with VENCLEXTA at 100 mg on Day 1, followed by a daily ramp-up dosing schedule to the recommended daily dose of 600 mg.
How Supplied	*Approved*:

Packaging Presentation	Number of Tablets	National Drug Code (NDC)
Starting Pack for patients with CLL	Each pack contains four weekly wallet blister packs: • Week 1 (14 x 10 mg tablets) • Week 2 (7 x 50 mg tablets) • Week 3 (7 x 100 mg tablets) • Week 4 (14 x 100 mg	0074-0579-28
Wallet containing 10 mg tablets	14 x 10 mg tablets	0074-0561-14

	Wallet containing 50 mg tablets	7 x 50 mg tablets	0074-0566-07
	Unit dose blister containing 10 mg tablets	2 x 10 mg tablets	0074-0561-11
	Unit dose blister containing 50 mg tablet	1 x 50 mg tablet	0074-0566-11
	Unit dose blister containing 100 mg tablet	1 x 100 mg tablet	0074-0576-11
	Bottle containing 100 mg tablets	120 x 100 mg tablets	0074-0576-22
	Proposed: Bottle containing 100 mg tablets	180 x 100 mg tablets	0074-0576-34
Storage	Store at or below 86˚F (30˚C)		
Container Closure	n/a		

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 15, 2018, we searched for previous DMEPA reviews relevant to this current review using the term, Venclexta. Our search identified four previous relevant reviews, and we confirmed that our previous recommendations were implemented or considered.

Garrison, N. Label and Labeling Review Memorandum for Venclexta NDA 208573/S-007 and S-010. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 31. RCM No.: 2018-825-1 and 2018-1838.
Garrison, N. Label and Labeling Review Memorandum for Venclexta NDA 208573/S-007. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 16. RCM No.: 2018-835.
Ogbonna, C. Label and Labeling Review for NDA 208573/S-004 and S-005. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 14. RCM No.: 2018-233.
Garrison, N. Human Factors, Label, and Labeling Review for NDA 208573. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JAN 26. RCM No.: 2015-2092.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On November 15, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR
Search Strategy and Terms	Match Exact Word or Phrase: Venclexta

D.2 Results

The search retrieved no relevant articles associated with label and labeling for Venclexta.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER SOURCES

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Venclexta labels and labeling submitted by AbbVie Inc..

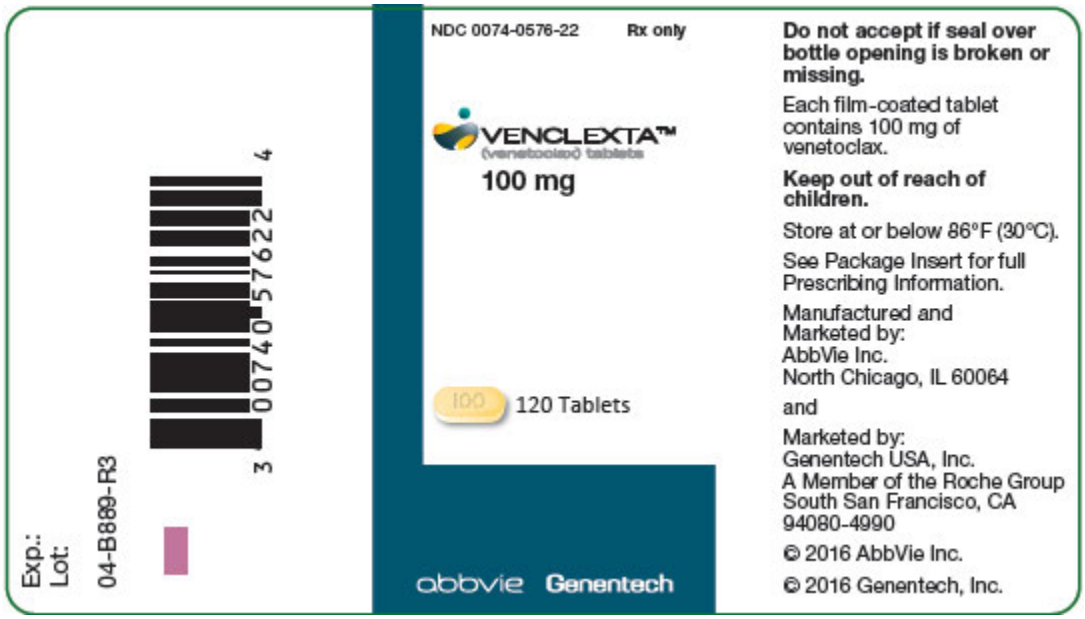
- Container label received on June 25, 2018
- Carton labeling received on June 25, 2018
- Prescribing Information (Image not shown) received on November 13, 2018

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

G.2 Label and Labeling Images (not to scale)

(b) (4)

Approved 100 mg - 120 tablets bottle label



(b) (4)

Approved 100 mg - 120 tablets carton labeling

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/s/

CARLOS M MENA-GRILLASCA
11/16/2018

HINA S MEHTA
11/16/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 8, 2018
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nisha Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	VENCLEXTA (venetoclax tablets), for oral use
Application Type/Number:	NDA 208573
Supplement Number:	S-009
Applicant:	AbbVie, Inc.

1 INTRODUCTION

On June 25, 2018, AbbVie, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 208573/S-009 for VENCLEXTA (venetoclax tablets), for oral use. With this supplement the Applicant is requesting accelerated approval of the proposed indication for VENCLEXTA (venetoclax tablets) in combination with a hypomethylating agent or in combination with low dose cytarabine for the treatment of newly diagnosed patients with acute myeloid leukemia (AML).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on October 29, 2018, and September 24, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VENCLEXTA (venetoclax tablets).

2 MATERIAL REVIEWED

- Draft VENCLEXTA (venetoclax tablets) MG received on June 25, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 1, 2018.
- Draft VENCLEXTA (venetoclax tablets) Prescribing Information (PI) received on June 25, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 1, 2018.
- Approved VENCLEXTA (venetoclax tablets) labeling dated September 7, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
11/08/2018

NISHA PATEL
11/08/2018

BARBARA A FULLER
11/08/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 8, 2018

To: Beatrice Kallungal, Regulatory Project Manager
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Team Leader, OPDP

Subject: OPDP Labeling Comments for VENCLEXTA® (venetoclax tablets) for oral use

NDA: 208573/S-009

In response to DHP's consult request dated September 24, 2018, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for VENCLEXTA® (venetoclax tablets) for oral use (Venclexta). This supplement (S-009) provides for a new indication: Venclexta in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 or older or who have comorbidities that preclude use of intensive induction chemotherapy.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on November 1, 2018. We have no comments on the draft PI at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on November 8, 2018.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

44 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NISHA PATEL
11/08/2018

CLINICAL INSPECTION SUMMARY

Date	October 22, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Lori Ehrlich, M.D., Ph.D., Medical Officer Tanya Wroblewski, M.D., CDTL Ann Farrell, M.D., Director Beatrice Kallungal, M.S., Regulatory Project Manager Division of Hematology Products
NDA	208573 S-009
Applicant	AbbVie Inc. [Genetech, A Member of the Roche Group]
Drug	Venclexta® (venetoclax)
NME	No
Therapeutic Classification/Status	Bcl-2 (B-cell lymphoma 2) family protein inhibitor
Proposed Indication	Treatment of newly diagnosed patients with acute myeloid leukemia (AML) ineligible for intensive chemotherapy, in combination with azacitidine, decitabine, or cytarabine
Consultation Request Date	August 16, 2018 (Priority Review)
Summary Goal Date	October 25, 2018 (original) November 2, 2018 (extension)
Action Goal Date	November 19, 2018
PDUFA Date	December 25, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Daniel Pollyea and Jing-Zhou Hou) were selected for inspection in support of NDA 208573 S-009. The study data from these clinical sites, as reported by the sponsor to the NDA, are considered to be reliable in support of the requested indication.

The preliminary regulatory classification of Dr. Pollyea is No Action Indicated. The preliminary regulatory classification pending receipt and review of the Establishment Inspection Report of Dr. Hou is Voluntary Action Indicated.

2. BACKGROUND

Venetoclax is an orally available small molecule Bcl-2 (B-cell lymphoma 2) family protein inhibitor. In vitro, ABT-199 (venetoclax) demonstrates broad cell killing activity against a panel of lymphoma and leukemia cells. This previously approved Bcl-2 inhibitor 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

For this submission, the sponsor seeks the following proposed label indication: venetoclax in combination with a hypomethylating agent (HMA) such as azacitidine and decitabine, or in combination with low dose cytarabine (LDAC) for the treatment of newly diagnosed patients with acute myeloid leukemia (AML) ineligible for intensive chemotherapy.

In review of this sNDA, the Division of Hematology Products (DHP) requested a single clinical study site inspection each for Study M14-358 and Study M14-387. These clinical study sites are critical to CDER DHP's efficacy and safety review of the application.

Study M14-358

Study M14-358 is a Phase1b, open-label, non-randomized, multicenter study evaluating the safety of orally administered venetoclax combined with decitabine or azacitidine and the preliminary efficacy of one of these combinations: venetoclax plus decitabine or venetoclax plus azacitidine in treatment naïve patients with AML at least 60 years old who are not eligible for standard induction therapy due to co-morbidity or other factors.

There were 19 study sites in the US, France, Germany and Australia. The first subject enrolled on November 19, 2014. As of the data cutoff date of December 22, 2017, a total of 212 subjects were enrolled and were treated with study drug; all 212 subjects received their first dose of study drug at least 6 months before the data cutoff date. The study is ongoing.

Overall response rate (complete response, complete remission with incomplete blood count recovery and partial remission) was the exploratory primary efficacy endpoint of interest for this early phase clinical trial. Other exploratory efficacy endpoints such as duration of treatment response, or overall survival could be considered as well.

Study M14-387

Study M14-387 is a Phase 1/2, non-randomized, multicenter study evaluating the pharmacokinetics (PK), safety, and preliminary efficacy of venetoclax in combination with LDAC in newly diagnosed subjects with AML at least 60 years old who were not eligible for standard induction therapy because of age, co-morbidity, or other factors. The study is ongoing.

The primary objectives of the Phase 1 portion were to assess the safety profile, characterize the PK, to determine the dose schedule and the maximum-tolerated dose (MTD), and the recommended Phase 2 dose (RPTD) of venetoclax in combination with low-dose cytarabine (LDAC).

The primary objectives of the initial Phase 2 portion of the study were to evaluate the preliminary estimates of efficacy, including the overall response rate (ORR), and to characterize the toxicities of the combination at the RPTD.

A total of nine sites participated in this trial in Australia, Italy, Germany and the United States. For the Phase 1 component, 18 subjects enrolled; for the Phase 2 component, 53 subjects enrolled; for Phase 2, Cohort C, 23 subjects enrolled (21 of 23 enrolled subjects received study drug). The first subject enrolled December 31, 2014. The study is ongoing; data cutoff for this interim report was November 8, 2017.

The following efficacy evaluations/endpoints were collected during the study: leukemia response rates (defined by International Working Group [IWG] for AML response criteria: complete response [CR], complete response with incomplete blood recovery [Cri], partial remission [PR], morphologic leukemia-free state [MLFS], resistant disease [RD], and progressive disease [PD]), duration of response (DOR), and overall survival (OS). In addition to the response determination using the IWG AML response criteria, each subject was evaluated for hematologic response (transfusion independence) and complete remission with partial hematologic recovery (CRh).

3. RESULTS (by site):

Name of Clinical Investigator Address	**Protocol #/ Site # # Subjects enrolled**	**Inspection Dates**	**Classification**
Dr. Daniel Pollyea University of Colorado 1665 Aurora Court, Room 3200 Mail Stop F-700 Denver, CO 80045	Study M14-358 Site# 50868 Total subjects =34	September 27–October 4, 2018	Preliminary: NAI
Dr. Jing-Zhou Hou University of Pittsburgh Medical Center Hillman Cancer Center 5115 Centre Avenue Lemieux Center for Blood Cancers Pittsburgh, PA 15232	Study M14-387 Site # 50863 Total subjects =16	September 5 – October 12, 2018	Preliminary: VAI*

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
* Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. **Daniel Pollyea, M.D.**

A total of 52 subjects were screened and 34 subjects were enrolled. All subjects received treatment. Ten study subjects completed the study (twenty-four patients discontinued mainly due to disease progression). The study is ongoing

For this inspection, a complete review of all regulatory documentation at the study site was performed, as well as the source records for twenty subjects enrolled at the site prior to the database lock. A review of 20 screened subjects' informed consent forms was completed. The source records reviewed included medical records, regulatory binder documents, source data worksheets, monitoring follow-up reports, and pharmacy records.

Source documents for twenty enrolled subjects whose records were reviewed were verified against the case report forms and sNDA subject line listings, in part, for primary efficacy endpoints, adverse events and serious adverse event reporting. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. **Jing-Zhou Hou, M.D., Ph.D.**

A total of 17 subjects were screened, and 16 subjects were enrolled (one was discontinued due to an adverse event prior to the first drug dose administered). Sixteen subjects received treatment; two subjects completed the treatment phase of this study [Fourteen subjects discontinued for the following reasons: eight study subjects discontinued treatment due to progressive disease (# (b) (6) # (b) (6) # (b) (6) # (b) (6) # (b) (6) # (b) (6) # (b) (6) three patients discontinued due to death (# (b) (6) # (b) (6) # (b) (6) one patient discontinued due to an adverse event (# (b) (6) and two study subjects withdrew consent(# (b) (6) # (b) (6) The study is ongoing.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents for all 17 enrolled subjects and sponsor-generated correspondence were also inspected.

Source documents for all 17 enrolled subjects whose records were reviewed were verified against the case report forms and sNDA subject line listings, in part, for primary study endpoint assessment, adverse event and serious adverse event reporting. A comprehensive audit of the inclusion and exclusion criteria for patient enrollment was evaluated at this site inspection. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for failure to follow the study protocol according to the investigational plan and inaccurate recording and transcription errors. The full 483 citation was shared with DHP. Specifically,

(a) The original protocol excluded the use of concomitant medications that were CYP3A inhibitors. Protocol Amendment 1 allowed the use of moderate CYP3A inhibitors after the dose ramp-up period if the venetoclax dose was reduced by two-fold. Six study subjects did not reduce or adjust the venetoclax dose for ciprofloxacin concomitant medication use. Additionally, the study site did not report these six protocol deviations and an additional dose reduction deviation in another subject to the IRB, within five business days, as part of the site reporting requirement for unanticipated problems.

Comment: Ciprofloxacin antibiotic was prescribed to six study patients, for a single episode, during the study treatment phase. There was no evidence that harms occurred to these newly diagnosed AML study patients [Note: According to the approved label, ciprofloxacin is a CYP3A4 moderate inhibitor when concomitantly used with venetoclax. Ciprofloxacin is also a strong CYP1A2 inhibitor in clinical drug interaction studies].

(b) Transcription errors in the efficacy treatment response were noted for eight subjects, at different time periods during the study visits, for various item subcomponents and classification in the International Working Group treatment response guidelines for Acute Myelogenous Leukemia.

1. For Subject # (b) (6)
    - Post-baseline D IWG-AML Criteria and Hematological Response Assessment case report form (CRF) showed that the IWG response was *Complete Remission with Incomplete Blood Count Recovery*, but both the neutrophils and platelets were below the required levels.
    - Post-baseline E IWG-AML Criteria and Hematological Response Assessment CRF showed that the IWG response was *Complete Remission with Incomplete Blood Count Recovery*, but both the neutrophils and platelets were below the required levels.

2. For Subject # (b) (6)
    - Post-baseline B IWG-AML Criteria and Hematological Response Assessment CRF showed that the IWG response was *Complete Remission with Incomplete Blood Count Recovery*, but both the neutrophils and platelets were below the required levels.
3. For Subject # (b) (6)
    - Post-baseline B IWG-AML Criteria and Hematological Response Assessment CRF showed that the IWG response was *Complete Remission with Incomplete Blood Count Recovery*, but both the neutrophils and platelets were below the required levels.
4. For Subject # (b) (6)
    - Post-baseline A IWG-AML Criteria and Hematological Response Assessment CRF showed that the IWG response was *Partial Remission*, but the correct response should have been *Resistant Disease*.

5. For Subject # (b) (6)
    - A hematologic response was reported as "yes", in the absence of an absolute neutrophil count (ANC) lab report.
    - Bone marrow blast count was 22.0% in the tumor CRF, but 33% in the bone marrow pathology report.
    - The Bone Marrow Aspirate and Biopsy for Response Assessment – Tumor CRF reported that the blast count was 1.0 %, but it was 6% in the bone marrow pathology report.
    - The Post-baseline B IWG-AML Criteria and Hematological Response Assessment CRF showed the bone marrow blasts were reported as less than 5%, but the Bone Marrow Pathology Report showed the bone marrow blasts were 6%.
    - Post-baseline B IWG-AML Criteria and Hematological Response Assessment CRF IWG response of *Morphologically Leukemia Free State* was incorrect, because the bone marrow blasts were not less than 5%.
6. For Subject # (b) (6)
    - The Baseline IWG-AML Criteria and Hematological Response Assessment CRF showed the peripheral blood platelets were reported as less than 100,000/mcL, but the actual result was 296,000 per microliter.
    - The Post-baseline A IWG-AML Criteria and Hematological Response Assessment CRF showed the peripheral blood neutrophils were reported as greater than 1000 per microliter, but the actual result was 30 per microliter.
7. For Subject # (b) (6)
    - The peripheral blood platelet report was recorded as less than 100,000 per microliter, but the actual report was 123,000 per microliter.
    - The bone marrow blasts were reported as less than 5%, but the actual report was 73.7%.
    - The treatment responses of (b) (6), respectively, were recorded as *Complete Remission with Incomplete Blood Count Recovery*, but the neutrophils and platelets did not meet the response criteria.
8. For Subject # (b) (6)
    - The Post-baseline B IWG-AML Criteria and Hematological Response Assessment CRF showed that the IWG response was *Complete Remission*, but according to the Bone Marrow Pathology Report the samples were inadequate for interpretation.

Comment: These inaccurate and incomplete recording, at different time points of the visit observation, occurred sporadically for a random set of the subcomponent items in the treatment response evaluation for eight patients. The impact is unlikely to be considered critical. DHP's independent assessment of the efficacy response is ongoing, concomitant with the biostatistical application team review.

Despite the above observed regulatory deficiencies, these inspectional observations were not considered critical.

{See appended electronic signature page}

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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10/29/2018

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