CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208573Orig1s020, s021

Trade Name:	VENCLEXTA
Generic or Proper Name:	venetoclax
Sponsor:	AbbVie Inc.
Approval Date:	October 16, 2020
Indications:	In combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy

CENTER FOR DRUG EVALUATION AND RESEARCH

208573Orig1s020, s021

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s020, s021

APPROVAL LETTER

NDA 208573/S-020
NDA 208573/S-021

SUPPLEMENT APPROVAL/
FULLFILLMENT OF POSTMARKETING
REQUIREMENT

AbbVie Inc.
Attention: Allan Bonsol
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72/Bldg. AP30
North Chicago, IL 60064

Dear Mr. Bonsol:

Please refer to your supplemental new drug applications (sNDA) dated May 22, 2020, received May 22, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VENCLEXTA (venetoclax tablets) for oral use.

These Prior Approval supplemental new drug applications provide for traditional approval of the following indication: 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 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. Approval of these supplements are based upon results from clinical studies M15-656 (VIALE-A) and M16-043 (VIALE-C).

We also refer to your supplemental new drug application, NDA 208573/S-009, approved November 21, 2018, under Title 21 of the Code of Federal Regulation (CFR) section 314.510 Subpart H for Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 FDA.gov.[1] 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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).

SUBPART H FULFILLED

As noted above, NDA 208573/S-009 was approved under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of these supplements (NDA 208573/S-020 and NDA 208573/S-021) fulfills Postmarketing Requirements 3545-1 and 3545-2 made under 21 CFR 314.510.

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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submissions dated May 7, 2020 and May 22, 2020, containing the final reports for the following postmarketing requirements listed in the November 21, 2018, approval letter for NDA 208573/S-009.

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 ≥ 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.

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 ≥ 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.

We have reviewed your submissions and conclude that the above requirements are fulfilled.

This completes all of your postmarketing requirements acknowledged in our November 21, 2018, approval letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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 Suria Yesmin, Senior Regulatory Project Manager, at 301-348-1725.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Acting Division Director
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

ROMEO A DE CLARO
10/16/2020 10:24:57 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s020, s021

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, AML (1.2)	10/2020
Dosage and Administration (2.1, 2.3, 2.5, 2.8)	10/2020
Warnings and Precautions, Tumor Lysis Syndrome (5.1)	10/2020
Warnings and Precautions, Neutropenia (5.2)	10/2020

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). (1.1)
- In combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. (1.2)

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for recommended VENCLEXTA dosages. (2.2, 2.3)
- Take VENCLEXTA tablets orally once daily with a meal and water. Do not chew, crush, or break tablets. (2.8)
- Provide prophylaxis for tumor lysis syndrome. (2.4)

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. (2.6, 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. (2.4, 5.1)
- Neutropenia: Monitor blood counts. Interrupt dosing and resume at same or reduced dose. Consider supportive care measures. (2 5, 5 2)
- Infections: Monitor for signs and symptoms of infection and treat promptly. Withhold for Grade 3 and 4 infection until resolution and resume at same or reduced dose. (2.5, 5.3)
- Immunization: Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery. (5.4)
- 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. (5.5)
- Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials. (5.6)

ADVERSE REACTIONS

In CLL/SLL, the most common adverse reactions (⩾20%) for VENCLEXTA when given in combination with obinutuzumab or rituximab or as monotherapy were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema. (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, edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, musculoskeletal pain, dizziness, cough, oropharyngeal pain, and hypotension. (6.1)

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. (2.6, 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)
- Hepatic Impairment: Reduce the VENCLEXTA dose by 50% in patients with severe hepatic impairment. (2.7, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2020

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).

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 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

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 (2.4) and Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA dosing begins with a 5-week ramp-up. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS.

VENCLEXTA 5-week Dose Ramp-Up Schedule

Administer VENCLEXTA according to the 5-week ramp-up dosing schedule to the recommended dosage of 400 mg orally once daily as shown in Table 1.

Table 1. Dosing Schedule for 5-Week Ramp-Up Phase for Patients with CLL/SLL

	VENCLEXTA Oral 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)]*.

In Combination with Obinutuzumab

Start obinutuzumab administration at 100 mg on Cycle 1 Day 1, followed by 900 mg on Cycle 1 Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle for a total of 6 cycles. Refer to the obinutuzumab prescribing information for additional dosing information.

On Cycle 1 Day 22, start VENCLEXTA according to the 5-week ramp-up dosing schedule (see Table 1). After completing the ramp-up phase on Cycle 2 Day 28, continue VENCLEXTA at a dose of 400 mg orally once daily from Cycle 3 Day 1 until the last day of Cycle 12.

In Combination with Rituximab

Start rituximab administration after the patient has completed the 5-week ramp-up dosing schedule for VENCLEXTA (see Table 1) and has received VENCLEXTA at the recommended dosage of 400 mg orally once daily for 7 days. Administer rituximab on Day 1 of each 28-day cycle for 6 cycles, at a dose of 375 mg/m^2 intravenously for Cycle 1 and 500 mg/m^2 intravenously for Cycles 2-6. Continue VENCLEXTA 400 mg orally once daily for 24 months from Cycle 1 Day 1 of rituximab.

Refer to the rituximab prescribing information for additional dosing information.

Monotherapy

The recommended dosage of VENCLEXTA is 400 mg once daily after completion of the 5-week ramp-up dosing schedule (see Table 1). Continue VENCLEXTA until disease progression or unacceptable toxicity.

2.3 Recommended Dosage for Acute Myeloid Leukemia

The recommended dosage and ramp-up of VENCLEXTA depends upon the combination agent. Follow the dosing schedule, including the 3-day or 4-day dose ramp-up, as shown in Table 2. Start VENCLEXTA administration on Cycle 1 Day 1 in combination with:

- Azacitidine 75 mg/m^2 intravenously or subcutaneously once daily on Days 1-7 of each 28-day cycle; OR
- Decitabine 20 mg/m^2 intravenously once daily on Days 1-5 of each 28-day cycle; OR
- Cytarabine 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle.

Table 2. Dosing Schedule for 3- or 4-Day Ramp-up Phase in Patients with AML

	VENCLEXTA Oral Daily Dose	
Day 1	100 mg	
Day 2	200 mg	
Day 3	400 mg	
Days 4 and beyond	400 mg orally once daily of each 28-day cycle in combination with **azacitidine or decitabine**	600 mg orally once daily of each 28-day cycle in combination with **low-dose cytarabine**

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

Refer to *Clinical Studies (14.2)* and Prescribing Information for azacitidine, decitabine, or cytarabine for additional dosing information.

2.4 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 to 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 to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5 to 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

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
				• 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 to 2 L) and intravenous (150 to 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), consider additional measures, including increased laboratory monitoring and reducing VENCLEXTA starting dose.

2.5 Dosage Modifications for Adverse Reactions

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The recommended dosage modifications for VENCLEXTA for adverse reactions are provided in Table 4 and the recommended dose reductions for VENCLEXTA for adverse reactions are provided in Table 5.

For patients who have had a dosage 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 re-initiation with a reduced dose is necessary (e.g., all or some levels of the dose ramp-up schedule) *[see Dosage and Administration (2.2, 2.4)]*.

Table 4. Recommended VENCLEXTA Dosage Modifications for Adverse Reactions[a] in CLL/SLL

Adverse Reaction	Occurrence	Dosage Modification
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS *[see Warnings and Precautions (5.1)]*	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at reduced dose (see Table 5).
		For any events of clinical TLS,[b] resume at reduced dose following resolution (see Table 5).
Non-Hematologic Adverse Reactions		
Grade 3 or 4 non-hematologic toxicities *[see Adverse Reactions (6.1)]*	1st occurrence	Interrupt VENCLEXTA. Upon resolution to Grade 1 or baseline level, resume VENCLEXTA at the same dose.
	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 Adverse Reactions		
Grade 3 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia) *[see Warnings and Precautions (5.2)]*	1st occurrence	Interrupt VENCLEXTA. Upon resolution to Grade 1 or baseline level, resume VENCLEXTA at the same dose.
	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.
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. Recommended Dose Reduction for Adverse Reactions for VENCLEXTA 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. Dose modification and interruptions for cytopenias are dependent on remission status. Dose modifications of VENCLEXTA for adverse reactions are provided in Table 6.

Table 6. Recommended VENCLEXTA Dosage Modifications for Adverse Reactions in AML

Adverse Reaction	Occurrence	Dosage Modification
Hematologic Adverse Reactions		
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia *[see Warnings and Precautions (5.2)]*	Occurrence prior to achieving remission[a]	In most instances, do not interrupt VENCLEXTA in combination with azacitidine, decitabine, or low-dose cytarabine due to cytopenias prior to achieving remission.
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent cycle of VENCLEXTA in combination with azacitidine, decitabine, or low-dose cytarabine and monitor blood counts. Upon resolution to Grade 1 or 2, resume VENCLEXTA at the same dose in combination with azacitidine, decitabine or low-dose cytarabine.
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent cycle of VENCLEXTA in combination with azacitidine, or decitabine, or low-dose cytarabine and monitor blood counts. Upon resolution to Grade 1 or 2, resume VENCLEXTA at the same dose in combination with azacitidine, decitabine or low-dose cytarabine, and reduce VENCLEXTA duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days.

Adverse Reaction	Occurrence	Dosage Modification
Non-Hematologic Adverse Reactions		
Grade 3 or 4 non-hematologic toxicities *[see Adverse Reactions (6.1)]*	Any occurrence	Interrupt VENCLEXTA if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume VENCLEXTA at the same dose.
[a]Recommend bone marrow evaluation.		

2.6 Dosage Modifications for Drug Interactions

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 a 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 a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor *[see 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]
Posaconazole	CLL/SLL	Contraindicated	Reduce VENCLEXTA dose to 70 mg.
	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.			

2.7 Dosage Modifications for Patients with Severe Hepatic Impairment

Reduce the VENCLEXTA once daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for adverse reactions *[see Use in Specific Populations (8.7)]*.

2.8 Administration

Instruct patients of the following:

- Take VENCLEXTA with a meal and water.
- Take VENCLEXTA at approximately the same time each day.
- Swallow VENCLEXTA tablets whole. Do not chew, crush, or break tablets prior to swallowing.

If the patient misses a dose of VENCLEXTA within 8 hours of the time it is usually taken, instruct the patient to 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, instruct the patient to take the missed dose and resume the usual dosing schedule the next day.

If the patient vomits following dosing, instruct the patient to not take an additional dose that day and to take the next prescribed dose 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 (2.6) 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)]*.

In patients with CLL who followed the current 5-week ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL monotherapy trials. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or 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)]*.

In patients with AML who followed the current 3-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 1.1% in patients who received VENCLEXTA in combination with azacitidine (VIALE-A). In patients with AML who followed a 4-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 5.6% and included deaths and renal failure in patients who received VENCLEXTA in combination with low-dose cytarabine (VIALE-C) *[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. Assess patients for risk and provide 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 (2.1, 2.2, 2.3, 2.4) and Use in Specific Populations (8.6)]*.

Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during ramp-up phase of VENCLEXTA. For patients with CLL/SLL, coadministration of VENCLEXTA with strong CYP3A inhibitors at initiation and during the 5-week ramp-up phase is contraindicated *[see Contraindications (4)]*. For patients with AML, reduce the dose of VENCLEXTA when coadministered with strong CYP3A inhibitors at initiation and during the 3- or 4-day ramp-up phase. For patients with CLL/SLL or AML, reduce the dose of VENCLEXTA when coadministered with moderate CYP3A4 inhibitors or P-gp inhibitors *[see Dosage and Administration (2.6) and Drug Interactions (7.1)]*.

5.2 Neutropenia

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

In patients with AML, baseline neutrophil counts worsened in 95% to 100% of patients treated with VENCLEXTA in combination with azacitidine, decitabine or low-dose cytarabine. Neutropenia can recur with subsequent cycles.

Monitor complete blood counts throughout the treatment period. For interruption and dose resumption of VENCLEXTA for severe neutropenia, see Table 4 for CLL and Table 6 for AML *[see Dosage and Administration (2.5)]*. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF).

5.3 Infections

Fatal and serious infections, such as pneumonia and sepsis, have occurred in patients treated with VENCLEXTA *[see Adverse Reactions (6.1)]*.

Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution. For dose resumptions, see Table 4 for CLL and Table 6 for AML *[see Dosage and Administration (2.5)]*.

5.4 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.

5.5 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, 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 a dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight.

Advise pregnant women of the potential risk to a fetus. 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, 8.3)]*

5.6 Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to Bortezomib and Dexamethasone

In a randomized trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Tumor Lysis Syndrome *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*
- Infections *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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.

In CLL/SLL, the safety population reflects exposure to VENCLEXTA as monotherapy in patients in M13-982, M14-032, and M12-175 and in combination with obinutuzumab or rituximab in patients in CLL14 and MURANO. In this CLL/SLL safety population, the most common adverse reactions (≥20%) for VENCLEXTA were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema.

In AML, the safety population reflects exposure to VENCLEXTA in combination with decitabine, azacitidine, or low-dose cytarabine in patients in M14-358, VIALE-A, and VIALE-C.

In this safety population, the most common adverse reactions (≥30% in any trial) were nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, musculoskeletal pain, dizziness, cough, oropharyngeal pain, and hypotension.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA in Combination with Obinutuzumab

The safety of VENCLEXTA in combination with obinutuzumab (VEN+G) (N=212) versus obinutuzumab in combination with chlorambucil (GClb) (N=214) was evaluated in CLL14, a randomized, open-label, actively controlled trial in patients with previously untreated CLL *[see Clinical Studies (14.1)]*. Patients randomized to the VEN+G arm were treated with VENCLEXTA and obinutuzumab in combination for six cycles, then with VENCLEXTA as monotherapy for an additional six cycles. Patients initiated the first dose of the 5-week ramp-up for VENCLEXTA on Day 22 of Cycle 1 and once completed, continued VENCLEXTA 400 mg orally once daily for a total of 12 cycles. The trial required a total Cumulative Illness Rating Scale (CIRS) >6 or CLcr <70 mL/min, hepatic transaminases and total bilirubin ≤2 times upper limit of normal and excluded patients with any individual organ/system impairment score of 4 by CIRS except eye, ear, nose, and throat organ system. The median duration of exposure to VENCLEXTA was 10.5 months (range: 0 to 13.5 months) and the median number of cycles of obinutuzumab was 6 in the VEN+G arm.

Serious adverse reactions were reported in 49% of patients in the VEN+G arm, most often due to febrile neutropenia and pneumonia (5% each). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection.

In the VEN+G arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 21%, and dose interruption in 74%. Neutropenia led to dose interruption of VENCLEXTA in 41% of patients, reduction in 13%, and discontinuation in 2%.

Table 9 presents adverse reactions identified in CLL14.

Table 9. Adverse Reactions (≥10%) in Patients Treated with VEN+G in CLL14

Adverse Reaction	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders				
Neutropenia[a]	60	56	62	52
Anemia[a]	17	8	20	7
Gastrointestinal disorders				
Diarrhea	28	4	15	1
Nausea	19	0	22	1
Constipation	13	0	9	0
Vomiting	10	1	8	1
General disorders and administration site conditions				

Adverse Reaction	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Fatigue[a]	21	2	23	1
Infections and infestations				
Upper respiratory tract infection[a]	17	1	17	1
[a]Includes multiple adverse reaction terms.				

Other clinically important adverse reactions (All Grades) reported in <10% of patients treated with VEN+G are presented below:

Blood and lymphatic system disorders: febrile neutropenia (6%)

Infection and infestations (all include multiple adverse reaction terms): pneumonia (9%), urinary tract infection (6%), sepsis (4%)

Metabolism and nutrition disorder: tumor lysis syndrome (1%)

During treatment with VENCLEXTA monotherapy after completion of VEN+G, the adverse reaction that occurred in ≥10% of patients was neutropenia (26%). The grade ≥3 adverse reactions that occurred in ≥2% of patients were neutropenia (23%) and anemia (2%).

Table 10 presents laboratory abnormalities CLL14.

Table 10. New or Worsening Clinically Important Laboratory Abnormalities (≥10%) in Patients Treated with VEN+G in CLL14

Laboratory Abnormality[a]	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Leukopenia	90	46	89	41
Lymphopenia	87	57	87	51
Neutropenia	83	63	79	56
Thrombocytopenia	68	28	71	26
Anemia	53	15	46	11
Chemistry				
Blood creatinine increased	80	6	74	2
Hypocalcemia	67	9	58	4
Hyperkalemia	41	4	35	3
Hyperuricemia	38	38	38	38
[a]Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.				

Grade 4 laboratory abnormalities that developed in ≥2% of patients treated with VEN+G included neutropenia (32%), leukopenia and lymphopenia (10%), thrombocytopenia (8%), hypocalcemia (8%), hyperuricemia (7%), blood creatinine increased (3%), hypercalcemia (3%), and hypokalemia (2%).

VENCLEXTA in Combination with Rituximab

The safety of VENCLEXTA in combination with rituximab (VEN+R) (N=194) versus bendamustine in combination with rituximab (B+R) (N=188) was evaluated in MURANO *[see Clinical Studies (14.1)]*. 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. At the time of analysis, the median duration of exposure to VENCLEXTA was 22 months and the median number of cycles of rituximab was 6 in the VEN+R arm.

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

In the VEN+R arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 15%, and dose interruption in 71%. 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 11 presents adverse reactions identified in MURANO.

Table 11. Adverse Reactions (≥10%) in Patients Treated with VEN+R in MURANO

Adverse Reaction	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders				
Neutropenia[a]	65	62	50	44
Anemia[a]	16	11	23	14
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Nausea	21	1	34	1
Constipation	14	<1	21	0
Infections and infestations				
Upper respiratory tract infection[a]	39	2	23	2
Lower respiratory tract infection[a]	18	2	10	2
Pneumonia[a]	10	7	14	10
General disorders and administration site conditions				
Fatigue[a]	22	2	26	<1

Adverse Reaction	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
[a]Includes multiple adverse reaction terms.				

Other clinically important adverse reactions (All Grades) reported in <10% of patients treated with VEN+R are presented below:

Blood and lymphatic system disorders: febrile neutropenia (4%)

Gastrointestinal disorders: vomiting (8%)

Infections and infestations: sepsis (<1%)

Metabolism and nutrition disorders: tumor lysis syndrome (3%)

During treatment with VENCLEXTA monotherapy after completion of VEN+R combination treatment, adverse reactions that occurred in ≥10% of patients were upper respiratory tract infection (21%), diarrhea (19%), neutropenia (16%), and lower respiratory tract infections (11%). The Grade 3 or 4 adverse reactions that occurred in ≥2% of patients were neutropenia (12%) and anemia (3%).

Table 12 presents laboratory abnormalities identified in MURANO.

Table 12. New or Worsening Clinically Important Laboratory Abnormalities (≥10%) in Patients Treated with VEN+R in MURANO

Laboratory Abnormality	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	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
Anemia	50	12	63	15
Thrombocytopenia	49	15	60	20
Chemistry				
Blood creatinine increased	77	<1	78	1
Hypocalcemia	62	5	51	2
Hyperuricemia	36	36	33	33
Hyperkalemia	24	3	19	2
[a]Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.				

Grade 4 laboratory abnormalities that developed 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%).

VENCLEXTA as Monotherapy

The safety of VENCLEXTA was evaluated in pooled data from three single-arm trials (M13-982, M14-032, and M12-175). Patients received VENCLEXTA 400 mg orally once daily after completing the ramp-up phase (N=352). 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.

In the pooled dataset, 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).

Serious adverse reactions were reported in 52% of patients, with the most frequent (≥5%) being pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). 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 often (2 patients) from septic shock.

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%).

Table 13 presents adverse reactions identified in these trials.

Table 13. Adverse Reactions Reported in ≥10% (All Grades) or ≥5% (Grade ≥3) of Patients with Previously Treated CLL/SLL Who Received VENCLEXTA Monotherapy

Adverse Reaction	VENCLEXTA (N = 352)	
	All Grades (%)	Grade ≥3 (%)
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
Infections and infestations		
Upper respiratory tract infection[a]	36	1
Pneumonia[a]	14	8
Lower respiratory tract infection[a]	11	2

Adverse Reaction	VENCLEXTA (N = 352)	
	All Grades (%)	Grade ≥3 (%)
General disorders and administration site conditions		
Fatigue[a]	32	4
Edema[a]	22	2
Pyrexia	18	<1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[a]	29	2
Arthralgia	12	<1
Respiratory, thoracic, and mediastinal disorders		
Cough[a]	22	0
Dyspnea[a]	13	1
Nervous system disorders		
Headache	18	<1
Dizziness[a]	14	0
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.		

Table 14 presents 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 14. New or Worsening Laboratory Abnormalities in ≥40% (All Grades) or ≥10% (Grade 3 or 4) of Patients with Previously Treated CLL/SLL Who Received VENCLEXTA Monotherapy

Laboratory Abnormality	VENCLEXTA (N = 352)	
	All Grades[a] (%)	Grade 3 or 4 (%)
Hematology		
Leukopenia	89	42
Neutropenia	87	63
Lymphopenia	74	40
Anemia	71	26
Thrombocytopenia	64	31
Chemistry		
Hypocalcemia	87	12

Laboratory Abnormality	VENCLEXTA (N = 352)	
	All Grades[a] (%)	Grade 3 or 4 (%)
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 in CLL/SLL

Tumor Lysis Syndrome

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

CLL14

The incidence of TLS was 1% (3/212) in patients treated with VEN+G *[see Warnings and Precautions (5.1)]*. All three events of TLS resolved and did not lead to withdrawal from the trial. Obinutuzumab administration was delayed in two cases in response to the TLS events.

MURANO

The incidence of TLS was 3% (6/194) in patients treated with VEN+R. After 77/389 patients were enrolled in the trial, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures described in sections 2.2 and 2.4 *[see Dosage and Administration (2.2, 2.4)]*. 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 *[see Dosage and Administration (2.2, 2.4)]*. Rates of laboratory abnormalities relevant to TLS for patients treated with VEN+R are presented in Table 12.

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 (2.2, 2.4)]*. 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 (2.2, 2.4)]*.

Acute Myeloid Leukemia

VENCLEXTA in Combination with Azacitidine

The safety of VENCLEXTA in combination with azacitidine (VEN+AZA) (N=283) versus placebo in combination with azacitidine (PBO+AZA) (N=144) was evaluated in VIALE-A, a double-blind, randomized trial, in patients with newly diagnosed AML *[see Clinical Studies (14.2)]*. At baseline, patients 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 ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr < 45 mL/min, or other comorbidity. Patients were randomized to receive VENCLEXTA 400 mg orally once daily after completion of the ramp-up phase in combination with azacitidine (75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle) or placebo in combination with azacitidine. Among patients who received VEN+AZA, the median duration of exposure to VENCLEXTA was 7.6 months (range: <0.1 to 30.7 months).

Serious adverse reactions were reported in 83% of patients who received VEN+AZA, with the most frequent (≥5%) being febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%), and hemorrhage (6%). Fatal adverse reactions occurred in 23% of patients who received VENCLEXTA in combination with azacitidine, with the most frequent (≥2%) being pneumonia (4%), sepsis (excluding fungal; 3%), and hemorrhage (2%).

Adverse reactions led to permanent discontinuation of VENCLEXTA in 24% of patients, dose reductions in 2%, and dose interruptions in 72%. Adverse reactions which led to discontinuation of VENCLEXTA in ≥2% of patients were sepsis (excluding fungal; 3%) and pneumonia (2%). The most frequent adverse reaction leading to dose reduction was pneumonia (0.7%). Adverse reactions which required a dose interruption in ≥5% of patients included febrile neutropenia (20%), neutropenia (20%), pneumonia (14%), sepsis (excluding fungal; 11%), and thrombocytopenia (10%). Among patients who achieved bone marrow clearance of leukemia, 53% underwent dose interruptions for ANC <500/microliter.

Table 15 presents adverse reactions identified in VIALE-A.

Table 15. Adverse Reactions (≥10%) in Patients with AML Who Received VEN+AZA with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Reactions Compared with PBO+AZA in VIALE-A

Adverse Reaction	VENCLEXTA + Azacitidine (N = 283)		Placebo + Azacitidine (N = 144)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	44	2	35	<1
Diarrhea[a]	43	5	33	3
Vomiting[b]	30	2	23	<1
Stomatitis[c]	18	1	13	0
Abdominal pain[d]	18	<1	13	0
Blood and lymphatic system disorders				
Febrile neutropenia	42	42	19	19
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[e]	36	2	28	1
General disorders and administration site conditions				
Fatigue[f]	31	6	23	2
Edema[g]	27	<1	19	0
Vascular disorders				
Hemorrhage[h]	27	7	24	3
Hypotension[i]	12	5	8	3
Metabolism and nutrition disorders				
Decreased appetite[j]	25	4	17	<1
Skin and subcutaneous tissue disorders				
Rash[k]	25	1	15	0
Infections and infestations				
Sepsis[l] (excluding fungal)	22	22	16	14
Urinary tract infection[m]	16	6	9	6
Respiratory, thoracic and mediastinal disorders				
Dyspnea[n]	18	4	10	2
Nervous system disorders				
Dizziness[o]	17	<1	8	<1

[a]Includes diarrhea and colitis
[b]Includes vomiting and hematemesis
[c]Includes stomatitis, mouth ulceration, mucosal inflammation, cheilitis, aphthous ulcer, glossitis and tongue ulceration.
[d]Includes abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.

Adverse Reaction	VENCLEXTA + Azacitidine (N = 283)		Placebo + Azacitidine (N = 144)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
[e]Includes arthralgia, back pain, pain in extremity, musculoskeletal pain, bone pain, myalgia, neck pain, non-cardiac chest pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, spinal pain, and musculoskeletal discomfort. [f]Includes fatigue and asthenia. [g]Includes edema peripheral, edema, generalized edema, eyelid edema, face edema, penile edema, periorbital edema, and swelling. [h]Includes epistaxis, hematuria, conjunctival hemorrhage, hemoptysis, hemorrhoidal hemorrhage, gingival bleeding, mouth hemorrhage, hemorrhage intracranial, vaginal hemorrhage, cerebral hemorrhage, gastrointestinal hemorrhage, muscle hemorrhage, skin hemorrhage, upper gastrointestinal hemorrhage, anal hemorrhage, eye hemorrhage, gastritis hemorrhagic, hemorrhage, hemorrhage urinary tract, hemorrhagic diathesis, hemorrhagic stroke, hemorrhagic vasculitis, lower gastrointestinal hemorrhage, mucosal hemorrhage, penile hemorrhage, post procedural hemorrhage, rectal hemorrhage, retinal hemorrhage, shock hemorrhagic, soft tissue hemorrhage, subdural hemorrhage, tongue hemorrhage, urethral hemorrhage, vessel puncture site hemorrhage, vitreous hemorrhage and wound hemorrhage. [i]Includes hypotension and orthostatic hypotension. [j]Includes decreased appetite and hypophagia. [k]Includes rash, rash maculo-papular, rash macular, drug eruption, rash papular, rash pustular, eczema, rash erythematous, rash pruritic, dermatitis acneiform, rash morbilliform, dermatitis, eczema asteatotic, exfoliative rash, and perivascular dermatitis. [l]Includes sepsis, escherichia bacteremia, escherichia sepsis, septic shock, bacteremia, staphylococcal bacteremia, klebsiella bacteremia, staphylococcal sepsis, streptococcal bacteremia, enterococcal bacteremia, klebsiella sepsis, pseudomonal bacteremia, pseudomonal sepsis, urosepsis, bacterial sepsis, clostridial sepsis, enterococcal sepsis, neutropenic sepsis, and streptococcal sepsis. [m]Includes urinary tract infection, escherichia urinary tract infection, cystitis, urinary tract infection enterococcal, urinary tract infection bacterial, pyelonephritis acute, and urinary tract infection pseudomonal. [n]Includes dyspnea, dyspnea exertional, and dyspnea at rest. [o]Includes dizziness and vertigo.				

Other clinically important adverse reactions (All Grades) at ≥10% that did not meet criteria for Table 15 or <10% are presented below:

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (4%)

Infections and infestations: pneumonia[b] (33%)

Metabolism and nutrition disorders: tumor lysis syndrome (1%)

Nervous system disorders: headache[c] (11%)

Investigations: weight decreased (13%).

[a]Includes cholecystitis acute, cholelithiasis, cholecystitis, and cholecystitis chronic

[b]Includes pneumonia, lung infection, pneumonia fungal, pneumonia klebsiella, atypical pneumonia, lower respiratory tract infection, pneumonia viral, lower respiratory tract infection fungal, pneumonia hemophilus, pneumonia pneumococcal, and pneumonia respiratory syncytial viral

[c]Includes headache and tension headache.

Table 16 presents laboratory abnormalities identified in VIALE-A.

Table 16. New or Worsening Laboratory Abnormalities (≥10%) in Patients with AML Who Received VEN+AZA with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Reactions Compared with PBO+AZA in VIALE-A

Laboratory Abnormality	VENCLEXTA + Azacitidine		Placebo + Azacitidine	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophils decreased	98	98	88	81
Platelet decreased	94	88	94	80
Lymphocytes decreased	91	71	72	39
Hemoglobin decreased	61	57	56	52
Chemistry				
Bilirubin increased	53	7	40	4
Calcium decreased	51	6	39	9
Sodium decreased	46	14	47	8
Alkaline phosphatase increased	42	1	29	<1
Blood bicarbonate decreased	31	<1	25	0
The denominator used to calculate the rate varied from 85 to 144 in PBO+AZA and from 125 to 283 in VEN+AZA based on the number of patients with at least one post-treatment value.				

VENCLEXTA in Combination with Azacitidine or Decitabine

The safety of VENCLEXTA in combination with azacitidine (n=67) or decitabine (n=13) was evaluated in M14-358, a non-randomized trial of patients with newly diagnosed AML. At baseline, patients 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 ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity *[see Clinical Studies (14.2)]*. Patients received VENCLEXTA 400 mg orally once daily after completion of the ramp-up phase in combination with azacitidine (75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle) or decitabine (20 mg/m^2 intravenously on Days 1-5 of each 28-day cycle).

Azacitidine

The median duration of exposure to VENCLEXTA when administered in combination with azacitidine was 6.5 months (range: 0.1 to 38.1 months). The safety of VENCLEXTA in combination with azacitidine in this trial is consistent with that of VIALE-A.

Decitabine

The median duration of exposure to VENCLEXTA when administered in combination with decitabine was 8.4 months (range: 0.5 to 39 months).

Serious adverse reactions were reported in 85% of patients who received VENCLEXTA with decitabine, the most frequent (≥10%) being sepsis (excluding fungal; 46%), febrile neutropenia (38%), and pneumonia (31%). One (8%) fatal adverse reaction of bacteremia occurred within 30 days of starting treatment.

Permanent discontinuation of VENCLEXTA due to adverse reactions occurred in 38% of patients. The most frequent adverse reaction leading to permanent discontinuation (≥5%) was pneumonia (8%).

Dosage interruptions of VENCLEXTA due to adverse reactions occurred in 69% of patients. The most frequent adverse reactions leading to dose interruption (≥ 10%) were neutropenia (38%), febrile neutropenia (23%), leukopenia (15%), and pneumonia (15%).

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

The most common adverse reactions (≥30%) were febrile neutropenia (69%), fatigue (62%), constipation (62%), musculoskeletal pain (54%), dizziness (54%), nausea (54%), abdominal pain (46%), diarrhea (46%), pneumonia (46%), sepsis (excluding fungal; 46%), cough (38%), pyrexia (31%), hypotension (31%), oropharyngeal pain (31%), edema (31%), and vomiting (31%). The most common laboratory abnormalities (≥30%) were neutrophils decreased (100%), lymphocytes decreased (100%), white blood cells decreased (100%), platelets decreased (92%), calcium decreased (85%), hemoglobin decreased (69%), glucose increased (69%), magnesium decreased (54%), potassium decreased (46%), bilirubin increased (46%), albumin decreased (38%), alkaline phosphatase increased (38%), sodium decreased (38%), ALT increased (31%), creatinine increased (31%), and potassium increased (31%).

VENCLEXTA in Combination with Low-Dose Cytarabine

VIALE-C

The safety of VENCLEXTA in combination with low-dose cytarabine (VEN+LDAC) (N=142) versus placebo with low-dose cytarabine (PBO+LDAC) (N=68) was evaluated in VIALE-C, a double-blind randomized trial in patients with newly diagnosed AML. At baseline, patients 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 ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity *[see Clinical Studies (14.2)]*. Patients were randomized to receive VENCLEXTA 600 mg orally once daily after completion of a 4-day ramp-up phase in combination with low-dose cytarabine (20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle) or placebo in combination with low-dose cytarabine. Among patients who received VEN+LDAC, the median duration of exposure to VENCLEXTA was 3.9 months (range: <0.1 to 17.1 months).

Serious adverse reactions were reported in 65% of patients who received VEN+LDAC, with the most frequent (≥10%) being pneumonia (17%), febrile neutropenia (16%), and sepsis (excluding fungal; 12%). Fatal adverse reactions occurred in 23% of patients who received VENCLEXTA in combination with LDAC, with the most frequent (≥5%) being pneumonia (6%) and sepsis (excluding fungal; 7%).

Adverse reactions led to permanent discontinuation of VENCLEXTA in 25% of patients, dose reductions in 9%, and dose interruptions in 63%. The most frequent adverse reaction (>2%) which resulted in permanent discontinuation of VENCLEXTA was pneumonia (6%). Adverse reactions which required a dose reduction in ≥1% of patients were pneumonia (1%) and thrombocytopenia (1%) and the adverse reactions which required a dose interruption in ≥5% of patients included neutropenia (20%), thrombocytopenia (15%), pneumonia (8%), febrile neutropenia (6%), and sepsis (excluding fungal; 6%). Among patients who achieved bone marrow clearance of leukemia, 32% underwent dose interruptions for ANC <500/microliter.

Table 17 presents adverse reactions identified in VIALE-C.

Table 17. Adverse Reactions (≥10%) in Patients with AML Who Received VEN+LDAC with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Compared with PBO+LDAC in VIALE-C

Adverse Reaction	VENCLEXTA + Low-Dose Cytarabine (N = 142)		Placebo + Low-Dose Cytarabine (N = 68)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	42	1	31	0
Diarrhea	28	3	16	0
Vomiting	25	<1	13	0
Abdominal pain[a]	15	<1	9	3
Stomatitis[b]	15	1	6	0
Blood and lymphatic system disorders				
Febrile neutropenia	32	32	29	29
Infections and infestations				
Pneumonia[c]	29	19	21	21
Vascular Disorders				
Hemorrhage[d]	27	8	16	1
Hypotension[e]	11	5	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[f]	23	3	18	0
General Disorders and Administration Site Conditions				
Fatigue[g]	22	2	21	0
Nervous System Disorders				
Headache	11	0	6	0

[a]Includes abdominal pain, abdominal pain upper, abdominal discomfort and abdominal pain lower.
[b]Includes stomatitis, mouth ulceration, aphthous ulcer, glossitis, mucosal inflammation and tongue ulceration.

Adverse Reaction	VENCLEXTA + Low-Dose Cytarabine (N = 142)		Placebo + Low-Dose Cytarabine (N = 68)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
[c]Includes pneumonia, lung infection, lower respiratory tract infection, pneumonia fungal, lower respiratory tract infection fungal, pneumocystis jirovecii pneumonia, pneumonia aspiration, pneumonia cytomegaloviral, and pneumonia pseudomonal. [d]Includes epistaxis, conjunctival hemorrhage, hemoptysis, gastrointestinal hemorrhage, gingival bleeding, mouth hemorrhage, upper gastrointestinal hemorrhage, hematuria, retinal hemorrhage, catheter site hemorrhage, cerebral hemorrhage, gastric hemorrhage, gastritis hemorrhagic, hemorrhage intracranial, hemorrhage subcutaneous, lip hemorrhage, mucosal hemorrhage, pharyngeal hemorrhage, post procedural hemorrhage, pulmonary alveolar hemorrhage, pulmonary hemorrhage, tooth pulp hemorrhage, uterine hemorrhage and vascular access site hemorrhage. [e]Includes hypotension and orthostatic hypotension. [f]Includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, arthritis, bone pain, musculoskeletal chest pain and spinal pain. [g]Includes fatigue and asthenia.				

Other clinically important adverse reactions (All Grades) at ≥10% that did not meet criteria for the Table 17 or <10% are presented below:

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (1%)

Infections and infestations: sepsis[b] (excluding fungal; 15%), urinary tract infection[c] (8%)

Metabolism and nutrition disorders: decreased appetite (19%), tumor lysis syndrome (6%)

Nervous system disorders: dizziness[d] (9%)

Respiratory, thoracic, and mediastinal disorders: dyspnea[e] (10%)

Investigations: weight decreased (9%).

[a]Includes cholecystitis and cholecystitis acute

[b]Includes sepsis, bacteremia, septic shock, neutropenic sepsis, staphylococcal bacteremia, streptococcal bacteremia, bacterial sepsis, Escherichia bacteremia, pseudomonal bacteremia, and staphylococcal sepsis

[c]Includes urinary tract infection and escherichia urinary tract infection

[d]Includes dizziness and vertigo

[e]Includes dyspnea and dyspnea exertional.

Table 18 describes laboratory abnormalities identified in VIALE-C.

Table 18. New or Worsening Laboratory Abnormalities (≥10%) in Patients with AML Who Received VEN+LDAC with Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Reactions Compared with PBO+LDAC in VIALE-C

Laboratory Abnormality	VENCLEXTA + Low-Dose Cytarabine		Placebo + Low-Dose Cytarabine	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Platelets decreased	97	95	92	90
Neutrophils decreased	95	92	82	71
Lymphocytes decreased	92	69	65	24
Hemoglobin decreased	63	57	57	54
Chemistry				
Bilirubin increased	61	7	38	7
Albumin decreased	61	6	43	4
Potassium decreased	56	16	42	14
Calcium decreased	53	8	45	13
Glucose increased	52	13	59	9
AST increased	36	6	37	1
Alkaline phosphatase increased	34	1	26	1
ALT increased	30	4	26	1
Sodium increased	11	3	6	1
The denominator used to calculate the rate varied from 38 to 68 in PBO+LDAC and from 65 to 142 in VEN+LDAC based on the number of patients with at least one post-treatment value.				

M14-387

The safety of VENCLEXTA in combination with low-dose cytarabine (n=61) was evaluated in M14-387, a non-randomized, open label trial of patients with newly diagnosed AML *[see Clinical Studies (14.2)]*. At baseline, patients 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 ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity. Patients received VENCLEXTA 600 mg orally once daily after completion of the ramp-up phase in combination with low-dose cytarabine (20mg/m^2 subcutaneously on Days 1-10 of each 28-day cycle). The safety of VENCLEXTA in combination with low-dose cytarabine is consistent with that of VIALE-C.

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 $AUC_{0\text{-}INF}$ *[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 monitor more frequently for adverse reactions *[see Dosage and Administration (2.5, 2.6)]*.

In patients with AML, adjust VENCLEXTA dosage and monitor more frequently for adverse reactions *[see Dosage and Administration (2.5, 2.6)]*.

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 (2.5, 2.6)]*.

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 $AUC_{0\text{-}INF}$ *[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 $AUC_{0\text{-}INF}$ *[see Clinical Pharmacology (12.3)]*, which may increase the risk of bleeding. Monitor international normalized ratio (INR) more frequently in patients using warfarin concomitantly with VENCLEXTA.

P-gp Substrates

Concomitant use of VENCLEXTA increases C_{max} and $AUC_{0\text{-}INF}$ 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

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1)]*, VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. There are no available data on VENCLEXTA use in pregnant women to inform a drug-associated risk. Administration of venetoclax to pregnant mice during the period of organogenesis was fetotoxic at exposures 1.2 times the human exposure at the recommended dose of 400 mg daily based on AUC. Advise pregnant women 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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 exposure at the recommended dose of 400 mg once 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 or the effects on the breastfed child or milk production. Venetoclax was present in the milk when administered to lactating rats *(see Data)*.

Because of the potential for serious adverse reactions in a breastfed, advise women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

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 when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating VENCLEXTA.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose.

Infertility

Based on findings in animals, VENCLEXTA may impair male fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of VENCLEXTA have not been established in pediatric patients.

Juvenile Animal Toxicity Data

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 clinically meaningful differences in safety and effectiveness were observed between older and younger patients in the combination and monotherapy studies.

Acute Myeloid Leukemia

Of the 283 patients who received VENCLEXTA with azacitidine in VIALE-A, 96% were ≥65 years of age and 60% were ≥75 years of age.

Of the 13 patients who received VENCLEXTA in combination with decitabine in M14-358, 100% were ≥65 years of age and 62% were ≥75 years of age.

Of the 142 patients who received VENCLEXTA in combination with low-dose cytarabine in VIALE-C, 92% were ≥65 years of age and 57% were ≥75 years of age.

Clinical studies of VENCLEXTA in patients with AML did not include sufficient numbers of younger adults to determine if patients 65 years of age and older respond differently from younger adults.

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 (2.1, 2.2, 2.3, 2.4) and Warnings and Precautions (5.1)]*.

No dose adjustment is recommended for patients with mild, moderate or severe renal impairment (CLcr ≥15 mL/min) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more frequently for adverse reactions *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

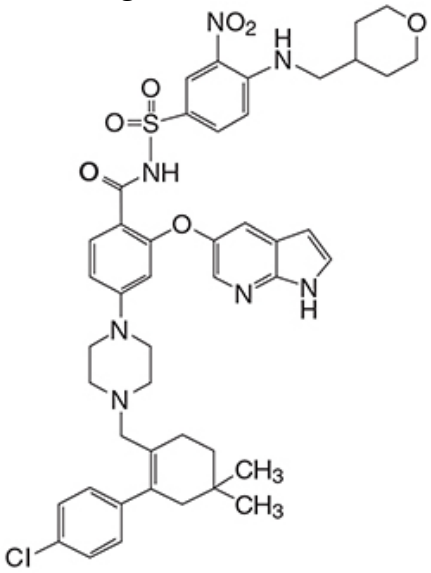
10 OVERDOSAGE

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, 2.4, 2.5)]*. 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 BCL-2 inhibitor. 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 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:



Venetoclax has very low aqueous solubility.

VENCLEXTA tablets for oral use 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 trial 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_{0-24h} 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 (21% 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 93 years), sex, weight, mild to severe renal impairment (CLcr 15 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 end-stage renal disease (CLcr <15 mL/min) or dialysis on venetoclax pharmacokinetics is unknown.

Racial or Ethnic Groups

No clinically significant differences in the pharmacokinetics of venetoclax were observed in White, Black, and Asian patients enrolled in the United States. Of 771 patients with AML, Asian patients from Asian countries [China (5.6%), Japan (5.5%), South Korea (2.1%), and Taiwan (0.9%)] had 63% higher venetoclax exposure than non-Asian populations.

Patients with Hepatic Impairment

Following a single dose of VENCLEXTA 50 mg, venetoclax systemic exposure ($AUC_{0\text{-}INF}$) was 2.7-fold higher in subjects with severe hepatic impairment (Child-Pugh C) compared to subjects with normal hepatic function *[see Dosage and Administration (2.7) and Use in Specific Populations (8.7)]*. No clinically relevant differences in venetoclax systemic exposure were observed between subjects with mild or moderate hepatic impairment and subjects with normal hepatic function.

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, obinutuzumab, 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 $AUC_{0\text{-}INF}$ 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 VENCLEXTA 50 mg and 100 mg for 7 days resulted in 61% and 86% higher venetoclax C_{max}, respectively, compared with VENCLEXTA 400 mg administered alone. The venetoclax AUC_{0-24h} was 90% and 144% higher, respectively *[see Drug Interactions (7.1)]*.

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_{0-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_{0-INF} by 71% *[see Drug Interactions (7.1)]*.

Warfarin

Concomitant use of a single 400 mg dose of VENCLEXTA with 5 mg of warfarin resulted in 18% to 28% increase in C_{max} and AUC_{0-INF} of R-warfarin and S-warfarin *[see Drug Interactions (7.2)]*.

Digoxin

Concomitant use of a single dose of VENCLEXTA 100 mg with digoxin (a P-gp substrate) 0.5 mg increased digoxin C_{max} by 35% and AUC_{0-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

Neither venetoclax nor M27, a major human metabolite, were carcinogenic in a 6-month transgenic (Tg.rasH2) mouse study at oral doses up to 400 mg/kg/day of venetoclax, and at a single oral dose level of 250 mg/kg/day of M27.

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 a dose of 400 mg.

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

In Combination with Obinutuzumab

CLL14 (BO25323) was a randomized (1:1), multicenter, open label, actively controlled trial (NCT02242942) that evaluated the efficacy and safety of VENCLEXTA in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) for patients with previously untreated CLL with coexisting medical conditions (total Cumulative Illness Rating Scale [CIRS] score >6 or CLcr <70 mL/min). The trial required hepatic transaminases and total bilirubin ≤2 times upper limit of normal and excluded patients with Richter's transformation or any individual organ/system impairment score of 4 by CIRS except eye, ear, nose, and throat organ system.

All patients received obinutuzumab at 1000 mg on Days 1 (the first dose could be split as 100 mg and 900 mg on Days 1 and 2), 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle for a total of 6 cycles. Patients in the VEN+G arm began the VENCLEXTA 5-week ramp-up dosing schedule *[see Dosage and Administration (2.2, 2.4)]* on Day 22 of Cycle 1 and received VENCLEXTA 400 mg orally once daily from Cycle 3 Day 1 until the last day of Cycle 12. Patients randomized to the GClb arm received chlorambucil 0.5 mg/kg orally on Day 1 and Day 15 of Cycles 1 to 12. Each cycle was 28 days.

A total of 432 patients were randomized, 216 to each arm. Baseline demographic and disease characteristics were similar between the arms. The median age was 72 years (range: 41 to 89 years), 89% were White, 67% were male; 36% and 43% were Binet stage B and C, respectively, and 88% had Eastern Cooperative Oncology Group (ECOG) performance status <2. The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CLcr <70 mL/min. A 17p deletion was detected in 8% of patients, *TP53* mutations in 10%, 11q deletion in 19%, and unmutated *IgVH* in 57%.

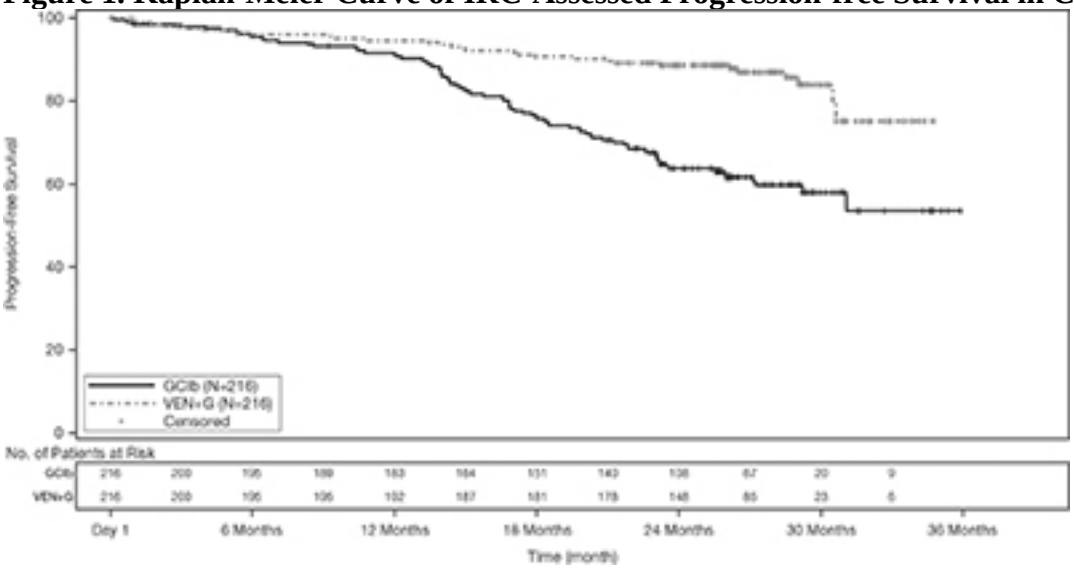
Efficacy was based on progression-free survival (PFS) as assessed by an Independent Review Committee (IRC). The median duration of follow-up for PFS was 28 months (range: 0 to 36 months). Efficacy results for CLL14 are shown in Table 19. The Kaplan-Meier curve for PFS is shown in Figure 1.

Table 19. Efficacy Results in CLL14

Endpoint	VENCLEXTA + Obinutuzumab (N = 216)	Obinutuzumab + Chlorambucil (N = 216)
Progression-free survival[a]		
Number of events, n (%)	29 (13)	79 (37)
Disease progression	14 (6)	71 (33)
Death	15 (7)	8 (4)
Median, months	Not Reached	Not Reached
HR (95% CI)[b]	0.33 (0.22, 0.51)	
p-value[b]	<0.0001	
Response rate[c], n (%)		
ORR[d]	183 (85)	154 (71)
95% CI	(79, 89)	(65, 77)
CR	100 (46)	47 (22)
CR+CRi[d]	107 (50)	50 (23)
PR	76 (35)	104 (48)

CI = confidence interval; HR = hazard ratio; CR = complete remission; CRi = complete remission with incomplete marrow recovery; PR = partial remission; ORR = overall response rate (CR + CRi + PR).
[a]From randomization until earliest event of disease progression or death due to any cause. IRC-assessed; Kaplan-Meier estimate.
[b]HR estimate is based on Cox-proportional hazards model stratified by Binet Stage 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.
[d]p-values based on Cochran-Mantel-Haenszel test; p=0.0007 for ORR; p <0.0001 for CR+CRi.

Figure 1. Kaplan-Meier Curve of IRC-Assessed Progression-free Survival in CLL14



At the time of analysis, median overall survival (OS) had not been reached, with fewer than 10% of patients experiencing an event. The median duration of follow-up for OS was 28 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. Rates of MRD negativity 3 months after the completion of treatment regardless of response and in patients who achieved CR are shown in Table 20. At this assessment, 134 patients in the VEN+G arm who were MRD negative in peripheral blood had matched bone marrow specimens; of these, 122 patients (91%) were MRD negative in both peripheral blood and bone marrow.

Table 20. Minimal Residual Disease Negativity Rates Three Months After the Completion of Treatment in CLL14

	VENCLEXTA + Obinutuzumab	**Obinutuzumab + Chlorambucil**
MRD negativity rate (ITT population)		
N	216	216
Bone marrow, n (%)	123 (57)	37 (17)
95% CI	(50, 64)	(12, 23)
p-value[a]	<0.0001	
Peripheral blood, n (%)	163 (76)	76 (35)
95% CI	(69, 81)	(29, 42)
p-value[a]	<0.0001	
MRD negativity rate in patients with CR		
N	100	47
Bone marrow, n (%)	69 (69)	21 (45)
95% CI	(59, 78)	(30, 60)
p-value[a]	0.0048	
Peripheral blood, n (%)	87 (87)	29 (62)

	VENCLEXTA + Obinutuzumab	Obinutuzumab + Chlorambucil
95% CI	(79, 93)	(46, 75)
p-value[a]	0.0005	
CI = confidence interval; CR = complete remission. [a]p-value based on Chi-square test		

Twelve months after the completion of treatment, MRD negativity rates in peripheral blood were 58% (126/216) in patients treated with VEN+G and 9% (20/216) in patients treated with GClb.

In Combination with Rituximab

MURANO was a randomized (1:1), multicenter, open label trial (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 VENCLEXTA 5-week ramp-up dosing schedule *[see Dosage and Administration (2.2, 2.4)]* and received VENCLEXTA 400 mg orally once daily for 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. Rituximab was initiated after the 5-week dose ramp-up at a dose of 375 mg/m^2 intravenously on Day 1 of Cycle 1 and 500 mg/m^2 intravenously on Day 1 of Cycles 2-6. Patients randomized to B+R received bendamustine 70 mg/m^2 intravenously on Days 1 and 2 for 6 cycles in combination with rituximab at the above described dose and schedule. Each cycle was 28 days.

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 to 85 years), 97% were White, 74% were male, and 99% had ECOG performance status <2. Median prior lines of therapy was 1 (range: 1 to 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 PFS as assessed by an 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 21. The Kaplan-Meier curve for PFS is shown in Figure 2.

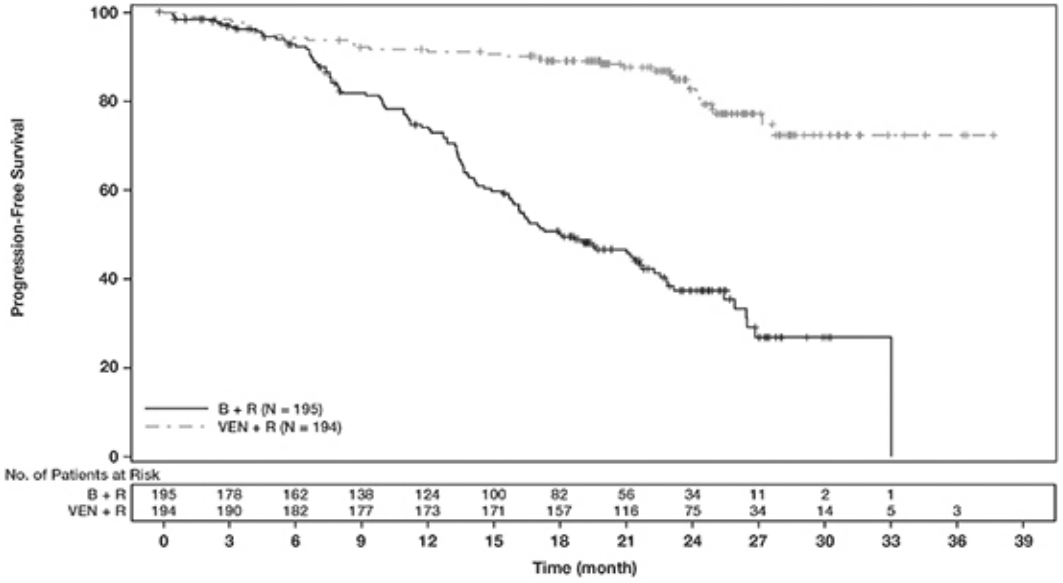
Table 21. IRC-Assessed Efficacy Results in MURANO

Endpoint	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (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	

Endpoint	VENCLEXTA + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
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 2. 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.

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 trials.

M13-982

M13-982 (NCT01889186) was an open-label, multicenter trial that enrolled 106 patients with CLL with 17p deletion who had received at least one prior therapy. In the trial, 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 400 mg orally once daily following completion of the ramp-up dosing schedule *[see Dosage and Administration (2.2, 2.4)]*.

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

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

Table 22. Baseline Patient Characteristics in 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)
ECOG = Eastern Cooperative Oncology Group. [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 23.

Table 23. Efficacy Results per IRC for Patients with Previously Treated CLL with 17p Deletion in M13-982

Endpoint	VENCLEXTA N = 106
ORR, n (%)[a] (95% CI)	85 (80) (71, 87)
CR + CRi, n (%) CR, n (%) CRi, n (%)	8 (8) 6 (6) 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);	

Endpoint	VENCLEXTA N = 106
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.

Minimal residual disease 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).

M12-175

M12-175 (NCT01328626) was an open-label, multicenter 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 VENCLEXTA 400 mg orally once daily following completion of a ramp-up dosing schedule. 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 71.7 months).

The median age was 65 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 was based on 2008 IWCLL guidelines and assessed by an IRC. The ORR was 76% (95% CI: 64%, 86%), with a CR + CRi rate was 10% and PR rate was 66%. The median DOR was 36.2 months (range: 2.4 to 52.4 months).

M14-032

M14-032 (NCT02141282) was an open-label, multicenter trial that enrolled patients with CLL who had been previously treated with and progressed on or after ibrutinib or idelalisib. Patients received VENCLEXTA 400 mg orally once daily following completion of the ramp-up dosing schedule *[see Dosage and Administration (2.2, 2.4)]*. Patients continued this dose until disease progression or unacceptable toxicity. At the time of analysis, the median duration of treatment was 19.5 months (range: 0.1 to 39.5 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 and was assessed by an IRC. The ORR was 70% (95% CI: 61%, 78%), with a CR + CRi rate of 5% and PR rate of 65%. The median DOR was not reached with a median follow-up time of 19.9 months (range: 2.9 to 36 months).

14.2 Acute Myeloid Leukemia

VENCLEXTA was studied in adult patients with newly diagnosed AML who were 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr < 45 mL/min, or other comorbidity.

In Combination with Azacitidine or Decitabine

VIALE-A was a randomized (2:1), double-blind, placebo-controlled, multicenter trial (NCT02993523) that evaluated the efficacy and safety of VENCLEXTA in combination with azacitidine (VEN+AZA) versus placebo with azacitidine (PBO+AZA).

Patients received VENCLEXTA 400 mg orally once daily on Days 1-28 following completion of the ramp-up dosing schedule *[see Dosage and Administration (2.3)]* or placebo in combination with azacitidine 75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring.

Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 × 10^3/microliter. For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated. Azacitidine was resumed on the same day as VENCLEXTA or placebo following interruption. Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity *[see Dosage and Administration (2.5)]*. Patients continued treatment until disease progression or unacceptable toxicity.

A total of 431 patients were randomized: 286 to the VEN+AZA arm and 145 to the PBO+AZA arm. The baseline demographic and disease characteristic are shown in Table 24.

Table 24. Baseline Demographic and Disease Characteristics in Patients with AML

Characteristic	VENCLEXTA + Azacitidine N = 286	Placebo + Azacitidine N = 145
Age, years; median (range)	76 (49, 91)	76 (60, 90)
Race		
White; %	76	75
Black or African American; %	1	1.4
Asian; %	23	23
Males; %	60	60
ECOG performance status; %		
0-1	55	56
2	40	41
3	5.6	3.4

Characteristic	VENCLEXTA + Azacitidine N = 286	Placebo + Azacitidine N = 145
Bone marrow blast; %		
<30%	30	28
≥30% to <50%	21	23
≥50%	49	49
Disease history; %		
De Novo AML	75	76
Secondary AML	25	24
Cytogenetic risk detected[a], %		
Intermediate	64	61
Poor	36	39
Mutation analyses detected; n/N[b] (%)		
IDH1 or IDH2	61/245 (25)	28/127 (22)
IDH1	23/245 (9.4)	11/127 (8.7)
IDH2	40/245 (16)	18/127 (14)
FLT3	29/206 (14)	22/108 (20)
NPM1	27/163 (17)	17/86 (20)
TP53	38/163 (23)	14/86 (16)

[a]Per the 2016 National Comprehensive Cancer Network (NCCN) Guidelines.
[b]Number of evaluable BMA specimens received at baseline.

Efficacy was based on overall survival (OS), measured from the date of randomization to death from any cause. The combination of VEN+AZA was superior in OS to PBO+AZA.

The Kaplan-Meier curve for OS is shown in Figure 3. The efficacy results of VIALE-A are shown in Table 25.

Figure 3. Kaplan-Meier Curve for Overall Survival in VIALE-A

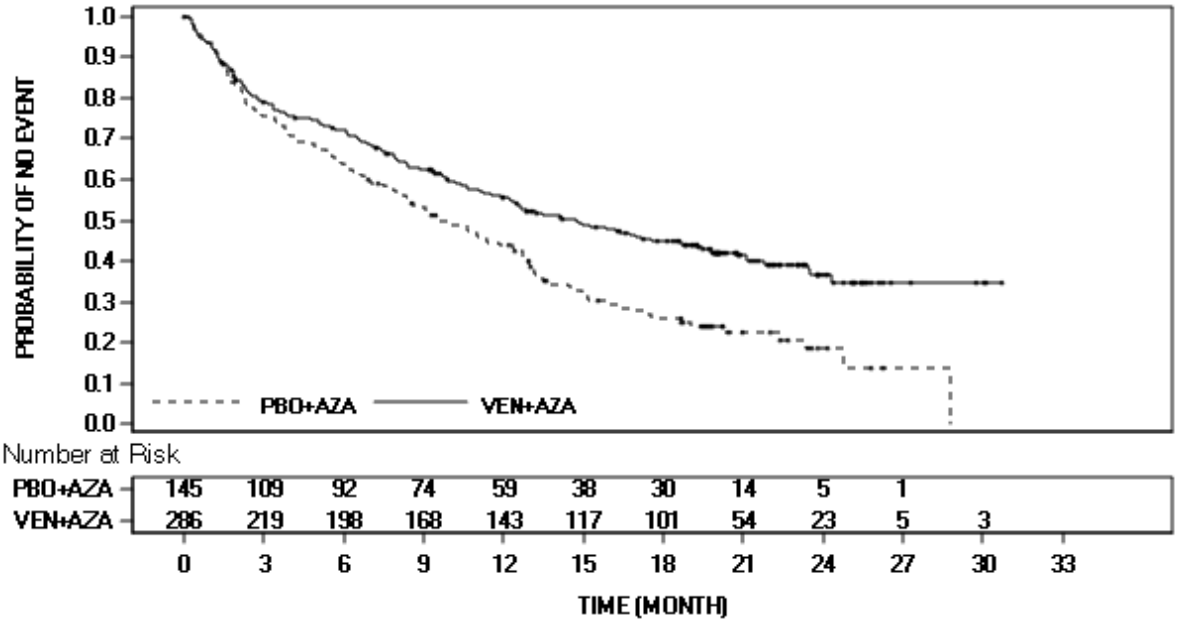


Table 25. Efficacy Results in VIALE-A

Endpoint	VENCLEXTA + Azacitidine (N = 286)	Placebo + Azacitidine (N = 145)
Overall survival		
Median[a], months (95% CI)	14.7 (11.9, 18.7)	9.6 (7.4, 12.7)
Hazard ratio[b] (95% CI)	0.66 (0.52, 0.85)	
p-value[b]	<0.001	
Response rate		
CR, n (%)	105 (37)	26 (18)
(95% CI)	(31, 43)	(12, 25)
p-value[c]	<0.001	
Median DOCR[a,d] (months)	18.0	13.4
95% CI	(15.3, -)	(8.7, 17.6)
CR+CRh, n (%)	185 (65)	33 (23)
(95% CI)	(59, 70)	(16, 30)
p-value[c]	<0.001	
Median DOCR+CRh[a,e] (months)	17.8	13.9
95% CI	(15.3, -)	(10.4, 15.7)

CI = confidence interval; HR = hazard ratio; CR = complete remission; CRh = complete remission with partial hematologic recovery; DOCR = duration of CR; - = 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%

Endpoint	VENCLEXTA + Azacitidine (N = 286)	Placebo + Azacitidine (N = 145)
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). [a]Kaplan-Meier estimate. [b]Hazard ratio estimate (VEN+AZA vs. PBO+AZA) is based on Cox-proportional hazards model stratified by cytogenetics (intermediate risk, poor risk) and age (18- <75, ≥75) as assigned at randomization; p-value based on log-rank test stratified by the same factors. [c]P-value is from Cochran-Mantel-Haenszel test stratified by age and cytogenetics risk. [d]Duration of CR is defined as the number of days from the date of first response of CR to the date of earliest evidence of confirmed morphologic relapse, confirmed progressive disease or death due to disease progression. [e]Duration of CR+CRh is defined as the number of days from the date of first response of CR+CRh (the first of either CR or CRh) to the date of earliest evidence of confirmed morphologic relapse, confirmed progressive disease, or death due to disease progression.		

Among the patients treated with VEN+AZA, 155 were dependent on red blood cell (RBC) and/or platelets transfusions at baseline; of these patients, 49% (76/155) became independent of RBC and platelet transfusions during any consecutive ≥56-day post-baseline period. Of the patients treated with VEN+AZA, 131 were independent of both RBC and platelet transfusions at baseline, 69% (90/131) remained transfusion independent during any consecutive ≥56-day post-baseline period. Among the patients treated with PBO+AZA, 81 were dependent on red blood cell (RBC) and/or platelets transfusions at baseline; of these patients, 27% (22/81) patients became independent of RBC and platelet transfusions during any consecutive ≥56-day post-baseline period. Of the patients treated with PBO+AZA, 64 were independent of both RBC and platelet transfusions at baseline, 42% (27/64) remained transfusion independent during any consecutive ≥56-day post-baseline period.

The median time to first response of CR or CRh was 1.0 months (range: 0.6 to 14.3 months) with VEN+AZA treatment.

M14-358

M14-358 (NCT02203773) was a non-randomized, open-label trial that evaluated the efficacy 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 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy.

Patients received VENCLEXTA 400 mg orally once daily following completion of the ramp-up dosing schedule *[see Dosage and Administration (2.3)]* in combination with azacitidine (75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1) or decitabine (20 mg/m^2 intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1). During the ramp-up phase, patients received TLS prophylaxis and were hospitalized for monitoring. Patients continued to treatment until disease progression or

unacceptable toxicity. Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts, with cytopenia following Cycle 1 treatment, VENCLEXTA was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 × 10^3/microliter. Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity. Dose reductions for decitabine were not implemented in the clinical trial.

Table 26. 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
Male; %	60	38
ECOG performance status; % 0-1 2 3	 64 33 3	 92 7.7 0
Disease history; % De Novo AML Secondary AML	 73 27	 85 15
Mutation analyses detected[a]; %		
TP53	15	31
IDH1 or IDH2	27	0
FLT3	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

ECOG = Eastern Cooperative Oncology Group.
[a]Includes 6 patients with insufficient sample for analysis in the azacitidine group and 4 in the

Characteristic	VENCLEXTA in Combination with Azacitidine N = 67	VENCLEXTA in Combination with Decitabine N = 13
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 27.

Table 27. 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 (%)	29 (43)	7 (54)
(95% CI)	(31, 56)	(25, 81)
CRh, n (%)	12 (18)	1 (7.7)
(95% CI)	(9.6, 29)	(0.2, 36)
CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematological recovery.		

The median follow-up was 15.9 months (range: 0.4 to 40.3 months) for VENCLEXTA in combination with azacitidine. The median duration of CR was 23.8 months (95% CI: 15.4, -), and the median duration of CR+CRh was 26.5 months (95% CI: 17.4, -).

The median follow-up was 11.0 months (range: 0.7 to 38.8 months) for VENCLEXTA in combination with decitabine. The median duration of CR was 12.7 months (95% CI: 1.4, -) and median duration of CR+CRh was 12.7 months (95% CI: 1.4, 20.0).

Duration of CR is defined as time from the first documentation of CR to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest. Duration of CR+CRh is defined as time from the first documentation of either CR or CRh to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest.

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, 12% (8/67) subsequently received stem cell transplant.

The trial enrolled 35 additional patients (age range: 65 to 74 years) who did not have known comorbidities that precluded 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%). Nine (53%) 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%). Four (22%) patients subsequently received stem cell transplant.

In Combination with Low-Dose Cytarabine

VIALE-C was a randomized (2:1), double-blind, placebo-controlled, multicenter trial (NCT03069352) that evaluated the efficacy and safety of VENCLEXTA in combination with low-dose cytarabine (VEN+LDAC) versus placebo with low-dose cytarabine (PBO+LDAC).

Patients received VENCLEXTA 600 mg orally once daily on Days 1-28 following completion of the ramp-up dosing schedule *[see Dosage and Administration (2.3, 2.4)]* or placebo in combination with cytarabine 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. During the ramp-up phase, patients received TLS prophylaxis and were hospitalized for monitoring.

Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 × 10^3/microliter. For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated. LDAC was resumed on the same day as VENCLEXTA or placebo following interruption. Patients continued to receive treatment until disease progression or unacceptable toxicity.

Table 28. Baseline Demographic and Disease Characteristics in Patients with AML

Characteristic	VENCLEXTA in Combination with Low-Dose Cytarabine N = 143	Placebo in Combination with Low-Dose Cytarabine N = 68
Age, years; median (range)	76 (36, 93)	76 (41, 88)
Race		
White; %	71	69
Black or African American; %	1.4	1.5
Asian; %	27	29
Male; %	55	57
ECOG performance status; % 0-1 2 3	 52 44 4.2	 50 37 13

Characteristic	VENCLEXTA in Combination with Low-Dose Cytarabine N = 143	Placebo in Combination with Low-Dose Cytarabine N = 68
Disease history; % De Novo AML Secondary AML	 59 41	 66 34
Mutation analyses detected; n/N[a] (%)		
TP53	22/112 (20)	9/52 (17)
IDH1 or IDH2	21/112 (19)	12/52 (23)
FLT3	20/112 (18)	9/52 (17)
NPM1	18/112 (16)	7/52 (13)
Cytogenetic risk detected[b]; %		
Favorable	<1	4
Intermediate	63	63
Poor	33	29

[a]Number of evaluable BMA specimens received at baseline.
[b]Per the 2016 National Comprehensive Cancer Network (NCCN) Guidelines.

Efficacy was based on the rate of CR and duration of CR with supportive evidence of rate of CR+CRh, duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The CR rate in the VEN+LDAC arm was 27% (95% CI: 20%, 35%) with a median duration of CR of 11.1 months (95% CI: 6.1, -), and the CR rate in the PBO+LDAC arm was 7.4% (95% CI: 2.4%, 16%) with a median duration of CR of 8.3 months (95% CI: 3.1, -). The CR+CRh rate in the VEN+LDAC arm was 47% (95% CI: 39%, 55%) and in the PBO+LDAC arm was 15% (95% CI: 7.3%, 25%) with a median duration of CR+CRh of 11.1 months with VEN+LDAC treatment and 6.2 months with PBO+LDAC treatment. The median time to first response of CR or CRh was 1.0 month (range: 0.7 to 5.8 months) with VEN+LDAC treatment.

Among the patients treated with VEN+LDAC, 111 were dependent on red blood cell (RBC) and/or platelets transfusions at baseline; of these patients, 33% (37/111) patients became independent of RBC and platelet transfusions during any consecutive ≥56-day post-baseline period. Of the patients treated with VEN+LDAC, 32 were independent of both RBC and platelet transfusions at baseline, 50% (16/32) remained transfusion independent during any consecutive ≥56-day post-baseline period.

Among the patients treated with PBO+LDAC, 55 were dependent on red blood cell (RBC) and/or platelets transfusions at baseline; of these patients, 13% (7/55) patients became independent of RBC and platelet transfusions during any consecutive ≥56-day post-baseline period. Of the patients treated with PBO+LDAC, 13 were independent of both RBC and platelet transfusions at baseline, 31% (4/13) remained transfusion independent during any consecutive ≥56-day post-baseline period.

VEN+LDAC did not significantly improve OS versus PBO+LDAC. The hazard ratio (HR) for OS was 0.75 (95% CI: 0.52, 1.07); p-value 0.114. The median OS for VEN+LDAC arm was 7.2 months (95% CI: 5.6, 10.1) and for PBO+LDAC arm was 4.1 months (95% CI: 3.1, 8.8).

M14-387

M14-387 (NCT02287233) was a non-randomized, open-label trial that evaluated the efficacy of VEN+LDAC (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 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy.

Patients received VENCLEXTA 600 mg orally once daily on Days 1-28 following completion of the ramp-up phase *[see Dosage and Administration (2.3)]* in combination with cytarabine 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. During the ramp-up, patients received TLS prophylaxis and were hospitalized for monitoring. Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia following Cycle 1 treatment, VENCLEXTA was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 × 10^3/microliter. Patients continued treatment until disease progression or unacceptable toxicity.

Table 29. 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	8.2
IDH1 or IDH2	23
FLT3	21
NPM1	9.8
Cytogenetic risk detected[b]; %	

Characteristic	VENCLEXTA in Combination with Low-Dose Cytarabine N = 61
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.

The median follow-up was 7.3 months (range: 0.3 to 54.0 months). The CR rate was 21% (95% CI: 12, 34) and CRh rate was 21% (95% CI: 12, 34).

The median duration of CR was 22.9 months (95% CI: 5.1, -) and the median duration of CR+CRh was 14.3 months (95% CI: 6.1, 31.2).

Median time to first CR or CRh for patients treated with VEN+LDAC was 1.0 month (range: 0.8 to 9.4 months).

The trial enrolled 21 additional patients (age range: 67 to 74 years) who did not have known comorbidities that precluded the use of intensive induction chemotherapy and were treated with VEN+LDAC. 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

Packaging Presentation	Number of Tablets	National Drug Code (NDC)
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 (2.4)]*.

Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Dosage and Administration (2.4)]*.

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)]*.

Infections

Advise patients to contact their HCP immediately if they develop a fever or any signs of infection *[see Warnings and Precautions (5.3)]*.

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 (5.4)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to the fetus. Advise females or reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)]*.

Advise female patients of reproductive potential to use effective contraception during therapy and for at least 30 days after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.2)]*.

Infertility

Advise males of reproductive potential that VENCLEXTA may impair fertility *[see Use in Specific Populations (8.3)]*.

Administration

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 (2.8)]*.

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 (2.8)]*.

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

20064516 October 2020

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).
- 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 liver 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 and for 1 week after the last dose of 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 and may pause dosing.
- **Infections**. Death and serious infections such as pneumonia and blood infection (sepsis) have happened during treatment with VENCLEXTA. Your healthcare provider will closely monitor and treat you right away if you have fever or any signs of infection 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 obinutuzumab or rituximab or alone in people with CLL or SLL include:

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

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 count
- constipation
- low white blood cell count
- fever with low white blood cell count
- tiredness
- vomiting
- swelling of arms, legs, hands, or feet
- fever
- infection in lungs
- shortness of breath
- bleeding
- low red blood cell count
- rash
- stomach (abdominal) pain
- infection in your blood
- muscle and joint pain
- dizziness
- cough
- sore throat
- low blood pressure

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. 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 or 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

20064516
For more information go to www.venclexta.com or call 1-800-633-9110

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

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 10/2020

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/

ROMEO A DE CLARO
10/16/2020 10:24:57 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s020, s021

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

Disclaimer: FDA's review was conducted in conjunction with Health Canada (HC), Therapeutic Goods Administration (TGA), Swissmedic (SMC), and Brazilian Health Regulatory Agency (ANVISA) under Project ORBIS. While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications submitted to the other Regulatory Authorities remain under review. In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA or the other Regulatory Authorities.

Application Type	sNDA
Application Number(s)	208573, S-020 and S-021
Priority or Standard	Priority
Submit Date(s)	RTOR submission 5/7/2020, full submission 5/22/2020
Received Date(s)	May 22, 2020
PDUFA Goal Date	November 22, 2020
Division/Office	Division of Hematologic Malignancies I, Office of Oncologic Diseases
Review Completion Date	October 15, 2020
Established Name	Venetoclax
Trade Name	VENCLEXTA
Pharmacologic Class	BCL-2 inhibitor
Code name	ABT-199
Applicant	AbbVie, Inc.
Formulation(s)	Tablets: 10, 50, and 100 mg
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)	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
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s)	In combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid

	leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP=Division of Medical Policy Programs

Health Canada Review Team for Assessment Aid

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Project Manager	
Medical Manager	
Clinical Reviewers	
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Statistical Reviewer	
Label Reviewer	

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Biostatistics Reviewer	
Clinical Reviewer	
Clinical Pharmacology Reviewer	
Risk Management Plan Reviewer	

Glossary

ADR	adverse drug reaction
AE	adverse event
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AUC	area under the plasma concentration-time curve
AUCss	area under curve at steady state
AZA	Azacitidine
BLA	biologics license application
CDx	Companion Diagnostics
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CML	chronic myeloid leukemia
COA	Clinical Outcome Assessment
CR	complete remission
CrCl	creatinine clearance
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete blood count recovery
CRF	case report form
CSR	clinical study report
CYP3A	cytochrome P450 3A isoform subfamily
DEC	Decitabine
DILI	drug-induced liver injury
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FDA	Food and Drug Administration
FMS	FMS-like tyrosine kinase
GCP	good clinical practice
GHS/QoL	Global Health Status/Quality of Life
HMA	hypomethylating agent
HR	hazard ratio
IA	interim analysis
ICH	International Council for Harmonisation
IDH	isocitrate dehydrogenase
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenously
IWG	International Working Group
LDAC	Low-dose cytarabine
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimum important difference
MLFS	morphologic leukemia-free state
MPN	myeloproliferative neoplasm
MR	morphologic relapse
MRD	minimal/measurable residual disease
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NR	not reached
OBF	O'Brien-Fleming
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBO	Placebo
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetics
PMR	postmarketing requirement
PR	partial remission
PRO	patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PSUR	Periodic Safety Update report
PT	preferred term
PTY	patient-treatment years
QD	once daily
RBC	red blood cell
RD	resistant disease
REMS	risk evaluation and mitigation strategy
ROW	Rest of World
RPTD	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan

SC	subcutaneously
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
sNDA	Supplementary New Drug Application
SOC	standard of care
TLS	tumor lysis syndrome
TP53	tumor protein p53
TTD	time to deterioration
US	United States
USPI	United States Package Insert
VEN	Venetoclax
WBC	white blood cell

1 Executive Summary

1.1. Product Introduction

Trade Name:	Venclexta®
Established Name:	Venetoclax
Also Known As:	ABT-199, GDC-0199
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 that was initially approved for the treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma. Venetoclax received accelerated approval in combination with azacitidine, or decitabine, or low-dose cytarabine (LDAC) 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, on November 21, 2018. Efficacy was established on the basis of durable complete remission (CR) and supported by CR with partial hematologic recovery (CRh) in Studies M14-358 (NCT02203773) of venetoclax in combination with azacitidine or decitabine and M14-387 (NCT02287233) of venetoclax in combination with LDAC. The Applicant now submits a supplementary New Drug Application (sNDA) to support regular approval and fulfill the accelerated approval requirements with results from randomized, Phase 3 Studies M16-043 (VIALE-C; NCT03069352) and M15-656 (VIALE-A; NCT02993523), postmarketing requirements (PMR 3545-1 and PMR 3545-2, respectively) under 21 CFR 314 Subpart H.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval for venetoclax “in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.” The recommendation is based on the findings of improved overall survival (OS) in Study VIALE-A and compelling evidence of benefit on several secondary endpoints in Study VIALE-C, including CR, CR+CRh, and conversion to and maintenance of transfusion independence (TI), despite the lack of a statistically significant benefit in OS at the time of the primary analysis. Supportive evidence of benefit was also demonstrated with long-term follow-up data on CR rates and duration of CR from Studies M14-358 and M14-387.

Venetoclax was evaluated in two randomized, double-blind, placebo-controlled Phase 3 studies 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 criterion of 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 VIALE-A was a randomized (2:1), double-blind, placebo-controlled trial of venetoclax in combination with azacitidine (n=286) versus placebo in combination with azacitidine (n=145). Randomization was stratified by age, cytogenetics, and region. The demographic and disease characteristics of the randomized patients were balanced between arms.

The final analysis of VIALE-A included a prespecified assessment of OS, measured form the date of randomization until death from any cause. At the time of analysis, median OS was significantly longer on the venetoclax + azacitidine arm at 14.7 months (95% CI 11.9, 18.7) compared to 9.6 months (95% CI 7.4, 12.7) on the placebo + azacitidine arm with HR 0.66 (95% CI 0.52, 0.85; p-value < 0.001).

In the final analysis of VIALE-A, FDA-adjudicated CRs were achieved by 105 (37%) patients on venetoclax + azacitidine and 26 (18%) patients on placebo + azacitidine (p < 0.001); median duration of CR (DOCR) was 18.0 (95% CI, 15.3 to not reached [NR]) versus 13.4 months (95% CI, 8.7 to 17.6), respectively. CR+CRh responses were seen in 185 (65%) of patients on venetoclax + azacitidine and 33 (23%) of patients on placebo + azacitidine (p < 0.001); median duration of CR+CRh (DOCR+CRh) was 17.8 (95% CI, 15.3 to NR) versus 13.9 months (95% CI, 10.4 to 15.7), respectively.

For patients who achieved a CR or CRh on the venetoclax + azacitidine arm, the median time to first response was 1.0 months (range, 0.6 to 14.3 months) compared to 2.6 months (range, 0.8 to 13.2 months) for patients on the placebo + azacitidine arm. The improvement in CR+CRh rate on the venetoclax + azacitidine arm vs the placebo + azacitidine arm was consistent across various disease subsets (e.g. IDH1/2 72% vs 7%; FLT3 66% vs 18%; intermediate cytogenetics 72% vs 24%; poor cytogenetics 52% vs 21%; primary AML 65% vs 24%; AML-MRC 60% vs 14%; secondary AML including t-AML 64% vs 20%).

Conversion to and maintenance of TI also supported the efficacy of venetoclax + azacitidine. Among the 155 patients who transfusion dependent (TD) on RBCs and/or platelets at baseline, 76 (49%) became TI of RBC and platelets during any 56-day post-baseline period (compared to 22/81 [27%] on the placebo + azacitidine arm). For the 131 patients who were TI of both RBC and platelets at baseline, 90 (69%) remained TI during any 56-day post-baseline period (compared to 27/64 [42%] on the placebo + azacitidine arm). Labeling should include these results.

Efficacy of venetoclax in combination with azacitidine or decitabine was supplemented by long-term follow-up data from Study M14-358. 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, who met the prespecified criteria of age ≥ 75 years or comorbidities that preclude the use of intensive induction chemotherapy. In combination with azacitidine, the CR rate was 43% (95% CI: 31, 56) with a median DOCR of 23.8 months (95% CI: 15.4-NR). In combination with decitabine, the CR rate was 54% (95% CI: 25, 81) with a median DOCR of 12.7 months (95% CI: 1.4-NR). The CRh rate was 18% and 8% in the venetoclax plus azacitidine and venetoclax plus decitabine groups, respectively.

Although there was no randomized, controlled trial to verify the clinical benefit of venetoclax + decitabine, the significant improvement in OS in combination with the other hypomethylating agent, azacitidine, coupled with similar durable response rates for the venetoclax + azacitidine and venetoclax + decitabine combinations on Study M14-358 are supportive of similar expected long-term efficacy of the decitabine combination.

Study VIALE-C was a randomized (2:1), double-blind, placebo-controlled trial of venetoclax in combination with LDAC (n=143) versus placebo in combination with LDAC (n=68). Randomization was stratified by AML status, age, and region. The demographic and disease characteristics of the randomized patients were generally balanced between arms.

The final analysis of VIALE-C included a prespecified assessment of OS, measured form the date of randomization until death from any cause. Patients randomized to venetoclax + LDAC had non-significantly longer survival compared to placebo + LDAC (HR 0.75; 95% CI: 0.52 – 1.07; p-value = 0.11). With an additional 6 months of follow-up, there was noted to be a further benefit in OS on the venetoclax + LDAC arm compared to placebo + LDAC (HR 0.70; p-value = 0.041). (b) (4)

In the primary analysis of VIALE-C, FDA-adjudicated CRs were achieved by 39 (27%) patients on venetoclax + LDAC and 5 (7%) patients on placebo + LDAC; median DOCR was 11.1 (95% CI, 6.1 to NR) versus 8.3 months (95% CI, 3.1 to NR), respectively. CR+CRh responses were seen in 67 (47%) of patients on venetoclax + LDAC and 10 (15%) of patients on placebo + LDAC; median DOCR+CRh was 11.1 versus 6.2 months, respectively. Due to failure of the primary endpoint to meet statistical significance, significant improvement in the secondary endpoints of CR or CR+CRh rate could not be declared for venetoclax + LDAC. However, these results are appropriate to display descriptively in labeling to demonstrate compelling confirmatory evidence of efficacy for the venetoclax + LDAC combination.

For patients who achieved a CR or CRh on the venetoclax + LDAC arm, the median time to first response was 1.0 month (range, 0.7 to 5.8 months) compared to 2.8 months (range, 0.9 to 6.5 months) for patients on the placebo + LDAC arm. The numerical improvement in CR+CRh rate on the venetoclax + LDAC arm vs the placebo + LDAC arm was consistent across various disease subsets (e.g. intermediate cytogenetics 53% vs 19%; poor cytogenetics 32% vs 10%; primary AML 59% vs 20%; AML-MRC 32% vs 11%; secondary AML 29% vs 4%; prior hypomethylating agent for MDS 18% vs 7%).

Conversion to and maintenance of TI also supported the efficacy of venetoclax + LDAC. Among the 111 patients who were TD on RBCs and/or platelets at baseline, 37 (33%) became TI of RBCs and platelets during any 56-day post-baseline period (compared to 7/55 [13%] on the placebo + LDAC arm). For the 32 patients who were TI of both RBCs and platelets at baseline, 16 (50%) remained TI during any 56-day post-baseline period (compared to 4/13 [31%] on the placebo + LDAC arm). Labeling should include these results as further evidence of clinical benefit with the addition of venetoclax to LDAC.

Efficacy of venetoclax in combination with LDAC was supplemented by long-term follow-up data from Study M14-387. Study M14-387 was an open-label, single-arm, multicenter clinical trial of venetoclax in combination with 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 who met the prespecified criteria of age ≥ 75 years or comorbidities that preclude the use of intensive induction chemotherapy. In combination with LDAC, the CR rate was 21% (95% CI: 12, 34) with a median DOCR of 22.9 months (95% CI: 5.1 to NR months). The CRh rate was 21%.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Venetoclax is an orally administered BCL-2 inhibitor that was initially approved for the treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma. Venetoclax received accelerated approval in combination with azacitidine, or decitabine, or LDAC for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy, on November 21, 2018. This supplemental NDA serves to convert the indication for treatment of patients with AML in combination with azacitidine, decitabine, or LDAC to regular approval.

AML is an aggressive hematological malignancy and has an increasing incidence with age. Standard of care intensive AML induction chemotherapy is often not an option for elderly patients or those with significant comorbidities due to the potential for excess toxicity and induction mortality. Existing standard of care non-intensive therapies for this patient population are associated with low response rates and poor long-term outcomes. Thus, this patient population has a significant unmet medical need.

The recommendation for regular approval is based on the efficacy results from two randomized controlled trials evaluating venetoclax in combination with azacitidine and LDAC, with supportive long-term follow-up data from two single arm studies evaluating venetoclax in combination with azacitidine, decitabine, and LDAC. Study VIALE-A was a randomized (2:1), double-blind, placebo-controlled trial of venetoclax in combination with azacitidine (n=286) versus placebo in combination with azacitidine (n=145). Randomization was stratified by age, cytogenetics, and region. Patients randomized to venetoclax + azacitidine had significantly longer survival compared to placebo + azacitidine (HR 0.66; 95% CI: 0.52 – 0.85; p-value < 0.001). The CR rate was 37% on the venetoclax + azacitidine arm and 18% on the placebo + azacitidine arm (p < 0.001); median DOCR was 18.0 months (95% CI, 15.3 to NR) versus 13.4 months (95% CI, 8.7 to 17.6), respectively. The CR+CRh rate was 65% on the venetoclax + azacitidine arm and 23% on the placebo + azacitidine arm (p < 0.001); median DOCR+CRh was 17.8 months (95% CI, 15.3 to NR) versus 13.9 months (95% CI, 10.4 to 15.7), respectively. Among patients who were TD on RBCs and/or platelets at baseline, 49% became TI of RBCs and platelets during any 56-day post-baseline period (compared to 27% on the placebo + azacitidine arm). Among patients who were TI of both RBCs and platelets at baseline, 69% remained TI during any 56-day post-baseline period (compared to 42% on the placebo + azacitidine arm).

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 served as the basis for the accelerated approval of venetoclax in combination with azacitidine and decitabine. 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, who met the prespecified criteria of age ≥ 75 years or comorbidities that preclude the use of intensive induction chemotherapy. For the venetoclax + azacitidine combination, the CR rate was 43% (95% CI: 31, 56) with a median DOCR of 23.8 months (95% CI: 15.4-NR). For the venetoclax + decitabine combination, the CR rate was 54% (95% CI: 25, 81) with a median DOCR of 12.7 months (95% CI: 1.4-NR months). The CRh rate was 18% and 8% in the venetoclax plus azacitidine and venetoclax plus decitabine groups, respectively.

Study VIALE-C was a randomized (2:1), double-blind, placebo-controlled trial of venetoclax in combination with LDAC (n=143) versus placebo in combination with LDAC (n=68). Randomization was stratified by AML status, age, and region. Patients randomized to venetoclax + LDAC had non-significantly longer survival compared to placebo + LDAC (HR 0.75; 95% CI: 0.52 – 1.07; p-value = 0.11). Supportive secondary endpoints at the time of the primary analysis included improvements in CR rate, CR+CRh rate, and conversion to and maintenance of TI. CR rate was 27% on the venetoclax + LDAC arm and 7% on the placebo + LDAC arm; median DOCR was 11.1 months (95% CI, 6.1 to NR) versus 8.3 months (95% CI, 3.1 to NR), respectively. CR+CRh responses were seen in 67 (47%) of patients on venetoclax + LDAC and 10 (15%) of patients on placebo + LDAC; median DOCR+CRh was 11.1 versus 6.2 months, respectively. Among patients who were TD on RBCs and/or platelets at baseline, 33% became TI of RBCs and platelets during any 56-day post-baseline period (compared to 13% on the placebo + LDAC arm). For the patients who were TI of both RBCs and platelets at baseline, 50% remained TI during any 56-day post-baseline period (compared to 31% on the placebo + LDAC arm).

Efficacy of venetoclax in combination with LDAC was supplemented by long-term follow-up data from Study M14-387. Study M14-387 was an open-label, single-arm, multicenter clinical trial of venetoclax in combination with 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 who met the prespecified criteria of age ≥ 75 years or comorbidities that preclude the use of intensive induction chemotherapy. In combination with LDAC, the CR rate was 21% (95% CI: 12, 34) with a median DOCR of 22.9 months (95% CI: 5.1 to NR months). The CRh rate was 21%.

Safety of the venetoclax combinations was demonstrated on the VIALE-A and VIALE-C randomized, phase 3 trials, as well as on the M14-358 and M14-387 single arm studies. Common adverse reactions (> 40%) not related to a laboratory evaluation for the combination of venetoclax and azacitidine from Study VIALE-A were nausea, diarrhea, constipation, and febrile neutropenia. Frequent serious adverse reactions (> 5%) included febrile neutropenia, pneumonia, sepsis, and hemorrhage. Common adverse reactions (> 40%) not related to a laboratory evaluation for the combination of venetoclax and decitabine from Study M14-358 were febrile neutropenia, fatigue, constipation, musculoskeletal pain, dizziness, nausea, abdominal pain, diarrhea, pneumonia, and sepsis. Frequent serious adverse reactions (> 10%) included sepsis, febrile

neutropenia, and pneumonia. Common adverse reactions (> 25%) not related to a laboratory evaluation for the combination of venetoclax and LDAC from Study VIALE-C were nausea, febrile neutropenia, pneumonia, diarrhea, and hemorrhage. Frequent serious adverse reactions (> 10%) included pneumonia, febrile neutropenia, and sepsis. In all combinations, the events were managed by anti-infectives, G-CSF, and transfusions as indicated. Tumor lysis syndrome (TLS) was infrequent and can be mitigated by the dose ramp-up, prophylaxis, and monitoring stipulated in labeling.

In conclusion, the endpoints used to assess efficacy in the presented studies were OS, CR rate and duration of CR, supported by CRh rate and conversion to and maintenance of TI. The median OS was 14.7 months (95% CI 11.9, 18.7) on the venetoclax + azacitidine arm of VIALE-A compared to 9.6 months (95% CI 7.4, 12.7) on the placebo + azacitidine arm with HR 0.66 (95% CI 0.52, 0.85); p-value < 0.001. CR rate was 37% versus 18%, respectively (p < 0.001). CR rate was similar at 43% for the venetoclax + azacitidine combination and 54% for the venetoclax + decitabine combination on the single arm trial M14-358. The survival benefit of venetoclax + azacitidine and the durability of responses of venetoclax + azacitidine and venetoclax + decitabine support effectiveness in this population. Median OS was 7.2 months (95% CI 5.6, 10.1) on the venetoclax + LDAC arm of VIALE-C compared to 4.1 months (95% CI 3.1, 8.8) on the placebo + LDAC arm with HR 0.75 (95% CI 0.52, 1.1); p-value 0.11. Failure to achieve statistical significance at the time of the primary analysis was thought to be a consequence of an underpowered study design. In the unplanned analysis with an additional 6 months of follow-up, the OS HR was 0.70 (95% CI: 0.50, 0.99) with a nominal p-value = 0.041. At the time of the primary analysis, CR rate was 27% versus 7% and CR+CRh rate was 47% versus 15%, respectively. CR rate was similar at 21% for the venetoclax + LDAC combination on the single arm trial M14-387. Furthermore, for venetoclax + LDAC versus venetoclax + placebo on VIALE-C, 33% versus 13% of patients who were TD at baseline became TI during any 56-day post-baseline period and 50% versus 31% of patients who were TI at baseline remained TI during any 56-day post-baseline period. The totality of the results, including compelling evidence of benefit on several secondary endpoints on VIALE-C (CR, CR+CRh, TI), durability of responses, and the OS benefit of venetoclax + azacitidine on VIALE-A, support effectiveness of venetoclax + LDAC in this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AML is a fatal disease • Most patients age ≥ 75 years or those with comorbidities would not tolerate intensive induction chemotherapy due to excess toxicities	AML is a fatal disease Elderly patients or those with comorbidities would not tolerate intensive chemotherapy

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Patients with newly-diagnosed AML who cannot receive intensive chemotherapy may use available therapy with reported CR rates of 8-20%. The median OS is approximately 5-10 months. • Gemtuzumab ozogamicin (GO) is approved for patients with newly-diagnosed CD33-positive AML in adults. The CR rate was 15% with median OS of 4.9 months. • Glasdegib + LDAC is approved for patients with newly-diagnosed AML in adult patients who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy. The CR rate was 18% with median OS of 8.3 months.	There is a need for effective therapies for patients with newly-diagnosed AML who are age >= 75 years or have comorbidities that preclude the use of intensive induction chemotherapy
Benefit	• In Study VIALE-A, a randomized (2:1), controlled trial, 286 patients age ≥ 75 years or with comorbidities received venetoclax in combination with azacitidine and 145 received placebo in combination with azacitidine. Median OS was significantly longer with venetoclax + azacitidine versus placebo + azacitidine (HR 0.66; 95% CI: 0.52 – 0.85; p-value < 0.001). CR rate was 37% versus 18% with median DOCR 18.0 months (95% CI, 15.3 to NR) versus 13.4 months (95% CI, 8.7 to 17.6), respectively. CR+CRh rate was 65% versus 23% with median DOCR+CRh 17.8 (95% CI, 15.3 to NR) versus 13.9 months (95% CI, 10.4 to 15.7). Among patients who were TD at baseline, 49% versus 27% became TI during any 56-day post-baseline period and among patients who were TI at baseline, 69% versus 42% remained TI during any 56-day post-baseline period, respectively. • 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 age ≥ 75 years or with comorbidities that precluded intensive chemotherapy. The CR rate was 43% for patients who received venetoclax and azacitidine and 54% in patients who received venetoclax and decitabine. The median DOCR for	The endpoints of OS, CR, durability of response, and conversion to/maintenance of TI support effectiveness in patients who are age ≥ 75 years or who have comorbidities that preclude the use of intensive chemotherapy. The addition of venetoclax to azacitidine shows an improvement in OS, CR rate, CR+CRh rate, and TI. The addition of venetoclax to decitabine appears to show an improvement in CR rates that is not attributable to either agent alone. CR rate with venetoclax + decitabine was similar to that of venetoclax + azacitidine. The addition of venetoclax to LDAC shows a non-significant trend towards improvement in OS, and clinically meaningful improvements in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the azacitidine combination was 23.8 months (95% CI: 15.4-NR) and for the decitabine combination was 12.7 months (95% CI: 1.4-NR months). • In Study VIALE-C, a randomized (2:1), controlled trial, 143 patients age ≥ 75 years or with comorbidities received venetoclax in combination with LDAC and 68 received placebo in combination with LDAC. Median OS was non-significantly longer with venetoclax + LDAC versus placebo + LDAC (HR 0.75; 95% CI: 0.52 – 1.07; p-value = 0.11). In an unplanned analysis with additional 6 months follow-up, HR for OS was 0.70 (95% CI: 0.50, 0.99); nominal p-value = 0.041. On the venetoclax + LDAC versus placebo + LDAC arms, CR rate was 27% versus 7% with median DOCR 11.1 months (95% CI, 6.1 to NR) versus 8.3 months (95% CI, 3.1 to NR), respectively. CR+CRh rate was 47% versus 15% with median DOCR+CRh 11.1 versus 6.2 months, respectively. Among patients who were TD at baseline, 33% versus 13% became TI during any 56-day post-baseline period and among patients who were TI at baseline, 50% versus 31% became TI during any 56-day post-baseline period, respectively. • In Study M14-387, a single-arm trial, 61 patients with age ≥ 75 years or with comorbidities that precluded intensive chemotherapy received venetoclax (600 mg) and LDAC. Twenty-one percent of patients achieved a CR. The median DOCR was 22.9 months (95% CI: 5.1 to NR months).	CR rate, CR+CRh rate, and TI.
Risk and Risk Management	• Common adverse reactions (> 40%) not related to a laboratory evaluation for venetoclax + azacitidine were nausea, diarrhea, constipation, and febrile neutropenia. • Frequent serious adverse reactions (> 5%) for venetoclax + azacitidine included febrile neutropenia, pneumonia, sepsis, and hemorrhage.	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 with azacitidine, decitabine, or LDAC can be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Common adverse reactions (> 40%) not related to a laboratory evaluation for venetoclax + decitabine were febrile neutropenia, fatigue, constipation, musculoskeletal pain, dizziness, nausea, abdominal pain, diarrhea, pneumonia, and sepsis. • Frequent serious adverse events (> 10%) for venetoclax + decitabine included sepsis, febrile neutropenia, and pneumonia. • Common adverse reactions (> 25%) not related to a laboratory evaluation for venetoclax + LDAC were nausea, febrile neutropenia, pneumonia, diarrhea, and hemorrhage. • Frequent serious adverse reactions (> 10%) for venetoclax + LDAC included pneumonia, febrile neutropenia, and sepsis. • TLS was an infrequent event	sufficiently addressed through warnings and precautions in the United States Prescribing Information.

1.4. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include:						Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as					
			☒	Patient-reported outcome (PRO)			Sections 8.1.2, 8.1.4, and 8.2.6
			☐	Observer reported outcome (ObsRO)			
			☐	Clinician reported outcome (ClinRO)			
			☐	Performance outcome (PerfO)			
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)					
	☐	Patient-focused drug development or other stakeholder meeting summary reports					
	☐	Observational survey studies designed to capture patient experience data					
	☐	Natural history studies					
	☐	Patient preference studies (e.g., submitted studies or scientific publications)					
	☐	Other: (Please specify)					
☐	Patient experience data that was not submitted in the application, but was considered in this review.						

X _____

Kelly Norsworthy, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:
Acute myeloid leukemia (AML) is an aggressive hematopoietic malignancy with increase in incidence among older patients, with a median age of diagnosis of 68 years, with 55% of the patients diagnosed at 65 years or older and approximately a third of them diagnosed over the age of 75.[1,2] It is characterized by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood, and occasionally extramedullary tissues which leads to disruption of normal hematopoiesis.[2] AML is defined as a myeloid neoplasm with 20% or more blasts in the peripheral blood or bone marrow by the World Health Organization.[2]

AML is the most common form of acute leukemia in adults, with a projected estimate of 21,450 new cases and 10,920 deaths in the United States (US) in 2019.[1] It has the lowest survival rate and accounts for the largest number of deaths among all types of leukemia, as patients are often elderly and unable to receive intensive therapy to achieve remission and long term benefit.[2,3,4] In older patients who are unable to receive intensive chemotherapy due to high rates of therapy-related toxicity, the 5-year survival is less than 5%.[4]

AML is a heterogeneous disease with many different recognized cytogenetic and molecular aberrations. Adverse cytogenetics, multi-drug resistance phenotype and higher incidence of secondary AML from antecedent hematologic disorders of myelodysplastic syndromes (MDS) or cytotoxic therapy for another disorder are identified as the most important disease-related prognostic indicators in AML. Prognostic factors that are related to the patient such as increasing age, coexisting conditions, and poor performance status commonly predict treatment-related early death.[5,6]

Therefore, treatment of older patients with AML remains challenging and the treatment options for older patients have historically been limited, with hypomethylating agents (HMA; i.e., azacitidine, decitabine) and low-dose cytarabine (LDAC) providing only modest response rates of less than 30% and a median survival benefit of less than 1 year.[7]

Even though there have been improvements in the treatment of AML, there remains an unmet need for the development of low-intensity combination regimens in patients who are ineligible for intensive therapy, particularly, treatments that are more tolerable, produce higher and more durable remissions, and provide improvement in overall survival (OS).

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment that AML is a serious disease with a substantial risk of mortality. There is a need for development of lower-intensity regimens for the treatment of

patients who are not candidates for intensive therapy based on age or comorbidities which accounts for approximately half of patients diagnosed with AML.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration[a]	Efficacy Information[b]	Important Safety and Tolerability Issues[b]
FDA Approved Treatments [combine by Pharmacologic Class, if relevant]					
Azacitidine (VIDAZA)[9]	Indicated for the treatment of patients with MDS: Recommended by NCCN as low intensity therapy for patients with newly diagnosed AML who are not candidates for intensive induction therapy	2004	For each cycle, 75 mg/m^2 daily for 7 days by SC injection or IV infusion. Repeat cycles every 4 weeks	In the Phase 3 Study AZA-AML-001,[16,17] patients (AML with blasts > 30%) treated with AZA monotherapy had a CR + CRi rate of 27.8% with a CR of 19.5% and a median OS of 10.4 months (vs. 6.5 months for conventional care regimens p=0.10); enrollment of patients eligible for intensive chemotherapy was allowed.	Any grade AEs with azacitidine[16]: nausea 27.1%; neutropenia 19.9%; thrombocytopenia 17.4%. Grade 3 or 4 AEs: febrile neutropenia 28%; neutropenia 26.3%; thrombocytopenia 23.7%; pneumonia 19.1%
Decitabine (DACOGEN) [10]	Indicated for treatment of adult patients with MDS: Recommended by NCCN as low intensity therapy for patients with newly diagnosed AML who are not candidates for intensive induction therapy	2006	Five-day regimen: administer at 20 mg/m^2 by continuous IV infusion over 1 hour repeated daily for 5 days. Repeat cycle every 4 weeks.	In the Phase 3 Study DACO-016,[18] patients treated with DEC monotherapy had a CR + CRi of 25.6% with a CR of 15.7% and a median OS of 7.7 months (vs. 5.0 months for treatment choice p=0.108); enrollment of patients eligible no active therapy was allowed.	Any grade AEs with decitabine[18]: thrombocytopenia 27%; neutropenia 24%; febrile neutropenia 21%; anemia 21%. Grade 3 or 4 AEs: thrombocytopenia 40%; febrile neutropenia 32%; neutropenia 32%; anemia 34%; pneumonia 21%
Gemtuzumab ozogamicin (MYLOTARG)[12]	Indicated for treatment of newly-diagnosed CD33-positive AML in adults and treatment of relapsed or refractory CD33-positive AML in adults and in pediatric	2017	Newly-diagnosed AML (single-agent regimen): *Induction*: 6 mg/m^2 on Day 1 and 3 mg/m^2 on Day 8. *Continuation*: For patients without evidence	In a Phase 3, randomized, open-label study (EORTC-GIMEMA AML-19),[19] gemtuzumab ozogamicin monotherapy resulted in a CR + CRi rate of 27.0%, CR of 15.3%, and a median OS of 4.9	Boxed warning: hepatotoxicity, including severe or fatal hepatic VOD. Study AML-19 Any grade ARs: 87% Grade ≥3 ARs: 17% Selected ARs [any grade; Grade ≥ 3]:

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration[a]	Efficacy Information[b]	Important Safety and Tolerability Issues[b]
	patients 2 years and older		of disease progression following induction, up to 8 continuation courses of MYLOTARG 2 mg/m^2 on Day 1 every 4 weeks.	months.	liver 51%; fatigue 46%; infection 44%; cardiac 28%; bleeding 25%; febrile neutropenia 18%; metabolic 16%; renal 6%
Glasdegib (DAURISMO)[14]	Indicated, in combination with LDAC, for the treatment of newly-diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy	2018	100 mg orally once daily on days 1 to 28 in combination with cytarabine 20 mg SC twice daily on days 1 to 10 of each 28-day cycle.	In a Phase 2, randomized, open-label study (NCT01546038),[20] glasdegib in combination with LDAC resulted in a CR of 17% and a median OS of 8.8 months.	Study BRIGHT AML 1003 Boxed warning: embryo-fetal death or severe birth defects. SAEs were reported in 79% of patients in DAURISMO+LDAC arm; most common (≥ 5%): febrile neutropenia (29%), pneumonia (23%), hemorrhage (12%), anemia (7%) and sepsis (7%). Grade ≥3 AEs reported in ≥ 15% in DAURISMO arm: anemia (41%), febrile neutropenia (31%), thrombocytopenia (30%), platelet count decreased (15%). Other clinically significant AEs (< 10%): QT interval prolongation (consider drug interaction with QTc prolonging drugs); alopecia; loose tooth and toothache.
Ivosidenib (TIBSOVO)[15]	Indicated for the treatment of AML with a susceptible IDH1 mutation as detected by an FDA-approved test in adult patients with newly-diagnosed AML who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction	2018	500 mg orally once daily with or without food until disease progression or unacceptable toxicity. Avoid a high-fat meal.		Boxed warning: differentiation syndrome, which can be fatal if not treated. Any grade AEs: leukocytosis 36%; differentiation syndrome 25%; diarrhea 61%; fatigue 50%; edema 43%; decreased appetite 39%; nausea 36%; abdominal pain 29% Grade ≥ 3 AEs: differentiation syndrome 11%; fatigue 14%; QT

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration[a]	Efficacy Information[b]	Important Safety and Tolerability Issues[b]
	chemotherapy, or adult patients with relapsed or refractory AML				prolongation 11%
Cytarabine[11]	Indicated for remission induction in ANLL of adults and pediatric patients. It has also been found useful in the treatment of ALL and the blast phase of CML. Intrathecal administration of Cytarabine Injection (preservative free preparations only) is indicated in the prophylaxis and treatment of meningeal leukemia.	1969	In the induction therapy of ANLL, the dose in combination with other anti-cancer drugs is 100 mg/m^2/day by continuous IV infusion (Days 1 to 7) or 100 mg/m^2 IV every 12 hours (Days 1 to 7). Cytarabine has been used intrathecally in acute leukemia in doses ranging from 5 mg/m^2 to 75 mg/m^2 of body surface area. The frequency of administration varied from once a day for 4 days to once every 4 days.	From Phase 3 study DACO-16,[18] LDAC monotherapy arm: CR = 7.9%; CR + CRi = 10.7%; PR = 3.7%; median OS = 5.0 months* * Median OS is derived from a patient population of N = 243; 215 patients were treated with LDAC monotherapy and 28 patients were treated with SoC treatment choice.	Grade ≥ 3 AEs: 90% patients Grade ≥ 3 AEs in ≥ 15% patients: thrombocytopenia 35%; anemia 27%; febrile neutropenia 25%; neutropenia 20%; pneumonia 19% SAEs: 72% patients SAEs in ≥ 10% patients: febrile neutropenia 16%; pneumonia 16%

AE = adverse event; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; ANLL = acute non-lymphocytic leukemia; AR = adverse reaction; BSC = best supportive care; CML = chronic myelocytic leukemia; CMMoL = chronic myelomonocytic leukemia; CNS = central nervous system; CRi = complete remission with incomplete blood count recovery; CR = complete remission; CR + CRi = composite complete remission; EORTC = European Organisation for Research and Treatment of Cancer; FDA = Food and Drug Administration; GI = gastrointestinal; IDH = isocitrate dehydrogenase; IV = intravenous; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; N/A = not available; NCCN = National Comprehensive Cancer Network; OS = overall survival; PR = partial remission; RA = refractory anemia; RAEB = RA with excess blasts; RAEB-T = RAEB in transformation; RARS = RA with ringed sideroblasts; SAE = serious AE; SC = subcutaneous; SoC = standard of care; VOD = veno-occlusive disease

[a] Doses listed for some products reflect the doses in the same indication discussed in this document.

[b] Data in these columns are presented for treatment in patients with AML. Azacitidine and decitabine are not approved for monotherapy treatment of AML and the efficacy and safety data may not be available in the USPI.

Although no single standard of care exists for newly-diagnosed AML patients who are not candidates for intensive therapy regimens,[8] these patients may be treated with low-intensity options recommended by National Comprehensive Cancer Network (NCCN) (i.e., HMAs [AZA[9] or DEC][10] or LDAC[11]), as well as MYLOTARG™ (gemtuzumab ozogamicin) monotherapy[12] or VENCLEXTA® (venetoclax)[13] combination therapy (HMAs or LDAC), and DAURISMO™ (glasdegib) combination therapy (LDAC).[14] In addition to these, TIBSOVO® (ivosidenib) monotherapy is indicated for newly-diagnosed patients with AML who are ineligible for intensive chemotherapy who are positive for the isocitrate dehydrogenase (IDH) 1 mutation.[15]

There are currently 3 products commonly used as standard of care for patients with newly diagnosed AML who are not candidates for standard induction chemotherapy:[8] AZA (VIDAZA®)[9], DEC (DACOGEN®)[10], and LDAC (Cytarabine)[11]. The safety and efficacy data are presented in Table 1 for each of these treatments. Neither pivotal, randomized study (Studies AZA-AML-001[16,17] and DACO-016[18]) showed statistically significant improvement in OS for HMA-treated patients compared to the standard treatment arms (which included intensive chemotherapy, LDAC, or best supportive care). However, these studies did provide robust clinical data with comparable patient populations and measures of outcomes in representative samples of the AML population.

The most common standard treatment choice in Studies AZA-AML-001[16,17] and DACO-016[18] was LDAC. In Study DACO-016,[18] patients were randomized to receive LDAC (20 mg/m^2 subcutaneously [SC], once daily [QD]). In Study AZA-AML-001,[16,17] patients were randomized to receive LDAC (20 mg flat-dose SC, twice daily [BID]).

The three additional therapies with a Food and Drug Administration (FDA)-approved indication for newly-diagnosed patients with AML who are ineligible for intensive chemotherapy include gemtuzumab ozogamicin (MYLOTARG™)[12] monotherapy, glasdegib (DAURISMO™)[14] combination therapy with LDAC, and ivosidenib (TIBSOVO®)[15] monotherapy.

Additionally, VENCLEXTA® (venetoclax)[13] combination therapy (AZA, DEC, or LDAC)[9,10,11] received accelerated approval in the US for the treatment of newly-diagnosed patients with AML who are 75 years of age or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

In summary, a significant and urgent unmet medical need exists for newly-diagnosed patients with AML who are ineligible for intensive therapy regimens necessitating the need for better treatment options that can offer clinically meaningful improvement in response rates and prolong survival. The Applicant proposes that venetoclax in combination with azacitidine, decitabine, or LDAC for the treatment of newly-diagnosed AML in adults who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy has the potential to fulfill this need.

Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment of approved therapies and commonly used therapies in patients with AML who are ineligible for intensive chemotherapy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

On 21 November 2018, FDA granted accelerated approval to venetoclax in combination with azacitidine, decitabine, or LDAC for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. FDA listed Study M16-043 (VIALE-C) and Study M15-656 (VIALE-A) as postmarketing requirements (PMR 3545-1 and PMR 3545-2, respectively) under 21 CFR 314 Subpart H upon approval (Reference ID: 4352962). In the 23 December 2019 Acknowledge Revised Postmarketing Requirement Milestones letter (Reference ID: 4538478), FDA acknowledged AbbVie's submissions dated 14 October 2019 to IND 110159 and 16 December 2019 to NDA 208573 containing a proposed revised milestone for VIALE-C (PMR 3545-1) that extends the submission of the VIALE-C Clinical Study Report (CSR) to June 2020 in order to facilitate inclusion in the proposed Supplementary New Drug Application (sNDA) submission to support the conversion from accelerated approval to full approval of venetoclax in combination with azacitidine, decitabine, or LDAC for the treatment of newly-diagnosed patients with AML who are ineligible for intensive chemotherapy.

Regulatory Authorities' Assessment:

FDA agrees with the Applicant's presentation of development of venetoclax in AML. Venetoclax initially 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. The CLL indication was subsequently expanded to include CLL and small lymphocytic leukemia (SLL) with or without 17p deletion.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Orphan Drug Designation

The FDA granted orphan drug designation for venetoclax for AML on 04 February 2016.

Breakthrough Therapy Designations

FDA granted Breakthrough Therapy Designations (BTD) for venetoclax in combination with HMAs (azacitidine or decitabine), and venetoclax in combination with LDAC, for newly-diagnosed patients with AML who are ineligible for intensive chemotherapy on 25 January 2016 and 21 July 2017, respectively.

Other Regulatory Interactions Relevant to the Proposed Application

In a Type C Guidance Meeting (Reference ID: 4495990) held on 19 September 2019, the Agency indicated that provided that VIALE-A meets its primary objective at the pre-specified 75% OS

interim analysis, the Agency has no objections to AbbVie's planned sNDA to include the additional follow-up data from Studies M14-358 and M14-387, primary analysis data from VIALE-C, and interim survival analysis data from VIALE-A. Additionally, the Agency agreed to review the results of the additional 6-month follow-up OS data from the VIALE-C study in context of the results of the VIALE-A study. The Agency also indicated that they would make a determination regarding the fulfillment of the PMRs at the time of the sNDA review.

Additionally, the Agency indicated that if the data from the VIALE-A study crosses the boundary at the pre-specified statistical interim analysis, AbbVie should send the Agency the topline efficacy and safety results, and the Agency would likely accept the sNDA for review under the Real-Time Oncology Review (RTOR) program.

On 17 April 2020, the Agency accepted the sNDA to be reviewed under RTOR and notified AbbVie to proceed with the proposed RTOR submission plan content and timeline. In addition, on 17 April 2020, the Agency confirmed the participation of Canada, Australia, and Switzerland in the review of the application under Project Orbis.

AbbVie formally submitted the Early Package Submission on 07 May 2020, comprised of sNDA elements agreed upon with the Agency. A completed sNDA submission was submitted on 22 May 2020.

Regulatory Authorities' Assessment:
FDA confirms the Applicant's assessment.

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

4.1. Office of Scientific Investigations (OSI)

Clinical inspections were not conducted for this sNDA. The Sponsor has been inspected previously with no significant issues identified. Several clinical trial sites have been inspected across the venetoclax development program, and with multiple approved indications, there have not been any significant issues identified that would alter the benefit:risk conclusions. For the phase 3 studies, VIALE-A and VIALE-C, there did not appear to be any sites that overly influenced the efficacy or safety evaluations.

4.2. Product Quality

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

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable. No devices or companion diagnostics are needed for this indication.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

Regulatory Authorities' Assessment:
The FDA agrees with the Applicant that there is no new information provided related to nonclinical pharmacology and toxicology in the current submission.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted efficacy supplements to support the conversion from accelerated approval to full approval of venetoclax in combination with a hypomethylating agent (HMA) (azacitidine or decitabine) or low-dose cytarabine (LDAC) for the treatment of patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

In the approval letter of venetoclax in combination with HMA or LDAC for patients with newly diagnosed AML, FDA issued Trial M15-656 (VIALE-A) and Trial M16-043 (VIALE-C) as postmarketing requirements. These Phase 3 confirmatory trials evaluated the efficacy and safety of venetoclax in combination with an HMA (VIALE-A) or LDAC (VIALE-C) in patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

Clinical pharmacokinetic (PK) analyses indicated that exposure of venetoclax in combination with an HMA (Studies M14-358 and VIALE-A) or LDAC (Studies M14-387 and VIALE-C) in patients with AML were within the range of that observed in patients with CLL/SLL or NHL. There were no significant drug-drug interactions (DDIs) between venetoclax and the combination agents azacitidine, decitabine or cytarabine.

Exposure-response (E-R) analyses for efficacy did not reveal any apparent E-R relationships between steady-state area under the plasma concentration-time curve (AUC_{ss}) of venetoclax and the efficacy endpoints (CR, CR+CRi, CR+CRh, OS, EFS, or the probabilities of conversion to post baseline transfusion independence for both platelets and RBCs) in patients with newly diagnosed AML who received venetoclax doses of 400 to 1200 mg QD in combination with a HMA (Studies M14-358 and VIALE-A) or venetoclax 600 to 800 mg QD in combination with LDAC (Studies M14-387 and VIALE-C). E-R analyses for safety showed that patients in the venetoclax arms in VIALE-A and VIALE-C had a higher probability of treatment-emergent Grade ≥ 3 neutropenia. When data from the placebo arm were excluded from the analysis, there was no apparent E-R relationships between venetoclax AUC_{ss} and safety measurements, e.g., treatment-emergent Grade ≥ 3 infections or thrombocytopenia, with the exception of a shallow but not statistically significant E-R relationship for treatment-emergent Grade ≥ 3 neutropenia in patients receiving venetoclax 400 to 1200 mg QD in combination with a HMA (Studies M14-358 and VIALE-A).

The updated population PK model is generally consistent with the legacy model and indicates that venetoclax PK in patients with AML are consistent with those observed previously in patients with CLL, SLL, and NHL. In addition, the updated population PK analysis continues to support the current labeling recommendations that no dose adjustment is needed based on age, sex, weight, mild to moderate renal impairment, or mild to moderate hepatic impairment. Additionally, the updated population PK analysis indicates that patients with severe renal impairment had comparable venetoclax exposure to those with normal renal function, supporting a labeling recommendation that no dose adjustment is needed for patients with severe renal impairment. The updated population PK analysis also indicates that Asian patients

with AML (mostly from Asian countries) had a 63% higher venetoclax exposure compared to non-Asian patients with AML. Further clinical pharmacology analyses for Asian patients from the US did not substantiate the findings observed in Asian patients from Asian countries. No differences in venetoclax exposure were observed between Asian and White patients with AML from the US.

In summary, the clinical pharmacology analyses support the Applicant's proposed venetoclax dosing regimens in combination with an HMA or LDAC in patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in Supplements 020 and 021 of NDA 208573 and concluded that these supplements are approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:
Collectively, the pharmacokinetics (PK) and exposure-response analyses continue to support the venetoclax dose regimen of venetoclax 400 mg QD in combination with an HMA (VEN + HMA) or 600 mg QD in combination with LDAC (VEN + LDAC), in patients with treatment-naïve AML who are ineligible for intensive chemotherapy:

- The clinical PK findings for venetoclax from Phase 1b/2 and Phase 3 AML studies of VEN + HMA (azacitidine or decitabine) [Studies M14-358 and VIALE-A] and VEN + LDAC [Studies M14-387 and VIALE-C] were consistent with those previously submitted in 2018 AML sNDA 208573.
- Race (Asian versus Non-Asian) was determined to be a significant covariate in the venetoclax population PK model with Asian patients having 67% higher relative bioavailability than non-Asian patients; however, the range of exposures (area under the plasma concentration curve; AUC) in Asian patients was generally comparable to the range of exposures in non-Asian patients. Similar results were also seen with the individual dose-normalized exposures (maximum observed plasma concentration [C_{max}] and AUC) of venetoclax from the non-compartmental analysis of intensive concentration data. Therefore, no dose adjustment is necessary for race.
- The current population PK analysis showed that venetoclax exposures in patients with mild, moderate, or severe renal impairment is comparable (median AUC ≤ 15% higher) to those with normal renal function. Hence, the data continues to support the current recommendation in the venetoclax United States Package Insert (USPI) that no dose adjustment is needed in patients with mild or moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min). While severe renal impairment (CrCl ≥ 15 mL/min and < 30 mL/min) did not affect venetoclax PK in 6 patients with AML, clinical experience is limited

and a recommended dose has not been determined for patients with severe renal impairment (CrCl < 30 mL/min) or patients on dialysis.

- Azacitidine was a significant covariate on the venetoclax apparent volume of distribution of the central compartment (24% higher), but with no meaningful impact on venetoclax exposure.
- The exposure-efficacy analyses showed a clear trend of higher efficacy with VEN + HMA than placebo in combination with AZA (PBO + AZA), or with VEN + LDAC than placebo in combination with LDAC (PBO + LDAC). Within patients receiving VEN + HMA or VEN + LDAC, there was no apparent relationship with venetoclax exposures.
- The exposure-safety analyses showed no apparent relationships between venetoclax exposure levels and treatment-emergent Grade ≥ 3 thrombocytopenia or treatment emergent Grade ≥ 3 infections with either VEN + HMA or VEN + LDAC.
- Consistent with the clinical observation of neutropenia as an identified risk of venetoclax administration (Section 8.2.5), venetoclax in combination with an HMA or with LDAC was associated with an increased risk for neutropenia compared to placebo in combination with AZA or LDAC. However, within patients who received venetoclax, there was only a shallow relationship (for VEN + HMA at a venetoclax dose of 400 to 1200 mg QD) or no apparent relationship (for VEN + LDAC at a venetoclax dose of 600 to 800 mg QD) with venetoclax exposure levels.

Please see Section 6.3.1 for more details.

Regulatory Authorities' Assessment:

The FDA concurs with the Applicant's assessment on clinical PK and E-R relationships of venetoclax in patients with newly diagnosed AML who are ineligible for intensive chemotherapy. The FDA also agrees, in general, with the results of the updated venetoclax population PK analysis. Since data from patients with severe renal impairment and patients of Asian race are available for the updated population PK model, the impact of severe renal impairment and Asian race on venetoclax PK are reviewed in this submission.

Patients with severe renal impairment:

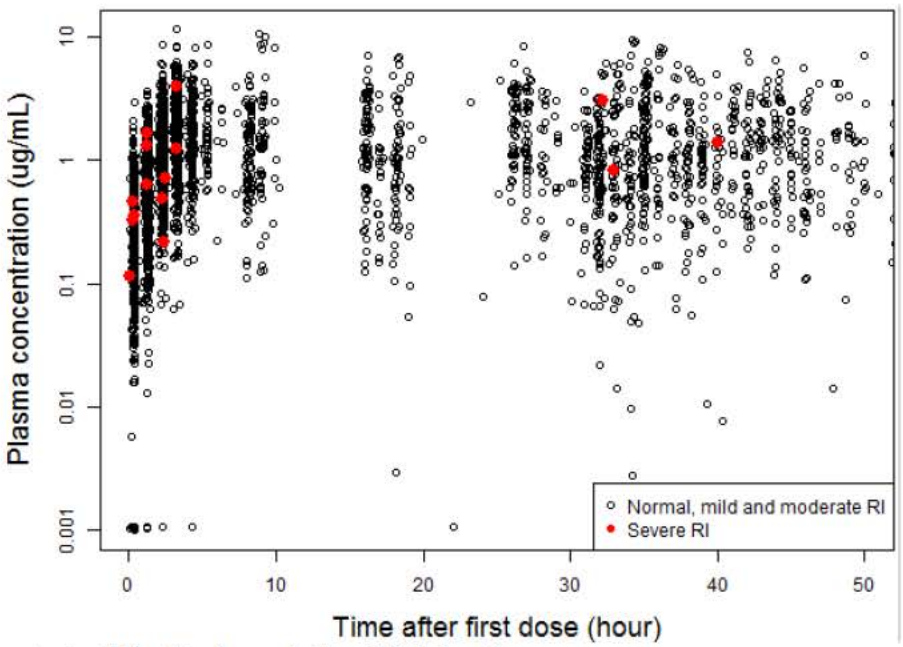
The impact of renal impairment on venetoclax exposure was previously evaluated during the original NDA submission using a population PK analysis of data from patients with CLL, SLL, and NHL. The use of population PK analysis to assess the impact of mild to moderate renal impairment on venetoclax exposure was acceptable and a dedicated renal impairment study was not necessary based upon the understanding of the elimination pathway (i.e., negligible renal excretion based on results from the mass balance study, M13-363).

The impact of severe renal impairment was not investigated during the original NDA submission because data for population PK analysis was only available from one patient with severe renal impairment.

In the updated population PK dataset submitted in this supplement, PK data from 5 patients with severe renal impairment (creatinine clearance of 15 – 29 mL/min) were available and used

to evaluate the effect of severe renal impairment on venetoclax exposure. The concentrations in patients with severe renal impairment generally fell within the PK range in patients with normal renal function and mild to moderate renal impairment, as shown in Figure 1. In addition, in the final population PK model, severe renal impairment was not a significant covariate on venetoclax PK.

Figure 1 Venetoclax plasma concentrations in patients with normal renal function and patients with mild, moderate, or severe renal impairment.

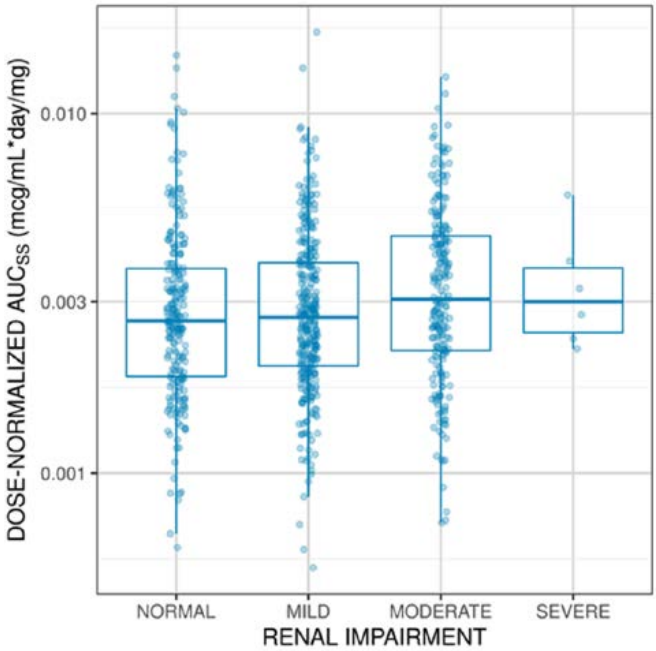


Source: FDA analysis of the final population PK dataset.

The FDA recommends revising section 8.6 (renal impairment) of the USPI to include no dose adjustment for patients with severe renal impairment for the following reasons:

- Negligible contribution of renal clearance to total clearance of venetoclax in humans.
- Based on the updated population PK analysis, there are no differences in dose-normalized venetoclax exposure between patients with normal kidney function, and patients with mild, moderate or severe renal impairment (Figure 2), showing no effect of severe renal impairment on venetoclax PK.

Figure 2 Distribution of dose-normalized venetoclax exposure by baseline renal function.



Source: Applicant's summary of clinical pharmacology, Figure 21.

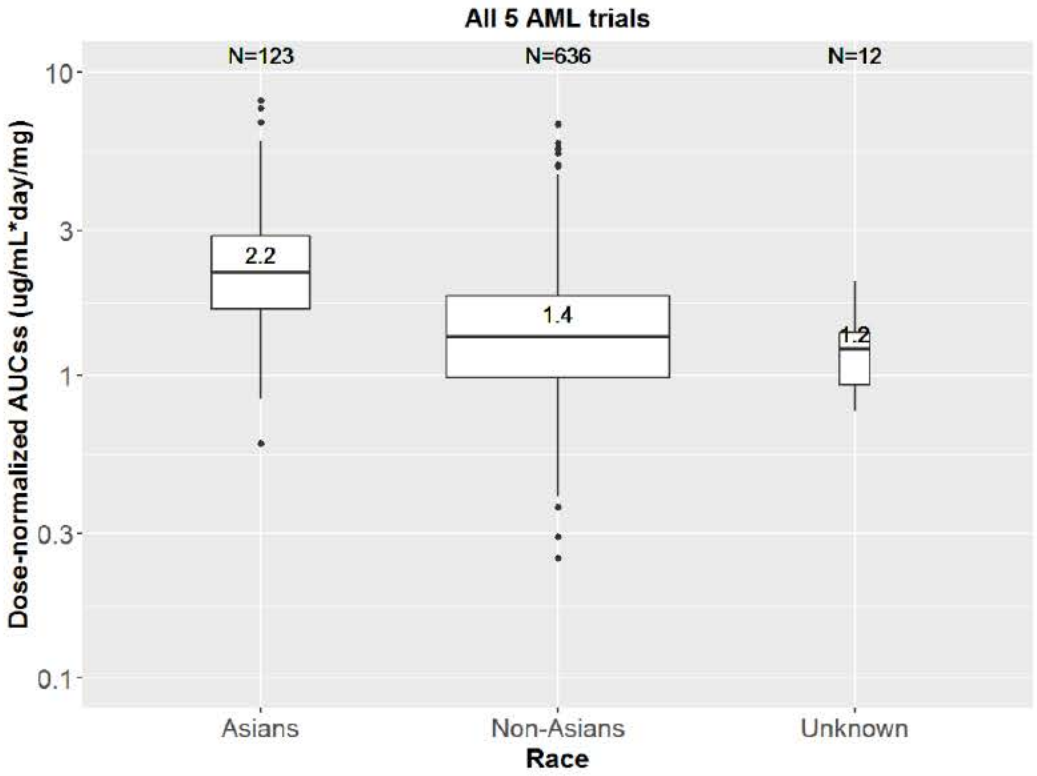
- Venetoclax is being evaluated for the treatment of patients with AML who are ineligible for intensive chemotherapy. Since renal dysfunction is a reason of ineligibility for intensive chemotherapy, expanding venetoclax use to patients with severe renal impairment will provide a treatment option for this patient population.

Patients of Asian race:

In the 5 AML studies included in the population PK analysis, there are 608 (79%) White, 123 (16%) Asian, and 21 (2.7%) African American/Black patients with AML. In the updated venetoclax population PK model, Asian versus non-Asian was found to be a significant covariate on venetoclax PK, with Asian patients having 63% higher dose-normalized AUC_{ss} (Figure 3).

In VIALE-A and VIALE-C, venetoclax safety and PK in Chinese patients with AML were evaluated in open-label cohorts in China prior to allowing Chinese patients to be fully enrolled into the double-blind, randomized portion of these studies. Non-compartmental analysis of data from intensive PK sampling from patients in the open-label cohorts showed an approximately 2-fold higher median steady-state venetoclax exposure (dose-normalized C_{max} and AUC_{24h}) in Chinese patients compared to non-Asian patients (Table 2).

Figure 3 Dose-normalized venetoclax AUC_{ss} in patients with AML based on race.



Source: FDA analysis of data from Studies VIALE A, VIALE-C, M14-358, M14-387, and M14-212.

Table 2 Comparison of median venetoclax dose-normalized C_{max} and AUC_{24} (Range) for Asian versus Non-Asian patients – Non-compartmental analysis of intensive PK data

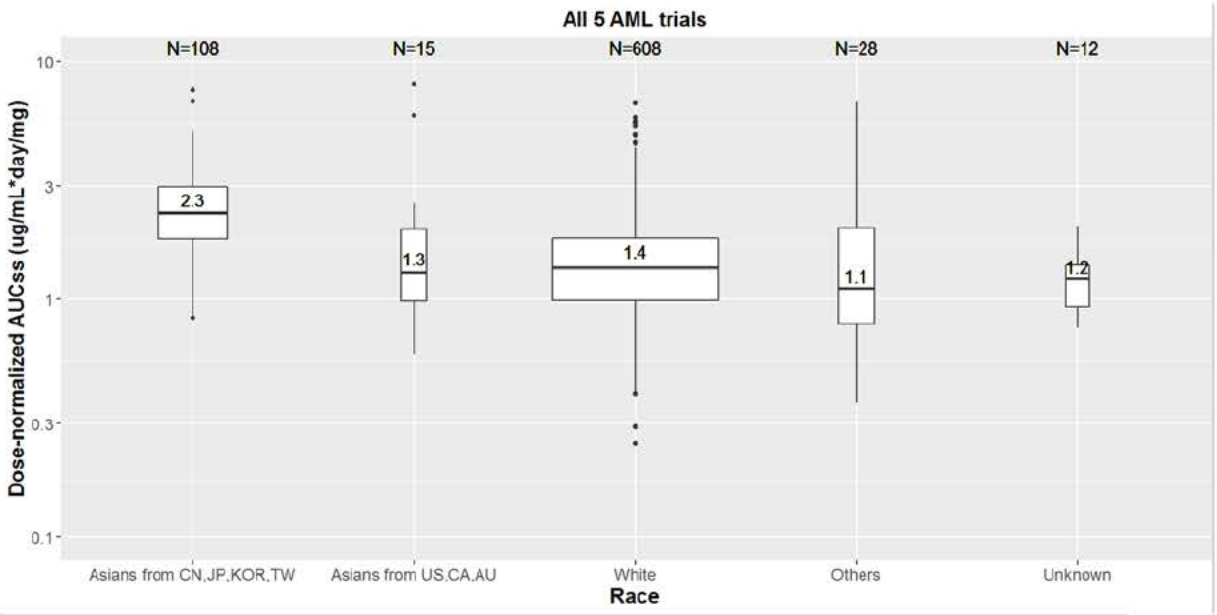
	VIALE-A (+ AZA) Chinese (N=9)	VIALE-C (+ LDAC) Chinese (N=6)	M14-358 (+ AZA) Non-Asian (N=17)	M14-387 (+ LDAC) Non-Asian (N=17)	M14-358 (+ DEC) Non-Asian (N=19)	Asian (AZA + LDAC) (N=15)	Non-Asian (AZA + LDAC) (N=34)	Non-Asian (AZA + LDAC + DEC) (N=53)
DN-C_{max} (ng/mL /mg)	8.2 (2-13)	5.3 (2-17)	3.7 (0.7-7)	2.9 (0.9-8)	3.6 (1.6-12)	7.4 (2-17)	3.3 (0.7-8)	3.3 (0.7-15)
DN-AUC_{24} (ng*h/mL /mg)	122 (31-218)	87 (37-361)	56 (11-93)	41 (12-148)	54 (20-250)	97 (31-361)	50 (11-148)	54 (11-250)

Source: FDA analysis of data from Studies VIALE A, VIALE-C, M14-358, and M14-387

However, FDA noted that most of the Asian patients enrolled in venetoclax AML studies are from Asian countries (Japan, China, South Korea, and Taiwan) and only 11 Asian patients from

the US were enrolled in the 5 AML studies. Using the updated population PK model, an analysis of venetoclax exposure for Asian patients with AML from the US (n = 11), Canada (n = 3) and Australia (n = 1) did not substantiate the findings observed in Asian patients from Asian countries and showed no differences in venetoclax exposure between Asian patients with AML from the US and White patients with AML (Figure 4).

Figure 4 Dose-normalized venetoclax AUC_{ss} in patients with AML based on race.



Source: FDA analysis of data from Studies VIALE A, VIALE-C, M14-358, M14-387, and M14-212.

Although Asians share a common ancestry, it is unknown if environmental or cultural differences between Asian patients with AML from the US and Asian patients from Asian countries can affect venetoclax exposure and it is not clear whether PK data from clinical trials conducted in Asian countries are generalizable to Asian patients in the US.

The contributing factors to the observed increases in venetoclax exposure in patients from Asian countries have not been determined. The body weight (median [min, max]) in Asian patients from Asian countries was 57.5 [32.6, 85.0] kg, Asian patients from Western countries was 69.6 [50.4, 84.4] kg, and non-Asian patients was 77.9 [35.0, 167.5] kg; although body weight was not identified as a significant covariate of venetoclax clearance in the updated population PK analysis. The predicted median CL/F [min, max] in Asian patients from Asian countries (425 [216, 845] L/day), Asian patients from Western countries (591 [256, 821] L/day) and non-Asian patients (458 [118, 1120] L/day) were generally comparable when not co-administered with strong and/or moderate CYP3A inhibitors. Therefore, the race effect is unlikely to be a result of a genetic variation in the metabolizing pathway (CYP3A4) that has been identified to contribute to venetoclax disposition. In addition, the observed race effect on PK cannot be explained by the differences in bioanalytical methods used to measure venetoclax concentration. Although a different method was used in Asian countries, this method was cross

validated with the method used to analyze the samples from the US patients and the two methods had the same linear range for venetoclax measurement (2-2000 ng/mL).

In VIALE-A and VIALE-C, there were no differences between Asian and non-Asian patients with AML in the overall incidence of treatment-emergent adverse events (TEAEs), Grade 3 or higher TEAEs, serious TEAEs, and TEAEs leading to venetoclax/placebo discontinuation, interruption or reduction (Table 3 and Table 4). Careful analysis of the safety data from VIALE-A, showed that Asian patients with AML had higher incidences of some hematological toxicities compared to non-Asian patients with AML (Table 4). However, Asian patients with AML in the placebo arm had also higher incidences of these hematological toxicities compared to the non-Asian patients in the placebo arm of VIALE-A (Table 5). Therefore, it is not clear whether the increased incidences of hematological toxicities are the result of increased venetoclax exposure or another, possibly genetic predisposition, in Asian patients with AML.

Table 3 Overview of number and percentage of patients with treatment-emergent adverse events - Asian vs. Non-Asian, VIALE-A

	Asian		Non-Asian	
	Placebo + Azacitidine (N=33) n (%)	Venetoclax 400 mg QD + Azacitidine (N=65) n (%)	Placebo + Azacitidine (N=111) n (%)	Venetoclax 400 mg QD + Azacitidine (N=218) n (%)
Any TEAE	33 (100)	65 (100)	111 (100)	218 (100)
Grade 3 or higher TEAEs	32 (97.0)	65 (100)	107 (96.4)	214 (98.2)
Treatment-emergent serious AE	17 (51.5)	49 (75.4)	88 (79.3)	186 (85.3)
TEAEs leading to Venetoclax/ Placebo discontinuation	5 (15.2)	6 (9.2)	24 (21.6)	63 (28.9)
TEAEs leading to Venetoclax/ Placebo dose interruption	13 (39.4)	41 (63.1)	69 (62.2)	163 (74.8)
TEAEs leading to Venetoclax/ Placebo dose reduction	0	1 (1.5)	6 (5.4)	6 (2.8)

Source: Applicant response to the FDA's issued IR.

Table 4 Overview of number and percentage of patients with treatment-emergent adverse events - Asian vs. Non-Asian, VIALE-C

	Asian		Non-Asian	
	Placebo + LDAC (N=20) n (%)	Venetoclax 600 mg QD + LDAC (N=39) n (%)	Placebo + LDAC (N=48) n (%)	Venetoclax 600 mg QD + LDAC (N=103) n (%)
Any TEAE	20 (100)	39 (100)	47 (97.9)	102 (99.0)
Grade 3 or higher TEAEs	19 (95.0)	38 (97.4)	46 (95.8)	100 (97.1)
Treatment-emergent serious AE	11 (55.0)	20 (51.3)	31 (64.6)	75 (72.8)
TEAEs leading to Venetoclax/ Placebo discontinuation	2 (10.0)	10 (25.6)	14 (29.2)	27 (26.2)
TEAEs leading to Venetoclax/ Placebo dose interruption	10 (50.0)	21 (53.8)	25 (52.1)	69 (67.0)
TEAEs leading to Venetoclax/ Placebo dose reduction	0	3 (7.7)	5 (10.4)	11 (10.7)

Source: Applicant response to the FDA's issued IR.

Table 5 Overview of number and percentage of subjects with hematological adverse events - Asian vs. Non-Asian

VIALE-A				
Toxicity	**Asian (N = 98)**		**Non-Asian (N = 329)**	
	Placebo + HMA (N = 33)	Venetoclax + HMA (N = 65)	Placebo + HMA (N = 111)	Venetoclax + HMA (N = 218)
Neutropenia	14 (42%)	35 (54%)	28 (25%)	84 (39%)
Thrombocytopenia	21 (64%)	36 (55%)	37 (33%)	94 (43%)
Anemia	13 (39%)	20 (31%)	17 (15%)	58 (27%)
Febrile Neutropenia	9 (27%)	31 (48%)	18 (16%)	87 (40%)
VIALE-C				
Toxicity	**Asian (N = 59)**		**Non-Asian (N = 146)**	
	Placebo + LDAC (N = 20)	Venetoclax + LDAC (N = 39)	Placebo + LDAC (N = 48)	Venetoclax + LDAC (N = 103)
Neutropenia	0 (0%)	12 (31%)	12 (25%)	57 (55%)
Thrombocytopenia	7 (35%)	17 (44%)	20 (42%)	48 (47%)
Anemia	3 (15%)	6 (15%)	12 (25%)	35 (34%)
Febrile Neutropenia	6 (30%)	14 (36%)	14 (29%)	32 (31%)

Source: Applicant response to the FDA issued IR.

The FDA recommends that no dose adjustment is necessary for Asian patients from the US for the following reasons:

- Findings from the updated population PK analysis showed no difference in venetoclax exposure between Asian patients from the US and White patients.
- Absence of safety signals that can be correlated with higher venetoclax exposure in Asian patients with AML. This is consistent with the finding of E-R analysis for safety which showed flat E-R relationships for the majority of AEs with venetoclax + HMA or venetoclax + LDAC, except for a shallow but not statistically significant E-R relationship between treatment-emergent Grade ≥ 3 neutropenia and higher venetoclax exposures.
- Data obtained from Asian patients in Asian countries may not be generalizable to Asian patients in the US due to factors such as environmental and cultural differences.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:
The recommended venetoclax dose regimen for AML patients ineligible for intensive chemotherapy is 400 mg QD when administered in combination with an HMA or 600 mg QD in combination with LDAC. The venetoclax dose regimen is supported by both population PK analysis and exposure-response analyses (see Sections 6.2.1, 6.3.1, and 6.3.2.2).

Regulatory Authorities' Assessment:
The FDA concurs with the Applicant's position that the proposed dosage regimens of venetoclax 400 mg QD in combination with an HMA or 600 mg QD in combination with LDAC are supported by the established efficacy and safety data and the results of population PK and E-R analyses.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:
Venetoclax exposure can be impacted by food, by severe hepatic impairment, and by interaction with coadministration of strong or moderate CYP3A inhibitors or P-glycoprotein (P-gp) inhibitors. These factors have been evaluated in the previously submitted clinical pharmacology studies, and the appropriate dosing recommendations are in the current USPI.

Regulatory Authorities' Assessment:
The FDA agrees that there are appropriate dose adjustments in the current USPI for coadministration with strong or moderate CYP3A or P-gp inhibitors, and severe hepatic impairment.

6.2.2.3. Outstanding Issues

The Applicant's Position:
There are no outstanding issues.

Regulatory Authorities' Assessment:
The FDA agrees with the Applicant that there are no outstanding clinical pharmacology related issues in the current submission.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
The information from prior clinical studies contributing to the clinical pharmacology evaluation of venetoclax was included in previous submissions.

The new clinical pharmacology information includes an evaluation of venetoclax PK and exposure-response (efficacy/safety) relationship using data from AML patients ineligible for intensive chemotherapy in the Phase 3 studies VIALE-A (VEN/PBO + AZA) and VIALE-C (VEN/PBO + LDAC), and updated data from Phase 1/2 AML studies M14-358 (VEN + HMA) and M14-387 (VEN + LDAC). Key new clinical pharmacology findings from this sNDA are summarized in Section 6.2.1.

The venetoclax exposure-efficacy and exposure-safety analyses on data from AML patients treated with VEN/PBO + HMA or VEN/PBO + LDAC are discussed in Section 6.3.2.2.

Regulatory Authorities' Assessment:
The FDA agrees with the Applicant on the general PK of venetoclax in patients with AML.

6.3.2. Clinical Pharmacology Questions

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

The Applicant's Position:
Evidence of positive benefit-risk is based on the efficacy and safety findings from the randomized portion of the pivotal Phase 3 studies, VIALE-A and VIALE-C. While clinical pharmacology evaluation does not include a direct assessment of benefit-risk, consistent PK with prior venetoclax studies and shallow or no apparent exposure-response (efficacy/safety) relationships in the respective dose range studied (400 mg to 1200 mg in combination with an HMA, 600 mg to 800 mg in combination with LDAC) support the 400 mg QD venetoclax dose in combination with azacitidine and the 600 mg QD venetoclax dose in combination with LDAC as evaluated in VIALE-A and VIALE-C, which is consistent with the approved dose regimens for the treatment of AML under accelerated approval based on response rates. Support for the venetoclax dose is provided in Section 6.3.2.2.

Regulatory Authorities' Assessment:
The FDA agrees with the Applicant's position on the supportive evidence of venetoclax effectiveness in patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

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

The Applicant's Position:
The recommended venetoclax dose for patients with AML is 400 mg QD when administered in combination with an HMA (azacitidine or decitabine) or 600 mg QD when in combination with LDAC, which are the approved dose regimens for the treatment of AML under accelerated approval based on response rates.

Key findings from population PK analysis are summarized in Section 6.2.1.

Details on exposure-response analyses are provided below. Separate analyses were performed for VEN + HMA and VEN + LDAC.

The exposure-efficacy analyses evaluated the relationship between venetoclax exposures and CR, CR + CRi, CR + complete remission with partial hematologic recovery (CRh), OS, event-free survival (EFS), and conversion from baseline transfusion dependence to post-baseline transfusion independence for platelets or red blood cells (RBCs). For all efficacy variables evaluated, venetoclax area under curve at steady-state (AUCss) quartile plots showed a clear trend of higher efficacy with VEN + HMA than PBO + AZA, or VEN + LDAC than PBO + LDAC. Within patients who received VEN + HMA or VEN + LDAC, there were no apparent exposure-response relationships. Model-based analyses excluding the data from PBO + AZA or PBO + LDAC confirmed this lack of significant exposure-response relationships in the dose range studied (400 mg to 1200 mg in combination with an HMA, 600 mg to 800 mg in combination with LDAC), indicating that the beneficial effect of venetoclax is already maximized at 400 mg with an HMA or at 600 mg with LDAC.

The exposure-safety analyses evaluated the relationship between venetoclax exposures and treatment-emergent Grade ≥ 3 neutropenia, Grade ≥ 3 infections, and Grade ≥ 3 thrombocytopenia. Only treatment-emergent Grade ≥ 3 neutropenia had higher incidence with VEN + HMA or VEN + LDAC than the corresponding placebo treatment arm (PBO + AZA or PBO + LDAC). Within patients receiving venetoclax, there was a shallow or no apparent relationship with venetoclax exposures in the dose ranges studied (400 mg to 1200 mg in combination with an HMA, 600 mg to 800 mg in combination with LDAC).

Collectively, the efficacy, safety, PK, and exposure-response analyses continue to support the venetoclax dose regimens of 400 mg QD in combination with an HMA and the 600 mg QD in combination with LDAC in patients with AML ineligible for intensive chemotherapy as

appropriate dosage regimens, with highly favorable efficacy achieved with a manageable safety profile and supportive of a positive benefit-risk profile.

Regulatory Authorities' Assessment:
The FDA concurs with the Applicant's position that efficacy, safety, PK, and E-R analyses continue to support the venetoclax dose regimens of 400 mg QD in combination with an HMA and the 600 mg QD in combination with LDAC in patients with AML.

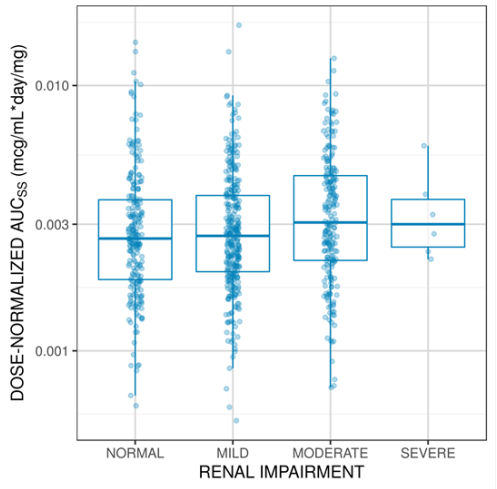
6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:
Based on the population PK analysis results as described in Section 6.2.1, dose adjustment is not necessary for race.

While severe renal impairment (CrCl ≥ 15 mL/min and < 30 mL/min) did not affect venetoclax PK in 6 patients with AML (Figure 5), clinical experience is limited and a recommended dose has not been determined for patients with severe renal impairment (CrCl < 30 mL/min) or patients on dialysis.

No other new intrinsic covariates were identified affecting venetoclax PK in AML patients that warrant dose adjustment of venetoclax.

Figure 5. Distribution of Dose-Normalized Venetoclax Exposure by Baseline Renal Function



AUCss = area under the plasma concentration-time curve at steady state
Note: Venetoclax AUCss values, normalized for designated cohort dose, are plotted versus categorical covariates.
Note: Normal (N = 224), Mild (N = 321), Moderate (N = 219), Severe (N = 6).
Source: Module 2, Section 2.7.2.3.2.3

Regulatory Authorities' Assessment:
The FDA generally agrees with the Applicant's conclusions on the updated venetoclax population PK model with the exception of the impact of severe renal impairment. The FDA recommends revising section 8.6 (renal impairment) of the USPI to include no dose adjustment for severe renal impairment. Refer to section 6.2.1.

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

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

Regulatory Authorities' Assessment:
The FDA agrees that there are appropriate management strategies for clinically relevant food-drug or drug-drug interactions of venetoclax.

X	X
Hisham Qosa, PhD Liang Li, PhD	Ruby Leong, PharmD Lian Ma, PhD
Primary Reviewers	Team Leaders

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

Table 6. Listing of Clinical Trials Relevant to this sNDA

Protocol Number; Phase; NCT Number	Trial Design	Regimen/Schedule/Route	Objective(s) of the Study	Treatment Duration[a]/ Follow Up[b]	Number of Patients Enrolled	Study Population	Number of Centers and Countries
Pivotal Studies to Support Efficacy and Safety of Venetoclax in Combination with Azacitidine or Cytarabine							
VIALE-A (M15-656) Phase 3 NCT02993523	Randomized, double-blind, placebo-controlled, multicenter study	Venetoclax or Placebo: 100 mg Day 1, 200 mg Day 2, 400 mg Day 3 (ramp-up); 400 mg/day thereafter, oral Azacitidine: 75 mg/m^2 SC or IV (per local label) administered QD for 7 days beginning on Day 1 of each 28-day cycle	Evaluate if venetoclax in combination with azacitidine improved overall survival and composite complete remission rate (CR + CRi) versus placebo in combination with azacitidine, in treatment-naïve patients with AML	VEN + AZA: 7.6 months; PBO + AZA: 4.3 months / Follow-up: 20.5 months	431 patients randomized[c] N =286 VEN + AZA; N = 145 PBO + AZA	Newly-diagnosed patients with AML who are ≥ 18 years of age and not eligible for standard induction therapy due to age or comorbidities	134 sites in 27 countries (see Section 8.1.2 for full list)
VIALE-C (M16-043) Phase 3 NCT03069352	Randomized, double-blind, placebo-controlled, multicenter study	Venetoclax or Placebo: 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, 600 mg Day 4 (ramp-up); 600 mg/day thereafter, oral from Day 1 to Day 28 each 28-day cycle LDAC: 20 mg/m^2 SC administered QD from Day 1 to Day 10 each 28-day cycle	Evaluate if venetoclax when co administered with LDAC improves overall survival versus LDAC and placebo, in treatment-naïve patients with AML	VEN + LDAC: 3.9 months; PBO + LDAC: 1.7 months / Follow up: 12.0 months	211 patients randomized N = 143 VEN (600 mg) + LDAC N = 68 PBO + LDAC	Newly-diagnosed patients with AML who are ≥ 18 years of age and who are ineligible for intensive chemotherapy	76 sites in 20 countries (see Section 8.1.2 for full list)

Protocol Number; Phase; NCT Number	Trial Design	Regimen/Schedule/Route	Objective(s) of the Study	Treatment Duration[a]/ Follow Up[b]	Number of Patients Enrolled	Study Population	Number of Centers and Countries
Supportive Studies to Support Efficacy and Safety of Venetoclax in Combination with Azacitidine, Cytarabine, or Decitabine							
M14-358 Phase 1b NCT02203773	Non-randomized, open-label, multicenter, dose-escalation and expansion study	Venetoclax: 400 mg, 800 mg, or 1200 mg, orally, QD, 28-day cycles AND Azacitidine: 75 mg/m^2, SC or IV, Days 1 – 7 for each cycle OR Decitabine: 20 mg/m^2, IV, Days 1 – 5 for each cycle	Dose escalation: Evaluate the safety and PK of venetoclax + decitabine or azacitidine in the target population, and to assess preliminary efficacy. Dose expansion: Confirm safety and project preliminary efficacy of venetoclax + decitabine or azacitidine in the target population. DDI substudy: Evaluate the effect of posaconazole on safety and PK of venetoclax when co-administered with posaconazole	VEN (400 mg) + AZA: 6.4 months; VEN (all doses) + AZA: 5.5 months; VEN (400 mg) + DEC: 5.7 months; VEN (all doses) + DEC: 6.7 months DDI substudy: 2.3 months / Follow up[d]: VEN + AZA: 34.3 months; VEN + DEC: 40.4 months; DDI: 42.9 months	212 patients enrolled; N = 127 VEN (all doses) + AZA; N = 73 VEN (all doses) + DEC; N = 12 DDI substudy	Newly-diagnosed elderly (≥ 60 years) patients with AML who are not eligible for standard induction therapy	18 sites in the United States, Australia, Germany, and France

Protocol Number; Phase; NCT Number	**Trial Design**	**Regimen/Schedule/Route**	**Objective(s) of the Study**	**Treatment Duration[a]/ Follow Up[b]**	**Number of Patients Enrolled**	**Study Population**	**Number of Centers and Countries**
M14-387 Phase 1/2 NCT02287233	Non-randomized, open-label, multicenter, dose-escalation and expansion study	Venetoclax: 600 mg or 800 mg, orally, QD Cytarabine: 20 mg/m^2, SC Days 1 – 10 for each 28-day cycle	Characterize PK and safety, determine maximum tolerated dose/recommended Phase 2 dose, and evaluate efficacy	VEN (600 mg) + LDAC: 4.2 months; VEN (600 or 800 mg) + LDAC: 4.1 months / Follow-up: VEN (all doses) + LDAC: 41.7 months	94 patients enrolled; N = 84 VEN (600 mg) + LDAC N = 10 VEN (800 mg) + LDAC	Newly-diagnosed patients with AML who are ≥ 60 years of age and who are not eligible for standard anthracycline-based induction therapy	9 sites in Australia, Germany, Italy, and the United States

AML = acute myeloid leukemia; AZA = azacitidine; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DDI = drug-drug interaction; DEC = decitabine; IV = intravenous; LDAC = low-dose cytarabine; PBO = placebo; PK = pharmacokinetics; QD = once daily; SC = subcutaneous; VEN = venetoclax

a. Median treatment duration for each study is presented as patient exposure to venetoclax (or placebo for randomized studies).

b. Median duration of follow-up is provided for the total number of patients in the study. The median duration of follow-up by treatment arm is provided in the Study Results section for each study.

c. In VIALE-A, in addition to the 431 patients randomized into Group 2 (stratified for age, cytogenetics, and region), there were 2 patients randomized into Group 1 (stratified for age and region only). Efficacy analyses are presented for the patients in Group 2 (N = 431); safety analyses are presented for patients in Group 1 and Group 2 who received at least 1 dose of study drug (N = 427). In addition to the 433 patients randomized into the blinded portion of the study, there were 10 patients from China enrolled into an open-label safety cohort for a total of N = 443 patients enrolled in VIALE-A.

d. Median follow-up values are presented for all doses of venetoclax.

Regulatory Authorities' Assessment:

We agree with the summary of clinical studies presented in Table 2 above. M14-358 and M14-387 were reviewed under supplement 9 for accelerated approval for the current indication. The proposed USPI included updated response rates (CRh conversion to CR) and duration of response. Refer to the prior supplement review for details of those studies with study summary provided in Sections 8.1.5 and 8.1.7. Updated response and durability from the single arm studies with additional follow up is included in section 8.1. This review provides detailed analysis of VIALE-A and VIALE-C.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Trial to Support Efficacy of Venetoclax and Azacitidine - VIALE-A

Trial Design

The Applicant's Description:

Basic Study Design
VIALE-A is an ongoing, randomized, double-blind, placebo-controlled, multicenter Phase 3 study investigating the efficacy and safety of VEN in combination with AZA in patients with treatment-naïve AML who were older or had comorbidities that precluded the use of intensive induction chemotherapy. VIALE-A excluded patients with prior exposure to HMAs for MDS and favorable risk cytogenetics. Patients randomized in VIALE-A were stratified by age (18 to < 75, ≥ 75 years), cytogenetics (intermediate, poor risk), and region (US, European Union [EU], China, Japan, Rest of world [ROW]).

Patients were randomized to VEN + AZA or PBO + AZA in a 2:1 ratio. Patients were evaluated at the Screening visit and had up to 21 days to complete screening procedures to be enrolled into the study. Patients were hospitalized during the VEN/PBO dose ramp-up period (each cycle was 28 days in length).

Trial Location
VIALE-A was conducted globally in North and South America, Europe, Asia, Africa, and Australia. The number of sites and list of countries where this study randomized patients are provided in Section 8.1.2.

Choice of Control Group
AML patients with significant comorbidities and the elderly are often not eligible for intensive chemotherapy treatment, so low-intensity treatment options are considered the standard of care for these patients.[21] Azacitidine, a standard of care treatment in the AML patient population ineligible for intensive therapy as per NCCN Guidelines Version 2, 2016,[7] was an appropriate control therapy to compare the combination of VEN with AZA in the study. Additional details are provided in Section 2.

The choice of control group allowed for a double-blind assessment of the contribution of VEN to the safety and efficacy of the backbone treatment of AZA.

Diagnostic Criteria
VIALE-A enrolled treatment-naïve patients with AML who were ineligible for intensive chemotherapy due to age or comorbidities.

Key Inclusion/Exclusion Criteria
Enrollment in the study was open to patients with AML ≥ 18 years of age with a potential life expectancy of at least 12 weeks. Patients must be considered ineligible for standard induction therapy as defined by the following:

- ≥ 75 years of age, or
- ≥ 18 to 74 years of age, with at least 1 of these comorbidities: cardiac history of congestive heart failure requiring treatment or ejection fraction ≤ 50% or chronic stable angina; Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) ≤ 65% or Forced Expiratory Volume in 1 Second (FEV1) ≤ 65%; CrCl ≥ 30 mL/min to < 45 mL/min; moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN; Eastern Cooperative Oncology Group (ECOG) Performance Status of 2 or 3; or any other comorbidity that the physician judges to be incompatible with intensive chemotherapy (as reviewed and approved by the Therapeutic Area Medical Director (TA MD) during screening).

Patients were excluded if they had a history of myeloproliferative neoplasm (MPN) including myelofibrosis, essential thrombocythemia, polycythemia vera, chronic myeloid leukemia (CML) with or without BCR-ABL1 translocation and transformation to AML with BCR-ABL1 translocation; or had favorable risk cytogenetics such as t(8;21), inv(16), t(16;16) or t(15;17) as per the NCCN Guidelines Version 2, 2016.[7]

Patients were also excluded if they had acute promyelocytic leukemia; known active central nervous system (CNS) involvement with AML; known HIV, Hep B, or Hep C infections; or had received strong and/or moderate cytochrome P450 3A isoform subfamily (CYP3A) inducers within 7 days prior to the initiation of study treatment. Patients with cardiovascular disability status of New York Heart Association Class > 2; malabsorption syndrome; chronic respiratory diseases; or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, any other medical condition or known hypersensitivity to any of the study medications were also excluded.

Patients were not eligible for study participation in VIALE-A if they were previously treated with any HMA, VEN, and/or any chemotherapeutic agent for MDS, CAR-T cell therapy, or if they were participating in another research or observational study.

Dose Selection and Study Treatments:
Venetoclax
For VIALE-A, the selected dose of VEN is based on the results from Study M14-358, an ongoing Phase 1b study of escalating doses of VEN in combination with AZA and DEC (as described in Section 8.1.5). In the dose escalation phase, patients were enrolled at 3 dose levels of VEN: 400 mg, 800 mg, and 1200 mg. While the efficacy and safety data at both 400 mg and 800 mg dose of VEN in combination with HMAs was comparable, prolonged neutropenia was reported in patients receiving 800 mg dose of VEN after achieving a CR/CRi compared to patients receiving 400 mg dose. An exposure-response analysis of the efficacy in Study M14-358 indicated that the predicted probability of achieving CRi or better was approximately 70% at

exposures associated with both the 400 mg and 800 mg daily dosage regimen of VEN in combination with the HMAs. The maximum tolerated dose (MTD) of VEN was not reached in Study M14-358 at the highest tested dose of venetoclax (1200 mg daily).

Azacitidine

The approved dosing regimen of azacitidine[9] is the dose specified for treatment of adult patients with AML in the EU Summary of Product Characteristics (SmPC) and for treatment of MDS in the US prescribing information. This dosing regimen is recommended as standard of care in the NCCN guidelines for AML patients ineligible for intensive therapy. Azacitidine was administered at a dose of 75 mg/m^2 QD either intravenously (IV) or SC on Days 1 to 7 of each 28-day cycle.

Assignment to Treatment

In VIALE-A, patients were randomized by the Interactive Response Technology (IRT) system into 2 treatment arms in a 2:1 ratio (VEN + AZA versus PBO + AZA). Patient randomization was stratified by age (18 to < 75, ≥ 75), cytogenetics (intermediate risk, poor risk) and region (US, EU, China, Japan, ROW). There were 2 patients randomized only by age and region; these patients were called Group 1 and all other patients were considered Group 2. Efficacy analyses are presented for patients in Group 2 only. Safety analyses are presented for all treated patients in Group 1 and Group 2.

Blinding

AbbVie personnel with direct management of the study sites (with the exception of AbbVie Clinical Drug Supply Management and AbbVie Pharmacovigilance Team), the Investigator, the study site personnel, and the patient remained blinded to each patient's treatment with VEN/PBO. All patients were treated with open-label AZA. An Independent Data Monitoring Committee (IDMC) reviewed safety and efficacy data in an unblinded fashion and provided recommendations to AbbVie per the IDMC charter.

Dose Modification, Dose Discontinuation

The following dose modifications for VEN and/or AZA were implemented to mitigate the risk of high-grade hematologic adverse events (AEs) and their clinical consequences such as serious infections or deaths:

- Duration of VEN/PBO was reduced to 21 days with two occurrences of Grade 4 neutropenia or thrombocytopenia.
- Azacitidine dose reduction was implemented for subsequent treatment cycles based on bone marrow cellularity and duration of count recovery.
- Prophylactic anti-infectives for bacterial, viral and fungal infections were required for absolute neutrophil count (ANC) of < 500/µL while on study treatment. After marrow leukemia clearance, venetoclax/placebo was interrupted between treatment cycles until ANC ≥ 500/µL or platelet count ≥ 50 × 10^3/µL or for up to 14 days, whichever occurred earlier.

Administrative Structure
This study is conducted globally under a collaboration agreement between AbbVie, Inc (AbbVie), Genentech Inc., and F. Hoffmann-La Roche, Ltd., (GNE/Roche) (Sponsors).

The study utilized an IDMC. The IDMC reviewed safety and efficacy data in an unblinded fashion and provided recommendations to the Sponsors, as per the IDMC charter. A formal interim analysis for safety was performed by the IDMC after about 20 patients were dosed and followed for 3 months. Additionally, the IDMC reviewed safety data every 3 months after the formal interim analysis for safety. Two interim analyses for efficacy were performed. The first interim analysis (IA1) was planned when 225 patients were randomized and followed for 6 months (226 patients were included in IA1 as the last 2 patients were randomized on the same date with 6-month follow-up by the cutoff date). The CR + CRi endpoint based on investigator's assessment was formally analyzed and reviewed by the IDMC at IA1. This was the primary analysis for CR + CRi. The second interim analysis (IA2) was performed when 270 death events (75% of the total 360 events) occurred. In each interim analysis, the IDMC reviewed the OS endpoint to ensure no potential detrimental OS effect defined as hazard ratio (HR) > 1.

The study was designed to utilize the dual primary endpoints of CR + CRi and OS for potential early regulatory interactions in the EU and other regions. The data from IA1 were reviewed by the IDMC; with a recommendation that the study be continued without modification. However, the results were not disclosed to the Sponsors or the investigator sites. The study continued in a blinded fashion until the IDMC made the recommendation to unblind after IA2 on 16 March 2020.

Procedures and Schedule
Screening tests were performed within 21 days prior to enrollment. During the treatment period, scheduled study visits were based on a 28-day (4 week) cycle, with Cycle 1 beginning on Day 1, and all patients were assessed for disease responses at the end of Cycle 1 and every 3 cycles thereafter. Patients with resistant disease (RD) at end of Cycle 1, were to have a repeat bone marrow at the end of Cycle 2 or Cycle 3 to assess for a response. For patients with a response of CR or CRi on two consecutive bone marrows assessments, additional bone marrow assessments were only performed when clinically indicated. Patients were also assessed for disease progression at a final study visit (regardless of whether the patient completed or prematurely discontinued study treatment) and had posttreatment visits performed every 2 months after the last study visit. All patients were followed for survival information (i.e., date and cause of death if known) unless the patients withdrew consent from survival follow-up.

Dietary Restrictions/Instructions
Patients were not to consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first study drug administration and until the last day of treatment due to possible CYP3A-mediated metabolic interaction. Each dose of VEN/PBO was to be taken orally QD with approximately 240 mL of water within approximately 30 minutes after the completion of a meal (preferably after breakfast).

Concurrent Medications
Medications that were cautionary in the VEN ramp-up period and during VEN treatment included strong and moderate CYP3A inhibitors, moderate CYP3A inducers, P-gp inhibitors, P-gp substrates with instructions for appropriate dose reductions of VEN/PBO when co-administered; for warfarin, coumarin derivatives patients were to be monitored closely for safety by investigators. Strong CYP3A inducers were excluded during ramp-up and throughout the study.

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

Patient Completion, Discontinuation, or Withdrawal
Patients continued their study treatment until documented disease progression (per Investigator assessment), unacceptable toxicity, withdrawal of consent, or the patients met other protocol criteria for discontinuation (whichever occurs first).

Patients could voluntarily discontinue study treatment or withdraw from the study at any time for any reason. The investigator also had the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Regulatory Authorities' Assessment:
We agree with the Applicant's description of the trial design of the Phase 3, VIALE-A study.

Study Endpoints

The Applicant's Description:
The Sponsors incorporated the Agency's feedback to designate OS as the primary endpoint in the VIALE-A prespecified Statistical Analysis Plan (SAP) for the US. Secondary endpoint definitions of composite remission in VIALE-A incorporated the Agency's 16 November 2017 advice provided for the June 2018 sNDA supporting the 21 November 2018 accelerated approval. The definition of the secondary endpoint of minimal/measurable residual disease (MRD) negative remission rate incorporated the Agency's feedback as provided in the 23 May 2019 Type C Guidance meeting. Primary, key secondary, and exploratory endpoints important to characterizing overall efficacy are presented below.

Endpoints: For VIALE-A, the primary endpoint was OS for US and US reference countries. The ranked key secondary endpoints for US and US reference countries are presented in Table 7.

Regulatory Authorities' Assessment:
We agree with the Applicant's description of the study endpoints of the Phase 3, VIALE-A study.

Statistical Analysis Plan and Amendments

The Applicant's Description:
VIALE-A was designed to enroll approximately 400 patients with 2:1 randomization ratio to VEN + AZA and PBO + AZA. For the US and US reference countries, this study had a single primary endpoint of OS. For Japan, EU and EU reference countries, this study had dual primary endpoints of CR + CRi rate (as assessed by investigator) and OS. The sample size and statistical analyses performed for these endpoints are discussed in the "Statistical Methodology for Multiplicity" section below.

Analysis Populations
The study randomized 2 patients (Group 1) under the original protocol with age and region as stratification factors and 431 patients (Group 2) under protocol amendment 1 and later versions with age, cytogenetic risk, and region as stratification factors. The study also enrolled 10 additional patients in the China open-label safety cohort, who are not included in the efficacy or safety analyses presented in this document.

Two analysis populations were defined in the VIALE-A SAP:

- The Full Analysis Set (termed the Efficacy Analysis Set) included all Group 2 patients who were randomized to the study regardless of whether they received any study treatment (N = 431).
- The Safety Analysis Set included all randomized patients in Groups 1 and 2 who received at least one dose of study drug (N = 427).

Efficacy Analysis
The analysis of OS included all Group 2 patients in the Efficacy Analysis Set and were analyzed according to the treatment arm and strata they were assigned at time of the randomization in the IRT system. The primary efficacy analysis was a comparison of the distribution of OS between the two treatment arms using a log-rank test stratified by age (18 to < 75, ≥ 75 years) and cytogenetic risk (intermediate, poor) from IRT. The HR and 95% confidence interval (CI) were estimated using a Cox proportional hazards model stratified by the stratification factors mentioned above.

The analyses of CR + CRh rate, CR rate, and CR + CRh rate by initiation of Cycle 2, and postbaseline RBC and platelet transfusion independence rate were based on Cochran-Mantel-Haenszel (CMH) test stratified by above mentioned stratification factors. In addition, the 95% CI for rates were provided based on the binomial distribution (Clopper-Pearson exact method) for each treatment arm. The CR + CRh rates in IDH1/IDH2 and FMS-like tyrosine kinase 3 (FLT3) subgroups and OS in IDH1/IDH2 and FLT3 were evaluated since the pre-specified requirement such as the sample size of biomarker subgroups described in the SAP were met. The CR + CRh rates in IDH1/IDH2 and FLT3 were compared between the two treatment arms using Fisher's exact test. The OS in IDH1/IDH2 and FLT3 were compared between two treatment arms using unstratified log-rank test. The HR and 95% CI were estimated using unstratified Cox proportional hazards model.

Disease assessments were performed by the investigators per the revised International Working Group (IWG) criteria for AML. Response criteria were defined as follows:

- CR: Absolute neutrophil count > 10^3/µL, platelets > 10^5/µL, RBC transfusion independence, and bone marrow with < 5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
- CRi: All criteria as CR except for residual neutropenia ≤ 10^3/µL (1000/µL) or thrombocytopenia ≤ 10^5/µL (100,000/µL). RBC transfusion dependence is also defined as CRi.
- Partial Remission (PR): All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.
- Morphologic leukemia-free state (MLFS): Less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells, absence of circulating blasts and extramedullary disease without peripheral blood count recovery that meet the thresholds for either CR or CRi.
- RD: Failure to achieve CR, CRi, PR, or MLFS; only for patients surviving at least 7 days following completion of Cycle 1 treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.
- Morphologic relapse (MR): Reappearance of ≥ 5% blasts after CR/CRi in peripheral blood or bone marrow or development of extramedullary disease.
- Progressive disease (PD; as defined by ELN criteria[8]):
  - 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline); or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5 × 10^9/L [500/µL], and/or platelet count to > 50 × 10^9/L [50,000/µL] non transfused); or
  - 50% increase in peripheral blasts (white blood cell [WBC] × % blasts) to > 25 × 10^9/L (> 25,000/µL); or
  - New extramedullary disease

In addition to the response assessments by these criteria, each patient was evaluated for CRh derived from the bone marrow and hematology lab values. A response of CRh is achieved when the following criteria are met:

- Bone marrow with < 5% blasts
- Peripheral blood neutrophil count of > 0.5 × 10^3/µL*
- Peripheral blood platelet count of > 0.5 × 10^5/µL*
  - * 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 will be used for CRh analysis.
  - * Patient must have platelet transfusion independence for ≥ 7 days prior to the

hematology lab results.

Safety Analysis

All safety analyses were based on the Safety Analysis Set. AE summaries were presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). All AEs, Grade 3 to 4 AEs, treatment-related AEs, serious adverse events (SAEs), AEs leading to treatment discontinuation, AEs leading to dose reduction or interruption, AEs leading to death, selected AEs, death and causes of death, the number (%) of patients with worse postbaseline laboratory data (Grade 0 at baseline to Grade 1 to 4 postbaseline, Grade 0 to 2 at baseline to Grade 3 to 4 postbaseline or Grade 3 at baseline to Grade 4 postbaseline), the number (%) of patients who met Howard criteria for tumor lysis syndrome (TLS), and the number (%) of patients who met Hy's law of potential drug-induced liver injury (DILI) were summarized by treatment arm. All safety summaries included only treatment-emergent events or assessments, i.e., those collected on or after the first date of study drug (VEN/PBO or AZA) administration and no later than 30 days after the last date of study drug administration.

Methods for Handling Missing Data

For the analysis of OS, data for patients who were alive at the time of data cutoff were censored at the last date they were known to be alive prior to or on the data cutoff. For the analyses of postbaseline transfusion independence rates, patients who did not receive any study drug were considered postbaseline transfusion dependent. Patients who were randomized but had no IWG disease assessment were considered as non-responders in the calculation of CR + CRh rate, and CR + CRh rate by initiation of Cycle 2.

Statistical Methodology for Multiplicity

For US and US reference countries, this study had a single primary efficacy endpoint of OS. The fixed sequence testing procedures were performed with a significance level of 0.05 (two-sided) for the primary endpoint of OS. Assuming a true HR of 0.70 (median OS of 10.4 and 14.9 months for PBO + AZA arm and VEN + AZA arm, respectively), and an interim efficacy analysis at 75% of OS events with Lan-DeMets alpha spending function with O'Brien-Fleming (OBF) boundary, a total of 360 OS events were required for the study to have 88.6% power to detect statistically significant improvement in OS for the VEN + AZA arm at 2-sided alpha of 0.05. An interim analysis for the OS endpoint was planned to be conducted when 270 OS events (75% of OS events) occurred. If the statistical test was not significant for the primary efficacy endpoint of OS, then statistical significance would not be declared for any of the secondary endpoints. The Lan-DeMets alpha spending function with OBF boundary was used to determine the efficacy boundaries for primary and ranked key secondary endpoints in the interim and final analyses. The actual alpha-spending boundaries and corresponding information fraction for ranked secondary endpoints at IA2 are described in Table 7.

The pre-specified requirement for biomarker subgroup analyses (CR + CRh in IDH1/IDH2 and FLT3; OS in IDH1/IDH2 and FLT3) were met. These endpoints were formally tested according to pre-specified sequential testing procedure.

For Japan, EU and EU reference countries, this study had dual primary endpoints of CR + CRi rate (as assessed by investigator) and OS. For the dual primary efficacy endpoints, a significance level of 0.01 (two-sided) was allocated for the analysis of CR + CRi rate and a significance level of 0.04 (two-sided) was allocated for the analysis of OS to ensure strong control of the familywise error rate (FWER). If the statistical test was significant for CR + CRi rate, the significance level of 0.01 allocated to CR + CRi rate analysis was to be recycled to OS analysis.

Table 7. VIALE-A: Actual Alpha-Spending Boundary and Information Fraction for Ranked Endpoints at IA2 (US and US Reference countries)

Endpoints for US and US reference countries	Information Fraction	Interim Boundary p-value (two-sided)
1. OS	75% (270 OS events)	0.02
2. CR + CRh	100%	0.05
3. CR + CRi	First 226 patients	0.05
4. CR + CRh rate by the initiation of Cycle 2	100%	0.05
5. Post-baseline RBC transfusion independence	98%	0.047
6. CR + CRh rate in IDH1/IDH2	100%	0.05
7. CR Rate	98%	0.047
8. CR + CRh rate in FLT3	100%	0.05
9. Post-baseline platelet transfusion independence	98%	0.047
10. EFS	87% (313/360 events)	0.032
11. OS in IDH1/IDH2	NA	0.0002
12. OS in FLT3	NA	0.0002
13. EORTC QLQ-C30 GHS/QoL	NA	0.0002
14. PROMIS Cancer Fatigue SF7a	NA	0.0002
15. MRD Negative Remission Rate	98%	0.047

CR = complete remission; CR + CRi = composite complete remission rate; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete blood count recovery; EFS = event-free survival; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core; FLT3 = FMS-like tyrosine kinase; GHS/QoL = Global Health Status Quality of Life; IA2 = interim analysis 2; IDH = Isocitrate dehydrogenase; MRD = minimal/measurable residual disease; NA = not applicable; OS = overall survival; PROMIS = Patient Reported Outcomes Measurement Information System; RBC = red blood cell

Interim Analysis

The CR + CRi endpoint is one of the dual primary endpoints for Japan, EU and EU reference countries. The first interim efficacy analysis (IA1) was conducted for CR + CRi (Primary Analysis for CR + CRi endpoint) at 2-sided alpha = 0.01 after patients completing 6 months follow up. Two patients were randomized on the same date 6 months prior to the data cut-off date which resulted in 226 patients included in IA1 instead of the preplanned 225 patients. The second interim efficacy analysis (IA2) was conducted for OS at 2-sided alpha = 0.02 when 270 OS events (75% of 360 total OS events) were observed. The study continued in a blinded fashion until the IDMC made the recommendation to unblind after IA2.

Planned Subgroup Analyses

Subgroup analyses of CR rate, CR + CRh rate, CR + CRh rate by the initiation of Cycle 2, and OS were performed to assess consistency of treatment effect based on Efficacy Analysis Set.

Subgroups investigated included demographic factors, baseline characteristics, mutational markers and stratification factors.

SAP Amendments

There have been 7 versions of SAP. All SAP amendments were finalized and submitted to the agency before each interim analysis was conducted and before the study team was unblinded. The SAP version 7 was used for the most recent interim analysis (IA2). Key changes to the SAP are noted in the Protocol Amendments section below. Of note, in SAP version 4, the total number of OS events was increased from 302 to 360 with the number of events for 75% OS IA increased from 227 to 270 to ensure adequate study power for OS endpoint (from 80% to 86.7% for dual endpoints with 2-sided alpha of 0.04, or 88.6% for single primary endpoint with 2-sided alpha of 0.05).

Regulatory Authorities' Assessment:

We agree with the Applicant's description of the SAP of the Phase 3, VIALE-A study.

Protocol Amendments

The Applicant's Description:

The initial VIALE-A study protocol, dated 25 October 2016, had 7 global amendments. These changes did not impact the integrity of the study or the interpretation of the results. The amendments and the rationale for each amendment were as follows:

- Amendment 1 (21 December 2016)
  This amendment was created to lower the age limit for study eligibility and enroll AML patients ≥ 18 years of age who are ineligible for standard induction therapies due to comorbidities instead of ≥ 60 years of age, as well as to clarify female patient birth control methods and to add pregnancy testing for females of childbearing age.
  - Although cytogenetic risk as a stratification factor was added in Amendment 2, the 2 patients enrolled under this amendment in October 2017 and April 2018 were stratified for cytogenetic risk as well, since the IRT updates for randomization had been put in place.
- Amendment 2 (20 February 2017)
  This amendment was created to clarify the definitions for progression of disease and event-free survival. To support venetoclax dose reductions during the ramp-up when co-administered with strong CYP3A inhibitors exposure-response analysis from a Phase 1b study of venetoclax with HMAs (M14-358) was included. Patient stratification groups were updated to include cytogenetic risk to evaluate the differences in biology of disease in younger AML patients.
- Amendment 2.01 – China only (29 March 2017)
  This amendment was created to allow for open label safety evaluation of venetoclax in combination with azacitidine in a subset of Chinese AML patients prior to China enrollment in the double blind, randomized portion of the study.
- Amendment 3 (10 May 2017)
  This amendment was created in response to request during Voluntary Harmonisation Procedure to clarify that Sponsors approval is not necessary for the investigator prior to

unblinding a patient and provide additional clarification of patients with or without a BCR-ABL mutation within the eligibility criteria of the study. This amendment also provided guidance on patient treatment with anti-emetics to ensure alignment with azacitidine SmPC and exclusion of patients who are hypersensitive to active substances of the study drugs.

- Amendment 4 (01 March 2018)
  This amendment was created to add and define CRh analysis to be done on study data, as well as to clarify that home administration of azacitidine was not allowed and administration of azacitidine per the local label which was utilized at the sites. This amendment also provided additional guidance regarding various study procedures, the use of concomitant therapies, and updated safety language.
- Amendment 5 (08 August 2018)
  This amendment was created to ensure alignment between the protocol and SAP of CR + CRi rate analysis for the study, as well as clarify that OS and CR + CRi dual primary endpoints will be utilized for Japan, the EU, and EU reference countries while OS will be the single primary endpoint of analysis for the US. The primary efficacy endpoint of CR + CRi rate is to be based on investigator assessment. Additionally, the secondary endpoints of this study were updated to include evaluation of MRD (including MRD threshold of $< 10^{-3}$), CRh, transfusion independence, and molecular markers. MLFS, CRi, and RD criteria were defined in further detail. The timeframe which allows for historic bone marrow data to be used, as well as language to understand the prevalence of molecular key subtypes within the trial population was clarified.
- Amendment 6 (15 May 2019)
  This amendment was created to update the total number of OS events (as enrollment in to the study was projected to continue at the anticipated time of the survival event accrual for the interim survival analysis), to increase the follow up of the patients after enrollment, and to increase the statistical power of the study. Timing of patient-reported outcome (PRO) assessment administration in relation to other procedures and study drug administration was clarified.
- Amendment 7 (21 August 2019)
  This amendment was created to revise the definition of CR as a neutrophil count > 1000/µL and platelet count of > 100,000/µL per IWG criteria and to clarify the version of the NCCN guidelines for AML used to assess cytogenetic risk stratification criterion.

Regulatory Authorities' Assessment:
We agree with the Applicant's description of the amendments of the Phase 3, VIALE-A study.

8.1.2. Study Results – VIALE-A (Study M15-656)

Compliance with Good Clinical Practices

The Applicant's Position:
This study was conducted in accordance with the Code of Federal Regulations (CFR) governing the protection of human patients, Institutional Review Boards (IRBs), and the obligations of clinical investigators in accordance with Good Clinical Practice (GCP).

Independent Ethics Committees (IECs)/IRBs: The IEC/IRB reviewed the ethical, scientific and medical appropriateness of the study before it was conducted. IEC/IRB approval of the protocol, informed consent, and patient information and/or advertising was obtained prior to the authorization of drug shipment to a study site. Amendments to the protocol received IEC/IRB approval prior to implementation of any changes made to the study design. Serious AEs that met the reporting criteria, as dictated by local regulations, were reported to both responsible IECs and Regulatory Agencies as required by local regulations. During the conduct of the study, the investigator was to promptly provide written reports to the IEC/IRB for any changes that affected the conduct of the study and/or increase the risk to patients.

Ethical Conduct of the Study: This study was conducted in accordance with the protocol, full conformance with the International Conference on Harmonization (ICH) E6 guideline for GCP, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki.

Patient Information and Consent: The Investigator or their representative explained the nature of the study to the patient and answered all questions. Prior to any study-related screening procedures being performed on the patient, the informed consent statement was reviewed, signed, and dated by the patient, the person administering the informed consent, and any other signatories according to local requirements. A copy of the informed consent form was given to the patient and the original was placed in the patient's medical record. An entry was made in the patient's dated source documents to confirm these actions.

In the event a patient withdrew consent to participate in the study, stored biomarker and exploratory research samples continued to be used for research and analysis. In the event that a patient wanted to withdraw consent for research using these samples, the patient could request that their samples be withdrawn. Upon receipt of the request, remaining biomarker and exploratory research samples would be destroyed. A separate informed consent, approved by an IEC/IRB, must be voluntarily signed and dated before samples are collected for the optional exploratory research.

Audits: Audit certificates are provided in the VIALE-A Interim CSR. The AbbVie Clinical Quality Assurance group or designee conducted audits at 8 investigator sites. No critical audit findings were observed. For all audit findings, appropriate corrective and preventive actions were undertaken.

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

Financial Disclosure

The Applicant's Position:
During the study site initiation process, AbbVie or its designee provided study-specific financial

disclosure forms to all principal investigators and sub-investigators for use in disclosing financial interest in, or receipt of, significant payments from AbbVie and/or GNE/Roche. AbbVie Inc. and GNE/Roche were listed as co-development partners in the financial disclosure forms that were distributed. During the course of the study, new or revised financial disclosure forms and other essential documents were collected.

Methods Used to Minimize Bias by the Sponsors for VIALE-A:

- VIALE-A is a multicenter, randomized study. Patients were enrolled at 134 sites across 27 countries for VIALE-A, including the US. The study is being conducted with a double-blind design. The Sponsors, investigators and patients were blinded to the study treatment. In addition, the study is monitored by an IDMC.
- All investigator-positive financial disclosures were reviewed by AbbVie and assessed whether their financial interest in AbbVie, Genentech and/or Roche was significant per the Agency's Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators, February 2013. To ensure potential bias has not affected study integrity, the number of patients enrolled by these positive disclosed investigators was also evaluated.

Summary of Findings: For VIALE-A, 1,315 out of 1,336 (98.43%) principal investigators and sub-investigators provided financial disclosure information. Of the investigators who responded, 11 of 1,336 (< 1%) were positive for disclosable financial interests. A total of 18 sub-investigators were determined to have been added to the site Form FDA 1572 (Investigator Information and Agreement) in error, left the site, or died prior to collection of the financial disclosure information. Despite due diligence on the part of AbbVie to obtain the information, a signed financial disclosure was not obtained for 3 sub-investigators. The reason the information could not be collected, as well as the Applicant's due diligence efforts in attempting to obtain the information are provided in Section 1.3.4.1 of the sNDA.

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

Patient Disposition

The Applicant's Position:
A total of 433 patients were randomized at 134 sites across 27 countries, including the US (76 patients randomized across 15 sites). The Efficacy Analysis Set included the 431 randomized patients in Group 2: 145 patients in PBO + AZA and 286 patients in VEN + AZA. The Safety Analysis Set was comprised of 427 patients who received at least 1 dose of study treatment: 144 patients in PBO + AZA and 283 patients in VEN + AZA. At the data cutoff date (4 January 2020), 287 patients had completed the study (113 patients in PBO + AZA and 174 patients in VEN + AZA).

At the data cutoff date (4 January 2020), 73 patients in VEN + AZA and 16 patients in PBO + AZA were actively receiving study treatment; 210 patients in the VEN + AZA arm and 128 patients in the PBO + AZA arm had discontinued study treatment. Of the 427 patients receiving study

treatment during this trial, 268 patients (62.8%) died (159 patients [56.2%] in the VEN + AZA arm and 109 patients [75.7%] in the PBO + AZA arm) (Section 8.2.4).

Trial Locations

The trial locations for VIALE-A included 134 sites in Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Norway, Poland, Portugal, Russia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, and the United States.

Regulatory Authorities' Assessment:

We confirm the Applicant's position. The Applicant clarified that two patients were excluded from the ITT population because they were enrolled in the trial prior to the plan to stratify randomization by cytogenetic risk (referred to as Group 1). One patient was in each arm of the study. The patient in the venetoclax arm had intermediate risk cytogenetics and the patient in the placebo arm had poor risk cytogenetics. We do not object to the ITT population based on patients in only Group 2 after the addition of cytogenetics as a stratification factor.

Protocol Violations/Deviations

Data and The Applicant's Position:

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. Deviations were assessed for their impact on analyses and data integrity or patient safety.

As of the data cut-off for this interim analysis, for the Efficacy Analysis Set, 113 patients (39.5%) in the VEN + AZA arm and 65 (44.8%) patients in the PBO + AZA arm had protocol deviations. These deviations were not considered to have affected the interpretation of the study results or conclusions. The types of deviations were as follows:

- Patient entered study and did not satisfy eligibility criteria: a total of 8 protocol deviations were reported in 8 patients.
- Patient received wrong treatment or incorrect dose: a total of 127 protocol deviations were reported in 99 patients.
  - Patient received wrong treatment due to incorrect kit dispensation at the site: 2 deviations were identified in 2 patients where a placebo kit was dispensed instead of venetoclax with patients receiving PBO for less than 2 weeks. Once identified, correct kits were dispensed for dosing consistent with original treatment assignment.
- Patient received excluded concomitant medications: A total of 9 protocol deviations were reported in 9 patients.
- Protocol Compliance - Study Procedures: A total of 79 protocol deviations were reported in 79 patients.
- Protocol Compliance - Patient Dosing Compliance: A total of 14 protocol deviations were reported in 10 patients.

- Investigational Product (IP) - Dispensation/Administration: A total of 9 protocol deviations reported in 8 patients.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. Protocol deviations were relatively balanced between arms, and the deviations were unlikely to bias the study in favor of the study drug. Therefore, all patients, including those with important protocol deviations, were included in our analysis of efficacy endpoints.

Table of Demographic Characteristics

Data:

Table 8. VIALE-A: Demographic Characteristics (Efficacy Analysis Set)

Demographic Parameters n (%)	PBO + AZA (N = 145)	VEN 400 mg QD + AZA (N = 286)
Gender		
Male	87 (60.0)	172 (60.1)
Female	58 (40.0)	114 (39.9)
Age		
Mean years (SD)	75.1 (5.70)	75.6 (6.08)
Median (years)	76.0	76.0
Min, max (years)	60.0, 90.0	49.0, 91.0
Age Category		
18 to < 65 years	5 (3.4)	10 (3.5)
65 to < 75 years	53 (36.6)	102 (35.7)
≥ 75 years	87 (60.0)	174 (60.8)
Race		
White	109 (75.2)	217 (75.9)
Black or African American	2 (1.4)	3 (1.0)
Asian	33 (22.8)	66 (23.1)
American Indian or Alaskan Native	1 (0.7)	0
Region		
United States	24 (16.6)	50 (17.5)
Rest of the World*	121 (83.4)	236 (82.5)

AZA = azacitidine; max = maximum; min = minimum; N = sample size; n = number of patients; PBO = placebo; QD = once daily; SD = standard deviation; VEN = venetoclax

* Rest of the World includes sites in Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Norway, Poland, Portugal, Russia, South Africa, South Korea, Spain, Sweden, Taiwan and Turkey.

Note: Data included are subject to a cutoff date of 04 January 2020.

Source: VIALE-A CSR Table 14.1__3.1.2.1. Source dataset: ADSL.

The Applicant's Position:
In VIALE-A, the demographic characteristics were balanced across treatment arms (Table 8). The patients were elderly (median age: 76.0 years); the majority (≥ 60% of patients) were aged ≥ 75 years; and > 95% of patients were ≥ 65 years of age. The majority of the patients were male and white.

Regulatory Authorities' Assessment:

We agree with the Applicant's assessment. We note that Black or African American patients are significantly underrepresented compared to the population of the US.

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

Data:

Table 9. VIALE-A: Summary of Baseline Disease Characteristics (Efficacy Analysis Set)

Baseline Disease Characteristics n (%)	PBO + AZA (N = 145)	VEN 400 mg QD + AZA (N = 286)
ECOG Performance Status		
0	23 (15.9)	37 (12.9)
1	58 (40.0)	120 (42.0)
2	59 (40.7)	113 (39.5)
3	5 (3.4)	16 (5.6)
Type of AML		
De novo AML	110 (75.9)	214 (74.8)
Secondary AML	35 (24.1)	72 (25.2)
Cytogenetics (from EDC)[a]		
Intermediate	89 (61.4)	182 (63.6)
Poor	56 (38.6)	104 (36.4)
Bone marrow blast count		
< 30%	41 (28.3)	85 (29.7)
≥ 30% - < 50%	33 (22.8)	61 (21.3)
≥ 50%	71 (49.0)	140 (49.0)
Mutation Analyses Detected – n/N[b] (%)		
IDH1[c] and/or IDH2[d]	28/127 (22.0)	61/245 (24.9)
IDH1[c]	11/127 (8.7)	23/245 (9.4)
IDH2[d]	18/127 (14.2)	40/245 (16.3)
FLT3[e]	22/108 (20.4)	29/206 (14.1)
NPM1[f]	17/86 (19.8)	27/163 (16.6)
TP53[f]	14/86 (16.3)	38/163 (23.3)

AML = acute myeloid leukemia; AZA = azacitidine; ECOG = Eastern Cooperative Oncology Group; EDC = Electronic Data Capture; FLT3 = FMS-like tyrosine kinase 3; IDH = isocitrate dehydrogenase; N = sample size; n = number of patients; NPM = nucleophosmin; PBO = placebo; QD = once daily; TP = tumor protein; VEN = venetoclax

a. Per the 2016 National Comprehensive Cancer Network (NCCN) Guidelines.
b. Number of evaluable biomarker mutation analysis specimens received at baseline
c. Detected by Abbott RealT*ime* IDH1 assay
d. Detected by Abbott RealT*ime* IDH2 assay
e. Detected by LeukoStrat® CDx FLT3 mutation assay
f. Detected by MyAML® assay

Note: Data included are subject to a cutoff date of 04 January 2020.
Source: VIALE-A CSR Table 14.1__3.1.2.1. Source dataset: ADSL.

The Applicant's Position:

In VIALE-A, the treatment arms were balanced and represented the intended patient population overall with respect to baseline disease characteristics and prognostic factors/cytogenetics thereby providing reassurance with regard to the interpretation of the treatment comparison and validity of the efficacy conclusions (Table 9).

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. Patients were enrolled using the modified Ferrara criteria which provided objective criteria to determine if patients were ineligible for intensive chemotherapy. The criteria were 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.

In the venetoclax arm, 61% were ≥75 years old, and of those patients, 57% had at least one additional comorbidity. In the placebo arm, 65% were ≥75 years old, and 47% had at least one additional comorbidity. For those <75 years old, 63% in the venetoclax arm and 59% in the placebo arm had only one comorbidity. Of those who were <75 years, 78% had ECOG score of 2-3, but may have had more than one comorbidity.

Transfusion independence is determined by those who were dependent on RBC and/or platelets at baseline. In VIALE-A, 155 (54%) in the venetoclax arm and 81 (56%) in the placebo arm were transfusion dependent at baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data and The Applicant's Position:
Treatment Compliance: Compliance was monitored and documented by the study coordinator on the appropriate form. The study coordinator questioned the patient regarding adherence to the dosing regimen, recorded the number of tablets and/or bottles returned and the date returned, and determined treatment compliance before dispensing new study drug to the patient. Some patients did not take the study drug within 30 minutes of completing a meal as specified in the protocol; however, these samples are not expected to have impacted the study outcome or interpretation of the study results or conclusions.

Concomitant Medications: Overall, the proportion of patients who required concomitant medication was similar in both treatment arms. Differences in concomitant medication use were not deemed large enough to impact any efficacy or safety outcomes in the study.

The most common concomitant medications taken by ≥ 20% of patients overall (Group 2) included ondansetron (55.7%), paracetamol (55.2%), furosemide (49.9%), potassium (43.4%), levofloxacin (43.2%), pip/tazo (39.0%), meropenem (35.0%), pantoprazole (32.0%), aciclovir (30.2%), metoclopramide (29.0%), sodium chloride (27.1%), filgrastim (26.7%), vancomycin (25.5%), allopurinol (24.8%), lactulose (24.1%), lidocaine (21.6%), ciprofloxacin (21.3%), Bactrim (21.1%), cefepime (20.9%), and amlodipine (20.2%).

Per protocol, to mitigate the potential risk of TLS, all patients were to receive prophylactic uric acid reducing agents. Concomitant TLS prophylaxis agents or hydration were administered to 424 patients (98.4%): 281 patients (98.3%) in VEN + AZA and 143 patients (98.6%) in PBO + AZA. TLS prophylaxis agents were provided to 410 patients (95.1%) overall. The most common

agents were allopurinol (78.4%), febuxostat (11.1%), sodium bicarbonate (7.2%), and rasburicase (6.7%).

Per protocol, anti-infective prophylaxis for bacterial, viral and fungal infections were required for all patients with ANC of < 500/µL. Institutional infectious organisms and their drug resistance patterns were to be considered and the choice of these agents were to be primarily based on regional guidelines or institutional standards. In VIALE-A, 236 patients (82.5%) in VEN + AZA and 117 patients (80.7%) in PBO + AZA received anti-infective prophylaxis agents while receiving study treatment.

Rescue Medication: Not relevant to the product and disease under study.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. In VIALE-A, 48 patients (17%) in VEN+AZA and 27 patients (18%) in PBO+AZA received posaconazole at any time during the treatment period. See Additional Analyses below for an evaluation of response rates by patients who received posaconazole and other CYP3A inhibitors.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

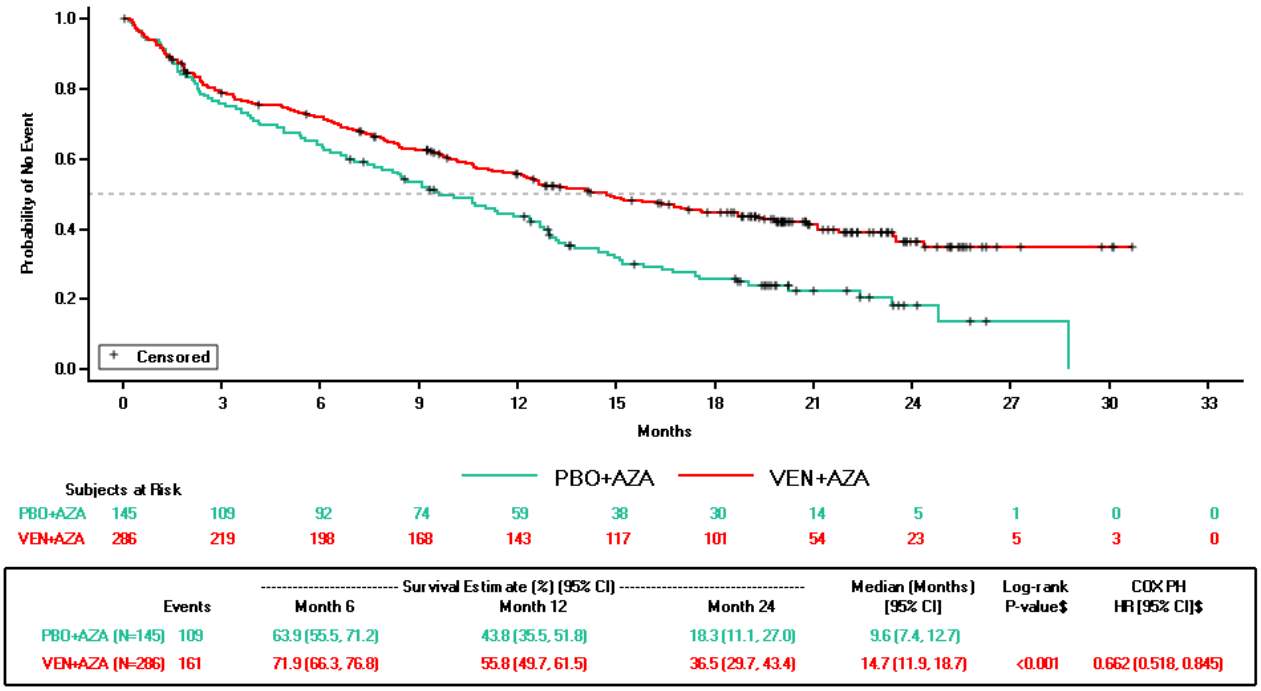
Data:
Two-sided p-value is presented in all efficacy results.

Table 10. VIALE-A: Analysis of Overall Survival (Efficacy Analysis Set)

	PBO + AZA (N = 145)	**VEN 400 mg QD + AZA (N = 286)**
Events (deaths) - n (%)	109 (75.2%)	161 (56.3%)
Duration of Overall Survival (months)		
25th (95% CI)	3.4 (2.1, 4.9)	4.8 (2.8, 6.5)
Median (95% CI)	9.6 (7.4, 12.7)	14.7 (11.9, 18.7)
75th (95% CI)	18.7 (14.7, 28.8)	NR
6-Month Survival Estimate (95% CI)	63.9% (55.5%, 71.2%)	71.9% (66.3%, 76.8%)
12-Month Survival Estimate (95% CI)	43.8% (35.5%, 51.8%)	55.8% (49.7%, 61.5%)
24-Month Survival Estimate (95% CI)	18.3% (11.1%, 27.0%)	36.5% (29.7%, 43.4%)
Treatment Comparison (Stratified[a])	**VEN + AZA vs. PBO + AZA**	
p-value from Log-rank Test	< 0.001***	
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)	0.662 (0.518, 0.845)	

AZA = azacitidine; CI = confidence interval; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; N = sample size; n = number of patients; NR = not reached; PBO = placebo; QD = once daily; VEN = venetoclax
a. Stratified by age (18 to < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk) from IVRS/IWRS.
Note: ***, **, * at p = 0.001, 0.01, 0.05 levels, respectively.
Note: Data included are subject to a cutoff date of 04 January 2020.
Source: VIALE-A CSR Table 14.2__1.1. Source datasets: ADSL and ADTTE.

Figure 6 VIALE-A: Analysis of Overall Survival (Efficacy Analysis Set)



	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	Log-rank P-value$	COX PH HR [95% CI]$
PBO+AZA (N=145)	109	63.9 (55.5, 71.2)	43.8 (35.5, 51.8)	18.3 (11.1, 27.0)	9.6 (7.4, 12.7)		
VEN+AZA (N=286)	161	71.9 (66.3, 76.8)	55.8 (49.7, 61.5)	36.5 (29.7, 43.4)	14.7 (11.9, 18.7)	<0.001	0.662 (0.518, 0.845)

AZA = azacitidine; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; PBO = placebo; VEN = venetoclax
$ Stratified by age (18 to < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk) from IVRS/IWRS.
Note: Data included are subject to a cutoff date of 04 January 2020.
Source: VIALE-A CSR, Figure 14.2__11.1. Source datasets: ADSL and ADTTE.

At data cutoff (4 January 2020), VEN + AZA reduced the risk of death in newly-diagnosed patients with AML ineligible for intensive chemotherapy by 33.8% (HR = 0.662; p-value < 0.001 [stratified log-rank test]). The median OS in the VEN + AZA arm was 14.7 months, compared to 9.6 months in the PBO + AZA arm (Table 10). The Kaplan-Meier plot for OS showed separation of curves in favor of the VEN + AZA arm beginning around 2 months; the separation was maintained over time (Figure 6).

The median duration of follow-up for patients in VEN + AZA arm was 20.7 months (range: 0.0 to 30.7) and 20.2 months (range: 0.2 to 28.8) for patients in PBO + AZA arm.

The Applicant's Position:
VIALE-A met its primary endpoint; OS was statistically significantly prolonged for patients in the VEN + AZA arm versus patients in the PBO + AZA arm.

Sensitivity and Supportive Analyses for OS
Data:
Sensitivity analysis of OS is performed using all data in the IA2 database extracted on 18 February 2020 without applying any cutoff date. The combination of VEN + AZA reduced the risk of death by 34.7% (HR = 0.653; p-value < 0.001). The median OS in VEN + AZA arm (N =

286) was 14.7 months (95% CI: 11.9, 18.7 months). In comparison, for patients in the PBO + AZA arm (N = 145), the median OS was 9.6 months (95% CI: 7.4, 12.7 months) (Table 11).

Table 11. VIALE-A: Sensitivity Analysis of Overall Survival – Including All Data in the Extracted Database (Efficacy Analysis Set)

	PBO + AZA (N = 145)	**VEN 400 mg QD + AZA (N = 286)**
Events (deaths) - n (%)	113 (77.9%)	165 (57.7%)
Duration of Overall Survival (months)		
25th (95% CI)	3.4 (2.1, 4.9)	4.8 (2.8, 6.5)
Median (95% CI)	9.6 (7.4, 12.7)	14.7 (11.9, 18.7)
75th (95% CI)	18.7 (14.9, 23.8)	NR (27.4, NR)
6-Month Survival Estimate (95% CI)	63.9% (55.5%, 71.2%)	71.9% (66.3%, 76.8%)
12-Month Survival Estimate (95% CI)	43.9% (35.6%, 51.9%)	56.0% (49.9%, 61.6%)
24-Month Survival Estimate (95% CI)	16.4% (9.6%, 24.9%)	37.8% (31.5%, 44.1%)
Treatment Comparison (Stratified[a])	**VEN + AZA vs. PBO + AZA**	
p-value from Log-rank Test	< 0.001***	
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)	0.653 (0.513, 0.832)	
p-value	< 0.001***	

AZA = azacitidine; CI = confidence interval; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; N = sample size; n = number of patients; NA = not available; NR = not reached; PBO = placebo; QD = once daily; VEN = venetoclax

a. Stratified by age (18 to < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk) from IVRS/IWRS.

Note: ***, **, * at p = 0.001, 0.01, 0.05 levels, respectively.

Note: Data included are subject to a cutoff date of 18 February 2020.

Source: VIALE-A CSR Table 14.2__1.2.1. Source datasets: ADSL and ADTTE.

The Applicant's Position:

Consistent with the result of primary OS analysis, similar OS improvement is observed in the VEN + AZA arm by sensitivity analysis of OS including all data in the extracted database at IA2.

Regulatory Authorities' Assessment:

We agree with the Applicant's assessment of OS results. We agree that the sensitivity analysis of OS using all data is consistent with the primary analysis. We note that the final analysis was originally planned for 270 OS events which was achieved at cutoff date 4 January 2020.

We note that there is minimal impact on the OS results based on hematopoietic stem cell transplantation (HSCT) as only 2 patients in the venetoclax arm and 1 patient in the placebo arm proceeded to HSCT.

As noted under patient disposition, two patients in Group 1 were excluded from the ITT population due to a change in stratification factors. After including these 2 patients from Group 1, the unstratified Cox regression and log rank test results were as follows: HR=0.683 (95% CI= 0.50, 0.81) with log-rank test P-value < 0.001. We note that these results are consistent with current VIALE-A OS results. The analyses below utilize the patients enrolled in Group 2. Note that inclusion of patients from Group 1 in these analyses will have negligible impact on the

results. In addition, patients from Group 1 were randomized over a continuous time period following the 2 patients randomized in Group 1.

Data Quality and Integrity

The Applicant's Position:
Prior to enrolling any patient in the study, an initiation meeting was held with AbbVie personnel, the Investigators, and the study coordinators/project managers. This meeting included a detailed discussion and review of the protocol and essential documents, performance of study procedures, case report form (CRF) completion, and specimen collection methods.
The AbbVie site monitor monitored the study site throughout the study. Source document reviews were made against entries on the CRFs and a quality assurance check was performed to ensure that the Investigator was complying with the protocol and regulations. In addition, after the CRFs were retrieved, a review of the data was conducted by a physician or representative at AbbVie.

After completion of the data entry process, computer logic and manual checks were created to identify such items as inconsistent study dates. Any necessary corrections were made to the database via the appropriate change form/electronic CRF.

Routine hematology, serum chemistry and serology, and urinalysis tests were conducted using a certified clinical laboratory. Laboratory reference ranges were obtained prior to the initiation of the study and updated as necessary throughout the course of the study. A review of all laboratory results was conducted by the AbbVie monitor, the Investigator and other appropriate personnel from AbbVie.

Regulatory Authorities' Assessment:
We agree with the data quality and integrity assessment.

Efficacy Results – Secondary and other relevant endpoints

Data:
Table 12 presents data from the key ranked secondary endpoints in VIALE-A. These endpoints are described in detail in the following sections. Data for endpoints not presented below (including CR + CRi rates, EFS, and MRD) are provided in the VIALE-A CSR. The primary analysis of all response-related endpoints is based on the investigator assessment. Two-sided p-value is presented in all efficacy results.

Table 12. VIALE-A: Summary of Key Secondary Efficacy Parameters

Parameter	PBO + AZA (N = 145)	VEN + AZA (N = 286)
CR + CRh Rate and Duration of Response		
Responders; n (%) [95% CI]	33 (22.8) [16.2, 30.5]	185 (64.7) [58.8, 70.2]
p-value (CMH test)	p < 0.001	
Duration of Response (months); median (95% CI)	13.9 (10.4, 15.7)	17.8 (15.3, NR)
CR + CRh Rate by the Initiation of Cycle 2		
Responders; n (%) [95% CI]	8 (5.5) [2.4, 10.6]	114 (39.9) [34.1, 45.8]
p-value (CMH test)	p < 0.001	
Postbaseline RBC Transfusion Independence		
Responders; n (%) [95% CI]	51 (35.2%) [27.4%, 43.5%]	171 (59.8%) [53.9%, 65.5%]
p-value (CMH test)	p < 0.001	
CR + CRh Rate in IDH1/IDH2		
Responders; n/N (%) [95% CI]	2/28 (7.1) [0.9, 23.5]	44/61 (72.1) [59.2, 82.9]
p-value (Fisher's exact test)	p < 0.001	
CR Rate and Duration of Response		
Responders; n/N (%) [95% CI]	26 (17.9) [12.1, 25.2]	105 (36.7) [31.1, 42.6]
p-value (CMH test)	p < 0.001	
Duration of Response (months); median (95% CI)	13.3 (8.5, 17.6)	17.5 (15.3, NR)
CR + CRh Rate in FLT3		
Responders; n/N (%) [95% CI]	4/22 (18.2) [5.2, 40.3]	19/29 (65.5) [45.7, 82.1]
p-value (Fisher's exact test)	p = 0.001	
Postbaseline Platelet Transfusion Independence		
Responders; n (%) [95% CI]	72 (49.7%) [41.3%, 58.1%]	196 (68.5%) [62.8%, 73.9%]
p-value (CMH test)	p < 0.001	
Overall Survival in IDH1/IDH2		
Number of patients with events; n/N	24/28	29/61
Median OS months (95% CI)	6.2 (2.3, 12.7)	NR (12.2, NR)
HR (p-value from unstratified log-rank test)	0.345 (p < 0.0001)	
Overall Survival in FLT3		
Number of patients with events; n/N	19/22	19/29
Median OS months (95% CI)	8.6 (5.9, 14.7)	12.7 (7.3, 23.5)
HR (p-value from unstratified log-rank test)	0.664 (p = 0.2054)	

AZA = azacitidine; CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; FLT3 = FMS-like tyrosine kinase 3; IDH = isocitrate dehydrogenase; N = sample size; n = number of patients; NR = not reached; RBC = red blood cell; VEN = venetoclax

Note: Data included are subject to a cutoff date of 04 January 2020.

Sources: VIALE-A CSR Tables 14.2__2.1.3, 14.2__3.3.1, 14.2__4.1.1, 14.2__3.2.1, and 14.2__2.4.2. VIALE-A Figures 14.2__11.4.1.1 and 14.2__11.4.3. Source datasets: ADSL, ADRS, and ADTTE.

CR + CRh Rate

The CR + CRh rate for patients in the VEN + AZA arm (N = 286) was 64.7% (95% CI: 58.8%, 70.2%), with a CR rate of 36.7% and a CRh rate of 28.0%. In comparison, the CR + CRh rate for patients in the PBO + AZA arm (N = 145) was 22.8% (95% CI: 16.2%, 30.5%) with a CR rate of 17.9% and a CRh rate of 4.8%. The CR + CRh rate was statistically significantly greater for patients in the VEN + AZA arm than for patients in the PBO + AZA arm (p-value < 0.001) (Table 13).

Among patients in the VEN + AZA arm who achieved a best response of CR + CRh, median time to first response was 1.0 months (range: 0.6 to 14.3 months) compared to a median time to

first response of 2.6 months (range: 0.8 to 13.2 months) for patients in the PBO + AZA arm. Median time to best response of CR + CRh was 2.3 months in the VEN + AZA arm and 3.6 months in the PBO + AZA arm (Table 13).

CR + CRh Rate by the Initiation of Cycle 2

The observed complete remissions were rapid and reported early in the course of study treatment. Venetoclax in combination with azacitidine statistically significantly (p-value < 0.001) improved the percentage of patients who achieved remission (CR + CRh) by the initiation of Cycle 2 (39.9% patients versus 5.5% patients in the PBO + AZA arm) (Table 13).

CR Rate

The CR rate for patients in the VEN + AZA arm was 36.7% (95% CI: 31.1%, 42.6%) compared to a CR rate of 17.9% (95% CI: 12.1%, 25.2%) for patients in the PBO + AZA arm. The CR rate was statistically significantly greater for patients in the VEN + AZA arm than for patients in the PBO + AZA arm (p-value < 0.001). Median time to best response of CR rate was 3.2 months (range: 0.9 to 24.5 months) in the VEN + AZA arm and 4.0 months (range: 1.0 to 13.2 months) in the PBO + AZA arm (Table 13).

Table 13. VIALE-A: Analysis of Best Response of CR + CRh (Efficacy Analysis Set)

	PBO + AZA (N = 145)	VEN 400 mg QD + AZA (N = 286)	p-value[a]
CR + CRh Rate (as best response) - n (%) [95% CI][b]			
CR	26 (17.9) [12.1, 25.2]	105 (36.7) [31.1, 42.6]	< 0.001***
CRh	7 (4.8) [2.0, 9.7]	80 (28.0) [22.8, 33.6]	
CR + CRh	33 (22.8) [16.2, 30.5]	185 (64.7) [58.8, 70.2]	< 0.001***
Patients with Best Response of CR + CRh – Mean (SD) Median [range]			
Time to First Response (months)			
CR + CRh	3.0 (2.35) 2.6 [0.8-13.2]	2.2 (2.23) 1.0 [0.6-14.3]	
Time to Best Response (months)			
CR	4.5 (2.95) 4.0 [1.0-13.2]	4.5 (4.38) 3.2 [0.9-24.5]	
CRh	2.7 (1.52) 2.8 [1.1-5.5]	2.6 (2.66) 1.0 [0.6-14.3]	
CR + CRh	4.1 (2.79) 3.6 [1.0-13.2]	3.6 (3.84) 2.3 [0.6-24.5]	
CR + CRh Rate (as best response) by Initiation of Cycle 2 - n (%) [95% CI][b]			
CR	3 (2.1) [0.4, 5.9]	37 (12.9) [9.3, 17.4]	
CRh	5 (3.4) [1.1, 7.9]	77 (26.9) [21.9, 32.5]	
CR + CRh	8 (5.5) [2.4, 10.6]	114 (39.9) [34.1, 45.8]	< 0.001***

AZA = azacitidine; CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; N = sample size; n = number of patients; PBO = placebo; QD = once daily; SD = standard deviation; VEN = venetoclax

a. P-value is from Cochran-Mantel-Haenszel test stratified by age (18 to < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk) from IVRS/IWRS.

b. 95% confidence interval is from the exact binomial distribution.

Note: ***, **, * at p = 0.001, 0.01, 0.05 levels, respectively.

Note: Data included are subject to a cutoff date of 04 January 2020.

Source: VIALE-A CSR Table 14.2__2.1.3. Source datasets: ADSL, ADRS, and ADTTE.

Postbaseline Red Blood Cell and Platelet Transfusion Independence
In the VEN + AZA arm, 166 patients (58.0%) achieved RBC and platelet transfusion independence compared to 49 patients (33.8%) in the PBO + AZA arm (Table 14).

At baseline, 155 patients (54.2%) in VEN + AZA arm and 81 patients (55.9%) in PBO + AZA arm were RBC or platelet transfusion dependent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were RBC or platelet transfusion dependent at baseline, 49.0% patients (76/155) in VEN + AZA arm and 27.2% patients (22/81) in PBO + AZA arm became transfusion independent (Table 14). These patients achieved a 56-day or greater transfusion-free period while actively receiving study drugs.

At baseline, 131 patients (45.8%) in VEN + AZA arm and 64 patients (44.1%) in PBO + AZA arm were RBC or platelet transfusion independent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were RBC or platelet transfusion independent at baseline, 68.7% patients (90/131) in VEN + AZA arm and 42.2% patients (27/64) in PBO + AZA arm remained transfusion independent for at least 56 days postbaseline (Table 14).

VEN + AZA statistically significantly improved the percentage of patients who achieved transfusion independence for RBC and platelets (p-value < 0.001). Rates of conversion from baseline transfusion dependence to independence while on study treatment was significantly higher in patients treated with VEN + AZA compared to patients treated with PBO + AZA. Patients who were transfusion independent at baseline maintained their transfusion independence at a higher rate in the VEN + AZA arm compared to the PBO + AZA arm during study treatment.

Postbaseline Red Blood Cell Transfusion Independence
In the VEN + AZA arm, 171 patients (59.8%) achieved RBC transfusion independence compared to 51 patients (35.2%) in the PBO + AZA arm (Table 14).

At baseline, 144 patients (50.3%) in VEN + AZA arm and 76 patients (52.4%) in PBO + AZA arm were RBC transfusion dependent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were RBC transfusion dependent at baseline, 49.3% patients (71/144) in VEN + AZA arm and 27.6% patients (21/76) in PBO + AZA arm became transfusion independent (Table 14). These patients achieved a 56-day or greater transfusion-free period while actively receiving study drugs.

At baseline, 142 patients (49.7%) in VEN + AZA arm and 69 patients (47.6%) in PBO + AZA arm were RBC transfusion independent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were RBC transfusion independent at baseline, 70.4% patients (100/142) in VEN + AZA arm and 43.5% patients (30/69) in PBO + AZA arm remained RBC transfusion independent for at least 56 days postbaseline (Table 14).

VEN + AZA statistically significantly improved the percentage of patients who achieved transfusion independence for RBC (p-value < 0.001). Rates of conversion from baseline RBC

transfusion dependence to independence while on study treatment was significantly higher in patients treated with VEN + AZA compared to patients treated with PBO + AZA. Patients who were RBC transfusion independent at baseline maintained their transfusion independence at a higher rate in the VEN + AZA arm compared to the PBO + AZA arm during study treatment.

Postbaseline Platelet Transfusion Independence
In the VEN + AZA arm, 196 patients (68.5%) achieved platelet transfusion independence compared to 72 patients (49.7%) in the PBO + AZA arm (Table 14).

At baseline, 68 patients (23.8%) in VEN + AZA arm and 32 patients (22.1%) in PBO + AZA arm were platelet transfusion dependent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were platelet transfusion dependent at baseline, 50.0% patients (34/68) in VEN + AZA arm and 37.5% patients (12/32) in PBO + AZA arm became transfusion independent (Table 14). These patients achieved a 56-day or greater transfusion-free period while actively receiving study drug.

At baseline, 218 patients (76.2%) in VEN + AZA arm and 113 patients (77.9%) in PBO + AZA arm were platelet transfusion independent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were platelet transfusion independent at baseline, 74.3% patients (162/218) in VEN + AZA arm and 53.1% patients (60/113) in PBO + AZA arm remained platelet transfusion independent for at least 56 days postbaseline (Table 14).

VEN + AZA statistically significantly improved the percentage of patients who achieved transfusion independence for platelets (p-value < 0.001). Rates of conversion from baseline transfusion dependence to independence while on study treatment was significantly higher in patients treated with VEN + AZA compared to patients treated with PBO + AZA. Patients who were platelet transfusion independent at baseline maintained their platelet transfusion independence at a higher rate in the VEN + AZA arm compared to the PBO + AZA arm during study treatment.

Table 14. VIALE-A: Summary of Postbaseline Transfusion Independence (Efficacy Analysis Set)

	PBO + AZA (N = 145)	VEN 400 mg QD + AZA (N = 286)	p-value[a]
Postbaseline Transfusion Independence Rate - n (%) [95% CI][b]			
RBC and Platelet	49 (33.8%) [26.2%, 42.1%]	166 (58.0%) [52.1%, 63.8%]	< 0.001***
RBC	51 (35.2%) [27.4%, 43.5%]	171 (59.8%) [53.9%, 65.5%]	< 0.001***
Platelet	72 (49.7%) [41.3%, 58.1%]	196 (68.5%) [62.8%, 73.9%]	< 0.001***
Postbaseline Transfusion Independence Rate by Baseline Transfusion Status – n/N (%) [95% CI][b]	**PBO + AZA (N = 145)**	**VEN 400 mg QD + AZA (N = 286)**	
Having RBC or Platelet Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	22/81 (27.2%) [17.9%, 38.2%]	76/155 (49.0%) [40.9%, 57.2%]	

	PBO + AZA (N = 145)	VEN 400 mg QD + AZA (N = 286)	p-value[a]
Without RBC or Platelet Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	27/64 (42.2%) [29.9%, 55.2%]	90/131 (68.7%) [60.0%, 76.5%]	
Having RBC Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	21/76 (27.6%) [18.0%, 39.1%]	71/144 (49.3%) [40.9%, 57.8%]	
Without RBC Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	30/69 (43.5%) [31.6%, 56.0%]	100/142 (70.4%) [62.2%, 77.8%]	
Having Platelet Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	12/32 (37.5%) [21.1%, 56.3%]	34/68 (50.0%) [37.6%, 62.4%]	
Without Platelet Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	60/113 (53.1%) [43.5%, 62.5%]	162/218 (74.3%) [68.0%, 80.0%]	

AZA = azacitidine; CI = confidence interval; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; N = sample size; n = number of patients; PBO = placebo; QD = once daily; RBC = red blood cell; VEN = venetoclax

a. P-value is from Cochran-Mantel-Haenszel test stratified by age (18 to < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk) from IVRS/IWRS.

b. 95% confidence interval is from the exact binomial distribution.

Note: ***, **, * at p = 0.001, 0.01, 0.05 levels, respectively.

Note: The postbaseline transfusion independence is defined as a period of at least 56 days with no RBC or platelet transfusion during the evaluation period. Postbaseline transfusion evaluation period is from the first dose of study drug to the last dose of study drug + 30 days, or disease progression, or confirmed morphological relapse, or death, or data cut-off date, whichever occurred earlier. Subjects not receiving any study drug were considered as postbaseline transfusion dependent.

Note: Non-treated patients are patients who did not receive any study treatment.

Note: Data included are subject to a cutoff date of 04 January 2020.

Source: VIALE-A CSR Table 14.2__4.1.1. Source datasets: ADSL, ADRS, and ADTTE.

CR + CRh Rate in IDH1/IDH2 Subgroup

There were 245 patients in the VEN + AZA arm and 127 patients in the PBO + AZA arm with results from companion diagnostics (CDx); patients with undetermined or missing values (non-evaluable) were not included in this total. As of the data cutoff date for the interim analysis, there were 61/245 patients (24.9%) in the VEN + AZA arm and 28/127 patients (22.0%) with IDH1/IDH2 mutations in the PBO + AZA arm. In the VEN + AZA arm, there were 23 patients (9.4%) with IDH1 mutations and 40 patients (16.3%) with IDH2 mutations; 11 patients (8.7%) had IDH1 mutations and 18 patients (14.2%) had IDH2 mutations in the PBO + AZA arm (Table 9).

For patients in the VEN + AZA arm, a CR + CRh rate of 72.1% (95% CI: 59.2%, 82.9%) with a CR rate of 42.6% and a CRh rate of 29.5% were obtained in patients with IDH1/IDH2 mutations. For patients in the PBO + AZA arm, a CR + CRh rate of 7.1% (95% CI: 0.9%, 23.5%) with a CR rate of 3.6% and a CRh rate of 3.6% were obtained in patients with IDH1/IDH2 mutations. VEN + AZA statistically significantly (p-value < 0.001) improved the percentage of patients who achieved remission (CR + CRh) among patients with IDH1/IDH2 mutations (Table 15).

Overall Survival in IDH1/IDH2 Subgroup

For patients with an IDH1/IDH2 mutation, the median OS was not reached for patients in the VEN + AZA arm (95% CI: 12.2 months, not reached [NR]), and 6.2 months (95% CI: 2.3, 12.7 months) for patients in the PBO + AZA arm (HR = 0.345; p-value < 0.0001) (Figure 7).

Table 15. VIALE-A: CR + CRh by Molecular Marker – IDH1/IDH2 (Efficacy Analysis Set)

	PBO + AZA (N = 28)	VEN 400 mg QD + AZA (N = 61)	p-value[a]
CR + CRh Rate (as best response) - n (%) [95% CI][b]			
CR	1 (3.6) [0.1, 18.3]	26 (42.6) [30.0, 55.9]	
CRh	1 (3.6) [0.1, 18.3]	18 (29.5) [18.5, 42.6]	
CR + CRh	2 (7.1) [0.9, 23.5]	44 (72.1) [59.2, 82.9]	<0.001***
Patients with Best Response of CR + CRh – Mean (SD)			
Median [range]			
Time to First Response (months)			
CR + CRh	2.6 (0.70) 2.6 [2.1-3.1]	1.9 (1.82) 1.0 [0.8-9.6]	
Time to Best Response (months)			
CR + CRh	3.7 (0.93) 3.7 [3.1-4.4]	3.2 (3.53) 1.4 [0.8-17.9]	

Aza = azacitidine; CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; N = sample size; n = number of patients; PBO = placebo; QD = once daily; SD = standard deviation; VEN = venetoclax

a. P-value is from Fisher's exact test.

b. 95% confidence interval is from the exact binomial distribution.

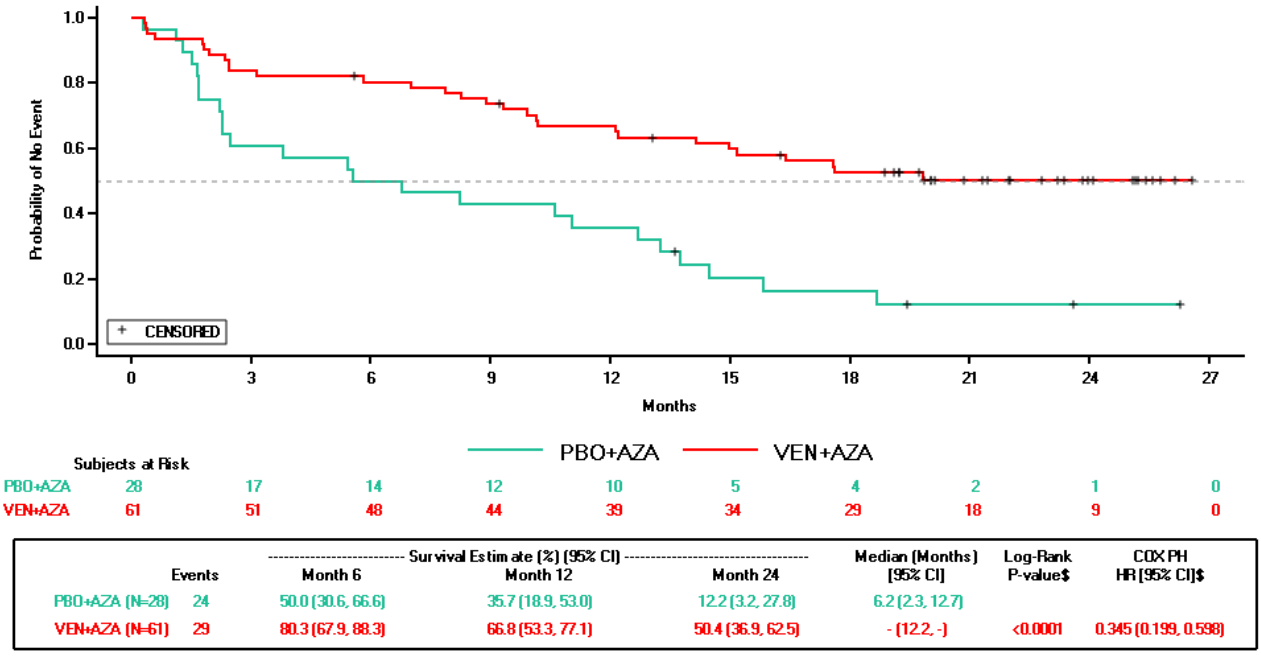
Note: IDH1 and IDH2 mutations were detected by Abbott RealT*ime* IDH1 and Abbott RealT*ime* IDH2 assays, respectively.

Note: ***, **, * at p = 0.001, 0.01, 0.05 levels, respectively.

Note: Data included are subject to a cutoff date of 04 January 2020.

Source: VIALE-A CSR Table 14.2__2.4.2. Source datasets: ADSL, ADRS, and ADTTE.

Figure 7. VIALE-A: Overall Survival by Molecular Marker IDH1/IDH2 (Efficacy Analysis Set)



AZA = azacitidine; CI = confidence interval; HR = hazard ratio; IDH = isocitrate dehydrogenase; N = sample size; NA = not available; PBO = placebo; PH = proportional hazard; VEN = venetoclax

$ Unstratified log-rank test and unstratified Cox model.

Note: IDH1/IDH2 are by CDx method. Data included are subject to a cutoff date of 04 January 2020.

Source: VIALE-A CSR Figure 14.2__11.4.1.1. Source datasets: ADSL and ADTTE.

CR + CRh Rate in FLT3 Subgroup

There were 206 patients in the VEN + AZA arm and 108 patients in the PBO + AZA arm with results from CDx; patients with undetermined or missing values (non-evaluable) were not included in this total. As of the data cutoff date for the interim analysis, there were 29/206 patients (14.1%) with FLT3 mutations in the VEN + AZA arm (11.2% with FLT3-ITD and 3.4% with FLT3-TKD) and 22/108 patients (20.4%) with FLT3 mutations in the PBO + AZA arm (12.0% with FLT3-ITD and 9.3% with FLT3-TKD). There were more patients in the PBO + AZA arm with FLT3-TKD mutations compared to the VEN + AZA arm (Table 9).

For patients in the VEN + AZA arm, a CR + CRh rate of 65.5% (95% CI: 45.7%, 82.1%) with a CR rate of 34.5% and a CRh rate of 31.0% were obtained in patients with FLT3 mutations. For patients in the PBO + AZA arm, a CR + CRh rate of 18.2% (95% CI: 5.2%, 40.3%) with a CR rate of 13.6% and a CRh rate of 4.5% were obtained in patients with FLT3 mutations. VEN + AZA statistically significantly (p-value = 0.001) improved the percentage of patients who achieved remission (CR + CRh) among patients with FLT3 mutations (Table 16).

Overall Survival in FLT3 Subgroup

For patients with a FLT3 mutation, the median OS was 12.7 months (95% CI: 7.3, 23.5 months) for patients in the VEN + AZA arm and 8.6 months (95% CI: 5.9, 14.7 months) for patients in the PBO + AZA arm (HR = 0.664; p-value = 0.2054) (Figure 8).

Table 16. VIALE-A: CR + CRh by Molecular Marker – FLT3 (Efficacy Analysis Set)

	PBO + AZA (N = 22)	VEN 400 mg QD + AZA (N = 29)	p-value[a]
CR + CRh Rate (as best response) - n (%) [95% CI][b]			
CR	3 (13.6) [2.9, 34.9]	10 (34.5) [17.9, 54.3]	
CRh	1 (4.5) [0.1, 22.8]	9 (31.0) [15.3, 50.8]	
CR + CRh	4 (18.2) [5.2, 40.3]	19 (65.5) [45.7, 82.1]	0.001**
Patients with Best Response of CR + CRh – Mean (SD) Median [range]			
Time to First Response (months)			
CR + CRh	2.9 (0.81) 3.2 [1.8-3.6]	1.9 (1.53) 1.0 [0.8-4.8]	
Time to Best Response (months)			
CR + CRh	2.9 (0.81) 3.2 [1.8-3.6]	3.9 (3.36) 4.1 [0.8-13.4]	

Aza = azacitidine; CI = confidence interval; CDx = companion diagnostics; CR = complete remission; CRh = complete remission with partial hematologic recovery; N = sample size; n = number of patients; PBO = placebo; QD = once daily; SD = standard deviation; VEN = venetoclax

a. P-value is from Fisher's exact test.

b. 95% confidence interval is from the exact binomial distribution.

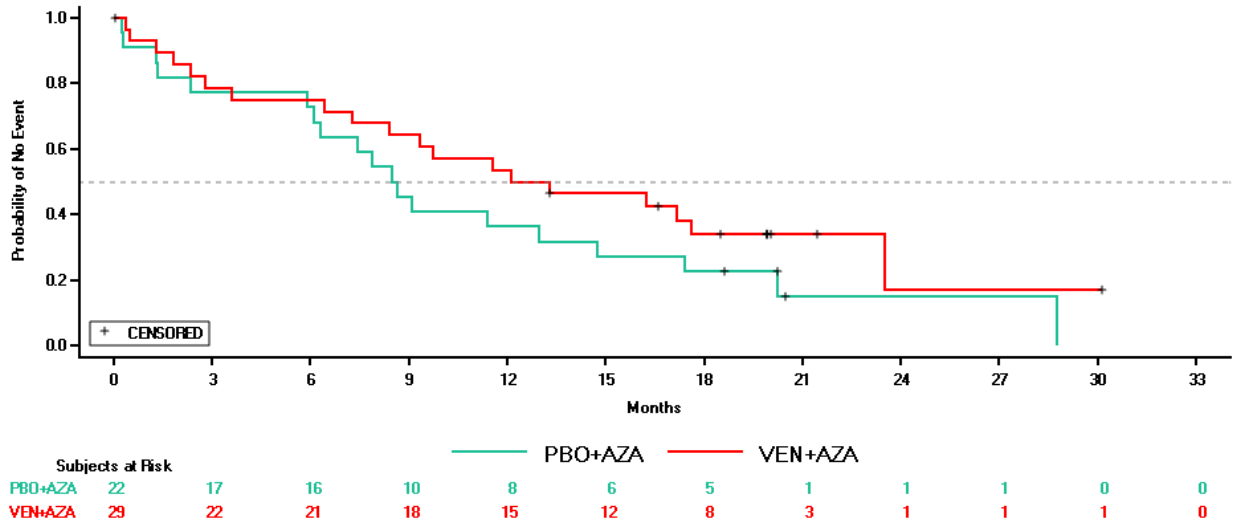
Note: FLT3 mutations were detected by LeukoStrat® CDx FLT3 mutation assay.

Note: ***, **, * at p = 0.001, 0.01, 0.05 levels, respectively.

Note: Data included are subject to a cutoff date of 04 January 2020.

Source: VIALE-A CSR Table 14.2__2.4.2. Source datasets: ADSL, ADRS, and ADTTE.

Figure 8. VIALE-A: Overall Survival by Molecular Marker FLT3 (Efficacy Analysis Set)



	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	Log-Rank P-value$	COX PH HR [95% CI]$
PBO+AZA (N=22)	19	72.7 (49.1, 86.7)	36.4 (17.4, 55.7)	15.2 (3.3, 35.1)	8.6 (5.9, 14.7)		
VEN+AZA (N=29)	19	75.0 (54.6, 87.2)	53.6 (33.8, 69.8)	17.0 (1.7, 46.5)	12.7 (7.3, 23.5)	0.2054	0.664 (0.351, 1.257)

AZA = azacitidine; CI = confidence interval; HR = hazard ratio; FLT3 = FMS-like tyrosine kinase 3; N = sample size; NA = not available; PBO = placebo; PH = proportional hazard; VEN = venetoclax
$ Unstratified log-rank test and unstratified Cox model.
Note: FLT3 mutations were detected by LeukoStrat® CDx FLT3 mutation assay
Note: Data included are subject to a cutoff date of 04 January 2020.
Source: VIALE-A CSR Figure 14.2__11.4.3. Source datasets: ADSL and ADTTE.

The Applicant's Position:

Venetoclax in combination with AZA demonstrated statistically significant improvement in OS, with high composite complete remission rates (CR + CRi) that are rapid and durable compared to the patients in the PBO + AZA arm who were ineligible for intensive therapy. The median OS was longer for patients treated with VEN + AZA (14.7 months) compared to patients treated with PBO + AZA (9.6 months), as demonstrated by stratified HR of 0.662. The OS data represent a 33.8% reduction in the risk of death for patients treated with VEN + AZA. These results represent a substantial improvement in OS for VEN + AZA compared to AZA monotherapy. The reduction in the risk of death in this population of newly diagnosed AML patients who are ineligible for chemotherapy is clinically meaningful.

Response rates for CR + CRh were statistically significantly greater in the VEN + AZA arm compared to the PBO + AZA arm for this AML population with rapid onset of remission. The percentage of patients achieving remission (CR + CRh) by the initiation of Cycle 2 was also statistically significantly higher in the VEN + AZA arm versus the PBO + AZA arm. The observed complete remissions were rapid and reported early in the course of study treatment. The majority of patients treated with VEN + AZA were RBC and platelet transfusion independent while actively receiving treatment compared to patients in the PBO + AZA arm.

Venetoclax combines synergistically with AZA in AML. The remission rates observed with VEN + AZA are substantially higher than AZA monotherapy, which is one of the current standards of care for low-intensity therapies for this population, with clinically meaningful and statistically significant improvement in both OS and remission rates.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of secondary endpoints. We note that the overall survival of the subjects with FLT3 mutation was not statistically significant across arms (HR=0.664; p = 0.2054). Consequently, formal testing in the testing hierarchy was stopped at this endpoint.

This clinical adjudication of CR and CRh responses agreed with the Applicant's assessment of these endpoints.

FDA defines duration of response to be time from response, measured as the time of the associated bone marrow evaluation, to relapse or death. The results presented above by the Applicant define the starting time of response as the date at which the hematology values met the CR criteria within 14 days. Based on the date of the marrow evaluation, 7 patients had the CBC meet CR criteria on day 15 and one patient on day 16. These patients were accepted as CR on the date of the marrow.

The results for CR and CR+CRh using FDA's definition are presented in Table 17.

Table 17: VIALE-A Response Endpoints with Duration of Response per FDA Definition

Parameter	PBO + AZA (N = 145)	VEN + AZA (N = 286)
CR Rate and Duration of Response		
Responders; n/N (%) [95% CI]	26 (17.9) [12.1, 25.2]	105 (36.7) [31.1, 42.6]
Duration of Response (months); median (95% CI)	13.4 (8.7, 17.6)	18.0 (15.3, NR)
CR + CRh Rate and Duration of Response		
Responders; n (%) [95% CI]	33 (22.8) [16.2, 30.5]	185 (64.7) [58.8, 70.2]
Duration of Response (months); median (95% CI)	13.9 (10.4, 15.7)	17.8 (15.3, NR)

Source: Reviewer's analysis based on updated dataset submitted 09/03/2020.

The Applicant specified the Cochran-Mantel-Haenszel (CMH) test to be the analysis method for all response endpoints and the log-rank test to be the analysis method for all time-to-event endpoints; both tests were to be stratified by age (18-<75, ≥75) and cytogenetic risk (intermediate, poor). No specific analyses were specified for analyses of these endpoints in the molecular subsets (IDH1/IDH2-mutated and FLT3-mutated). Consequently, according to the SAP the analyses for endpoints within these subsets should be the CMH and log-rank stratified by age and cytogenetic risk. However, the Applicant analyzed CR+CRh and OS in these subgroups using Fisher's exact test and the unstratified log-rank test, respectively. The analyses implied by the SAP are presented in Table 18 and Table 19.

Table 18: CR+CRh in Molecular Subgroups per SAP-Specified Analysis

Subgroup	Odds Ratio (95% CI)	p-value[1] (2-sided)	Interim Boundary p-value[2]
CR+CRh rate in IDH1/IDH2	25.6 (5.5, 118.7)	<0.0001	0.05
CR+CRh rate in FLT3	NE[3]	NE[3]	0.05

[1]P-value as calculated via the CMH test stratified by age (18-<75, ≥75) and cytogenetic risk (intermediate, poor).
[2]As reported in Table 7.
[3]Not estimable. The stratum of ≥75 years of age and poor risk contains only one patient.

Table 19: OS in Molecular Subgroups per SAP-Specified Analysis

Subgroup	Hazard Ratio (95% CI)	p-value[1] (2-sided)	Interim Boundary p-value[2]
OS in IDH1/IDH2	0.43 (0.24, 0.76)	0.0032	0.0002
OS in FLT3	0.67 (0.35, 1.32)	0.2452	0.0002

[1]P-value as calculated via the log-rank test stratified by age (18-<75, ≥75) and cytogenetic risk (intermediate, poor).
[2]As reported in Table 7.

These estimates are unstable due to small patient numbers within the strata. Indeed, the CMH test cannot be carried out in the FLT3 subgroup since only 1 patient is in the stratum containing patients who are ≥75 years of age with poor risk. In addition, note that using the SAP-specified test for OS in IDH1/IDH2 results in a p-value that does not cross the interim boundary. While such results call into question whether the test should be considered to have formally rejected the null hypothesis, results in these subgroups provide only supportive evidence in any case. Furthermore, the treatment effects observed in these subgroups may not provide useful information beyond the results in the broader ITT population. Consequently, whether one considers these tests to formally reject the null hypothesis or not, they are not likely to provide useful additional information in labeling.

Transfusion independence

Transfusion independence (TI) is determined based on those who were dependent on RBC and/or platelets at baseline and became independent of both RBC and platelets for 56-days or more while on study therapy. As noted in Table 14 provided by the Applicant, in the venetoclax arm, 49% of patients who were transfusion dependent (TD) at baseline became TI on study treatment. Of those who were not TD at baseline, 69% remained TI while on study treatment. This is an improvement over the placebo arm which showed 27% of patients became TI and 42% remained TI.

Dose/Dose Response

The Applicant's Position:
The target dose and regimen for VEN 400 mg QD + AZA in AML patients was supported by the exposure-efficacy and exposure-safety analyses of VEN. The VEN 400 mg QD dose was

approved under accelerated approval and the data from VIALE-A confirms this venetoclax dosing regimen (see Section 3.1 and Section 0).

Regulatory Authorities' Assessment:
Agree with the Applicant's assessment.

Durability of Response

Data and The Applicant's Position:
Duration of responses for patients who achieved CR + CRh and CR are presented below. Duration of CR + CRh and CR responses are defined as the number of days from the date of first response (CR or CRh, as appropriate) per the revised IWG criteria for AML to the earliest evidence of confirmed MR or confirmed PD prior to any posttreatment therapy or death due to disease progression. If a patient did not have above events, data was censored at the last adequate disease assessment on or prior to the earliest posttreatment therapy (if applicable) or data cutoff date.

Overall, the responses with VEN + AZA are durable with duration of remission for all response categories of CR + CRh and CR being longer in the VEN + AZA arm compared to PBO + AZA arm.

Duration of CR + CRh
The median duration of response for CR + CRh was 17.8 months (95% CI: 15.3, NR) in the VEN + AZA arm and 13.9 months (95% CI: 10.4, 15.7) in the PBO + AZA arm (Table 12). For VEN + AZA patients who achieved CR or CRh, the event-free rates at Months 12 and 18 were 63.2% and 48.7%, respectively. In comparison, for PBO + AZA patients who achieved CR or CRh, the event-free rates at Months 12 and 18 were 61.2% and 24.5%, respectively.

The number of patients with events were 79 patients (42.7%) in the VEN + AZA arm and 17 patients (51.5%) in the PBO + AZA arm. There were 5 patients (6.3%) in the VEN + AZA arm and 2 patients (11.8%) in the PBO + AZA arm who died as a result of disease progression.

Duration of Complete Remission (CR)
The median duration of response for CR was 17.5 months (95% CI: 15.3, NR) in the VEN + AZA arm and 13.3 months (95% CI: 8.5, 17.6) in the PBO + AZA arm (Table 12). There were 39 patients (37.1%) in the VEN + AZA arm and 13 patients (50.0%) in the PBO + AZA arm with events. There was 1 patient (2.6%) in the VEN + AZA arm and 1 patient (7.7%) in the PBO + AZA arm who died as a result of disease progression.

Regulatory Authorities' Assessment:
We agree with the Applicant's description of duration of CR+CRh and duration of complete response. See Table 17 above for the duration of CR and CR+CRh based on the date of the bone marrow evaluation instead of the date of hematologic recovery resulting in minor differences in duration of up to 14 days.

Persistence of Effect

The Applicant's Position:
Survival was favorable and response rates were durable for patients with AML treated with VEN in combination with HMAs. Patients sustained long-term benefits with ongoing treatment.

Regulatory Authorities' Assessment:
We agree with the Applicant's description.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:
The Patient Reported Outcomes Measurement Information System (PROMIS) Cancer Fatigue SF-7A assessment and EORTC QLQ-C30 Global Health Status/Quality of Life (GHS/QoL) assessment were ranked secondary endpoints for the VIALE-A study. Patients receiving VEN + AZA showed no clinically meaningful differences in the mean change from baseline in the PROMIS Cancer Fatigue score than patients treated with PBO + AZA (–3.036 vs. –0.796, –2.263 vs. –1.976, –3.377 vs. –0.990, –2.209 vs. –1.745, and –1.644 vs. –1.453 at Cycles 5, 7, 9, 11, and 13, respectively). Patients in the VEN + AZA arm (median: 16.5 months; 95% CI: 9.76, not estimated) experienced a longer time to deterioration (TTD) in quality of life as determined by the EORTC QLQ-C30 GHS/QoL assessment versus patients in the PBO + AZA arm (median: 9.3 months; 95% CI: 4.67, 16.6). The PROMIS Cancer Fatigue SF-7A assessment and the EORTC QLQ-C30 GHS/QoL assessment are also discussed in Section 8.2.6.

Regulatory Authorities' Assessment:
We agree with the Applicant's description. Note that mean change from baseline is difficult to interpret in trials where there is a high rate of dropout due to progression and death. In general, it is not clear whether a treatment effect on this estimand would be clinically meaningful. In addition, the TTD analysis used a threshold of 10 points, which may not represent a clinically meaningful deterioration in GHS/QoL score.

Additional Analyses Conducted on the Individual Trial

Data:
Intermediate Cytogenetic Risk: The CR + CRh rate for patients with intermediate cytogenetic risk was 72.0% in VEN + AZA, with a median OS of 20.8 months. In comparison, the CR + CRh rate was 23.6% for patients in PBO + AZA, with a median OS of 12.4 months. The HR of OS was 0.566 (95% CI: 0.407, 0.786).
Poor Cytogenetic Risk: The CR + CRh rate for patients with poor cytogenetic risk was 51.9% in VEN + AZA, with a median OS of 7.6 months. In comparison, the CR + CRh rate was 21.4% for patients in PBO + AZA, with a median OS of 6.0 months. The HR of OS was 0.775 (95% CI: 0.538, 1.117).
Primary AML: The CR + CRh rate for patients with primary AML was 65.0% in VEN + AZA, with a median OS of 14.1 months. In comparison, the CR + CRh rate was 23.6% for patients in PBO + AZA, with a median OS of 9.6 months. The HR of OS was 0.674 (95% CI: 0.508, 0.895).

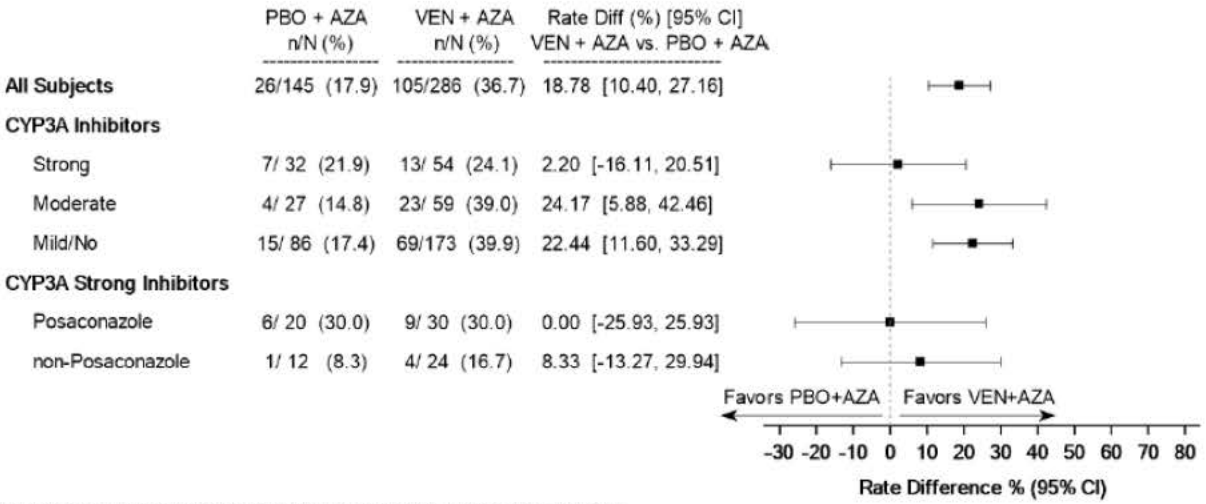
AML with Myelodysplasia-Related Changes (MRC): The CR + CRh rate for patients with AML-MRC was 59.8% in VEN + AZA versus 14.3% for patients in PBO + AZA. The HR of OS was 0.732 (95% CI: 0.484, 1.107).
Secondary AML, including Therapy Related: The CR + CRh rate for patients with secondary AML was 63.9% in VEN + AZA, with a median OS of 16.4 months. In comparison, the CR + CRh rate was 20.0% for patients in PBO + AZA, with a median OS of 10.6 months. The HR of OS was 0.561 (95% CI: 0.346, 0.910).

The Applicant's Position:
AML in elderly patients is a biologically and clinically distinct disease with a diminished response to chemotherapy, low remission rates, as well as short disease-free and overall survival. Higher proportion of unfavorable cytogenetics, higher frequency of antecedent hematologic disorders or prior therapy for previous malignancies, and more frequent expression of the multidrug resistance phenotype accounts for the poor outcomes associated with current therapy. Venetoclax in combination with AZA improved remission rates and OS compared to PBO + AZA for patients with AML in the intermediate or poor risk cytogenetic groups. Venetoclax + AZA also improved the remission rates and OS in patients with primary or secondary AML, as well as remission rates for patients with AML-MRC, compared to treatment with PBO + AZA.

Regulatory Authorities' Assessment:
We agree with the Applicant's description of additional analyses.

In an information request query, the Applicant performed an evaluation of response rates by CYP3A inhibitors, and by posaconazole vs. non-posaconazole for those on strong CYP3A inhibitors. We note that the response rate trends toward inferior response in patients with strong CYP3A inhibitors. However, the dose modification criteria in VIALE-A for patients on strong CYP3A inhibitors required escalation to only 50 mg of venetoclax where the current USPI recommends a dose of 70 mg for patients on posaconazole and 100 mg for patients on other strong CYP3A inhibitors. We note that the current recommendation in the USPI is based on a dedicated DDI study with posaconazole. The efficacy evaluation shown below is an exploratory, post-hoc analysis, and is not designed to fully assess the effect of concomitant CYP3A inhibitors on the efficacy of venetoclax. Patients on strong CYP3A inhibitors tended to have higher rate of poor cytogenetic risk in the venetoclax arm compared to the placebo arm which also may have contributed to the difference. We note that <15% of patients were on posaconazole for this evaluation.

CR rate based on Investigator's Assessment by Concomitant Use of CYP3A inhibitors in VIALE-A (Full Analysis Set Group 2)



Group 2: Enrolled not under original protocol. AZA = Azacitidine. PBO = Placebo. VEN = Venetoclax.
95% CI is exact unconditional confidence limits.
Arrow indicates confidence interval extended more than current range.
Note: Data included are subject to a cutoff date of 04JAN2020.

Source: Applicant's analysis, Response to IR received Sept 4, 2020.

8.1.3. Pivotal Trial to Support Efficacy of Venetoclax and Low Dose Cytarabine – VIALE-C

Trial Design

The Applicant's Description:

Basic Study Design

VIALE-C is an ongoing, randomized, double-blind, placebo-controlled, multicenter Phase 3 study investigating the efficacy and safety of venetoclax in combination with LDAC in patients with treatment-naïve AML ineligible to receive intensive chemotherapy. This study was similar to VIALE-A study design, eligibility criteria, duration of treatment, and objectives evaluated. Patient randomizations in VIALE-C were stratified by AML status (de novo, secondary AML), age (18 to < 75, ≥ 75 years), and region (US, EU, China, Japan, ROW).

Patients were randomized to VEN + LDAC or PBO + LDAC in a 2:1 ratio. Patients were enrolled at the screening visit and had up to 21 days to complete screening procedures. Patients were hospitalized during the venetoclax/placebo dose ramp-up period (each cycle was 28 days in length). Patients could continue their study treatment until documented disease progression per Investigator assessment, unacceptable toxicity, withdrawal of consent, or the patient meets other protocol criteria for discontinuation (whichever occurs first).

Trial Location

VIALE-C was conducted globally in North and South America, Europe, Asia, Africa, and Australia. The number of sites and list of countries where this study randomized patients are provided in Section 8.1.4.

Choice of Control Group

Because AML patients with significant comorbidities and the elderly are often not eligible for intensive chemotherapy treatment, low-intensity treatment options are considered the standard of care for these patients.[21] Currently, LDAC is one of the therapies recommended by the NCCN guidelines[7] for the treatment of AML in patients aged ≥ 60 years, based on performance status and cytogenetics.

This study compared VEN + LDAC to an active control of PBO + LDAC. A discussion for the choice of control group is provided in the section on Dose Selection (below). The choice of control group allowed for a double-blind assessment of the contribution of VEN to the safety and efficacy of the backbone regimen of LDAC.

Diagnostic Criteria

Like VIALE-A, the VIALE-C study enrolled treatment-naïve patients with AML who were ineligible for intensive chemotherapy due to age or comorbidities.

Key Inclusion/Exclusion Criteria

There were only few differences in eligibility criteria between VIALE-A and VIALE-C: VIALE-A

excluded patients with prior exposure to HMAs for MDS, while VIALE-C allowed patients treated with an HMA for this indication; VIALE-A enrolled only patients with an intermediate or poor cytogenetic risk, while VIALE-C also allowed patients with favorable cytogenetic risk. Key inclusion and exclusion criteria for VIALE-C were similar to those of the VIALE-A study. In addition to the criteria noted in the VIALE-A section on inclusion/exclusion criteria:

- Patients were excluded if they had a history of MPN including myelofibrosis, essential thrombocythemia, polycythemia vera, CML with or without BCR-ABL1 translocation and AML with BCR-ABL1 translocation.
- Patients were not eligible for study participation in VIALE-C if they were previously treated with VEN, CAR-T cell therapy, or if they were participating in another research or observational study.

Dose Selection and Study Treatments:

Venetoclax

For VIALE-C, the selected dosage of VEN was based on the results from Study M14-387, an ongoing Phase 1b/2 study of escalating doses of VEN + LDAC (as described in Section 8.1.7). In the dose escalation phase (Phase 1), VEN began on Day 2 to allow PK assessments of LDAC monotherapy of Cycle 1 followed by a ramp-up to continuous daily dosing at the doses of 600 mg for Cohort 1 (8 patients) and 800 mg for Cohort 2 (10 patients). An additional 53 patients were enrolled in Phase 2 at the 600 mg dose.

Low-Dose Cytarabine (LDAC)

LDAC has been a global treatment option for decades and typically dosed either once or twice daily by SC injection to a total daily dose of approximately 20 mg/m^2 for 10 days of a 28-day cycle. The same dosing schedule has been used as a comparator arm in previous trials of AML therapy,[6] and was the regimen used in the preceding Phase 1/2 Study M14-387. Cytarabine was administered at a dose of 20 mg/m^2 SC QD on Days 1 to 10 of each 28-day cycle.

Assignment to Treatment

In VIALE-C, patients were randomized by the IRT system into 2 treatment arms in a 2:1 ratio (VEN + LDAC versus PBO + LDAC). Patient randomization was stratified by AML status (de novo, secondary), age (18 to < 75, ≥ 75 years) and region (US, EU, China, Japan, ROW).

Blinding

AbbVie personnel with direct management of the study sites (with the exception of AbbVie Clinical Drug Supply Management and AbbVie Pharmacovigilance Team), the Investigator, the study site personnel, and the patient remained blinded to each patient's treatment with VEN/PBO. All patients were treated with open-label LDAC. An IDMC reviewed safety and efficacy data in an unblinded fashion and provided recommendations to AbbVie per the IDMC charter.

Dose Modification, Dose Discontinuation

The following dose modifications for VEN were implemented to mitigate the risk of high-grade hematologic AEs and their clinical consequences such as serious infections or deaths:

- After achieving a morphologic leukemia-free bone marrow, in the occurrence of Grade 4 hematologic toxicity, dose interruptions were allowed until count recovery (until ANC ≥ 500 to 1000/µL and platelet count ≥ 25 to 100 × 10^3/µL).
- In case of persistent occurrences of cytopenias (occurring after Day 28 during Cycle 2 and beyond), the duration of VEN/PBO was reduced in 7 days in the following order: from 28 days to 21 days, then from 21 days to 14 days. As a last attempt to manage persistent cytopenias, VEN/PBO dose could be reduced from 600 mg daily × 14 days to 400 mg daily × 14 days.
- Prophylactic anti-infectives for bacterial, viral, and fungal infections were required for ANC of < 500/µL while on study treatment.

Administrative Structure
This study is being conducted globally by AbbVie, Inc (AbbVie). The study utilized an IDMC.

The IDMC reviewed safety and efficacy data for VIALE-C study in an unblinded fashion and provided recommendations to the Sponsors, as per the IDMC charter. A formal interim analysis for safety was performed by the IDMC approximately 3 months after the 20th patient was enrolled and dosed. Subsequently, reviews of unblinded safety data were performed by IDMC every 6 months after the first review of unblinded safety data.

One interim analysis (IA1) for efficacy was performed at the time of the 100th death event and the final efficacy analysis was performed at the time of the 133rd death event. The IDMC oversaw the efficacy analysis of OS. The data from IA1 were reviewed by the IDMC with a recommendation that the study should be continued without modification. The study continued in a blinded fashion until after the final analysis was performed, and a protocol amendment was approved in order to allow the Sponsors to unblind each patient's treatment assignments to be provided to the investigators (Protocol Amendment 5, 29 May 2019).

Procedures and Schedule
Screening tests were performed within 21 days prior to enrollment. During the treatment period, scheduled study visits were based on a 28-day cycle, with Cycle 1 beginning at Day 1. All patients were assessed for disease response at the end of Cycle 1, end of Cycle 4 and every 3 cycles thereafter. For patients with RD at end of Cycle 1, a repeat bone marrow should be performed at the end of Cycle 2 or Cycle 3 to assess for CR or CRi. For any patient with a CRi on two consecutive bone marrows, an additional bone marrow test should be performed to confirm CR once peripheral blood count recovery was noted. Patients were also assessed for disease response upon concern of relapse or disease progression, at the final study visit (regardless of whether the patient completed or prematurely discontinued study treatment), at posttreatment visits, and at survival follow-up visits performed every 2 months after the last study visit.

Dietary Restrictions/Instructions
In this study, the dietary restrictions and instructions for taking VEN/PBO were similar to the

restrictions and instructions in VIALE-A.

Concurrent Medications
Medications that were cautionary in the VEN ramp-up period and during VEN treatment included strong and moderate CYP3A inhibitors, moderate CYP3A inducers, P-gp inhibitors, warfarin and coumarin derivatives, and P-gp substrates. Strong CYP3A inducers were excluded during ramp-up and throughout the study.

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

Patient Completion, Discontinuation, or Withdrawal
Patients continued their study treatment until documented disease progression (per Investigator assessment), unacceptable toxicity, withdrawal of consent, or if the patient met other protocol criteria for discontinuation, as defined in the protocol.

Patients could voluntarily discontinue study drug or withdraw from the study at any time for any reason. The investigator also had the right to discontinue a patient from study drug or withdraw a patient from the study at any time.

Regulatory Authorities' Assessment:
We agree with the Applicant's description of the trial design of the Phase 3, VIALE-C study. We note that reference 6 above (Kantarjian 2010) is likely an incorrect reference as it does not include any patients treated with LDAC. The publication by Kantarjian et al in 2012 (JCO) included a treatment choice control arm that included treatment with LDAC. The Kantarjian 2012 study used the same dose of LDAC (20 mg/m2, once daily for 10 days) as in VIALE-C.

Study Endpoints

The Applicant's Description:
The Sponsors incorporated the Agency's feedback to designate OS as the primary endpoint in the VIALE-C prespecified SAP. Secondary endpoint definitions of composite remission, including CRh, in VIALE-C incorporated the Agency's 16 November 2017 advice provided for the June 2018 sNDA supporting the 21 November 2018 accelerated approval. Primary, key secondary, and exploratory endpoints important to characterizing overall efficacy are presented below.

Primary Endpoint: For VIALE-C, the primary endpoint was OS.

Key Secondary Endpoints: The ranked key secondary endpoints in VIALE-C were as follows:

- CR + CRh Rate
- CR + CRi Rate
- Postbaseline platelet transfusion independence

- CR + CRh rate in IDH1/IDH2 subgroup
- CR rate
- CR + CRh rate by initiation of Cycle 2
- Postbaseline RBC transfusion independence
- MRD and CR + CRh response rate
- MRD and CR + CRi response rate
- PROMIS Cancer Fatigue SF-7a
- EORTC QLQ-C30 GHS/QoL
- OS in IDH1/IDH2 subgroup
- OS in FLT3 subgroup
- CR + CRh rate in FLT3 subgroup
- Event-free survival

Exploratory Endpoints Important to Characterize Overall Efficacy:

- Remaining subscales/items from the EORTC QLQ-C30 and EQ-5D-5L
- Evaluate BCL-2 expression and outcome measures of OS and CR rate

Regulatory Authorities' Assessment:
We agree with the Applicant's description of the study endpoints of the Phase 3, VIALE-C study.

Statistical Analysis Plan and Amendments

The Applicant's Description:
VIALE-C was designed to enroll 210 patients. A total of 133 OS events were required for the final analysis of OS, giving 90% power to detect HR = 0.545 for the comparison of VEN + LDAC versus LDAC alone, with assumed median OS for VEN + LDAC increased from 6 to 11 months. An interim analysis was planned to be conducted when 100 OS events (75% of total planned OS events) occurred. The SAP version 3 was finalized before the interim analysis was conducted and was used for both interim and final analyses.

Analysis Populations
Two analysis populations were defined in the VIALE-C SAP:

- The Full Analysis Set included all patients who were randomized to the study, regardless of whether they received any study treatment, and was the basis of all efficacy analyses (N = 211).
- The Safety Analysis Set included all randomized patients who received any dose of study drug and was the basis for all safety analyses (N = 210).

Efficacy Analysis
The primary analysis of OS included all patients who were randomized to the study. According to the intent-to-treat principle, patients were analyzed according to the treatment arm and strata they were assigned to during the randomization process. The primary efficacy analysis was a comparison of the distribution of OS between the two treatment arms using a log-rank

test stratified by AML status (de novo, secondary) and age (18 to < 75, ≥ 75 years). The HR was estimated using a Cox proportional hazards model stratified by AML status (de novo, secondary) and age (18 to < 75, ≥ 75 years).

The analyses of CR + CRh rate, CR rate, CR + CRh rate by initiation of cycle 2, and postbaseline RBC and platelet transfusion independence rate were based on the CMH test stratified by AML status (de novo, secondary) and age (18 to < 75, ≥ 75 years).

Disease assessments were performed by the investigators per the revised IWG criteria for AML. Definitions for the response criteria, including CRh, are presented in Section 8.1.1 (Efficacy Analysis; VIALE-A).

Safety Analysis
All safety analyses were based on the Safety Analysis Set. Patient data were analyzed according to the treatment actually received. AE summaries were presented by MedDRA SOC and PT. All AEs, Grade 3-4 AEs, treatment-related AEs, SAEs, AEs leading to treatment discontinuation, AEs leading to dose reduction or interruption, AEs leading to death, selected AEs, deaths and causes of death, the number (%) of patients with worse postbaseline laboratory data (Grade 0 at baseline to Grade 1 to 4 postbaseline, Grade 0 to 2 at baseline to Grade 3 to 4 postbaseline or Grade 3 at baseline to Grade 4 postbaseline), the number (%) of patients who met Howard criteria for TLS, and the number (%) of patients who met Hy's law of potential DILI were summarized by treatment arm. All safety summaries included only treatment-emergent events or assessments, i.e., those collected on or after the first date of study drug administration and no later than 30 days after the last date of study drug administration.

Methods for Handling Missing Data
For the analysis of OS, data for patients who were alive at the time of data cutoff were censored at the last date they were known to be alive. For the analyses of response rates, patients without any postbaseline disease assessment were considered non-responders. For the analyses of postbaseline transfusion independence rates, patients who did not receive any study drug were consider postbaseline transfusion dependent.

Statistical Methodology for Multiplicity
The fixed sequence testing procedure was performed with a significance level of 0.05 (two-sided) for the primary endpoint OS and key secondary efficacy endpoints sequentially. If the statistical test was not significant for the primary efficacy endpoint, then statistical significance would not to be declared for any of the secondary endpoints.

Interim Analysis
A pre-specified interim analysis was conducted with a cutoff date of 01 October 2018 when 100 OS events were observed. The Lan-DeMets alpha spending function with OBF boundary was used to determine the efficacy boundary at the interim analysis and to ensure that the overall false positive rate for each primary or key secondary efficacy endpoint was 0.05 (two-sided) or less. The IDMC recommended to continue the study as planned, and the study was

continued in a blinded fashion.

Planned Subgroup Analyses
Subgroup analyses of OS, CR rate, and CR + CRh rate were performed to assess consistency of treatment effect based on Full Analysis Set, with the results displayed in forest plots. Subgroups investigated included demographic factors, baseline characteristics and stratification factors.

SAP Amendments
There have been 3 versions of SAP. All SAP amendments were finalized and submitted to the agency before the interim analysis was conducted and before the study team was unblinded. The SAP version 3 was used for the interim and final analyses for VIALE-C. Key changes to the SAP are noted in the Protocol Amendments section below. Of note, in SAP version 2, the required number of OS events was updated from 101 to 133 death events and the total sample size was increased from approximately 175 to approximately 210 in accordance with Protocol Amendment 3.

Regulatory Authorities' Assessment:
We agree with the Applicant's description of the SAP of the Phase 3, VIALE-C study.

Protocol Amendments

The Applicant's Description:
At the time of the 6-month follow-up analysis for VIALE-C, the original protocol (10 November 2016) had 5 amendments and 4 administrative changes. These changes did not impact the integrity of the study or the interpretation of the results. Key changes for each amendment are listed below:

- Amendment 1 (17 February 2017)
  The main purpose of this amendment was to update the protocol to include AML patients ≥ 18 years of age ineligible to intensive chemotherapy due to comorbidities, and to include female patients of child-bearing potential due to the revised lower age limit. Additionally, the secondary efficacy endpoint of EFS and the VEN dose justification at 600 mg were updated.
- Amendment 2 (06 October 2017)
  The main purposes of this amendment were to clarify that patients who had previously been treated with VEN or were receiving other concurrent investigational agents could not be enrolled into the study, clarify previous MPN exclusion, specifically patients with or without BCR-ABL mutation were not allowed to be enrolled in the study, and clarify exclusion of patients who were hypersensitive to active substances of the study drugs.
- Amendment 3 (22 June 2018)
  The main purposes of this amendment were to update the required number of OS events (from 101 to 133 death events) and the total number of patients to be enrolled (from approximately 175 to approximately 210), to add evaluation of CR + CRh as a secondary endpoint and add evaluation of transfusion independence during any consecutive 56 days

during the study treatment period as an exploratory endpoint.

- Amendment 4 (29 November 2018)
  The main purpose of this amendment was to clarify that the endpoints of transfusion independence rates, MRD response rate, CR + CRh by the initiation of Cycle 2 and OS in molecular subgroups were secondary objectives. Additionally, this amendment clarified that CR rate was to be evaluated.
- Amendment 5 (29 May 2019)
  The purpose of this amendment was to allow the Sponsor to unblind patient treatment assignments following the final analysis results and provide the investigators with this information if requested by them or by the patients, so that a decision could be made with regard to the treatment continuation for patients.

Regulatory Authorities' Assessment:
We agree with the Applicant's description of the protocol amendments of the Phase 3, VIALE-C study. We note that it is possible that Amendment 5 may have impacted the integrity of the study with regards to the updated OS analysis, as patients and investigators could request to be unblinded at this time. We also note that the CSR does not report on how many patients were unblinded and therefore the impact of this practice is unknown.

8.1.4. Study Results – VIALE-C (Study M16-043)

Compliance with Good Clinical Practices

The Applicant's Position:
This study was conducted in accordance with the CFR governing the protection of human patients, IRBs, and the obligations of clinical investigators in accordance with GCP. IEC/IRB reviews, conformance with ICH GCP, and Patient Information and Consent were performed as described for the VIALE-A study (Section 8.1.2).

Audits: Audit certificates are provided in the VIALE-C Interim CSR. The AbbVie Clinical Quality Assurance group or designee conducted audits at 6 investigator sites. No critical audit findings were observed. For all audit findings, appropriate corrective and preventive actions were undertaken.

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

Financial Disclosure

The Applicant's Position:
During the study site initiation process, AbbVie or its designee provided study-specific financial disclosure forms to all principal investigators and sub-investigators for use in disclosing financial interest in, or receipt of, significant payments from AbbVie.

GNE/Roche is not a Sponsor of the covered clinical study, VIALE-C. During the conduct of this study, AbbVie changed its process to include GNE/Roche as a co-development partner on the financial disclosure certification for VIALE-C, and all new VEN studies, regardless of whether GNE/Roche co-sponsored the study or not. Although, GNE/Roche did not co-sponsor VIALE-C, to stay consistent across the VEN program, a new version of the financial disclosure certification that included GNE/Roche as co-development partner was requested from sites prior to submitting this marketing application.

The methods used to minimize bias by AbbVie for VIALE-C were similar to the methods used for the VIALE-A study; these are summarized in Section 8.1.2.

Summary of Findings:
For VIALE-C, 575 out of 575 (100%) principal investigators and sub-investigators provided financial disclosure information. Of the investigators who responded, 4 out of 575 (< 1%) of the investigators were positive for disclosable financial interests.

While GNE/Roche is not a Sponsor of the covered clinical study, VIALE-C, as mentioned above, for consistency purposes, an updated version of the financial disclosure information including GNE/Roche as a co-development partner was requested for active investigators; 414 out of 575 (72.0%) principal investigators and sub-investigators of these sites provided an updated financial disclosure certification. An updated version of the signed financial disclosure was not obtained for 161 members (3 principal investigators and 158 sub-investigators).

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

Patient Disposition

The Applicant's Position:
A total of 211 patients were randomized at 76 sites across 20 countries, including the US (19 patients randomized to 4 sites). The Full Analysis Set included the 211 randomized patients: 68 patients in PBO + LDAC and 143 patients in VEN + LDAC. The Safety Analysis Set was comprised of 210 patients who received at least 1 dose of study treatment: 68 patients in PBO + LDAC and 142 patients in VEN + LDAC.

VIALE-C had 2 data cutoff dates: a primary cutoff (15 February 2019) and a 6-month follow-up cutoff (15 August 2019). This Multi-disciplinary Review and Evaluation presents efficacy data from the primary analysis (data cut-off 15 February 2019) as well as a 6-month follow-up data cut-off (15 August 2019). Safety is presented for patients through the 6-month follow-up.

At the data cutoff date for the primary analysis (15 February 2019), a total of 166 patients (78.7%) discontinued VEN/PBO treatment (105 patients [73.4%] in VEN + LDAC and 61 patients [89.7%] in PBO + LDAC).

At the data cutoff date for the 6-month follow-up (15 August 2019), a total of 180 patients (85.3%) discontinued venetoclax/placebo treatment (117 patients [81.8%] in VEN + LDAC and 63 patients [92.6%] in PBO + LDAC). There were 159 patients (75.3%) who had discontinued the study (103 patients [72%] in VEN + LDAC and 56 patients [82.3%] in PBO + LDAC). Of the 210 patients receiving study treatment during this trial, 99 patients (69.7%) in VEN + LDAC and 54 patients (79.4%) in PBO + LDAC died.

Trial Locations

The trial locations for VIALE-C included 76 sites in Australia, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Greece, Hungary, Japan, New Zealand, Norway, Russia, South Africa, South Korea, Spain, Taiwan, United Kingdom, and the United States.

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

Protocol Violations/Deviations

The Applicant's Position:
Protocol deviations were defined in accordance with the ICH guidelines and were defined similarly to the VIALE-A study.

As of the data cut off for the primary analysis (data cut-off 15 February 2019), 45 patients (31.5%) in the VEN + LDAC arm and 18 patients (26.5%) in the PBO + LDAC arm had protocol deviations. These deviations were not considered to have affected the interpretation of the study results or conclusions. The types of deviations were as follows:

- 46 protocol deviations (reported in 41 patients) of incorrect dose in patients who received a strong CYP3A, moderate CYP3A, or P-gp inhibitor without modifying the dose of venetoclax/placebo as instructed in the protocol.
- 9 protocol deviations (reported in 8 patients) of incorrect dose in patients who received study treatment at the wrong time or at the incorrect dose level.
- 3 protocol deviations (reported in 3 patients) of wrong treatment due to incorrect kit dispensation at the site:
  - 1 patient received kit with PBO instead of VEN for 1 cycle; once identified, the correct kit was dispensed with original treatment assignment.
  - 1 patient randomized to VEN arm received VEN from a wrong kit number; however, the patient received the correct treatment.
  - 1 patient received kit with VEN instead of PBO for 1 cycle.
- 1 protocol deviation due to dosing non-compliance (patient was below the treatment compliance specified by protocol).
- 24 protocol deviations (reported in 23 patients) due to non-compliant protocol procedures.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. Protocol deviations were relatively balanced between arms, and the deviations were unlikely to bias the study in favor of the study drug.

Therefore, all patients, including those with important protocol deviations, were included in our analysis of efficacy endpoints.

Table of Demographic Characteristics

Data:

Table 20. VIALE-C: Demographic Characteristics (Full Analysis Set)

Demographic Parameters n (%)	PBO + LDAC (N = 68)	VEN 600 mg QD + LDAC (N = 143)
Gender		
Male	39 (57.4)	78 (54.5)
Female	29 (42.6)	65 (45.5)
Age		
Mean years (SD)	74.3 (8.63)	75.1 (8.09)
Median (years)	76.0	76.0
Min, max (years)	41.0, 88.0	36.0, 93.0
Age Category		
18 to < 65 years	9 (13.2)	11 (7.7)
65 to < 75 years	19 (27.9)	50 (35.0)
≥ 75 years	40 (58.8)	82 (57.3)
Race		
White	47 (69.1)	102 (71.3)
Black or African American	1 (1.5)	2 (1.4)
Asian	20 (29.4)	39 (27.3)
Region		
United States	6 (8.8)	13 (9.1)
Rest of the World*	62 (91.2)	130 (90.9)

LDAC = low-dose cytarabine; max = maximum; min = minimum; N = sample size; n = number of patients; PBO = placebo; SD = standard deviation; VEN = venetoclax

* Rest of the World includes sites in Australia, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Greece, Hungary, Japan, New Zealand, Norway, Russia, South Africa, South Korea, Spain, Taiwan, and the United Kingdom.

Source: VIALE-C CSR Table 14.1__1.5.1 (Primary analysis). Source dataset: ADSL.

The Applicant's Position:

Overall, patients were predominantly male (117 patients [55.5%]) and white (149 patients [70.6%]). In the overall patient population, patients were elderly (median age: 76.0 years); the majority (≥ 57.8% patients) were aged ≥ 75 years; and > 90% of patients were > 65 years of age. The VEN + LDAC arm had a lower proportion of patients aged 18 to < 65 years and, consequently, a higher proportion of elderly patients aged ≥ 65 years, compared to PBO + LDAC arm (Table 19).

Regulatory Authorities' Assessment:

We agree with the Applicant's assessment. We again note that Black or African American patients are significantly underrepresented compared to the population of the US.

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

Data:

Table 21. VIALE-C: Summary of Baseline Disease Characteristics (Full Analysis Set)

Baseline Disease Characteristics n (%)	PBO + LDAC (N = 68)	VEN 600 mg QD + LDAC (N = 143)
ECOG Performance Status		
0	11 (16.2)	22 (15.4)
1	23 (33.8)	52 (36.4)
2	25 (36.8)	63 (44.1)
3	9 (13.2)	6 (4.2)
Type of AML (from EDC)		
De novo AML	45 (66.2)	85 (59.4)
Secondary AML	23 (33.8)	58 (40.6)
AML with Myelodysplasia-Related Changes (AML-MRC)		
Yes	27 (39.7)	57 (39.9)
No	41 (60.3)	86 (60.1)
Cytogenetics (from EDC) [a]		
Favorable	3 (4.5)	1 (0.7)
Intermediate	43 (65.2)	90 (65.2)
Poor	20 (30.3)	47 (34.1)
Missing	2	5
Prior HMA Used		
Yes	14 (20.6)	28 (19.6)
No	54 (79.4)	115 (80.4)
Antecedent Hematologic History of MDS		
Yes	17 (25.0)	47 (32.9)
No	51 (75.0)	96 (67.1)
Mutation Analyses Detected – n/N[b] (%)		
IDH1 and/or IDH2	12/52 (23.1)	21/112 (18.8)
IDH1 R132X	5 (9.6)	11 (9.8)
IDH2 R140X	8 (15.4)	9 (8.0)
IDH2 R172X	0	3 (2.7)
FLT3	9/52 (17.3)	20/112 (17.9)
NPM1	7/52 (13.5)	18/112 (16.1)
TP53	9/52 (17.3)	22/112 (19.6)

AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; EDC = Electronic Data Capture; FLT3 = FMS-like tyrosine kinase; HMA = hypomethylating agent; IDH = isocitrate dehydrogenase; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; N = sample size; n = number of patients; NPM = nucleophosmin; PBO = placebo; QD = once daily; RBC = red blood cell; TP = tumor protein; VEN = venetoclax

a. Per the 2016 National Comprehensive Cancer Network (NCCN) Guidelines.

b: Number of evaluable BMA specimens received at baseline with mutations detected by MyAML® assay

Note: Data included are subject to a cutoff date of 15 February 2019.

Source: VIALE-C CSR Table 14.1__1.5.1 (Primary analysis). Source dataset: ADSL.

The Applicant's Position:

Baseline disease characteristics are presented in Table 20. ECOG performance status ranged from 0 to 3 and ECOG performance status of 2 was the most frequent in both arms. There were also more patients with secondary AML in the VEN + LDAC arm (40.6%) compared to the PBO + LDAC arm (33.8%); more patients had primary AML in the PBO + LDAC arm (66.2%) compared to the VEN + LDAC arm (59.4%). The majority of patients in the VEN + LDAC and PBO + LDAC arms did not use a prior HMA (115 [80.4%] patients and 54 [79.4%] patients, respectively), and more

patients in the VEN + LDAC arm (32.9%) had antecedent hematologic history of MDS compared to the PBO + LDAC arm (25.0%). The majority of patients (65.2%) had intermediate cytogenetic risk, and 32.8% had poor cytogenetic risk. The VEN + LDAC arm had a slightly higher percentage of patients with poor cytogenetic risk compared to the PBO + LDAC arm (34.1% vs 30.3%, respectively), while a favorable cytogenetic risk was reported in a lower percentage of patients in the VEN + LDAC arm versus the PBO + LDAC arm (0.7% vs 4.5%, respectively). Overall, IDH1/IDH2, FLT3, NPM1, and tumor protein p53 (TP53) mutations were identified in 33 (20.1%), 29 (17.7%), 25 (15.2%), and 31 (18.9%) patients, respectively.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. Notably, VIALE-C allowed enrollment of patients with favorable risk cytogenetics which was not allowed in VIALE-A. Relatively few patients with favorable risk cytogenetics were enrolled, and it was slightly skewed toward the PBO+LDAC arm, but only 3 patients were enrolled vs. 1 patient in the VEN+LDAC arm. This should not influence the overall results. VIALE-C also allowed enrollment of patients who received prior HMAs for antecedent MDS, which was balanced between arms.

Patients were enrolled using the modified Ferrara criteria which provided objective criteria to determine if patients were ineligible for intensive chemotherapy. The criteria were 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.

In the venetoclax arm, 57% were ≥75 years old, and of those patients, 48% had at least one additional comorbidity. In the placebo arm, 59% were ≥75 years old, and 52% had at least one additional comorbidity. For those <75 years old, 53% in the venetoclax arm and 72% in the placebo arm had only one comorbidity. Of those who were <75 years, 80% had ECOG score of 2-3, but may have had more than one comorbidity.

Transfusion independence is determined by those who were dependent on RBC and/or platelets at baseline. In VIALE-C, 111 (78%) in the venetoclax arm and 55 (81%) in the placebo arm were transfusion dependent at baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:
Treatment Compliance: Compliance was monitored and documented by the study coordinator on the appropriate form. The study coordinator questioned the patient regarding adherence to the dosing regimen, recorded the number of tablets and/or bottles returned and the date returned, and determined treatment compliance before dispensing new study drug to the patient. Some patients did not take the study drug within 30 minutes of completing a meal as specified in the protocol; however, these samples are not expected to have impacted the study outcome or interpretation of the study results or conclusions.

Concomitant Medications: Overall, the proportion of patients who required concomitant medication was similar in both treatment arms. Differences in concomitant medication use were not deemed large enough to impact any efficacy or safety outcomes in either study.

The most common concomitant medications taken by ≥ 20% of patients overall were furosemide (44.1%), paracetamol (43.6%), potassium (41.2%), ondansetron (34.1%), meropenem (33.2%), levofloxacin (32.7%), pip/tazo (31.8%), metoclopramide (28.4%), aciclovir (26.5%), omeprazole (23.2%), sodium chloride and valaciclovir (22.3%, each), Bactrim (21.8%), and filgrastim (20.4%).

Per protocol, to mitigate the potential risk of TLS, all patients were to receive TLS prophylaxis during the study, which included any uric acid reducing agents and/or hydration. Prior or concomitant TLS prophylaxis agents or hydration elements were provided to 208 patients (98.6%): 142 patients (99.3%) in VEN + LDAC and 66 patients (97.1%) in PBO + LDAC. TLS prophylaxis agents were provided to 201 patients (95.3%) overall. The most common agents were allopurinol (72.5%), febuxostat (15.6%), and rasburicase (10.0%).

Per protocol, anti-infective prophylaxis for bacterial, viral and fungal infections were required for all patients with ANC of < 500/µL. Institutional infectious organisms and their drug resistance patterns were to be considered and the choice of these agents were to be primarily based on regional guidelines or institutional standards. In VIALE-C, 96 patients (67.1%) in VEN + LDAC and 42 patients (61.8%) in PBO + LDAC received anti-infective prophylaxis agents while receiving study treatment.

Rescue Medication: Not relevant to the product and disease under study.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. In VIALE-C, 17 patients (12%) in VEN+LDAC and 6 patients (9%) in PBO+LDAC received posaconazole at any time during the treatment period. Posaconazole use appears to be less frequent than in the VIALE-A study but balanced between arms. See Additional Analyses below for an evaluation of response rates by patients who received posaconazole and other strong CYP3A inhibitors.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
Two-sided p-value is presented in all efficacy results.

Table 22. VIALE-C: Analysis of Overall Survival (Full Analysis Set)

	PBO + LDAC (N = 68)	VEN 600 mg QD + LDAC (N = 143)
Events (deaths) - n (%)	47 (69.1%)	86 (60.1%)
Duration of Overall Survival (months)		
25th (95% CI)	1.7 (1.0, 3.0)	2.8 (1.8, 4.1)
Median (95% CI)	4.1 (3.1, 8.8)	7.2 (5.6,10.1)
75th (95% CI)	10.2 (8.8, NR)	NR (11.2, NR)
6-Month Survival Estimate (95% CI)	45.8% (33.4%, 57.3%)	55.4% (46.4%, 63.4%)
12-Month Survival Estimate (95% CI)	24.4% (14.1%, 36.2%)	33.5% (24.8%, 42.5%)
24-Month Survival Estimate (95% CI)	NA	NA
Treatment Comparison (Stratified[a])	**VEN + LDAC vs. PBO + LDAC**	
p-value from Log-rank Test	0.114	
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)	0.749 (0.524, 1.071)	
p-value	0.114	

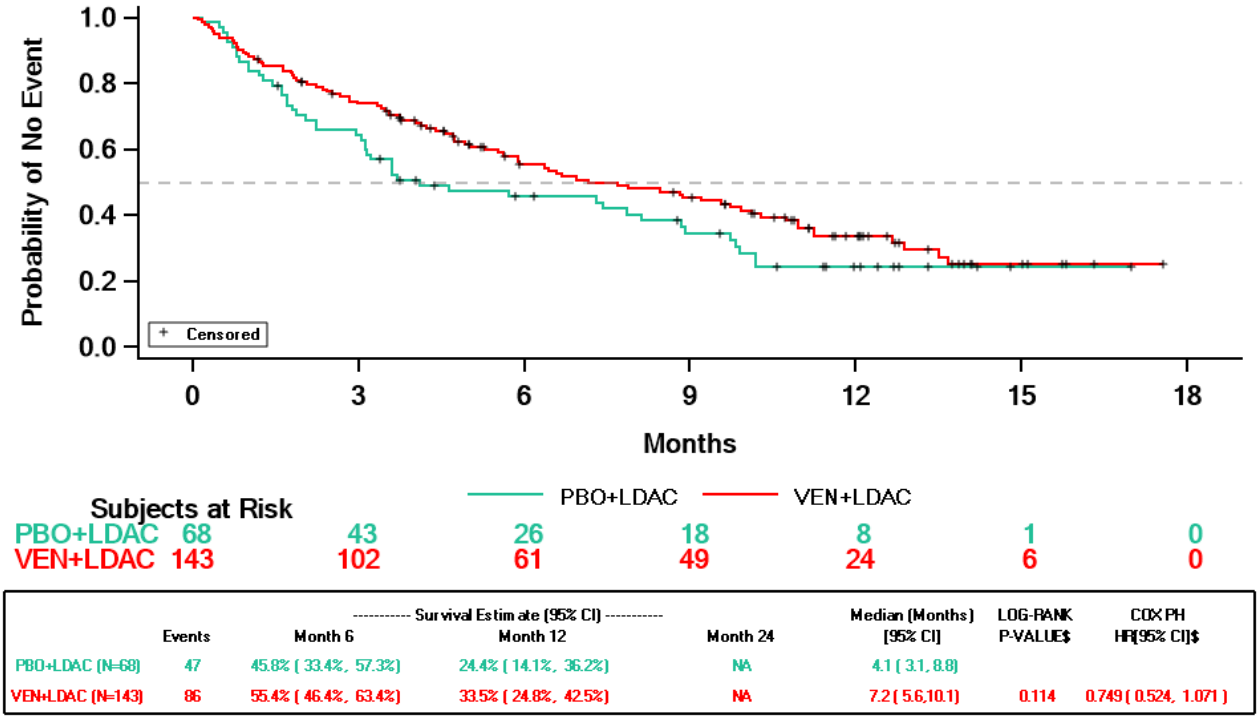
AML = acute myeloid leukemia; CI = confidence interval; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LDAC = low-dose cytarabine; N = sample size; n = number of patients; NA = not available; NR = not reached; PBO = placebo; QD = once daily; VEN = venetoclax

a. Stratified by AML status (de novo, secondary) and age (18 to < 75, ≥ 75) from IVRS/IWRS.

Note: Data included are subject to a cutoff date of 15 February 2019.

Source: VIALE-C CSR Table 14.2__1.1 (Primary Analysis). Source datasets: ADSL and ADTTE.

Figure 9. VIALE-C: Analysis of Overall Survival (Full Analysis Set)



IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LDAC = low-dose cytarabine; PBO = placebo; VEN = venetoclax

$ Stratified by AML status (de novo, secondary) and age (18 to < 75, ≥ 75) from IVRS/IWRS.

Note: Data included are subject to a cutoff date of 15 February 2019.

Source: VIALE-C CSR Figure 14.2__1.1 (Primary Analysis). Source datasets: ADSL and ADTTE.

The Applicant's Position:
For VIALE-C, at data cutoff (15 February 2019; primary analysis), VEN + LDAC reduced the risk of death in newly-diagnosed patients with AML ineligible for chemotherapy by 25% (HR = 0.749; p-value =0.114 [stratified log-rank test]), although the primary endpoint was not statistically significant.

The median OS in the VEN + LDAC arm was 7.2 months, compared to 4.1 months in the PBO + LDAC arm (Table 21; Figure 10). At primary analysis of OS, the median duration of follow-up for patients in both arms was 12.0 months (95% CI: 10.6, 12.8 months).

With additional 6 months of follow-up (15 August 2019), there was an improvement in median OS for VEN + LDAC arm, now with a reduction of 30% (HR = 0.704; p-value =0.041 [stratified log-rank test]) in the risk of death. The median OS was 8.4 months in VEN + LDAC arm, compared to 4.1 months in PBO + LDAC arm. The Kaplan-Meier plot for OS showed separation of curves in favor of the VEN + LDAC arm beginning around 1 month; the separation was maintained over time. At this analysis, the median duration of follow-up for patients in VEN + LDAC arm was 17.5 months (range: 0.1 to 23.5) and 17.7 months (range: 0.2 to 20.8) for patients in PBO + LDAC arm.

Sensitivity and Supportive Analyses
Data:
A stepwise multivariate Cox regression analysis was performed based on the primary analysis datasets to identify pretreatment factors associated with survival. Baseline factors included in the stepwise variable selection were treatment arm, age, sex, AML status, bone marrow blast count, ECOG performance score, cytogenetic risk, prior HMA use, geographic region, FLT3 mutation status, IDH mutation status, and NPM1 mutation status. TP53 mutation status was not included because it was identified to be highly correlated with poor cytogenetic risk in the observed data. Based on the stepwise selection, 5 covariates (treatment arm, age, AML status, ECOG performance score, and cytogenetic risk) were identified to be significantly correlated with OS.

The covariate-adjusted HR (95% CI) was 0.671 (0.467, 0.964) with a p-value = 0.031, demonstrating an important treatment effect for the VEN + LDAC arm as compared to the PBO + LDAC arm (Table 22). The same sensitivity analysis was also done for the 6-month follow-up data (cutoff date of 15 August 2019); the results were consistent with the ones observed in the primary analyses, now with a covariate-adjusted HR of 0.647 (95% CI: 0.461, 0.909) and a p-value = 0.012.

Table 23. VIALE-C: Multivariate Analysis of Overall Survival Including Identified Baseline Demographics and Disease Characteristics as Covariates (Full Analysis Set)

Cox Regression Analysis Using Stepwise Selection			
Covariate	Adjusted HR	95% CI	p-value
Arm (VEN + LDAC vs PBO + LDAC)	0.671	0.467, 0.964	0.031
Age group (< 75 vs ≥ 75 years)	0.555	0.368, 0.838	0.005
AML status (de novo vs secondary)	0.591	0.412, 0.847	0.004
Baseline ECOG (< 2 vs ≥ 2)	0.479	0.326, 0.703	< 0.001
Cytogenetics risk (intermediate vs poor)	0.570	0.395, 0.822	0.003

AML = acute myeloid leukemia; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; HR = hazard ratio; LDAC = low-dose cytarabine; PBO = placebo; VEN = venetoclax; vs = versus

Note: Baseline factors included in the stepwise variable selection were treatment arm, age, AML status, baseline bone marrow blast count, baseline ECOG score, cytogenetics risk, sex, prior hypomethylating agent use, region, FLT3 mutation status, IDH mutation status, and NPM1 mutation status. Age and AML status were from EDC. TP53 mutation status was not included because it was identified to be highly correlated with the cytogenetic risk in the observed data.

Note: Data included are subject to a cutoff date of 15 February 2019.

Source: VIALE-C CSR Table 14.2__1.4.1 (Primary analysis). Source datasets: ADSL and ADTTE.

The Applicant's Position:

Prolonged overall survival in VEN + LDAC arm is demonstrated based on the sensitivity analyses by including identified baseline demographics and disease characteristics as covariates. Greater OS in VEN + LDAC arm compared to the PBO + LDAC arm is demonstrated across the sensitivity analyses (including analysis with additional 6 months follow up data) consistent with the primary analysis.

Regulatory Authorities' Assessment:

We agree with the Applicant's assessment of the primary efficacy results. We note that the additional 6 months follow-up analysis was not planned and specified in the SAP, VIALE-C study. The results of the sensitivity analysis should be interpreted with caution. In general, data-driven stepwise model selection is fraught with a variety of issues, including low probability of choosing the correct model, underestimated standard errors, and biased estimates. In addition, including the chosen baseline characteristics as covariates rather than stratification factors in the Cox model makes the strong assumption of a common baseline hazard, which may not be met.

We also note that the above OS results are not consistent with the CR results provided below. To investigate this further, we plan to study the difference in OR among patients with CR vs. No-CR across treatment arms.

Association Between OS and CR:

During our analysis of the study endpoints, we found that the primary endpoint OS was not significantly different between the treatment arms, though OS was numerically higher in the VEN+LDAC arm. We note that the response-based secondary endpoints (e.g., CR, CR+CRh) were numerically higher in the VEN-LDAC arm, with large magnitude. To investigate this further, we used Cox regression analysis to study the association between OS and CR. We proposed to

study the difference in OS among patients with observed CR vs. No CR across treatment arms.

In this exploratory analysis, the OS of patients in the VEN+LDAC arm with observed CR was 81% higher as compared to patients with No-CR (HR (95% CI) = 0.19 (0.09,0.37)) (Table 23)). No association was found between OS and CR within the PBO+LDAC arm. We note that the number of responders in this arm is small (n=5).

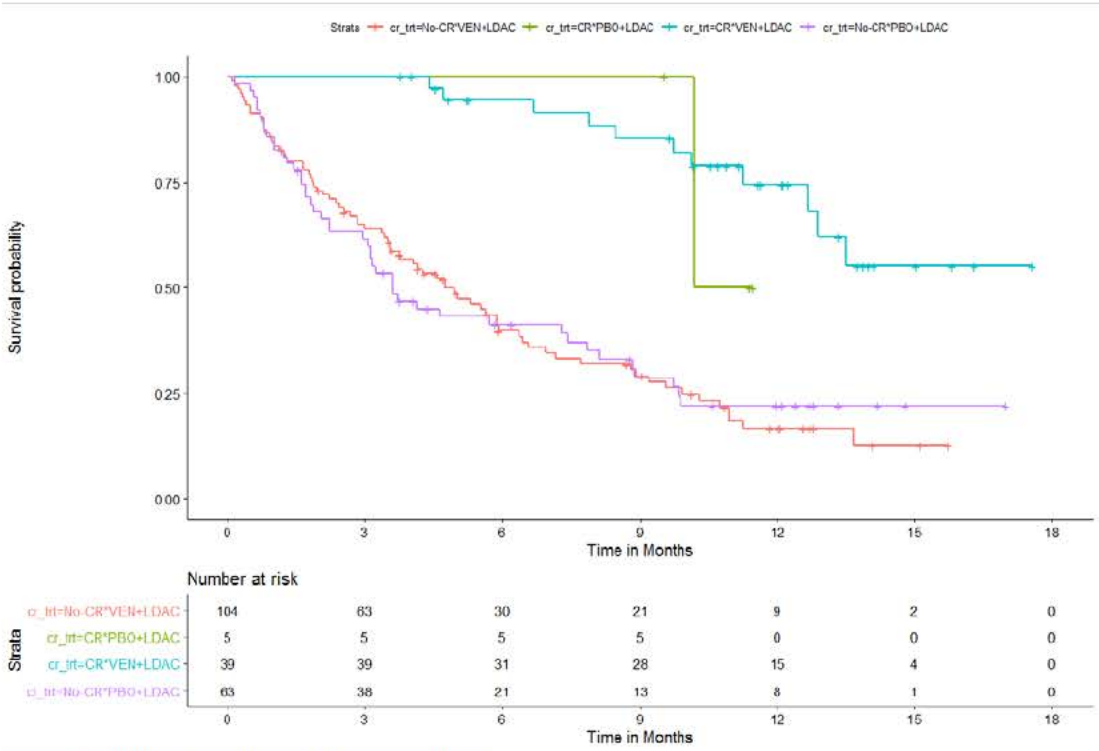
The OS Kaplan-Meier curves across CR and treatment arms are provided in Figure 11..

Table 24: VIALE-C: Association between OS and CR using Cox regression model

	Events	Median OS (95% CI)	HR (95% CI)
No-CR*VEN+LDAC (n=104)	75 (72%)	4.74 (3.55,5.92)	Ref
CR*VEN+LDAC (n=39)	11 (28%)	NA (12.66,NA)	0.19 (0.09,0.37)
No-CR*PBO+LDAC (n=63)	45 (71%)	3.62 (2.24,7.43)	0.98 (0.67,1.42)
CR*PBO+LDAC (n=5)	2 (40%)	10.2 (10.2,NA)	0.26 (0.06,1.07)

Source: Reviewer's analysis using ADSL and ADTTE

Figure 10: VIALE-C: Analysis of OS across CR and treatment arm



Source: Reviewer's analysis using ADSL and ADTTE

Note that these analyses do not adjust for the fact that CR is a post-randomization event. As the number of responders was small, the usual methods to account for such a phenomenon (e.g., propensity score methods) could not be employed credibly.

Data Quality and Integrity

The Applicant's Position:
The Data Quality and Integrity information for VIALE-C was similar to that for the VIALE-A study (as summarized in Section 8.1.2).

Regulatory Authorities' Assessment:
We agree with the Applicant's description of data quality and integrity, VIALE-C study.

Efficacy Results – Secondary and other relevant endpoints

Data:
Table 24 presents data from the key ranked secondary endpoints in VIALE-C. These endpoints are described in detail in the following sections. Data for endpoints not presented below (including CR + CRi rates, EFS, and MRD) are provided in the VIALE-C CSR. The primary analysis of all response-related endpoints is based on the investigator assessment. Two-sided p-value is presented in all efficacy results.

Table 25. VIALE-C: Summary of Key Ranked Secondary Efficacy Parameters – Primary Analysis and 6-month Follow-Up Analysis

Parameter	PBO + LDAC (N = 68)	VEN + LDAC (N = 143)
CR + CRh Rate		
Primary Analysis		
Responders; n (%) [95% CI]	10 (14.7) [7.3, 25.4]	67 (46.9) [38.5, 55.4]
p-value	p < 0.001[a]	
Duration of Response (months); median (95% CI)	6.2 (1.1, -)	11.1 (5.5, -)
6-Month Follow-Up		
Responders; n (%) [95% CI]	10 (14.7) [7.3, 25.4]	69 (48.3) [39.8, 56.8]
p-value	p < 0.001[a]	
Duration of Response (months); median (95% CI)	8.3 (1.1, -)	11.7 (6.1, -)
CR + CRh by the Initiation of Cycle 2		
Primary Analysis		
Responders; n (%) [95% CI]	3 (4.4) [0.9, 12.4]	44 (30.8) [23.3, 39.0]
p-value	p < 0.001[a]	
6-Month Follow-Up		
Responders; n (%) [95% CI]	3 (4.4) [0.9, 12.4]	44 (30.8) [23.3, 39.0]
p-value	p < 0.001[a]	
CR Rate		
Primary Analysis		
Responders; n (%) [95% CI]	5 (7.4) [2.4, 16.3]	39 (27.3) [20.2, 35.3]
p-value	p < 0.001[a]	
Duration of Response (months); median (95% CI)	8.3 (3.1, 8.3)	11.1 (5.9, -)
6-Month Follow-Up		
Responders; n (%) [95% CI]	5 (7.4) [2.4, 16.3]	40 (28.0) [20.8, 36.1]
p-value	p < 0.001[a]	
Duration of Response (months); median (95% CI)	8.3 (2.8, -)	17.1 (8.2, -)
Postbaseline RBC Transfusion Independence		
Primary Analysis		
Responders; n (%) [95% CI]	12 (17.6%) [9.5%, 28.8%]	58 (40.6%) [32.4%, 49.1%]
p-value	p = 0.001[a]	
6-Month Follow-Up		
Responders; n (%) [95% CI]	13 (19.1%) [10.6%, 30.5%]	62 (43.4%) [35.1%, 51.9%]
p-value	p < 0.001[a]	
Postbaseline Platelet Transfusion Independence		
Primary Analysis		
Responders; n (%) [95% CI]	22 (32.4%) [21.5%, 44.8%]	68 (47.6%) [39.1%, 56.1%]
p-value	p = 0.040[a]	
6-Month Follow-Up		
Responders; n (%) [95% CI]	22 (32.4%) [21.5%, 44.8%]	70 (49.0%) [40.5%, 57.4%]
p-value	p = 0.024[a]	

CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; LDAC = low-dose cytarabine; MRD = minimal residual disease; N = sample size; n = number of patients; PBO = placebo; RBC = red blood cell; VEN = venetoclax

a. p-value is from Cochran-Mantel-Haenszel test stratified by age (18 - < 75, ≥ 75) and AML status (de novo, secondary) from IVRS/IWRS. Because statistical significance was not met for the primary objective in VIALE-C, statistical significance cannot be declared for any of the secondary efficacy endpoints. Therefore, these p-values are only descriptive in nature.

Note: Data included are subject to a cutoff date of 15 February 2019 for Primary Analysis and 15 August 2019 for the 6-Month Follow-Up Analysis.

Sources: VIALE-C CSR Tables 14.2__2.2, 14.2__2.2A, 14.2__3.2.1, 14.2__3.2.1A, 14.2__4.1, and 14.2__4.1A. Source datasets: ADSL, ADRS, and ADTTE (for Primary Analysis and 6-Month Follow-Up Analysis).

The Applicant's Position:

CR + CRh

At the primary analysis (15 February 2019), the remission rate (CR + CRh) for patients in the VEN + LDAC arm was greater than that of patients in the PBO + LDAC arm (46.9% [95% CI; 38.5, 55.4] vs 14.7% [95% CI; 7.3, 25.4], p-value from CMH test < 0.001) (Table 25). The median time to first remission (CR + CRh) was 1.0 month (range: 0.7 to 5.8 months) in the VEN + LDAC arm compared to 2.8 months (range: 0.9 to 6.5 months) in the PBO + LDAC arm.

At the time of the 6-month follow-up data cut-off (15 August 2019), the remission rate (CR + CRh) for patients in the VEN + LDAC arm was also greater than that of patients in the PBO + LDAC arm (48.3% [95% CI; 39.8, 56.8] vs 14.7% [95% CI; 7.3, 25.4], p-value from CMH test < 0.001) (Table 24). The median time to first remission (CR + CRh) was 1.0 months (range: 0.7 to 16.3 months) in the VEN + LDAC arm compared to 2.8 months (range: 0.9 to 6.5 months) in the PBO + LDAC arm.

CR + CRh by the Initiation of Cycle 2

Venetoclax in combination with LDAC also improved early remission at the primary analysis; CR + CRh by initiation of Cycle 2 was greater for patients in the VEN + LDAC arm compared to patients in the PBO + LDAC arm (30.8% VEN + LDAC arm vs 4.4% PBO + LDAC arm; p-value < 0.001) (Table 25). This improvement was maintained at the 6-month follow-up analysis (Table 24).

CR Rate

The CR rate for patients in the VEN + LDAC arm was 27.3% (95% CI: 20.2%, 35.3%) compared to a CR rate of 7.4% (95% CI: 2.4%, 16.3%) for patients in the PBO + LDAC arm (p-value < 0.001). Median time to best response of CR rate was 1.3 months (range: 0.9 to 5.9 months) in VEN + LDAC and 3.7 months (range: 0.9 to 9.2 months) in PBO + LDAC (Table 25). At the 6-month follow-up analysis, the CR rate for patients in VEN + LDAC was 28.0% (95% CI: 20.8%, 36.1%) compared to 7.4% (95% CI: 2.4%, 16.3%) for patients in PBO + LDAC (Table 24).

Table 26. VIALE-C: Analysis of Best Response of CR + CRh (Full Analysis Set – Primary Analysis)

	PBO + LDAC (N = 68)	VEN 600 mg QD + LDAC (N = 143)	p-value[a]
CR + CRh Rate (as best response) - n (%) [95% CI] [b]			
CR	5 (7.4) [2.4, 16.3]	39 (27.3) [20.2, 35.3]	< 0.001***
CRh	5 (7.4) [2.4, 16.3]	28 (19.6) [13.4, 27.0]	
CR + CRh	10 (14.7) [7.3, 25.4]	67 (46.9) [38.5, 55.4]	< 0.001***
Patients with Best Response of CR + CRh – Mean (SD) Median [range] Time to First Response (months)			
CR + CRh	2.8 (1.83) 2.8 [0.9 - 6.5]	1.8 (1.33) 1.0 [0.7 - 5.8]	

	PBO + LDAC (N = 68)	VEN 600 mg QD + LDAC (N = 143)	p-value[a]
Time to Best Response (months)			
CR	3.7 (3.39) 3.7 [0.9 - 9.2]	2.3 (1.66) 1.3 [0.9 - 5.9]	
CRh	3.4 (2.19) 3.7 [1.0 - 6.5]	2.2 (1.50) 1.4 [0.8 - 5.8]	
CR + CRh	3.5 (2.70) 3.7 [0.9 - 9.2]	2.3 (1.58) 1.3 [0.8 - 5.9]	
CR + CRh Rate (as best response) by Initiation of Cycle 2 - n (%) [95% CI][b]			
CR	2 (2.9) [0.4, 10.2]	23 (16.1) [10.5, 23.1]	
CRh	1 (1.5) [0.0, 7.9]	21 (14.7) [9.3, 21.6]	
CR + CRh	3 (4.4) [0.9, 12.4]	44 (30.8) [23.3, 39.0]	< 0.001***

AML = acute myeloid leukemia; CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LDAC = low dose cytarabine; N = sample size; n = number of patients; QD = once daily; SD = standard deviation

a. p-value is from Cochran-Mantel-Haenszel test stratified by age (18 to < 75, ≥ 75) and AML status (de novo, secondary) from IVRS/IWRS.

b. 95% CI is from the exact binomial distribution.

Note: ***, **, * statistically significant at p = 0.001, 0.01, 0.05 levels, respectively. Because statistical significance was not met for the primary objective, statistical significance cannot be declared for any of the secondary efficacy endpoints. Therefore, these p-values are only descriptive in nature.

Note: Data included are subject to a cutoff date of 15 February 2019 (Primary Analysis)

Source: VIALE-C CSR Table 14.2__2.2. Source datasets: ADSL, ADRS, and ADTTE.

Postbaseline Red Blood Cell and Platelet Transfusion Independence

At the primary analysis (15 February 2019), in the VEN + LDAC arm, 53 patients (37.1%) achieved RBC and platelets transfusion independence compared to 11 patients (16.2%) in the PBO + LDAC arm (Table 26).

At baseline, 111 patients (77.6%) in VEN + LDAC arm and 55 patients (80.9%) in PBO + LDAC arm were RBC or platelet transfusion dependent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were RBC or platelet transfusion dependent at baseline, 33.3% patients (37/111) in VEN + LDAC arm and 12.7% patients (7/55) in PBO + LDAC arm became transfusion independent. These patients achieved a 56-day or greater transfusion-free period while actively receiving study drugs.

At baseline, 32 patients (22.4%) in VEN + LDAC arm and 13 patients (19.1%) in PBO + LDAC arm were RBC or platelet transfusion independent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were RBC or platelet transfusion independent at baseline, 50.0% patients (16/32) in VEN + LDAC arm and 30.8% patients (4/13) in PBO + LDAC arm remained transfusion independent for at least 56 days postbaseline.

At the 6-month follow-up, the RBC and platelet transfusion independence rates were 39.2% in the VEN + LDAC arm and 17.6% in the PBO + LDAC arm. In patients who had an RBC or platelet transfusion within 8 weeks prior to the first dose of study drug, transfusion independence was achieved in a higher percentage of patients in the VEN + LDAC arm (35.1%; 39/111 patients) compared to the PBO + LDAC arm (14.3%; 8/56 patients). In patients who were RBC or platelet transfusion independent within 8 weeks prior to the first dose of study drug, a higher percentage of patients in the VEN + LDAC arm (53.1%; 17/32 patients) compared to PBO + LDAC

arm (33.3%; 4/12 patients) remained transfusion independent for at least 56 days postbaseline.

Postbaseline Red Blood Cell Transfusion Independence

At the primary analysis (15 February 2019), in the VEN + LDAC arm, 58 patients (40.6%) achieved RBC transfusion independence compared to 12 patients (17.6%) in the PBO + LDAC arm (Table 26).

At baseline, 104 patients (72.7%) in VEN + LDAC arm and 53 patients (77.9%) in PBO + LDAC arm were RBC transfusion dependent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were RBC transfusion dependent at baseline, 37.5% patients (39/104) in VEN + LDAC arm and 15.1% patients (8/53) in PBO + LDAC arm became transfusion independent (Table 26). These patients achieved a 56-day or greater transfusion-free period while actively receiving study drugs.

At baseline, 39 patients (27.3%) in VEN + LDAC arm and 15 patients (22.1%) in PBO + LDAC arm were RBC transfusion independent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were RBC transfusion independent at baseline, 48.7% patients (19/39) in VEN + LDAC arm and 26.7% patients (4/15) in PBO + LDAC arm remained RBC transfusion independent for at least 56 days postbaseline.

At the 6-month follow-up, an increase in the RBC transfusion independence rates were observed when compared to the primary analysis in the VEN + LDAC and PBO + LDAC arms (43.4% and 19.1%, respectively). In patients who had an RBC transfusion within 8 weeks prior to the first dose of study drug, transfusion independence was achieved in a higher percentage of patients in the VEN + LDAC arm (40.4%; 42/104 patients) compared to the PBO + LDAC arm (16.7%; 9/54 patients). In patients who were RBC transfusion independent within 8 weeks prior to the first dose of study drug, a higher percentage of patients in the VEN + LDAC arm (51.3%; 20/39 patients) compared to PBO + LDAC arm (28.6%; 4/14 patients) remained RBC transfusion independent for at least 56 days postbaseline.

Postbaseline Platelet Transfusion Independence

At the primary analysis (15 February 2019), in the VEN + LDAC arm, 68 patients (47.6%) achieved platelet transfusion independence compared to 22 patients (32.4%) in the PBO + LDAC arm (Table 26).

At baseline, 53 patients (37.1%) in VEN + LDAC arm and 24 patients (35.3%) in PBO + LDAC arm were platelet transfusion dependent within 8 weeks prior to the first dose of study drug or randomization. Of these patients who were platelet transfusion dependent at baseline, 30.2% patients (16/53) in VEN + LDAC arm and 12.5% patients (3/24) in PBO + LDAC arm became transfusion independent, respectively. These patients achieved a 56-day or greater transfusion-free period while actively receiving study drugs.

At baseline, 90 patients (62.9%) in VEN + LDAC arm and 44 patients (64.7%) in PBO + LDAC arm were platelet transfusion independent within 8 weeks prior to the first dose of study drug or

randomization. Of these patients who were platelet transfusion independent at baseline, 57.8% patients (52/90) in VEN + LDAC arm and 43.2% patients (19/44) in PBO + LDAC arm remained platelet transfusion independent for at least 56 days postbaseline.

At the 6-month follow-up, an increase in the platelet transfusion independence rates were observed when compared to the primary analysis in the VEN + LDAC arm (49.0%), while PBO + LDAC arm maintained the same rate of 32.4%. In patients who had a platelet transfusion within 8 weeks prior to the first dose of study drug, transfusion independence was achieved in a higher percentage of patients in the VEN + LDAC arm (28.8%; 15/52 patients) compared to the PBO + LDAC arm (12.5%; 3/24 patients). In patients who were platelet transfusion independent within 8 weeks prior to the first dose of study drug, a higher percentage of patients in the VEN + LDAC arm (60.4%; 55/91 patients) compared to PBO + LDAC arm (43.2%; 19/44 patients) remained platelet transfusion independent for at least 56 days postbaseline.

Table 27. VIALE-C: Summary of Postbaseline Transfusion Independence (Full Analysis Set)

	PBO + LDAC (N = 68)	VEN 600 mg QD + LDAC (N = 143)	p-value[a]
Postbaseline transfusion independence rate - n (%) [95% CI][b]			
RBC and Platelet	11 (16.2%) [8.4%, 27.1%]	53 (37.1%) [29.1%, 45.5%]	0.002**
RBC	12 (17.6%) [9.5%, 28.8%]	58 (40.6%) [32.4%, 49.1%]	0.001**
Platelet	22 (32.4%) [21.5%, 44.8%]	68 (47.6%) [39.1%, 56.1%]	0.040*

Postbaseline Transfusion Independence Rate by Baseline Transfusion Status – n/N (%) [95% CI][b]	**PBO + LDAC (N = 68)**	**VEN 600 mg QD + LDAC (N = 143)**
Having RBC or Platelet Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	7/55 (12.7%) [5.3%, 24.5%]	37/111 (33.3%) [24.7%, 42.9%]
Without RBC or Platelet Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	4/13 (30.8%) [9.1%, 61.4%]	16/32 (50.0%) [31.9%, 68.1%]
Having RBC Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	8/53 (15.1%) [6.7%, 27.6%]	39/104 (37.5%) [28.2%, 47.5%]
Without RBC Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	4/15 (26.7%) [7.8%, 55.1%]	19/39 (48.7%) [32.4%, 65.2%]
Having Platelet Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	3/24 (12.5%) [2.7%, 32.4%]	16/53 (30.2%) [18.3%, 44.3%]
Without Platelet Transfusion within 8 Weeks Prior to First Dose of Study Drug, or Randomization for Non-Treated	19/44 (43.2%) [28.3%, 59.0%]	52/90 (57.8%) [46.9%, 68.1%]

AML = acute myeloid leukemia; CI = confidence interval; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LDAC = low dose cytarabine; max = maximum; min = minimum; N = sample size; n = number of patients; PBO = placebo; QD = once daily; RBC = red blood cell; SD = standard deviation; VEN = venetoclax

a. p-value is from Cochran-Mantel-Haenszel test stratified by age (18 - < 75, ≥ 75) and AML status (de novo, secondary) from IVRS/IWRS.

b. 95% CI is from the exact binomial distribution.

Note: ***, **, * statistically significant at p = 0.001, 0.01, 0.05 levels, respectively. Because statistical significance was not met for the primary objective, statistical significance cannot be declared for any of the secondary efficacy endpoints. Therefore, these p-values are only descriptive in nature.

Note: The postbaseline transfusion independence is defined as a period of at least 56 days with no RBC or platelet transfusion during the evaluation period. Postbaseline transfusion evaluation period is from the first dose of study drug to the last dose

of study drug + 30 days, or disease progression, or confirmed morphological relapse, or death, or data cut-off date whichever occurred earlier. Subjects not receiving any study drug were considered as postbaseline transfusion dependent.
Note: Non-treated patients are patients who did not receive any study treatment.
Source: VIALE-C CSR Table 14.2__4.1 (Primary Analysis; 15 February 2019). Source datasets: ADSL, ADRS, and ADTTE.

The Applicant's Position:

Venetoclax in combination with LDAC reduced the risk of death by 25% (OS HR = 0.749) in newly diagnosed AML patients ineligible to receive intensive chemotherapy. The median OS was longer for the patients treated with venetoclax (600 mg) in combination with LDAC compared to patients treated with placebo in combination with LDAC.

Venetoclax in combination with LDAC also resulted in increases in the remission rates (CR + CRh and CR) compared to patients treated with placebo in combination with LDAC. Rapid achievement of CR + CRh and CR was also observed for patients treated with VEN + LDAC as measured by the response rates at the initiation of Cycle 2. Transfusion independence rates for RBCs and platelets were greater in the VEN + LDAC arm compared to the PBO + LDAC arm.

Venetoclax in combination with LDAC presents a clinically meaningful benefit over the current standard of care for this population, with improvements in OS, remission rates, and transfusion independence rates.

Regulatory Authorities' Assessment:

We agree with the Applicant's description of results of secondary endpoints, VIALE-C study. CR and CR+CRh appear to be consistent with the results from the Phase 2 trial. As noted above in the footnotes, the p-values presented should be considered descriptive only, as no formal testing could be conducted due to the failure to reject the null hypothesis associated with OS.

The results for CR and CR+CRh using FDA's definition are presented in Table 27. All patients had hematologic recovery meeting criteria for CR within the 14-day window from the bone marrow date, and the date of CR or CRh was based on the date of the marrow evaluation.

Table 28: VIALE-C Response Endpoints with Duration of Response per FDA Definition

Parameter	PBO + LDAC (N = 68)	VEN + LDAC (N = 143)
CR Rate		
Primary Analysis		
Responders; n (%) [95% CI]	5 (7.4) [2.4, 16.3]	39 (27.3) [20.2, 35.3]
Duration of Response (months); median (95% CI)	8.3 (3.1, NE)	11.1 (6.1, NE)
CR + CRh Rate		
Primary Analysis		
Responders; n (%) [95% CI]	10 (14.7) [7.3, 25.4]	67 (46.9) [38.5, 55.4]
Duration of Response (months); median (95% CI)	6.2 (1.1, NE)	11.1 (5.5, NE)

Source: Reviewer's analysis based on updated dataset submitted 09/03/2020.

Use of subsequent therapy was imbalanced between the two arms, with 44% of patients randomized to the PBO+LDAC arm utilizing subsequent therapy and 23% in the VEN+LDAC arm. This imbalance is due in part to a numerically longer duration of response. In general, use of subsequent therapy is expected to impact OS. A summary of subsequent therapy is provided in the following Table 27.

Table 29: Summary of Post-treatment therapy: VIALE-C study

SUMMARY OF POST-STUDY TREATMENT THERAPY
(FULL ANALYSIS SET)

	PLACEBO + LDAC (N=68) n (%)	VENETOCLAX 600 MG QD + LDAC (N=143) n (%)
ANY POST-STUDY TREATMENT THERAPY	30 (44.1)	33 (23.1)
ACLARUBICIN HYDROCHLORIDE	3 (4.4)	1 (0.7)
ANTITHYMOCYTE IMMUNOGLOBULIN	0	1 (0.7)
AZACITIDINE	7 (10.3)	6 (4.2)
BUSULFAN	0	2 (1.4)
CC-90009	1 (1.5)	0
CEFIXIME	0	1 (0.7)
CLADRIBINE	2 (2.9)	1 (0.7)
COMBINATIONS OF ANTINEOPLASTIC AGENTS	2 (2.9)	2 (1.4)
CYTARABINE	18 (26.5)	13 (9.1)
CYTARABINE OCFOSFATE	1 (1.5)	1 (0.7)
CYTARABINE;DAUNORUBICIN	0	1 (0.7)
DAUNORUBICIN	3 (4.4)	3 (2.1)
DAUNORUBICIN HYDROCHLORIDE	0	1 (0.7)
DECITABINE	1 (1.5)	2 (1.4)
ENOCITABINE	1 (1.5)	1 (0.7)
ETOPOSIDE	2 (2.9)	0
FILGRASTIM	2 (2.9)	1 (0.7)
FLUCONAZOLE	0	1 (0.7)
FLUDARABINE	3 (4.4)	6 (4.2)
GEMTUZUMAB OZOGAMICIN	4 (5.9)	4 (2.8)
GILTERITINIB	0	2 (1.4)
HYDROXYCARBAMIDE	6 (8.8)	5 (3.5)
IDARUBICIN	2 (2.9)	5 (3.5)
IMGN632	0	1 (0.7)
JOSAMYCIN	0	1 (0.7)
LEVETIRACETAM	0	1 (0.7)
MERCAPTOPURINE	2 (2.9)	1 (0.7)
METHOTREXATE	1 (1.5)	0
METHYLPREDNISOLONE	1 (1.5)	1 (0.7)
MITOXANTRONE	0	1 (0.7)
MITOXANTRONE HYDROCHLORIDE	1 (1.5)	0
VENETOCLAX	2 (2.9)	0
VINCRISTINE	1 (1.5)	0

LDAC = LOW DOSE CYTARABINE.
NOTE: DATA INCLUDED ARE SUBJECT TO A CUTOFF DATE OF 15FEB2019.

Program Source Code: /caikx/SDA/ABT-199/AML/CSR/M16-043/O_UPDATE/14.2/PCMS_RUN/m16043-cm.sas

Source: M16-043 CSR Table 14.2__6.1.1, page 901.

Transfusion independence

Transfusion independence (TI) is determined based on those who were dependent on RBC and/or platelets at baseline and became independent of both RBC and platelets for 56-days or more while on study therapy. As noted in Table 26 provided by the Applicant, in the venetoclax arm, 33% of patients who were transfusion dependent (TD) at baseline became TI on study

treatment. Of those who were not TD at baseline, 50% remained TI while on study treatment. This is an improvement over the placebo arm which showed 13% of patients became TI and 31% remained TI.

Dose/Dose Response

The Applicant's Position:
The recommended dose and regimen for VEN 600 mg QD + LDAC in AML patients was supported by the exposure-efficacy and exposure-safety analyses of VEN. The 600 mg QD dose was consistent with both the approved VEN dose and regimen for the treatment of patients with AML (see Section 0).

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment.

Durability of Response

The Applicant's Position:
Duration of responses for patients who achieved CR + CRh and CR are presented below. Duration of CR + CRh and CR responses are defined as the number of days from the date of first response (CRh or CR) per revised IWG criteria for AML to the earliest evidence of confirmed MR, PD or death due to disease progression.

Overall, the responses with venetoclax in combination with LDAC are durable with duration of remission for all response categories of CR + CRh, and CR being longer in the VEN + LDAC arm compared to the PBO + LDAC arm. Responses were durable in the primary analysis and in the 6-month follow-up analysis.

Duration of CR + CRh
For CR + CRh, at the primary analysis, the median duration of response was 11.1 months for the VEN + LDAC arm compared to 6.2 months for the PBO + LDAC arm. At the 6-month follow-up analysis, the median duration of response was 11.7 months for the VEN + LDAC arm compared to 8.3 months for the PBO + LDAC arm (Table 24).

Duration of Complete Remission (CR)
For CR, at the primary analysis, the median duration of response was 11.1 months for the VEN + LDAC arm compared to 8.3 months for the PBO + LDAC arm. At the 6-month follow-up analysis, the median duration of response was 17.1 months for the VEN + LDAC arm compared to 8.3 months for the PBO + LDAC arm (Table 24).

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of duration of CR+CRh and duration of complete response results, VIALE-C study. See Table 27 above for the duration of CR and CR+CRh based on the date of the bone marrow evaluation instead of the date of hematologic recovery

resulting in minor differences in duration of up to 14 days.

Persistence of Effect

The Applicant's Position:
Survival was favorable and response rates were durable for patients with AML treated with VEN in combination with LDAC. Patients sustained long-term benefits with ongoing treatment.

Regulatory Authorities' Assessment:
We agree that the OS was numerically longer in the treatment group vs. the control group in VIALE-C. However, this finding did not reach statistical significance. The duration of response appears to be longer in the treatment arm vs. the control arm, though response endpoints could not be formally tested due to the failure to reject the null hypothesis of OS.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:
The PROMIS Cancer Fatigue SF-7A assessment and EORTC QLQ-C30 GHS/QoL assessment were ranked secondary endpoints for the VIALE-C study. The PROMIS Cancer Fatigue SF-7A assessment and the EORTC QLQ-C30 GHS/QoL assessment are also discussed in Section 8.2.6.

Between-group differences in mean score change from baseline were assessed at the minimum important difference (MID) of 3 points for the PROMIS Cancer Fatigue assessment and 5 points for the EORTC GHS/QoL. Relative to PBO + LDAC, patients receiving VEN + LDAC observed reduction in PROMIS Cancer Fatigue scores by Day 1 of Cycles 3 and 5 (–2.940 versus 1.567, –5.259 versus –0.336, respectively, with lower score indicating improvement in fatigue symptoms). Patients receiving VEN + LDAC observed improvement in GHS/QoL on Day 1 of Cycles 5, 7 and 9 vs PBO + LDAC (16.015 vs 2.627, 10.599 vs 3.481, and 13.299 vs 6.918, respectively, with higher score indicating improvement in QoL). However, these differences were not clinically meaningful differences between the groups. Patients receiving VEN + LDAC did not experience meaningful decrement in fatigue or QoL than PBO + LDAC.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of secondary or exploratory endpoints, VIALE-C study.

Additional Analyses Conducted on the Individual Trial

Data:
Intermediate Cytogenetic Risk: The CR + CRh rate for patients with intermediate cytogenetic risk was 53.3% in VEN + LDAC versus 18.6% for patients in PBO + LDAC.
Poor Cytogenetic Risk: The CR + CRh rate for patients with poor cytogenetic risk was 31.9% in VEN + LDAC versus 10.0% for patients in PBO + LDAC.
Primary AML: The CR + CRh rate for patients with primary AML was 58.8% in VEN + LDAC versus 20.0% for patients in PBO + LDAC.

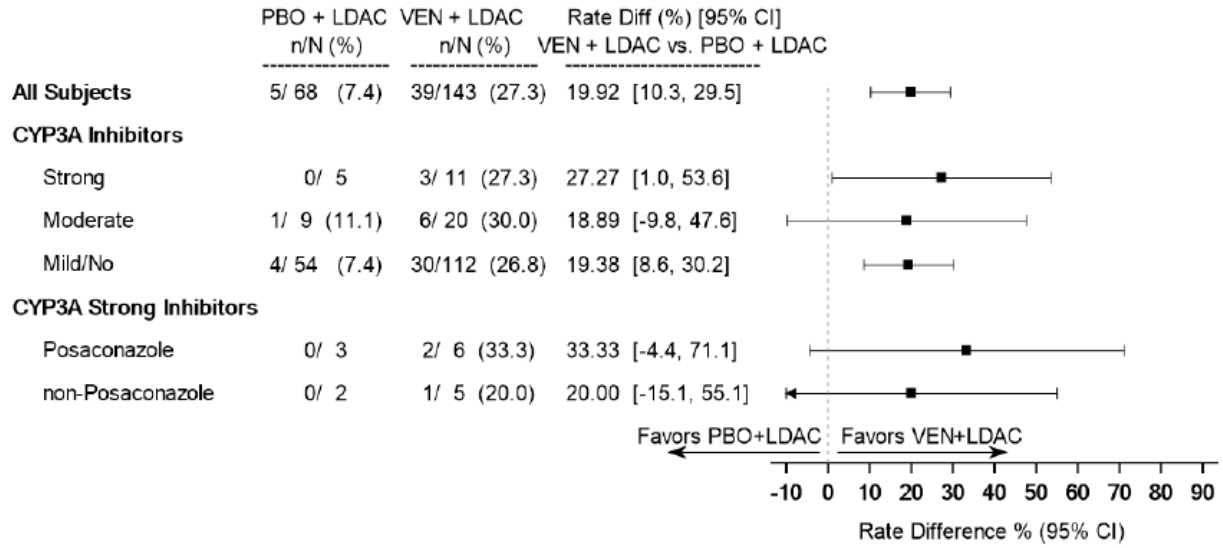
Secondary AML: The CR + CRh rate for patients with secondary AML was 29.3% in VEN + LDAC versus 4.3% for patients in PBO + LDAC.
AML-MRC: The CR + CRh rate for patients with AML-MRC was 31.6% in VEN + LDAC versus 11.1% for patients in PBO + LDAC.
Patients Who Received Prior HMAs for Myelodysplasia Syndrome (MDS): The CR + CRh rate for patients who received prior HMAs for MDS was 17.9% in VEN + LDAC versus 7.1% for patients in PBO + LDAC.

The Applicant's Position:
AML in elderly patients is a biologically and clinically distinct disease with a diminished response to chemotherapy, low remission rates, as well as short disease-free and overall survival. Higher proportion of unfavorable cytogenetics, higher frequency of antecedent hematologic disorders or prior therapy for previous malignancies, and more frequent expression of the multidrug resistance phenotype accounts for the poor outcomes associated with current therapy. Venetoclax in combination with LDAC improved remission rates compared to PBO + LDAC for patients with AML in the intermediate- or poor-risk cytogenetic groups. Venetoclax + LDAC also improved the remission rates for patients with primary or secondary AML, as well as patients with AML-MRC, compared to treatment with PBO + LDAC.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of results from additional analyses, VIALE-C study.

In an information request query, the Applicant performed an evaluation of response rates by CYP3A inhibitors, and by posaconazole vs. non-posaconazole for those on strong CYP3A inhibitors. See Additional Analyses section under VIALE-A for discussion of the effect of strong CYP3A inhibitors on efficacy. This effect was less prominent in VIALE-C as shown in the Figure below. While the patient numbers are much lower in this analysis, this indicates that other factors could be contributing to the differences in response rate in addition to the venetoclax treatment.

CR Rate Based on Investigators Assessment by Concomitant Use of CYP3A Inhibitors (Full Analysis Set), VIALE-C



LDAC = Low dose Cytarabine. PBO = Placebo. VEN = Venetoclax. Rate Diff = Rate Difference.
95% CI is exact unconditional confidence limits.
Arrow indicates confidence interval extended more than current range.
Note: Data included are subject to a cutoff date of 15FEB2019.

Source: Applicant's analysis, Response to IR received Sept 4, 2020.

8.1.5. Supportive Studies for Efficacy – Study M14-358

Trial Design

The Applicant's Position:

Study M14-358 is an ongoing, Phase 1b, open-label, non-randomized, multicenter study to evaluate the efficacy, PK, and safety of orally administered venetoclax combined with azacitidine (AZA) or decitabine (DEC), respectively, in newly-diagnosed patients with AML ≥ 60 years of age and who are not eligible for standard induction therapy due to comorbidity or other factors. Only patients with intermediate- or poor-risk cytogenetics were eligible.

The study consists of 2 stages (dose escalation and dose expansion), as well as a DDI substudy.

- A Phase 1 dose-escalation stage (N = 45 enrolled/48 planned) to assess ramp-up and/or target doses of venetoclax escalated across 4 cohorts, in combination with the HMAs, comprised of up to 24 patients each. These patients were treated with escalating doses of venetoclax (400, 800, and 1200 mg) in combination with AZA or DEC to establish the safety profiles of these combinations.
- A Phase 1 dose-expansion stage (N = 155 enrolled/155 planned in 2 expansions) to assess venetoclax at doses of 400 and 800 mg in combination with AZA or DEC to confirm safety and preliminary efficacy of these combinations.
  - Expansion 1 (N = 100) enrolled patients ≥ 65 years of age with 50 patients each treated with venetoclax (400 or 800 mg; 25 patients each) in combination with AZA or DEC
  - Expansion 2 (N = 55) enrolled patients ≥ 60 years of age treated with venetoclax

(400 mg) in combination with AZA

In addition, a DDI substudy (N = 12) was conducted at a single center to evaluate the effect of posaconazole (coadministered on Cycle 1, Days 21 to 28), a strong CYP3A inhibitor, on the PK and safety of venetoclax.

For Study M14-358, patients were enrolled at 18 sites in the United States, Australia, Germany, and France. This was an open-label study. There was no randomization of patients nor blinding. This study was conducted globally under a collaboration agreement between AbbVie and GNE/Roche. At study start, sites were required to choose their preferred HMA treatment (AZA or DEC); sites providing AZA control treatment were different from sites providing DEC.

This study enrolled newly-diagnosed AML patients ≥ 60 years old and who were ineligible for standard induction therapy due to comorbidities. 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. Patients must have received no prior treatment for AML with the exception of hydroxyurea. Patients must have ECOG performance status of 0 to 2 (if ≥ 75 years of age) or 0 to 3 (if ≥ 60 to 75 years of age), adequate renal function, and adequate liver function. Patients enrolled in Expansion 2 must have fulfilled objective medical criteria (also known as the Ferrara criteria) for ineligibility for intensive chemotherapy.

Study M14-358 was the first study to assess escalating doses of venetoclax in combination with HMAs (AZA or DEC) in newly-diagnosed patients with AML who are not eligible for standard induction therapy due to age or comorbidities. A daily dose ramp-up regimen was designed to escalate the dose of venetoclax rapidly in combination with AZA or DEC to mitigate the risk of TLS, as well as to optimize the opportunity for achieving a response and enable close patient monitoring. The dosing regimen also enabled interruptions at dose levels if rapid tumor lysis was observed. This study also evaluated interactions between the continuous coadministration of venetoclax and posaconazole.

Azacitidine (75 mg/m^2)[9] and decitabine (20 mg/m^2)[10] were dosed according to their respective package insert guidelines. Modifications for the azacitidine dose is covered in Section 8.1.1. If a dose modification for decitabine was believed necessary, a discussion with the Medical Monitor was required.

Regulatory Authorities' Assessment:
The trial design for M14-358 was reviewed under supplement 9. No additional patients were enrolled.

8.1.6. Efficacy Results – Study M14-358

For Study M14-358, the following assessments were evaluated: objective response rate (ORR: CR + CRi + PR), CR + CRi rate, CR rate, CRi rate, CR + CRh rate, CRh rate, DOR, OS, MRD, and transfusion independence. This study also evaluated the percentage of patients who received

subsequent stem cell transplants. The results of key efficacy endpoints are presented in the following sections.

This study evaluated response rates using modified IWG criteria to define CR (modified for ANC and platelet counts), as requested by the FDA. Reclassified response rates were assessed; DOR for the reclassified CR rate was also evaluated. The results for response by IWG criteria, presented below, are presented with the reclassified rates. The modified CR definition is:

- CR: ANC > 10^3/µL, platelet counts > 10^5/µL, RBC transfusion independence, and bone marrow with < 5% blasts; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease

Data and The Applicant's Position:

Results for Venetoclax 400 mg in Combination with Azacitidine

For patients in the VEN 400 mg + AZA arm (N = 84), the majority of patients were male (60.7%) and white (91.0%). The patients were elderly (median age: 74.5 years); 50.0% of patients were aged ≥ 75 years of age and 96.4% of patients were ≥ 65 years of age. Most of the patients (83.3%) were from the US.

For this treatment arm, at baseline, there were 59.5% patients with intermediate and 39.3% patients with poor cytogenetic risks (also 1.2% patients with no mitoses). Most patients had primary AML (75.0%) and 25.0% patients had secondary AML; 26.2% of patients had a history of AML-MRC. The majority of patients (67 patients; 79.8%) had sufficient information in the clinical database to determine that they fulfilled the objective medical criteria (known as Ferrara criteria) used in the pivotal Phase 3 studies, VIALE-A and VIALE-C, to determine intensive chemotherapy ineligibility.

Response by IWG Criteria

Patients meeting the objective medical criteria (N = 67) had a CR + CRh rate of 61.2% (95% CI: 48.5%, 72.9%) and a CR rate of 43.3% (95% CI: 31.2%, 56.0%). For patients who achieved CR, the median duration of response was 14.7 months (range: 0.4 to 30.2 months).

Patients who did not meet the objective medical criteria (N = 17) had a CR + CRh rate of 76.5% (95% CI: 50.1%, 93.2%) and a CR rate of 35.3% (95% CI: 14.2%, 61.7%).

Overall Survival

For all patients treated with VEN 400 mg + AZA (N = 84), median duration of study follow-up was 28.9 months (range: 0.4 to 42.0 months). For patients treated with VEN + AZA who met the objective medical criteria (N = 67), the median duration of study follow-up was 27.6 months (range: 0.4 to 40.3 months). For patients treated with VEN + AZA who did not meet the objective medical criteria (N = 17), the median duration of study follow-up was 40.6 months (range: 3.9 to 42.0 months).

Patients meeting the objective medical criteria (N = 67) had a median OS of 16.4 months (95% CI: 10.6, 26.7 months). Patients who did not meet the objective medical criteria (N = 17) had a median OS of 16.9 months (95% CI: 6.5 months, NR).

Postbaseline RBC Transfusion Independence
Among the 84 patients treated with VEN 400 mg + AZA, 54 patients (64.3%) achieved RBC transfusion independence.

Postbaseline Platelet Transfusion Independence
Among the 84 patients treated with VEN 400 mg + AZA, 59 patients (70.2%) achieved platelet transfusion independence.

Subsequent Stem Cell Transplant
Venetoclax (400 mg) in combination with AZA in patients who were ineligible to receive intensive therapy resulted in early remissions that enabled a few patients to receive an allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning regimens for a potential cure. For patients who met the objective medical criteria (N = 67), 8 patients (11.9%) treated with VEN + AZA received an allogeneic hematopoietic stem cell transplant. Of these 8 patients, 5 patients achieved CR/CRh and received a stem cell transplant.

For patients not meeting the objective medical criteria (N = 17), 9 patients (52.9%) received a stem cell transplant. Of these 9 patients, 8 patients achieved CR/CRh and received a stem cell transplant.

Data and The Applicant's Position:

Results for Venetoclax 400 mg in Combination with Decitabine
For patients in the VEN 400 mg + DEC arm (N = 31), the majority of patients were white (87.1%); 51.6% of patients were female and 48.4% were male. The patients were elderly (median age: 72.0 years) and 100% of patients were ≥ 65 years of age (25.8% were ≥ 75 years of age). Most of the patients (93.5%) were from the US.

For this treatment arm, at baseline, there were 51.6% patients with intermediate and 48.4% patients with poor cytogenetic risks. Most patients had primary AML (71.0%) and 29.0% patients had secondary AML; 41.9% of patients had AML-MRC. There were 13 patients (41.9%) with sufficient information in the clinical database to determine that they fulfilled the objective medical criteria (known as Ferrara criteria) used in the pivotal Phase 3 studies, VIALE-A and VIALE-C, to determine intensive chemotherapy ineligibility.

Response by IWG Criteria
Patients meeting the objective medical criteria (N = 13) had a CR + CRh rate of 61.5% (95% CI: 31.6%, 86.1%) and a CR rate of 53.8% (95% CI: 25.1%, 80.8%). For patients who achieved CR, the median duration of response was 6.9 months (range: 1.0 to 20.9 months).

Patients who did not meet the objective medical criteria (N = 18) had a CR + CRh rate of 77.8% (95% CI: 52.4%, 93.6%) and a CR rate of 55.6% (95% CI: 30.8%, 78.5%).

Overall Survival

For patients treated with VEN 400 mg + DEC (N = 31), median duration of study follow-up was 40.4 months (range: 0.7 to 42.7 months). For patients treated with VEN + DEC who met the objective medical criteria (N = 13), the median duration of study follow-up was 38.8 months (range: 0.7 to 38.8 months). For patients treated with VEN + DEC who did not meet the objective medical criteria (N = 18), the median duration of study follow-up was 40.6 months (range: 0.7 to 42.7 months).

Patients treated with all doses of VEN in combination with DEC and meeting the objective medical criteria (N = 39) had a median OS of 11.0 months (95% CI: 6.7, 18.2 months). Patients treated with all doses of VEN in combination with DEC and who did not meet the objective medical criteria (N = 34) had a median OS of 29.7 months (95% CI: 15.1 months, NR).

Postbaseline RBC Transfusion Independence

Among the 31 patients treated with VEN 400 mg + DEC, 19 patients (61.3%) achieved RBC transfusion independence.

Postbaseline Platelet Transfusion Independence

Among the 31 patients treated with VEN 400 mg + DEC, 27 patients (87.1%) achieved platelet transfusion independence.

Subsequent Stem Cell Transplant

Venetoclax (400 mg) in combination with DEC in patients who were ineligible to receive intensive therapy resulted in early remissions that enabled a few patients to receive an allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning regimens for a potential cure. For patients who met the objective medical criteria (N = 13), no patients treated with VEN + DEC received an allogeneic hematopoietic stem cell transplant.

For patients not meeting the objective medical criteria (N = 18), 4 patients (22.2%) received a stem cell transplant. All 4 of these patients achieved CR/CRh and received a stem cell transplant.

Regulatory Authorities' Assessment:

The original data cut used for Supplement 9 was 02/13/2018. In this data cut, the CR rate for patients who met the modified Ferrara criteria and were treated with VEN+AZA was 37% and the CR+CRh rate was 61.2%. For VEN+DEC, the CR rate was 54% and the CR+CRh rate was 61.5%. The data cut for the current submission is 07/19/2019. The CR rate for VEN+AZA is 43.3% and the CR+CRh rate is 61.2%, indicating that with additional follow up, 3 patients had continued count recovery meeting CR criteria from prior CRh determination. For VEN+DEC, the CR rate is 53.8% and CR+CRh rate is 61.5%, unchanged from the prior data cut.

The results for CR and CR+CRh using FDA's definition are presented in Table 29.

Table 30: M14-358 Response Endpoints with Duration of Response per FDA Definition

Parameter	VEN + AZA (N = 67)	VEN + DEC (N = 13)
CR Rate		
Updated cut-off date of 07/19/2020		
Responders; n (%) [95% CI]	29 (43.3) [31.2, 56.0]	7 (53.8) [25.1, 80.8]
Duration of Response (months); median (95% CI)	23.8 (15.4, NE)	12.7 (1.4, NE)
CR + CRh Rate		
Updated cut-off date of 07/19/2020		
Responders; n (%) [95% CI]	41 (61.2) [48.5, 72.9]	8 (61.5) [31.6, 86.1]
Duration of Response (months); median (95% CI)	26.5 (17.4, NE)	12.7 (1.4, 20.0)

Source: Reviewer's analysis based on updated dataset submitted 09/03/2020.

We note the limited data available on patients treated with decitabine which included only 31 patients overall, 13 of whom had objective criteria to determine they were ineligible for intensive chemotherapy. While the response rate in the 13 patients appears comparable or slightly higher than the azacitidine combination, the durability of CR may be shorter in this small subset of patients. In the broader 31 patient cohort, 17 patients achieved a CR (55%) with a median duration of CR of 21.3 months (95% CI: 6.9, -) by the Applicants definition of duration. This additional information provides assurance that the decitabine combination appears to have similar outcomes to the azacitidine combination.

8.1.7. Supportive Studies for Efficacy – Study M14-387

Trial Design

The Applicant's Position:
Study M14-387 is an ongoing, Phase 1/2, open-label, non-randomized, multicenter study to evaluate 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, comorbidity, or other factors. Only patients with intermediate- or poor-risk cytogenetics were eligible.

The study consisted of 3 distinct portions.

- A Phase 1 dose-escalation portion (N = 18 enrolled/42 planned) to evaluate the safety and PK profile of venetoclax administered in combination with LDAC with the objectives of defining the MTD and generating data to support a recommended Phase 2 dose (RPTD).
- A subsequent initial Phase 2 portion (N = 53 enrolled/50 planned) to evaluate whether the RPTD had sufficient efficacy and acceptable toxicity to warrant further development of the combination therapy.
- A Phase 2, Cohort C (N = 23 enrolled/20 planned [21/23 patients received study drug]) to evaluate the ORR of patients who were allowed additional supportive medications (e.g., strong CYP3A inhibitors), if medically indicated.

Patients were enrolled at 9 sites in the United States, Australia, Germany, and Italy. This was an open-label study. There was no randomization of patients nor blinding. This study was conducted globally under a collaboration agreement between AbbVie and GNE/Roche.

Patients enrolled in the study had newly-diagnosed AML and were ineligible for intensive chemotherapy because of age, comorbidity, or other factors. Patients were ≥ 65 years of age in the Phase 1 and the initial Phase 2 portions of the study. Patients enrolled in Phase 2, Cohort C portion must have been either ≥ 75 years of age or ≥ 60 to 74 years of age who were ineligible for standard induction therapy due to at least 1 comorbidity. Patients must have received no prior treatment for AML with the exception of hydroxyurea (patient may have been treated for prior MDS) and were to have a projected life expectancy of at least 12 weeks. Patients were to have adequate renal function and adequate liver function, as well as an ECOG performance status of 0 to 2 for patients ≥ 75 years of age or 0 to 3 for patients ≥ 60 to 74 years of age (if 0 to 1, another comorbidity was required).

Low-dose cytarabine (LDAC; 20 mg/m^2, the standard dose)[11] was prepared per package insert and administered SC on Days 1 to 10 of each 28-day cycle by a trained provider meeting local qualifications for administration of SC cytarabine.

Regulatory Authorities' Assessment:
The trial design for M14-388 was reviewed under supplement 9. No additional patients were enrolled.

8.1.8. Efficacy Results – Study M14-387

For Study M14-387, the following assessments were evaluated: ORR (CR + CRi + PR), CR + CRi rate, CR rate, CRi rate, CR + CRh rate, CRh rate, DOR, OS, MRD, and transfusion independence. The results of key efficacy endpoints are presented in the following sections.

This study evaluated response rates using modified IWG criteria to define CR (modified for ANC and platelet counts) as requested by the FDA. Reclassified response rates were assessed; DOR for the reclassified CR rate was also evaluated. The results for response by IWG criteria, presented below, are presented with the reclassified rates. The modified CR definition is:

- CR: ANC > 10^3/µL, platelet counts > 10^5/µL, RBC transfusion independence, and bone marrow with < 5% blasts

Data and The Applicant's Position:
All 92 patients were included in efficacy analysis in Study M14-387. The majority of patients (N = 82) were treated with venetoclax 600 mg + LDAC and 10 patients were treated with venetoclax 800 mg + LDAC in the Phase 1 dose-escalation portion of the study. Based on similar efficacy and improved safety of the 600-mg versus the 800-mg dose of venetoclax, the RPTD is venetoclax (600 mg) in combination with LDAC. This venetoclax dose in combination with LDAC is the target dose; therefore, efficacy data will be presented in this Assessment Aid for the venetoclax (600 mg) in combination with LDAC treatment arm only.

Results for Venetoclax 600 mg in Combination with LDAC
The majority of patients were male (64.6%) and white (94.9%). The patients were elderly (median age: 74.0 years) with 48.8% of patients aged ≥ 75 years of age. Most of the patients (62.2%) were from the US.

At baseline, there were 59.8% patients with intermediate-risk and 31.7% patients with poor-risk cytogenetics (8.5% patients with no mitoses). About half of patients (51.2%) had primary AML and 48.8% had secondary AML. There were 48.8% patients who had a history of AML-MRC and 24 patients (29.3%) had prior HMA use for antecedent hematologic disorders. The majority of patients (61 patients; 74.4%) had sufficient information in the clinical database to determine that they fulfilled the objective medical criteria (known as Ferrara criteria) used in the pivotal Phase 3 studies, VIALE-A and VIALE-C, to determine intensive chemotherapy ineligibility.

Response by IWG Criteria
Patients meeting the objective medical criteria (N = 61) had a CR + CRh rate of 42.6% (95% CI: 30.0%, 55.9%) and a CR rate of 21.3% (95% CI: 11.9%, 33.7%). For patients who achieved CR, the median duration of response was 14.8 months (range: 0.0 to 45.0 months).

Patients who did not meet the Ferrara criteria (N = 21) had a CR + CRh rate of 57.1% (95% CI: 34.0%, 78.2%) and a CR rate of 33.3% (95% CI: 14.6%, 57.0%).

Overall Survival
For all patients treated with VEN 400 mg + LDAC (N = 82), median duration of study follow-up was 41.7 months (range: 0.3 to 54.0 months). For patients in this treatment arm who met the objective medical criteria (N = 61), the median duration of study follow-up was 40.3 months (range: 0.3 to 54.0 months). For patients in this treatment arm who did not meet the objective medical criteria (N = 21), the median duration of study follow-up was 44.3 months.

Patients meeting the objective medical criteria (N = 61) had a median OS of 9.0 months (95% CI: 5.6, 14.0 months). Patients who did not meet the objective medical criteria (N = 21) had a median OS of 11.4 months (95% CI: 2.6, 16.9 months).

Postbaseline Red Blood Cell Transfusion Independence
Among the 82 patients treated with VEN 600 mg + LDAC, 39 patients (47.6%) achieved RBC transfusion independence.

Postbaseline Platelet Transfusion Independence
Among the 82 patients treated with VEN 600 mg + LDAC, 48 patients (58.5%) achieved platelet transfusion independence.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment.

The original data cut used for Supplement 9 was 01/30/2018. In this data cut, the CR rate for patients who met the modified Ferrara criteria (n=61) was 21% and the CR+CRh rate was 43%. The data cut for the current submission is 07/19/2019, with CR rate 21% and CR+CRh rate 43%, unchanged from the prior data cut. One patient had a missing bone marrow date, and the date of CR assessment was applied at the date of the CBC. All other patients had hematologic recovery within 14 days of the marrow and the date of CR or CRh was assessed at the time of the marrow.

The results for CR and CR+CRh using FDA's definition are presented in Table 30.

Table 31: M14-387 Response Endpoints with Duration of Response per FDA Definition

Parameter	VEN + LDAC (N = 67)
CR Rate	
Updated cut-off date of 07/19/2020	
Responders; n (%) [95% CI]	13 (21.3) [11.9, 33.7]
Duration of Response (months); median (95% CI)	22.9 (5.1, NE)
CR + CRh Rate	
Updated cut-off date of 07/19/2020	
Responders; n (%) [95% CI]	26 (42.6) [30.0, 55.9]
Duration of Response (months); median (95% CI)	14.3 (6.1, 31.2)

Source: Reviewer's analysis based on updated dataset submitted 09/03/2020.

8.1.9. Integrated Review of Effectiveness

Regulatory Authorities' Assessment:
See below sections for our integrated assessment of effectiveness.

8.1.10. Assessment of Efficacy Across Trials

Primary Endpoints

Data:
For all patients who received VEN 400 mg in combination with AZA or DEC, or VEN 600 mg in combination with LDAC, efficacy was demonstrated based on the OS, remission rates of CR + CRh and CR, DOR, and transfusion independence.

Overall Survival
In the placebo-controlled VIALE-A study, VEN + AZA led to a statistically significant and clinically meaningful reduction in the risk of death in newly-diagnosed patients with AML ineligible to receive intensive chemotherapy with an HR of 0.662 (p-value < 0.001). The median OS was 14.7 months for patients receiving VEN + AZA in VIALE-A and the median OS was 16.4 months for patients receiving VEN 400 mg + AZA in Study M14-358 and meeting objective medical criteria (known as the Ferrara criteria). This represents a substantial improvement in OS compared to AZA monotherapy in VIALE-A which resulted in a median OS of 9.6 months and a median OS of 10.4 months in historical AZA monotherapy trials.[16]

In Study M14-358, the median OS was 11.0 months for patients receiving all doses of VEN in combination with DEC (N = 39) and meeting objective medical criteria. This represents a substantial improvement in OS compared to historical DEC monotherapy trials which resulted in a median OS of 7.7 months;[18] this is consistent with the median OS for patients treated with VEN + AZA.

In the placebo-controlled VIALE-C study, the reduced risk of death was clinically meaningful for newly-diagnosed patients ineligible to receive intensive chemotherapy treated with VEN + LDAC. In the primary analysis (15 February 2019), although not statistically significant, the risk of death was reduced by 25% (HR of 0.749, p-value = 0.114 [stratified log-rank test]). The median OS was 7.2 months compared to 4.1 months in patients treated with VEN + LDAC versus PBO + LDAC, respectively. An important treatment effect of VEN + LDAC vs PBO + LDAC continued to be observed with the 6-month additional follow-up data; the risk of death was further reduced to 30% (HR = 0.704) for patients treated with VEN + LDAC. With 6-month follow-up data, the median OS was improved to 8.4 months for patients treated with VEN + LDAC while patients treated with PBO + LDAC continued to have a median OS of 4.1 months.

In Study M14-387, the median OS was 9.0 months for patients treated with VEN 600 mg + LDAC and meeting objective medical criteria (N = 61). This represents a substantial improvement in

OS compared to LDAC monotherapy, which resulted in a median OS of 4.1 months in the PBO + LDAC arm of VIALE-C and a median OS of 5.0 in historical LDAC monotherapy trials.[18]

The Applicant's Position:
Venetoclax in combination with AZA, DEC, or LDAC all compared favorably to AZA, DEC, or LDAC monotherapy treatments.[16,18] In both randomized trials, VIALE-A and VIALE-C, the median OS in the VEN combination arms was longer compared to the control arms with AZA and LDAC, respectively.

Regulatory Authorities' Assessment:
We agree that the OS was numerically longer in the treatment arms vs. the control arm in both VIALE-A and VIALE-C. However, we note that the strength of evidence is higher for VIALE-A, as it met its primary OS objective, while the test of OS in VIALE-C did not reach statistical significance. In addition, the 6-month update to OS in the VIALE-C should be considered post-hoc and exploratory only. Consequently, only the primary analyses of OS from these trials should be included in labeling.

Bayesian Analyses of OS:
We further investigated the impact of treatment arms on the OS of patients by borrowing treatment effect (VEN+LDAC) from the phase 2 study (M14-387) using a Bayesian approach. We also noted that the demographic variables and baseline characteristic of patients in both Phase 2 and Phase 3 studies were approximately similar therefore justifying performing exploratory Bayesian analyses. For instance, the median age was 74 years in Phase 2 study and 76 years in Phase 3 study. There were 61% patients with intermediate cytogenetic risk in Phase 2 study vs. 65% in Phase 3 study.

The proportional hazard model was defined as follows:

$$h\,(t|h_0\,,\,\beta) = \,h_0(t)\exp\{x^T\beta\}$$

where baseline hazard is defined using Weibull distribution $h_0(t) = \lambda\alpha t^{\alpha-1}$, α and λ = exp($\beta_0$) are shape and scale parameters and $x^T\beta = \beta_1 I_{Treatment}$ and HR=exp(β_1). The following steps were implemented:

Step1: Estimate the posterior distribution of α and β_0 using OS data from the Phase 2 (M14-387) trial. Normal distributions were matched based on mean and variance.

Step2: Build a Bayesian model for Phase 3 (VIALE-C))+6months trial using posterior distribution of α and β_0 from Phase 2 as an informative prior for Phase 3 Bayesian model

Step3: Estimate the posterior distribution of α, β_0, and HR= exp(β_1) for Phase 3 (VIALE-C)+6months

The Bayesian analyses was performed from within R, using the JAGS software. The results in Table 30 show that the OS of patients in Phase 2 (M14-387) and Phase 3 (VIALE-C) are consistent. Although the OS of patients in both studies (Phase 2 and Phase 3) are not exactly

same but with additional analyses performed with more diffuse priors yielded robust results. Based on the 95% credible interval we can conclude that the Pr(HR<1) is high.

Table 32: VIALE-C Posterior Estimates from Bayesian Analyses of Final OS as Observed by Final Analysis and 6-Month Update

		Posterior estimates (95% Credible Interval)		
Data cut	Data set	α	β_0	HR=exp(β_1)
Final[a]	Phase 2 only	0.84 (0.65,1.04)	-2.48 (-3.17,-1.85)	
Final[b]	Phase 3 only	0.97 (0.65,1.04)	-1.99 (-2.43,-1.63)	0.75 (0.53,1.07)
Additional 6-months[b]	Phase 3 only	0.89 (0.77,1.02)	-1.90 (-2.28,-1.15)	0.72 (0.52,1.00)
Final[c]	Phase 3 with informative prior borrowed from Phase 2	0.98 (0.85,1.13)	-2.02 (-2.44,-1.64)	0.74 (0.53,1.07)
Additional 6-months[c]	Phase 3 with informative prior borrowed from Phase 2	0.90 (0.78,1.02)	-1.93 (-2.30,-1.56)	0.72 (0.52,1.00)

a: Using OS data from Phase 2 study with non-informative priors $\alpha \sim Gamma(0.01,0.01)$, $\beta_0 \sim Normal(0,0.0001)$
b: Using final OS or additional 6 months OS data from Phase 3 study with non-informative priors $\alpha \sim Gamma(0.01,0.01)$, $\beta_0 \sim Normal(0,0.001)$ and $\beta_1 \sim Normal(0,0.001)$
c: Using final OS or additional 6 months OS data from Phase 3 study with informative priors borrowed from Phase 2 $\alpha \sim Gamma(2.9,0.3)$, $\beta_0 \sim Normal(-2.49,0.6)$ and $\beta_1 \sim Normal(0,0.001)$

Secondary and Other Endpoints

Remission Rates

Data:

In VIALE-A, the CR + CRh rate for patients randomized to receive VEN + AZA was statistically significantly greater than that of patients randomized to receive PBO + AZA (64.7% vs. 22.8%, respectively; p-value < 0.001). Statistically significant increases in the CR rates were also observed for patients receiving VEN + AZA versus PBO + AZA (36.7% vs. 17.9%, respectively; p-value < 0.001).

In Study M14-358, the CR + CRh and CR rates were consistently higher for patients treated with VEN 400 mg + AZA or VEN 400 mg + DEC than historically seen for patients treated with AZA or DEC monotherapy.[16,18] For patients who met the objective medical criteria, the CR + CRh rates were 61.2% in the VEN + AZA arm (N = 67) and 61.5% in the VEN + DEC arm (N = 13) compared to 22.8% for patients treated with AZA monotherapy (in VIALE-A). The CR rates were 43.3% for patients treated with VEN + AZA and 53.8% for patients treated with VEN + DEC compared to 19.5% and 15.7% for patients treated with historical AZA or DEC monotherapy, respectively.[16,18]

In VIALE-C (primary analysis; 15 February 2019), the CR + CRh rate for patients treated with VEN + LDAC was greater than that for patients treated with PBO + LDAC (46.9% vs. 14.7%, respectively). Greater CR rates were also observed for patients treated with VEN + LDAC versus patients treated with PBO + LDAC (27.3% vs. 7.4%, respectively). At the 6-month follow-up analysis (15 August 2019), rates of CR + CRh (48.3% vs. 14.7%) and CR (28.0% vs. 7.4%) were also higher for VEN + LDAC arm versus PBO + LDAC arm. Rates for CR + CRh and CR in the VEN + LDAC arm were higher at the 6-month follow-up analysis compared to the primary analysis;

rates for the PBO + LDAC arm remained 14.7% for CR + CRh and 7.4% for CR.

In Study M14-387, for patients meeting the objective medical criteria (N = 61), the rates of CR + CRh (42.6%) and CR (21.3%) were greater for patients treated with VEN 600 mg + LDAC than for patients treated with LDAC monotherapy in VIALE-C (CR + CRh: 14.7%; CR: 7.4%). The CR rates in this study were also higher than CR rates for patients treated with historical LDAC monotherapy (7.9%).[18]

In VIALE-A, the proportion of patients who achieved CR + CRh by initiation of Cycle 2 was statistically significantly higher (p-value < 0.001) in the VEN + AZA arm (39.9%) versus the PBO + AZA arm (5.5%). Median time to first response of CR + CRh was 1.0 month for patients in the VEN + AZA arm versus 2.6 months for patients in the PBO + AZA arm.

In Study M14-358, CR + CRh rates at the initiation of Cycle 2 was 36.9% for patients in the VEN 400 mg + AZA arm and 25.8% for patients in the VEN 400 mg + DEC arm. For patients meeting the objective medical criteria, median time to first response of CR + CRh was 1.0 month for patients in the VEN + AZA arm and 1.9 months for patients in the VEN + DEC arm.

In VIALE-C (primary analysis), 30.8% patients in VEN + LDAC achieved CR + CRh by initiation of Cycle 2 versus 4.4% patients in PBO + LDAC (p-value < 0.001; statistical significance cannot be inferred). Median time to first response of CR + CRh (primary analysis) was 1.0 month for patients in the VEN + LDAC arm versus 2.8 months for patients in the PBO + LDAC arm.
In Study M14-387, CR + CRh rate at the initiation of Cycle 2 was 30.5% for patients in the VEN 600 mg + LDAC arm. For patients meeting the objective medical criteria, median time to first response of CR + CRh was 1.0 month in the VEN + LDAC arm.

The Applicant's Position:
Venetoclax in combination with HMAs or LDAC substantially increases the rates of CR + CRh and CR compared to remission rates for AZA or LDAC monotherapy in the randomized trials or historical AZA, DEC, or LDAC monotherapy.[16,18] The response rates of CR + CRh and CR in both the randomized trials, VIALE-A and VIALE-C, were early and 2 to 3 times higher in the VEN combination arms compared to the control arms with AZA and LDAC, respectively. Responses to VEN in combination with AZA, DEC, or LDAC were rapid compared to the reported median time to response for these agents when given as monotherapy.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of remission rates across trials. We further note that remission rates were generally consistent across trials. In particular, the CR rate for VEN+AZA was 36.7% in VIALE-A and 43.3% in M14-358. The CR rate for VEN+LDAC was 27.3% in VIALE C and 21.3% in M14-387. Furthermore, the CR+CRh rate for VEN+AZA was 64.7% in VIALE-A and 61.2% in M14-358; the CR+CRh rate for VEN+LDAC was 46.9% in VIALE-C and 42.6% in M14-387.

These response rates are supportive for the VEN+AZA combination. As the OS endpoint was not met in VIALE-C, OS alone cannot constitute substantial efficacy for this combination. While this trial did not meet its primary objective, it did provide robust results on the secondary endpoints consistent with M14-387.

Post-hoc analyses such as those conducted when Type I error is no longer controlled should be interpreted with caution. In general, the validity of such analyses is stronger when 1) they have been pre-specified, 2) they have been replicated in another experiment, and 3) the magnitude of benefit is compelling. In the case of the analyses of CR and CR+CRh in VIALE-C, these comparisons were pre-specified in the testing hierarchy, the rates were similar to those observed in M14-387, and the magnitude of benefit vs. PBO+LDAC is compelling.

Transfusion Independence

Data:

In VIALE-A, a statistically significantly (p-value < 0.001) greater percentage of patients in the VEN + AZA arm (59.8%) achieved RBC transfusion independence versus the PBO + AZA arm (35.2%). A statistically significantly (p-value < 0.001) greater percentage of patients in the VEN + AZA arm (68.5%) achieved platelet transfusion independence versus PBO + AZA arm (49.7%).

In Study M14-358, for patients in the VEN 400 mg + AZA arm meeting the objective medical criteria (N = 41), 82.9% of patients achieved RBC transfusion independence and 87.8% of patients achieved platelet transfusion independence.

In Study M14-358, for patients in the VEN 400 mg + DEC arm meeting the objective medical criteria (N = 8), 87.5% of patients achieved RBC transfusion independence and 100% of patients achieved platelet transfusion independence.

In VIALE-C (primary analysis), 40.6% of patients in the VEN + LDAC arm achieved RBC transfusion independence versus 17.6% patients in the PBO + LDAC arm (p-value = 0.001); 47.6% of patients in the VEN + LDAC arm achieved platelet transfusion independence versus 32.4% patients in the PBO + LDAC arm (p-value = 0.040). Higher RBC and platelet transfusion independence rates in patients treated with VEN + LDAC were also observed in the 6-month follow-up analysis.

In Study M14-387, for patients in the VEN 600 mg + LDAC arm meeting the objective medical criteria (N = 26), 88.5% of patients achieved RBC transfusion independence and 88.5% of patients achieved platelet transfusion independence.

The Applicant's Position:

Venetoclax in combination with AZA, DEC, or LDAC significantly improved the percentage of patients who achieved transfusion independence (RBC and platelets).

Transfusion independence rates were similar across all 3 venetoclax combination regimens. RBC transfusion independence rates ranged from 38% to 57% for patients who were RBC

transfusion-dependent at baseline. Platelet transfusion independence rates ranged from 30% to 61% for patients who were platelet transfusion-dependent at baseline.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment.

Biomarkers
Data:
IDH1/IDH2: In VIALE-A, VEN + AZA was statistically significantly (p-value < 0.001) more effective than PBO + AZA with CR + CRh rate of 72.1% versus 7.1%. The median OS for patients treated with VEN + AZA and IDH1/IDH2 mutations was statistically significantly longer versus patients treated with PBO + AZA and IDH1/IDH2 mutations (HR = 0.345, p-value < 0.0001).

In VIALE-C, VEN + LDAC was more effective than PBO + LDAC with CR + CRh rate of 57.1% versus 33.3%. The median OS for patients treated with VEN + AZA and IDH1/IDH2 mutations was longer versus patients treated with PBO + AZA and IDH1/IDH2 mutations (HR = 0.724).

FLT3: In VIALE-A, response rates of CR + CRh for patients with FLT3 mutations treated with VEN + AZA was statistically significantly greater at 65.5% versus 18.2% for patients with FLT3 treated with PBO + AZA (p-value = 0.001). The HR for OS was consistent with the overall population (HR = 0.664), and the median OS was 12.7 months for VEN + AZA compared to 8.6 months for PBO + AZA.

In VIALE-C, FLT3 mutations of any type and mutational burden were detected in a total of 29 patients: 9 patients in the PBO + LDAC arm and 20 patients in the VEN + LDAC arm. The median OS for patients in the VEN + LDAC arm with FLT3 mutations was 5.9 months, compared to 9.8 months in the PBO + LDAC arm (HR = 1.113).

Response rates for patients with FLT3 mutations treated with VEN + LDAC were comparable to the remission rates for all patients randomized to the VEN + LDAC arm, whereas the rate among the 9 patients with FLT3 mutations treated with PBO + LDAC was higher than the response rates for the overall population randomized to PBO + LDAC. In the VEN + LDAC arm, a CR + CRh rate of 45.0% was obtained in patients with FLT3 mutations, compared to a CR + CRh rate of 44.4% in the PBO + LDAC arm.

The Applicant's Position:
Among patients with common or prognostically relevant mutational profiles (IDH1/IDH2 and FLT3 mutations), VEN in combination with AZA or LDAC was effective.

Across all 4 studies, VEN in combination with AZA or LDAC was more effective than AZA or LDAC monotherapy for patients with IDH1/IDH2 mutations. Response rates for patients with IDH1/IDH2 mutations were greater than response rates for the overall population which is consistent with nonclinical findings that IDH1/IDH2 mutated AML cells may have increased

sensitivity to apoptosis upon treatment with venetoclax.[25] Furthermore, improvement in the remission rates correlate with a longer median OS.

In VIALE-A, VEN + AZA demonstrates a greater response compared to AZA monotherapy for patients with FLT3 mutations. In VIALE-C, the response rates for patients with FLT3 mutations treated with VEN + LDAC were generally consistent with the response rates for the overall population. However, the 9 patients with FLT3 mutations treated with PBO + LDAC had a much higher response rate than the overall population. Therefore, no difference was observed in response rates between treatment arms in VIALE-C. In VIALE-A, VEN + AZA has shown improved survival for patients with FLT3 mutations compared to the survival observed for AZA alone (HR = 0.664), whereas improved survival was not observed in VIALE-C for patients with FLT3 mutations (HR = 1.113).

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of these biomarkers. We note that the sample size of these subpopulations is small. In addition, the treatment effects reported in these subgroups do not provide meaningful additional information beyond the results obtained in the ITT populations. Consequently, treatment effects in these subgroups should not be reported in labeling.

Minimal/Measurable Residual Disease

Data:
The ELN MRD working group reviewed over 40 publications which evaluated MRD in AML and concluded that MRD has prognostic significance and the working group recommended a threshold of $< 10^{-3}$ as clinically meaningful for survival. A reduction in MRD levels below 1 leukemic cell in 1,000 ($< 10^{-3}$) was prognostic for OS and risk of relapse after intensive chemotherapy and, therefore, was considered a relevant metric to evaluate the quality of the remission (CR, CRi, or CRh) in response to these lower intensity regimens of VEN + AZA and VEN + LDAC.

In VIALE-A, MRD was assessed centrally in the bone marrow by multicolor flow cytometry (MFC) as a secondary endpoint. MRD response defined as $< 10^{-3}$ was evaluated. In the VEN + AZA arm, 64 patients (22.4%) achieved CR + CRh and had a best MRD value of $< 10^{-3}$ compared to 9 patients (6.2%) in the PBO + AZA arm (p-value < 0.001). The 64 patients in the VEN + AZA arm who achieved CR + CRh and a best MRD value of $< 10^{-3}$ had a median OS that was not yet reached (95% CI: 24.4 months, NR). The 9 patients in the PBO + AZA arm had a median OS that was 28.8 months (95% CI: 7.0, 28.8 months).

In VIALE-C, MRD was assessed centrally in the bone marrow by MFC as a secondary endpoint. In VIALE-C, bone marrow MRD assessment was not required after CR was achieved, potentially resulting in fewer MRD assessments over time during the study. In the VEN + LDAC arm, 8 patients (5.6%) achieved CR + CRh and had a best MRD value of $< 10^{-3}$ compared to 1 patient (1.5%) in the PBO + LDAC arm (p-value = 0.162). The 8 patients in the VEN + LDAC arm who achieved CR + CRh and a best MRD value of $< 10^{-3}$ had a median OS that was not yet reached

(95% CI: 7.2 months, NR).

The Applicant's Position:
Patients treated with VEN in combination with AZA or LDAC demonstrated deep responses as determined by MFC. The rates of these deep responses (CR + CRh and MRD < 10^{-3}) were higher in patients treated with VEN in combination with AZA or LDAC in the 2 randomized trials. In VIALE-A and VIALE-C, patients who achieved a CR + CRh and MRD levels of < 10^{-3} experienced long median OS.

While the MRD negative rate has not been formally tested according to the US SAP, the high rate of deep responses (MRD < 10^{-3} remission) and prolonged OS observed across the studies add context to the depth and durability of the response achieved with the VEN combinations.

Regulatory Authorities' Assessment:

Minimal residual disease (MRD) was evaluated in all studies by multicolor flow cytometry from bone marrow aspirate samples using an MRD threshold of <0.1% (10^{-3}). MRD results presented in the CSRs were not confirmed by the FDA. 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. (b) (4)

Subpopulations

Venetoclax (400 mg) in Combination with an HMA (AZA or DEC)
Data:
In VIALE-A, VEN (400 mg) + AZA was a more effective treatment in the evaluated subgroups (cytogenetic risk, age, AML type [de novo or secondary], and AML-MRC) as measured by median OS and remission rates (CR + CRh and CR) compared to PBO + AZA. Results for these subgroups are presented in Section 8.1.2, under the subheading of "Additional Analyses Conducted on the Individual Trial". Results for other subgroups of interest are presented in Table 31.

Table 33. VIALE-A: Summary of OS by Subgroup (Efficacy Analysis Set)

	VEN + AZA (N = 286)		PBO + AZA (N = 145)		
Subgroup	**n**	**Median (months) (95% CI)**	**n**	**Median (months) (95% CI)**	**HR (95% CI)[a]**
Sex					
Female	114	16.8 (10.4, NA)	58	11.0 (6.8, 13.7)	0.68 (0.46, 1.02)
Male	172	13.5 (10.8, 18.7)	87	8.6 (6.0, 12.4)	0.62 (0.46, 0.85)
Age					
< 75	112	15.2 (10.8, 20.8)	58	13.2 (8.2, 23.4)	0.89 (0.59, 1.33)
≥ 75	174	14.1 (10.4, 21.8)	87	8.5 (6.0, 10.7)	0.54 (0.39, 0.73)
Race					

	VEN + AZA (N = 286)		PBO + AZA (N = 145)		
Subgroup	**n**	**Median (months) (95% CI)**	**n**	**Median (months) (95% CI)**	**HR (95% CI)[a]**
White	217	14.1 (10.4, 17.6)	109	10.6 (7.0, 12.7)	0.65 (0.50, 0.86)
Black or African American	3	NE	2	NE	NE
Asian	66	19.5 (10.6, NR)	33	10.1 (3.4, 20.3)	0.64 (0.35, 1.15)
American Indian or Alaska Native	0	NE	1	NE	NE

AZA = azacitidine; CI = confidence interval; HR = hazard ratio; N = sample size; n = number of patients; NE = not evaluable; NR = not reached; OS = overall survival; PBO = placebo; VEN = venetoclax

a From unstratified Cox proportional hazards model

Note: Median (95% CI) and HR (95% CI) are only calculated for subgroups with available data.
Data included are subject to a cutoff date of 04 January 2020.

Sources: VIALE-A CSR Figure 14.2__11.4.6.1, Figure 14.2__11.4.6.2, Figure 14.2__11.4.7.3, Figure 14.2__11.4.7.4; AAid Ad Hoc Figure 14.2__F1. Source datasets: ADSL, ADTTE and ADRS (VIALE-A).

In Study M14-358, VEN in combination with AZA was more effective in all evaluated subgroups as measured by remission rates (CR + CRh and CR) compared to PBO + AZA (in VIALE-A). Additionally, for patients with intermediate or poor cytogenetic risks or secondary AML and randomized to receive VEN + AZA in VIALE-A, the CR + CRh and CR rates were greater than the CR + CRh and CR rates for patients randomized to receive PBO + AZA. Overall, median OS was longer than previously reported OS in AZA monotherapy historical trials[16] for every subgroup with contextual historical data, including patients with poor-risk cytogenetics and secondary AML. Additionally, the CR + CRi rates were 2- to 3-fold greater for patients treated with VEN (400 mg) + AZA versus AZA monotherapy.

In Study M14-358, VEN in combination with DEC was effective in all evaluated subgroups as measured by remission rates (CR + CRh and CR). Overall, median OS was longer than previously reported OS in DEC monotherapy historical trials[18] for every subgroup with contextual historical data, including patients with poor-risk cytogenetics and secondary AML.

The Applicant's Position:
Similar trends across the VIALE-A and Study M14-358 evaluating VEN in combination with an HMA (AZA or DEC) were observed for subgroup populations. Overall, VEN (400 mg) in combination with either of the HMAs (AZA or DEC) was an effective treatment in newly-diagnosed patients with AML who were ineligible for intensive therapy, inclusive of all subpopulations.

Venetoclax (600 mg) in Combination with LDAC

Data:
Recent literature reports present outcomes for patients with AML treated with LDAC in high risk AML populations (intermediate- and poor-risk cytogenetics, secondary AML, and ≥ 75 years of age). Results for the subgroups of cytogenetic risk (intermediate, poor), type of AML (de novo, secondary, and AML-MRC), and patients who received prior HMAs for MDS are presented in Section 8.1.4, under the subheading of "Additional Analyses Conducted on the Individual Trial". Results for other subgroups of interest are presented in Table 32.

Table 34. VIALE-C: Summary of OS by Subgroups (Full Analysis Set)

	VEN + LDAC (N = 143)		PBO + LDAC (N = 68)		
Subgroup	**n**	**Median (months) (95% CI)**	**n**	**Median (months) (95% CI)**	**HR (95% CI)[a]**
Sex					
Female	65	6.7 (5.5, 13.7)	29	7.3 (1.6, 9.9)	0.66 (0.38, 1.15)
Male	78	7.7 (4.0, 10.1)	39	4.1 (3.1, 9.7)	0.82 (0.52, 1.31)
Age					
< 75	61	8.8 (5.5, 10.9)	28	7.3 (2.0, NR)	0.85 (0.47, 1.52)
≥ 75	82	6.6 (4.7, 9.7)	40	3.6 (3.0, 8.8)	0.69 (0.44, 1.09)
Race					
White	102	6.7 (5.0, 10.1)	47	4.1 (3.0, 7.9)	0.69 (0.45, 1.05)
Black or African American	2	NE	1	NE	NE
Asian	39	7.7 (4.7, 12.7)	20	5.9 (1.7, NR)	0.79 (0.40, 1.56)

CI = confidence interval; HR = hazard ratio; LDAC = low-dose cytarabine; N = sample size; n = number of patients; NE = not evaluable; NR = not reached; OS = overall survival; PBO = placebo; VEN = venetoclax

a From unstratified Cox proportional hazards model

Note: Median (95% CI) and HR (95% CI) are only calculated for subgroups with available data.
Data included are subject to a cutoff date of 15 February 2019.

Source: AAid Ad Hoc Figure 14.2_1.1. Source datasets: ADSL and ADTTE (VIALE-C).

The observed response rates for VEN + LDAC in VIALE-C and Study M14-358 appear much higher than previously reported for historical LDAC monotherapy treatments[18] across the subgroups. The combination of VEN and LDAC improves outcomes for patients across all reported risk groups, though historically prognostic features appear to retain prognostic significance with VEN in combination with LDAC. Remission rates (CR + CRh) were greater for patients treated with VEN + LDAC versus LDAC monotherapy.

The Applicant's Position:
Similar trends across VIALE-C and Study M14-387 evaluating VEN in combination with LDAC were observed for subgroup populations. Overall, VEN (600 mg) in combination with LDAC was an effective treatment in newly-diagnosed patients with AML who were ineligible for intensive therapy, inclusive of all subpopulations.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of subpopulation results for both VIALE-A and VIALE-C studies. These results should be considered exploratory only.

Additional Efficacy Considerations

Regulatory Authorities' Assessment:
No further efficacy considerations.

8.1.11. Integrated Assessment of Effectiveness

The Applicant's Position:
Venetoclax in combination with an HMA (AZA or DEC) or LDAC was substantially more effective in patients with AML who were ineligible for intensive therapy, inclusive of all subpopulations and including those with poor prognosis, compared to HMA or LDAC monotherapy. Venetoclax

in combination with an HMA or LDAC resulted in longer OS, rapid, durable responses with clinically meaningful improvements in response rates, and greater transfusion independence rates compared to HMA or LDAC monotherapies or currently available therapies for patients who were ineligible for intensive therapy. Venetoclax in combination with AZA or LDAC did not have any decrement in fatigue over and above that due to AZA or LDAC alone as assessed by the PROMIS Cancer Fatigue SF 7a score. VEN + AZA patients also experienced longer time to deterioration in quality of life compared to patients treated with AZA alone as assessed by the EORTC-QLQ-C30 GHS/QoL.

In the double-blind, multicenter, randomized Phase 3 study, VIALE-A, VEN in combination with AZA statistically significantly reduced the risk of death (HR = 0.662 [95% CI: 0.518, 0.845]; p-value < 0.001 [stratified log-rank test]) in newly-diagnosed AML patients ineligible to receive intensive chemotherapy. The median OS for patients randomized to receive VEN (400 mg) in combination with AZA was statistically significantly longer compared to patients randomized to receive PBO in combination with AZA.

In the double-blind, multicenter, randomized Phase 3 study, VIALE-C, VEN in combination with LDAC reduced the risk of death in newly-diagnosed AML patients ineligible to receive intensive chemotherapy (HR = 0.749 [95% CI: 0.524, 1.071]; primary analysis). The median OS was longer for patients treated with VEN (600 mg) in combination with LDAC compared patients treated with PBO in combination with LDAC. The 6-month follow-up analysis showed even longer median OS for patients receiving VEN + LDAC with a further reduction in the risk of death for these patients.

In the 2 nonrandomized studies, the median OS for patients treated with VEN (400 mg) in combination with AZA or DEC (Study M14-358) and VEN (600 mg) in combination with LDAC (Study M14-387) was longer than the median OS reported in the PBO treatment arms for VIALE-A and VIALE-C, respectively, and for the median OS reported in the literature for patients treated with AZA, DEC, or LDAC monotherapy.[16,18] All 3 combination therapies demonstrated a consistent improvement in survival.

In the 2 randomized studies (VIALE-A and VIALE-C), VEN in combination with AZA or LDAC resulted in significant increases in the remission rates (CR + CRh and CR) compared to patients treated with PBO in combination with AZA or LDAC, respectively. In VIALE-A, remission rates were statistically greater for patients randomized to receive VEN (400 mg) + AZA versus patients randomized to receive PBO + AZA (p-values < 0.001). In VIALE-C, remission rates were greater for patients receiving VEN (600 mg) + LDAC versus patients receiving PBO + LDAC (p-value < 0.001; statistical significance cannot be inferred since the study did not meet its primary endpoint of OS).

In the 2 nonrandomized studies (Study M14-358 and Study M14-387), the CR + CRh and CR rates were substantially greater than the remission rates reported for the reference therapy in the PBO treatment arms of VIALE-A and VIALE-C, respectively, and greater than the previously reported remission rates for patients treated with AZA, DEC, or LDAC monotherapy.[16,18]

In VIALE-A and VIALE-C, VEN in combination with AZA or LDAC improved the percentage of patients who achieved transfusion independence (RBC and platelet) compared to patients treated with PBO in combination with AZA or LDAC, respectively. In VIALE-A, a statistically significantly greater percentage of patients randomized to receive VEN (400 mg) in combination with AZA achieved transfusion independence compared to patients randomized to receive PBO in combination with AZA (p-value < 0.001). In VIALE-C, more patients in the VEN (600 mg) + LDAC arm achieved transfusion independence compared to patients in the PBO + LDAC arm (p-value = 0.002).

The totality of the efficacy data from pivotal studies, VIALE-A and VIALE-C, and the supportive studies, Study M14-358 and Study M14-387, demonstrate that venetoclax in combination with an HMA (azacitidine or decitabine) or LDAC represents a significant advancement for the treatment of newly-diagnosed patients with AML who are otherwise ineligible to receive standard intensive therapies. Additionally, the efficacy data including rapid, durable, and higher remission rates of CR/CRh across multiple biologic subsets of AML results in improvement in survival over the available standard of care treatment options.

Regulatory Authorities' Assessment:
We note that in the VIALE-C study, the treatment arm VEN+LDAC did not significantly improve OS versus PBO+LDAC. As noted above, the observed CR and CR+CRh was similar across VIALE-C and M14-387, with compelling magnitude of treatment effect vs. PBO+LDAC in VIALE-C. In addition, the observed effect on CR+CRh was accompanied by an increase transfusion independence. Taken together, the improvement on CR and duration of CR may be considered to be clinical benefit. Supportive evidence of benefit can be provided by the rate of CR+CRh, duration of CR+CRh, and the rate of conversion to and maintenance of transfusion independence.

8.2. Review of Safety

The Applicant's Position:
The safety profile of venetoclax in combination with AZA, LDAC, or DEC in previously untreated patients with AML has been assessed in 4 studies: VIALE-A (pivotal) and Study M14-358 assessed VEN + AZA, VIALE-C (pivotal) and Study M14-387 assessed VEN + LDAC, and Study M14-358 also assessed VEN + DEC. VIALE-A and VIALE-C are placebo-controlled studies and have enrolled a larger number of patients, so they provide the highest level of evidence to assess the safety profile in AML of VEN in combination with AZA and LDAC. Phase 1-2 studies, Study M14-358 and Study M14-387, were previously submitted to the FDA in 2018; these studies have been updated with an interim analysis and report for this submission. The study designs for all 4 studies are provided in Section 8.1.

VIALE-A provides evidence for the safety assessment of the combination VEN 400 mg + AZA based on 283 AML patients; this assessment is supported by the 84 patients exposed to VEN 400 mg + AZA in Study M14-358.

VIALE-C provides similar evidence for the safety assessment of the combination VEN 600 mg + LDAC based on 142 AML patients; this assessment is supported by the 82 patients exposed to VEN 400 mg + LDAC in Study M14-387.

The safety assessment of the combination VEN 400 mg + DEC is based on 31 AML patients from Study M14-358.

Pooled analyses for each of the therapies (VEN + AZA and VEN + LDAC) have been provided in Module 5 of the dossier. Safety data are presented for 367 patients treated with VEN 400 mg + AZA, as well as for 350 patients treated with VEN 400 mg + AZA and meeting the objective medical criteria (known as Ferrara criteria). Safety data are also presented for 224 patients treated with VEN 600 mg + LDAC, as well as for 203 patients treated with VEN 600 mg + LDAC and meeting the objective medical criteria.

The key safety findings from these 4 studies are presented in the following sections, with data cutoff dates of 4 January 2020 for VIALE-A, 15 August 2019 (6-month follow-up analysis) for VIALE-C, 30 August 2019 for Study M14-358, and 16 October 2019 for Study M14-387. The safety profile demonstrated by VIALE-A and VIALE-C in the treatment of newly-diagnosed AML patients is consistent with that of the previously analyzed nonrandomized studies and reflects the known safety profiles of VEN, AZA, LDAC, and DEC together with the natural history of AML.

Regulatory Authorities' Assessment:
We agree with the Sponsor's assessment of the safety database for venetoclax in combinations with low-intensity therapy. Due to the differences in the expected AE profile of azacitidine compared to low-dose cytarabine, the safety analysis was not pooled between the backbones. The population of patients treated with decitabine was relatively small compared to the other combinations and was also not pooled with the azacitidine group.

The 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. The age restriction and comorbidities were defined with the Agency's input during the conduct of the single-arm studies and is reviewed in S-009. These criteria were a modification of the consensus criteria in Ferrara et al 2013 and referred to as the "modified Ferrara criteria". Initial enrollment in the single-arm studies did not require these objective definitions to describe patients who were unfit for intensive therapy. However, the randomized studies only enrolled patients who met the objective modified Ferrara criteria. To ensure an adequate evaluation of the safety of venetoclax in this potentially frail population, pooled safety analyses were performed for patients who met those criteria referred to as the modified Ferrara criteria in this review. Therefore, the pooled analyses for safety for VEN/AZA was 350 patients (283 in VIALE-A and 67 in M14-358), for VEN/DEC was 13 patients (in M14-358), and for VEN/LDAC was 203 (142 in VIALE-C and 61 in M14-387).

The efficacy evaluation for VIALE-C in the USPI will be presented at the time of the protocol specified final analysis (15 February 2019); therefore, the safety analysis for purposes of the USPI will also be presented from that timepoint. In this review, the analyses presented by the Applicant used the 6-month follow up timepoint (15 August 2019). Full safety analyses at the earlier timepoint conducted by the FDA will not be presented here, but areas of significant differences in the timepoints will be noted.

8.2.1. Safety Review Approach

The Applicant's Position:
The safety profile of AZA, LDAC, and DEC, are well established in the AML patient population. The focus of the safety review in this clinical program was, therefore, to confirm the safety profile of these drugs when used in combination with VEN in previously untreated patients with AML who are older or have comorbidities.

The analyses presented hereafter is of treatment-emergent AEs, i.e., any event not present prior to the initiation of study treatment, or any event already present that worsened in either intensity or frequency following exposure to study treatment.

The safety profile of VEN in combination with AZA, LDAC, or DEC was assessed by analyzing the frequency of AEs, SAEs (including Grade 5 AEs), AEs of special interest (AESIs)/selected AEs, AEs leading to discontinuation, AEs leading to dose modification (dose reduction or interruption), vital sign measurements, and clinical laboratory assessments. All AEs were to be reported until 30 days after the last dose of study treatment (for VEN, AZA, LDAC, or DEC).

To assess clinically meaningful differences between treatment arms in VIALE-A and VIALE-C, incidence rates with < 5% difference between treatment arms for any AEs, and incidence rates with < 2% difference between treatment arms for SAEs and AEs Grade ≥ 3 were considered comparable. Difference in incidence rates between VEN and PBO arms, internal consistency of data within a study, consistency across AML studies, and biologic plausibility were considered in assessing potential new adverse drug reactions (ADRs).

Regulatory Authorities' Assessment:
Because the randomized data is more useful to evaluate the contribution of venetoclax to the safety profile, the prescribing information in the US will describe VIALE-A for VEN/AZA and VIALE-C for VEN/LDAC. The pooled analyses are used for signal seeking for other important AEs.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 35. Safety Population, Size, and Denominators

Safety Database for the Study Drug[a] Individuals exposed to the study drug in this development program for the indication under review N[b] = 834		
Clinical Trial Groups	**Venetoclax (n = 622)**	**Placebo[e] (n = 212)**
Controlled trials conducted for this indication[c]	425	212
All other than controlled trials conducted for this indication[d]	197	0

[a] Study drug means the drug being considered for approval.
[b] N is the sum of all available numbers from the columns below
[c] To be used in product's labeling
[d] If placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
[e] Placebo control patients were patients who received placebo + azacitidine or placebo + LDAC
Note: The N and n values reported in this table are limited to subjects who received venetoclax at the proposed doses and do not include all subjects who received venetoclax in the uncontrolled studies (Study M14-358 and Study M14-387).

Data from a total of 622 AML patients who received venetoclax and 212 patients who received placebo in the ongoing studies were evaluated for extent of exposure (Table 33). This includes data from patients who received VEN 400 mg + AZA (N = 283) in VIALE-A; VEN 400 mg + AZA (N = 84) and VEN 400 mg + DEC (N = 31) in Study M14-358; VEN 600 mg + LDAC (N = 142) in VIALE-C; and VEN 600 mg + LDAC (N = 82) in Study M14-387. Data from patients who received PBO + AZA (N = 144) in VIALE-A and PBO + LDAC (N = 68) in VIALE-C are also included.

Across the 4 studies of VEN in combination with HMAs or LDAC, treatment cycles were 28 days long.

In VIALE-A, patients treated with VEN 400 mg + AZA had a median duration of exposure of 7.6 months of VEN (range: < 0.1 [rounded to 0.0 in source table] to 30.7) and a median of 7.0 months of AZA (range: < 0.1 [rounded to 0.0 in source table] to 30.5). Patients treated with PBO + AZA had a median duration of exposure of 4.3 months of PBO (range: 0.1 to 24.0) with a median of 3.8 months of AZA (range: 0.1 to 23.4). Patients received both VEN and AZA for a median of 7.0 cycles (range: 1.0 to 30.0) and received both PBO and AZA for a median of 4.5 cycles (range: 1.0 to 26.0).

Table 36. VIALE-A: Dose Intensity of Venetoclax/Placebo and Azacitidine by Cycle

	VEN + AZA (N = 283)					PBO + AZA (N = 144)				
Cycle	**n**	**VEN dose intensity[a] < 80% n (%)**	**VEN dose intensity[b] < 80% n (%)**	**n[c]**	**AZA dose intensity[d] < 80% n (%)**	**n**	**PBO dose intensity[a] < 80% n (%)**	**PBO dose intensity[b] < 80% n (%)**	**n**	**AZA dose intensity[d] < 80% n (%)**
1	283	44 (15.5)	96 (33.9)	282	7 (2.5)	144	25 (17.4)	19 (13.2)	144	5 (3.5)
2	238	38 (16.0)	80 (33.6)	237	6 (2.5)	111	19 (17.1)	22 (19.8)	111	4 (3.6)
3	206	56 (27.2)	92 (44.7)	205	9 (4.4)	95	15 (15.8)	16 (16.8)	95	3 (3.2)
4	190	76 (40.0)	98 (51.6)	189	15 (7.9)	83	9 (10.8)	14 (16.9)	83	0
5	175	96 (54.9)	111 (63.4)	174	25 (14.4)	72	15 (20.8)	15 (20.8)	72	2 (2.8)
6	162	96 (59.3)	106 (65.4)	161	35 (21.7)	61	12 (19.7)	14 (23.0)	61	5 (8.2)
7	143	99 (69.2)	92 (64.3)	142	37 (26.1)	53	12 (22.6)	15 (28.3)	53	4 (7.5)

8	123	88 (71.5)	89 (72.4)	122	40 (32.8)	50	15 (30.0)	14 (28.0)	50	5 (10.0)
9	114	89 (78.1)	84 (73.7)	113	47 (41.6)	46	14 (30.4)	16 (34.8)	46	3 (6.5)
10	106	81 (76.4)	84 (79.2)	105	42 (40.0)	42	13 (31.0)	14 (33.3)	42	2 (4.8)
> 10	101	82 (81.2)	83 (82.2)	100	52 (52.0)	34	13 (38.2)	14 (41.2)	34	3 (8.8)

AZA = azacitidine; BSA = body surface area; CYP3A = cytochrome P450 3A isoform subfamily; N = sample size; n = number of patients; PBO = placebo; P-gp = P-glycoprotein; VEN = venetoclax

[a] VEN/PBO dose intensity by cycle, based on the planned 28-day cycle length, is defined as the actual total VEN/PBO dose (mg) in Cycle X divided by the planned total VEN/PBO (mg) from the first dose date of Cycle X to 27 days after the first dose date of Cycle X (first dose date of VEN/PBO of Cycle X + 27 days) or cutoff date whichever is earliest. The planned total VEN/PBO dose also considers protocol-planned VEN dose reduction with concomitant use of CYP3A and P-gp inhibitors and washout of CYP3A and P-gp inhibitors with continued VEN/PBO dose reduction.

[b] VEN/PBO dose intensity by cycle, accounting for dose reductions and all dose interruptions (within cycle and between cycles), is defined as the actual total VEN/PBO dose (mg) divided by the planned total VEN/PBO dose (mg) during the treatment period for each cycle. Treatment period for each cycle is defined as the first dose date of VEN/PBO in Cycle X to the day prior to the first dose date of VEN/PBO in Cycle (X + 1), or to the last dose date if Cycle X is the last cycle. The planned total VEN/PBO dose also considers protocol planned VEN dose reduction with concomitant use of CYP3A and P-gp inhibitors and washout of CYP3A and P-gp inhibitors with continued VEN/PBO dose reduction.

[c] There is one patient who has height missing at baseline. The dose intensity of AZA cannot be calculated for this patient due to missing BSA.

[d] Azacitidine dose intensity by cycle, based on the planned 28-day cycle length, is defined as the actual total AZA dose in mg divided by the planned total AZA dose in mg for each cycle. The planned total AZA dose in mg for each cycle is defined as 75 mg/m^2 * BSA * 7 days. BSA is derived from baseline height (cm) and weight (kg) using DuBois method.[26] The first postbaseline height or weight are used if baseline height or weight are not available.

Note: Percentages are calculated for non-missing dose intensity values. Percentages are calculated using the number of patients in each cycle.

Source: AAid Ad Hoc Table 14.1__T2, Table 14.1__T1, and Table 14.1__T3. Source filename: M15656-adhoc-US-aaid.

The dose intensity of VEN and AZA by cycle in VIALE-A is presented in Table 34. In column 3 (VEN dose intensity[a] < 80%) and column 8 (PBO dose intensity[a] < 80%) of this table, VEN/PBO dose intensity within each cycle based on a planned 28-day cycle length is presented. VEN/PBO dose intensity results in column 4 (VEN dose intensity[b] < 80%) and column 9 (PBO dose intensity[b] < 80%) were based on the duration of a treatment in a cycle (from Cycle X Day 1 to 1 day before Cycle [X + 1] Day 1); these are analogous to the values reported in the CSR for overall VEN/PBO dose intensity except for VEN/PBO dosage adjustment for P-gp inhibitors and the washout period for CYP3A and P-gp inhibitors. The results for columns 4 and 9 accounted for all dose interruptions (between cycles and within cycle). Both calculations accounted for planned VEN/PBO dosage adjustment for concomitant use of CYP3A and P-gp and 2 to 3 days washout period for VEN/PBO dose reduction after CYP3A and P-gp discontinuation as such reductions in ingested dose still results in comparable drug exposure and therapeutically is comparable to full dose intensity. Columns 6 and 11 present the dose intensity of AZA within each cycle.

In Study M14-358, patients treated with VEN 400 mg + AZA had median duration of exposure of 6.4 months of VEN (range: 0.1 to 38.1) and a median of 6.0 cycles of VEN (range: 1.0 to 37.0) and 4.0 cycles of AZA (range: 1.0 to 29.0).

In Study M14-358, patients treated with VEN 400 mg + DEC had median duration of exposure of 5.7 months of VEN (range: 0.5 to 41.8) and a median of 6.0 cycles for VEN and DEC (range: 1.0 to 38.0).

In VIALE-C, patients treated with VEN 600 mg + LDAC had median duration of exposure of 4.1 months of VEN (range: < 0.1 [rounded to 0.0 in source table] to 23.5) and a median of 3.5 months of LDAC (range: < 0.1 [rounded to 0.0 in source table] to 23.4). Patients treated with PBO + LDAC had a median duration of exposure of 1.7 months of PBO (range: 0.1 to 20.2) and 1.3 months of LDAC (range: < 0.1 [rounded to 0.0 in source table] to 19.9). Patients received both VEN and LDAC for a median of 4.0 cycles (range: 1.0 to 22.0) and received both PBO and AZA for a median of 2.0 cycles (range: 1.0 to 21.0).

Table 37. VIALE-C: Dose Intensity of Venetoclax/Placebo and LDAC by Cycle

	VEN + LDAC (N = 142)				PBO + LDAC (N = 68)			
Cycle	n	VEN dose intensity[a] < 80% n (%)	VEN dose intensity[b] < 80% n (%)	LDAC dose intensity[c] < 80% n (%)	n	PBO dose intensity[a] < 80% n (%)	PBO dose intensity[b] < 80% n (%)	LDAC dose intensity[c] < 80% n (%)
1	142	28 (19.7)	38 (26.8)	9 (6.3)	68	21 (30.9)	15 (22.1)	3 (4.4)
2	110	17 (15.5)	28 (25.5)	2 (1.8)	42	9 (21.4)	3 (7.1)	2 (4.8)
3	89	15 (16.9)	28 (31.5)	5 (5.6)	28	5 (17.9)	1 (3.6)	3 (10.7)
4	79	19 (24.1)	30 (38.0)	2 (2.5)	20	2 (10.0)	3 (15.0)	0
5	66	21 (31.8)	29 (43.9)	2 (3.0)	17	2 (11.8)	2 (11.8)	1 (5.9)
6	59	22 (37.3)	30 (50.8)	4 (6.8)	16	2 (12.5)	2 (12.5)	0
7	52	20 (38.5)	23 (44.2)	6 (11.5)	15	2 (13.3)	2 (13.3)	1 (6.7)
8	41	11 (26.8)	19 (46.3)	2 (4.9)	11	2 (18.2)	1 (9.1)	0
9	37	16 (43.2)	18 (48.6)	3 (8.1)	9	1 (11.1)	1 (11.1)	0
10	32	15 (46.9)	15 (46.9)	2 (6.3)	9	1 (11.1)	1 (11.1)	1 (11.1)
> 10	28	12 (42.9)	14 (50.0)	4 (14.3)	7	2 (28.6)	1 (14.3)	1 (14.3)

BSA = body surface area; CYP3A = cytochrome P450 3A isoform subfamily; LDAC = low-dose cytarabine; N = sample size; n = number of patients; PBO = placebo; P-gp = P-glycoprotein; VEN = venetoclax

[a] VEN/PBO dose intensity by cycle, based on the planned 28-day cycle length, is defined as the actual total VEN/PBO dose (mg) in Cycle X divided by the planned total VEN/PBO (mg) from the first dose date of Cycle X to 27 days after the first dose date of Cycle X (first dose date of VEN/PBO of Cycle X + 27 days) or cutoff date whichever is earliest. The planned total VEN/PBO dose also considers protocol-planned VEN dose reduction with concomitant use of CYP3A and P-gp inhibitors and washout of CYP3A and P-gp inhibitors with continued VEN/PBO dose reduction.

[b] VEN/PBO dose intensity by cycle, accounting for dose reductions and all dose interruptions (within cycle and between cycles), is defined as the actual total VEN/PBO dose (mg) divided by the planned total VEN/PBO dose (mg) during the treatment period for each cycle. Treatment period for each cycle is defined as the first dose date of VEN/PBO in Cycle X to the day prior to the first dose date of VEN/PBO in Cycle (X + 1), or to the last dose date if Cycle X is the last cycle. The planned total VEN/PBO dose also considers protocol planned VEN dose reduction with concomitant use of CYP3A and P-gp inhibitors and washout of CYP3A and P-gp inhibitors with continued VEN/PBO dose reduction.

[c] LDAC dose intensity by cycle, based on the planned 28-day cycle length, is defined as the actual total LDAC dose in mg divided by the planned total LDAC dose in mg for each cycle. The planned total LDAC dose in mg for each cycle is defined as 20 mg/m^2 * BSA * 10 days. BSA is derived from baseline height (cm) and weight (kg) using the DuBois method.[26] The first postbaseline height or weight are used if baseline height or weight are not available.

Note: Percentages are calculated for non-missing dose intensity values. Percentages are calculated using the number of patients in each cycle.

Source: AAid Ad Hoc Table 14.1__1.2, Table 14.1__1.1, and Table 14.1__1.3 (6-month follow-up analysis; 15 August 2019). Source filename: M16043-adhoc-US-aaid.

The dose intensity of VEN and LDAC by cycle in VIALE-C is presented in Table 35. In column 3 (VEN dose intensity[a] < 80%) and column 7 (PBO dose intensity[a] < 80%) of this table, VEN/PBO dose intensity within each cycle based on a planned 28-day cycle length is presented. VEN/PBO dose intensity results in column 4 (VEN dose intensity[b] < 80%) and column 8 (PBO dose intensity[b] < 80%) were based on the duration of a treatment in a cycle (from Cycle X Day 1 to 1

day before Cycle [X + 1] Day 1); these are analogous to the values reported in the CSR for overall VEN/PBO dose intensity except for VEN/PBO dosage adjustment for P-gp inhibitors and the washout period for CYP3A and P-gp inhibitors. The results for columns 4 and 8 accounted for all dose interruptions (between cycles and within cycle). Both calculations accounted for planned VEN/PBO dosage adjustment for concomitant use of CYP3A and P-gp and 2 to 3 days washout period for VEN/PBO dose reduction after CYP3A and P gp discontinuation as such reductions in ingested dose still results in comparable drug exposure and therapeutically is comparable to full dose intensity. Columns 5 and 9 present the dose intensity of LDAC within each cycle.

In Study M14-387, patients treated with VEN 600 mg + LDAC had median duration of exposure of 4.2 months of VEN (range: 0.2 to 41.8), as well as a median of 5.0 cycles of VEN (range: 1.0 to 43.0) and 3.0 cycles of LDAC (range: 1.0 to 36.0).

The Applicant's Position:
Compared to placebo controls (in the randomized Phase 3 studies), duration of exposure to VEN in combination with AZA or LDAC was consistently higher, as measured by median duration of exposure and median number of cycles. These results also suggest that, duration of exposure was not reduced by combining VEN to the treatment regimen.

Duration of exposure to DEC was also not reduced by combining VEN, when compared to historical data values of 4 cycles of DEC (range: 1 to 29 cycles).[18]

Regulatory Authorities' Assessment:
Table 23 presented by the Applicant at the presents the dose intensity of venetoclax and azacitidine separately by cycle. An intensity of <80% for venetoclax indicates 22 days or less of a planned 28-day cycle and for azacitidine represents 5 days or less of 7 planned per cycle. In the venetoclax arm, after the initial cycles, the dose intensity falls from approximately 15% of patients receiving less than 80% intensity to 70-80% of patients in the later cycles. The intensity of azacitidine appears relatively independent of the venetoclax treatment in early cycles, but in later cycles, significantly more patients were receiving less than full doses of azacitidine in the venetoclax arm compared to the placebo arm. This evaluation indicates that even though there is a clear survival benefit, perhaps the dose of venetoclax that is tolerable over a 28-day cycle has not been identified. However, in the absence of efficacy data with lower doses, it is acceptable to plan for 28-day dosing of venetoclax with dose modifications on an individual basis in response to adverse reactions and/or cytopenias.

A similar pattern of dose intensity was observed in the VIALE-C study in combination with LDAC as presented in Table 24. The decrease in dose intensity is not as pronounced in the LDAC combination with about 15% of patients receiving less than 80% intensity in the initial cycles, then falling to 30-45% of patients in the later cycles, likely reflecting the overall lower intensity of the LDAC regimen compared to the AZA regimen. The intensity of the LDAC backbone is more stable here also indicating a less intense regimen.

Relevant characteristics of the safety population:

Data:

The majority of patients in the ongoing studies had discontinued VEN as of the data cutoff dates for those individual studies. However, 122 patients treated with VEN + AZA (VIALE-A, n = 113; Study M14-358, n = 9), 3 patients treated with VEN + DEC (Study M14-358, n = 3), and 44 patients treated with VEN + LDAC (VIALE-C, n = 40; Study M14-387, n = 4), remained ongoing for disease progression and/or survival follow-up. Also ongoing for disease assessment and/or survival follow-up were 33 patients treated with PBO + AZA (VIALE-A) and 12 patients treated with PBO + LDAC (VIALE-C).

The median age of patients across studies ranged from 73 to 76 years. More than half of patients were male. One hundred and two patients (25.4%) treated with VEN 400 mg in combination with HMAs had secondary AML, and 71 patients (17.7%) reported an antecedent hematologic disorder of either MDS or MPN. Among patients treated with VEN 600 mg in combination with LDAC, 98 patients (43.6%) had secondary AML, and 86 patients (38.2%) reported an antecedent hematologic disorder of either MDS or MPN.

At baseline, the majority of patients across studies had Grade 3 or 4 neutropenia, Grade ≥ 2 anemia, and Grade 3 or 4 thrombocytopenia. Baseline hepatic impairment was present in 23.7% of patients in VIALE-A and in 27.5% of patients in VIALE-C. Baseline renal impairment was present in 76.0% of patients in VIALE-A and in 77.7% of patients in VIALE-C. Baseline hepatic impairment was categorized as mild or moderate and was defined as bilirubin ≤ 1 mg/dL and aspartate aminotransferase (AST) > 40 or bilirubin > 1 mg/dL. Baseline renal impairment was categorized as mild or moderate and was defined as CrCl of ≥ 30 mL/min to < 90 mL/min.

The Applicant's Position:

The demographics and baseline characteristics of the patient population were mostly well balanced between treatment arms and are described in Section 8.1. These demographic data and baseline disease characteristics define a group of AML patients with pre-existing comorbidities who are at risk of adverse outcomes. The patients enrolled in these studies are representative of patients who could receive venetoclax upon approval.

Regulatory Authorities' Assessment:

The safety population was nearly identical to the efficacy population. Baseline characteristics of the efficacy population are described in section 8.1 and represent the safety population in the randomized studies. In VIALE-A, 427 patients received venetoclax or placebo: 283 with VEN/AZA and 144 with PBO/AZA. In VIALE-C, 210 patients received venetoclax or placebo: 142 with VEN/LDAC and 68 with PBO/LDAC.

Adequacy of the safety database:

Data:

As of 28 November 2019, a total of 3,974 patients in the venetoclax development program and programs for other oncology compounds have known exposure to venetoclax across company-

sponsored clinical studies (open-label and unblinded data available in the clinical databases). This includes 3,481 adult patients (≥ 18 years of age) enrolled in oncology studies for monotherapy or combination therapy.

There were 622 adult patients with AML have been exposed to at least 1 dose of venetoclax in VIALE-A (VEN 400 mg + AZA), VIALE-C (VEN 600 mg + LDAC), Study M14-358 (VEN 400 mg + AZA and VEN 400 mg + DEC), and Study M14-387 (VEN 600 mg + LDAC). The duration of exposure for the combination therapies is presented in the "Overall Exposure" section.

The most recent Periodic Safety Update Report (PSUR) summarizes interval and cumulative benefit-risk information regarding venetoclax for the reporting interval of 05 June 2019 through 04 December 2019. The estimated cumulative patient exposure from company-sponsored interventional clinical trials for venetoclax was 4,243 patients. The worldwide postmarketing patient exposure to venetoclax was estimated to be 5,964 patient-treatment years (PTY) for all approved indications (chronic lymphocytic leukemia and AML) during the reporting interval. The estimated cumulative postmarketing patient exposure since first approval is 16,784 PTY.

The Applicant's Position:
The safety profiles of VEN, AZA, LDAC, and DEC as monotherapies have been established. The size of the study database for these studies is considered adequate to support the benefit-risk assessment for the use of venetoclax in combination with AZA, LDAC, or DEC in patients with previously untreated AML and adequately represents the target patient population.

Regulatory Authorities' Assessment:
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 for the indicated population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections; data in the CRFs and AE databases were consistent.

Regulatory Authorities' Assessment:
The quality of the safety data submitted was adequate to allow substantial primary review.

Categorization of Adverse Event

The Applicant's Position:
For classification purposes, lower-level terms were assigned by the Sponsors to the original

terms entered on the eCRF, using the most up-to-date version of MedDRA (Version 21.0) terminology for AEs and diseases. AEs were then presented by PT and SOC.

For the analysis of selected AEs across studies, the following search criteria (MedDRA PT, AE Group Term [AEGT], Standardized MedDRA Query [SMQ], or MedDRA SOC) were applied:

- Grade ≥ 3 neutropenia: PTs of neutropenia and neutrophil count decreased. The following MedDRA PTs were used to identify Grade ≥ 3 events of "extended search neutropenia": neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.
- Anemia: PTs of anaemia and haemoglobin decreased
- Thrombocytopenia: PTs of thrombocytopenia and platelet count decreased
- Grade ≥ 3 infection: SOC of Infections and Infestations.
- Hemorrhage: SMQ of Haemorrhages (narrow)
- TLS (AE): SMQ of Tumour Lysis Syndrome (narrow)

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

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. Adverse events were assessed by frequency (i.e., events per patient). Additional group terms were evaluated based on common related terms (see Appendix 19.5). The grouped terms are included in safety analyses throughout the review and will be indicated with an "*" in safety tables and the text of the review.

Routine Clinical Tests

The Applicant's Position:
Key assessments for each study included AE assessments, routine clinical laboratory tests (hematology, chemistry, etc.), vital sign assessments, and pregnancy tests (for applicable patients).

For VIALE-A and VIALE-C, AE assessments were performed at every study visit, beginning at Screening through the 30-day Safety Follow-up visit. Hematology and chemistry tests (drawn pre-dose) were evaluated at Screening; Cycle 1 Days 1 to 5 for VIALE-A or Days 1 to 6 for VIALE-C; Cycle 1 Days 8, 15, and 22; Day 1 of Cycles ≥ 2; Final Visit; and 30-day Safety Follow-up visit. Coagulation and urinalysis tests were performed at Screening, Cycle 1 Day 1, and at the Final Visit. Vital signs and physical exams (including weight) were assessed at Screening, Day 1 of every cycle, Final Visit, and the 30-day Safety Follow-up visit; physical exams were also performed prior to patient discharge from the hospital during Cycle 1 Days 5 to 7. Assessments for electrocardiograms (ECG) (12-lead and MUGA) were performed at Screening; 12-lead ECG was also assessed at the Final Visit. Serum pregnancy tests were performed at Screening and urine pregnancy tests were performed on Day 1 of each cycle prior to dosing.

For Study M14-358, AE assessments, hematology and chemistry assessments (drawn pre-dose), and vital signs assessments were performed at every study visit, beginning at Screening through the 30-day Safety Follow-up visit (except on Day –1 [for hematology and chemistry], at the end of Cycles 1, 4, and end of every 3 cycles thereafter). Coagulation and urinalysis tests were performed at Screening, Day 1 of Cycles 1 and 2, Final Visit, and 30-day Safety Follow-up visit. Assessments for ECG (12-lead and MUGA) were performed at Screening; 12-lead ECG was also assessed at the Final Visit.

For Study M14-387, AE assessments, hematology and chemistry assessments (drawn pre-dose), and vital signs assessments were performed at every study visit, beginning at Screening through the 30-day Safety Follow-up visit (except on Day 1 of Cycles 2, 4, and every 3 cycles thereafter). Coagulation tests were performed at Screening, Day 1 of Cycles 1 and 2, Final Visit, and 30-day Safety Follow-up visit. Urinalysis tests were performed at Screening. Assessments for ECG (12-lead and MUGA) were performed at Screening; 12-lead ECG was also assessed at the Final Visit.

Regulatory Authorities' Assessment:
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

Data:
Thirty- and 60-day mortality rates in AML are often considered to be a reflection of treatment-related morbidity.

In VIALE-A, patients who received VEN + AZA had 30-day and 60-day mortality rates of 7.4% and 15.2%, respectively; patients who received PBO + AZA had 30-day and 60-day mortality rates of 6.3% and 16.7%, respectively. In Study M14-358, patients treated with VEN 400 mg + AZA had 30-day and 60-day mortality rates of 2.4% and 8.3%, respectively.

In Study M14-358, patients treated with VEN 400 mg + DEC had 30-day and 60-day mortality rates of 6.5% and 9.7%, respectively.

In VIALE-C, 30- and 60-day mortality rates were numerically lower in patients treated with VEN + LDAC compared to PBO + LDAC. Patients who received VEN + LDAC had 30-day and 60-day mortality rates of 12.7% and 20.4%, respectively, compared to rates of 16.2% and 30.9%, respectively, for patients who received PBO + LDAC. In Study M14-387, patients treated with VEN 600 mg + LDAC had 30-day and 60-day mortality rates of 6.1% and 14.6%, respectively.

The majority of deaths were caused by disease progression. A summary of deaths among patients receiving proposed doses of venetoclax or placebo in combination with HMAs or LDAC is presented in Table 36. AEs leading to death are presented by SOC and PT in Table 37.

Across all studies, infections were the most common AEs that resulted in death; the PTs of pneumonia, sepsis, and septic shock were the most frequently reported AEs of infection. In the Phase 3 studies, the percentage of patients with AEs of infection leading to death was higher among patients who received VEN + AZA compared to those who received PBO + AZA (9.2% vs 7.6%) and among patients who received VEN + LDAC compared to PBO + LDAC (14.8% vs 10.3%) (Table 37).

The Applicant's Position:

Early mortality was not increased with the addition of VEN to AZA or LDAC, compared to PBO with AZA or LDAC. Among patients treated with VEN at the proposed doses in combination with AZA or LDAC, 30-day and 60-day mortality rates were 7.4% and 15.2%, respectively, in combination with AZA, and 12.7% and 20.4%, respectively, in combination with LDAC. These rates were not worse than those of patients who received PBO in combination with AZA or LDAC and suggest that patients treated with VEN in combination with AZA or LDAC are not at increased risk of early mortality.

Despite a numerically higher incidence of fatal infections among patients who received VEN in combination with AZA or LDAC compared to those who received PBO with AZA or LDAC, the differences were < 5% and were not considered clinically notable. Further, upon medical review, these deaths were deemed consistent with a patient population with advanced AML and other risk factors.

Table 38. Summary of Deaths Among AML Patients Receiving Proposed Doses of Venetoclax or Placebo in Combination with HMAs or LDAC

	VIALE-A PBO +AZA (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
All deaths by occurrence, n (%)							
Occurring ≤ 30 days after first dose	9 (6.3)	21 (7.4)	2 (2.4)	2 (6.5)	11 (16.2)	18 (12.7)	5 (6.1)
Occurring ≤ 60 days after first dose	24 (16.7)	43 (15.2)	7 (8.3)	3 (9.7)	21 (30.9)	29 (20.4)	12 (14.6)
All deaths by cause, n (%)							
Disease progression	65 (45.1)	75 (26.5)	34 (40.5)	17 (54.8)	37 (54.4)	61 (43.0)	54 (65.9)
Non-disease progression	35 (24.3)	78 (27.6)	21 (25.0)	8 (25.8)	14 (20.6)	36 (25.4)	13 (15.9)
Missing/unknown	9 (6.3)	6 (2.1)	1 (1.2)	0	3 (4.4)	2 (1.4)	0

AZA = azacitidine; DEC = decitabine; HMA = hypomethylating agent; LDAC = low-dose cytarabine; N = sample size; n = number of patients; PBO = placebo; VEN = venetoclax
Sources: VIALE-A Interim CSR Table 14.3__2.6.1.1; Study M14-358 Interim CSR Table 14.3__2.3.2.1, Table 14.3__2.3.2.2; VIALE-C Interim CSR Table 14.3__2.6.1A; Study M14-387 Interim CSR Table 14.3__2.3.2. Source datasets: ADSL, SDTM.DM, and SDTM.DD (VIALE-A); ADSL, SDTM.DM, and SDTM.DD (Study M14-358); ADSL (6-Month Follow-Up Analysis), SDTM.DM, and SDTM.DD (VIALE-C); and ADSL, SDTM.DM, and SDTM.DD (Study M14-387).

Table 39. Treatment-Emergent Adverse Events Leading to Death, by SOC and PT, Among AML Patients Receiving Proposed Doses of Venetoclax or Placebo in Combination with HMAs or LDAC

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO +AZA (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Any AE	29 (20.1)	64 (22.6)	13 (15.5)	6 (19.4)	14 (20.6)	33 (23.2)	16 (19.5)
Blood and lymphatic system disorders	1 (0.7)	0	0	0	0	2 (1.4)	0
Anaemia	0	0	0	0	0	1 (0.7)	0
Febrile neutropenia	1 (0.7)	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	1 (0.7)	0
Cardiac disorders	6 (4.2)	8 (2.8)	1 (1.2)	0	2 (2.9)	3 (2.1)	0
Acute myocardial infarction	1 (0.7)	0	0	0	0	0	0
Atrial fibrillation	0	2 (0.7)	0	0	0	0	0
Cardiac arrest	2 (1.4)	3 (1.1)	0	0	1 (1.5)	0	0
Cardiac failure	0	1 (0.4)	0	0	0	0	0
Cardiac failure acute	0	1 (0.4)	0	0	1 (1.5)	3 (2.1)	0
Cardio-respiratory arrest	1 (0.7)	0	0	0	0	0	0
Cardiovascular insufficiency	1 (0.7)	0	0	0	0	0	0
Myocardial infarction	0	1 (0.4)	1 (1.2)	0	0	0	0
Myocardial ischaemia	1 (0.7)	0	0	0	0	0	0
Gastrointestinal disorders	0	2 (0.7)	1 (1.2)	0	0	1 (0.7)	0

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO +AZA (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Gastritis erosive	0	0	0	0	0	1 (0.7)	0
Gastritis haemorrhagic	0	1 (0.4)	0	0	0	0	0
Intestinal haemorrhage	0	1 (0.4)	0	0	0	0	0
Intestinal ischaemia	0	0	1 (1.2)	0	0	0	0
General disorders and administration site conditions	7 (4.9)	9 (3.2)	3 (3.6)	0	3 (4.4)	2 (1.4)	2 (2.4)
Catheter site haemorrhage	1 (0.7)	0	0	0	0	0	0
Death	2 (1.4)	4 (1.4)	0	0	1 (1.5)	0	1 (1.2)
General physical health deterioration	1 (0.7)	1 (0.4)	0	0	1 (1.5)	0	0
Multiple organ dysfunction syndrome	1 (0.7)	2 (0.7)	2 (2.4)	0	1 (1.5)	1 (0.7)	0
Sudden cardiac death	1 (0.7)	0	0	0	0	0	0
Sudden death	0	1 (0.4)	1 (1.2)	0	0	1 (0.7)	1 (1.2)
Systemic inflammatory response syndrome	1 (0.7)	2 (0.7)	0	0	0	0	0
Hepatobiliary disorders	0	0	0	0	0	0	1 (1.2)
Acute hepatic failure	0	0	0	0	0	0	1 (1.2)
Infections and infestations	11 (7.6)	26 (9.2)	5 (6.0)	2 (6.5)	7 (10.3)	21 (14.8)	6 (7.3)
Anal abscess	0	1 (0.4)	0	0	0	0	0
Aspergillus infection	0	0	0	0	0	1 (0.7)	0
Bacteraemia	0	0	0	1 (3.2)	0	0	0
Bronchopulmonary aspergillosis	0	0	0	0	0	1 (0.7)	0
Candida sepsis	0	1 (0.4)	0	0	1 (1.5)	0	0
Enterococcal infection	0	1 (0.4)	0	0	0	0	0
Escherichia infection	1 (0.7)	0	0	0	0	0	0
Escherichia sepsis	0	1 (0.4)	0	0	0	0	0
Fungal sepsis	0	1 (0.4)	0	0	0	0	0
Gastroenteritis salmonella	0	1 (0.4)	0	0	0	0	0
Influenza	0	1 (0.4)	0	0	0	0	0
Klebsiella bacteraemia	0	0	1 (1.2)	0	0	0	0
Klebsiella infection	1 (0.7)	1 (0.4)	0	0	0	0	0
Lung infection	0	0	0	0	0	0	2 (2.4)
Lung infection pseudomonal	0	0	0	0	1 (1.5)	0	0
Neutropenic sepsis	0	0	0	0	0	1 (0.7)	0
Pneumocystis jirovecii pneumonia	0	0	0	0	0	1 (0.7)	0
Pneumonia	3 (2.1)	11 (3.9)	1 (1.2)	1 (3.2)	0	7 (4.9)	1 (1.2)
Pneumonia fungal	0	0	1 (1.2)	0	0	0	0
Pneumonia staphylococcal	0	0	0	0	1 (1.5)	0	0
Psoas abscess	0	0	0	0	0	1 (0.7)	0
Pulmonary sepsis	0	0	0	0	0	0	1 (1.2)
Rhinovirus infection	1 (0.7)	0	0	0	0	0	0

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO +AZA (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Sepsis	5 (3.5)	6 (2.1)	0	0	1 (1.5)	4 (2.8)	2 (2.4)
Septic shock	1 (0.7)	3 (1.1)	1 (1.2)	0	3 (4.4)	5 (3.5)	0
Sinusitis fungal	0	0	1 (1.2)	0	0	0	0
Staphylococcal sepsis	0	0	0	0	1 (1.5)	1 (0.7)	0
Injury, poisoning and procedural complications	1 (0.7)	0	0	0	0	0	0
Subdural haematoma	1 (0.7)	0	0	0	0	0	0
Metabolism and nutrition disorders	1 (0.7)	1 (0.4)	0	0	0	2 (1.4)	0
Failure to thrive	0	1 (0.4)	0	0	0	0	0
Metabolic acidosis	1 (0.7)	0	0	0	0	0	0
Tumour lysis syndrome	0	0	0	0	0	2 (1.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.4)	0	2 (6.5)	0	0	3 (3.7)
Brain neoplasm	0	1 (0.4)	0	0	0	0	0
Malignant neoplasm progression	0	0	0	2 (6.5)	0	0	3 (3.7)
Nervous system disorders	1 (0.7)	10 (3.5)	0	0	1 (1.5)	3 (2.1)	3 (3.7)
Cerebral haematoma	0	1 (0.4)	0	0	0	0	0
Cerebral haemorrhage	1 (0.7)	1 (0.4)	0	0	0	1 (0.7)	1 (1.2)
Cerebral infarction	0	1 (0.4)	0	0	0	0	0
Cerebrovascular accident	0	1 (0.4)	0	0	0	1 (0.7)	0
Coma	0	1 (0.4)	0	0	0	0	0
Haemorrhage intracranial	0	3 (1.1)	0	0	1 (1.5)	0	2 (2.4)
Haemorrhagic stroke	0	1 (0.4)	0	0	0	0	0
Ischaemic stroke	0	1 (0.4)	0	0	0	0	0
Seizure	0	1 (0.4)	0	0	0	0	0
Transient ischaemic attack	0	0	0	0	0	1 (0.7)	0
Renal and urinary disorders	0	2 (0.7)	0	0	0	0	0
Renal failure	0	2 (0.7)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	3 (2.1)	5 (1.8)	3 (3.6)	2 (6.5)	1 (1.5)	1 (0.7)	1 (1.2)
Acute respiratory distress syndrome	0	1 (0.4)	0	0	0	0	0
Acute respiratory failure	1 (0.7)	1 (0.4)	1 (1.2)	0	0	0	0
Haemoptysis	1 (0.7)	0	0	0	0	0	0
Pneumonitis	1 (0.7)	0	0	0	0	0	0
Pulmonary alveolar haemorrhage	0	0	0	0	0	1 (0.7)	0
Respiratory arrest	0	0	0	1 (3.2)	0	0	0
Respiratory failure	0	3 (1.1)	2 (2.4)	1 (3.2)	1 (1.5)	0	1 (1.2)
Vascular disorders	1 (0.7)	1 (0.4)	0	0	0	0	0
Coeliac artery occlusion	0	1 (0.4)	0	0	0	0	0
Hypotension	1 (0.7)	0	0	0	0	0	0

AE = adverse event; AZA = azacitidine; DEC = decitabine; HMA = hypomethylating agent; LDAC = low-dose cytarabine; MedDRA = Medical Dictionary for Regulatory Activities; N = sample size; n = number of patients; PBO = placebo; PT = preferred term; SOC = system organ class; VEN = venetoclax

Sources: VIALE-A Interim CSR Table 14.3__2.5.2.1; Study M14-358 Interim CSR Table 14.3__2.3.1.1, Table 14.3__2.3.1.2; VIALE-C Interim CSR Table 14.3__2.5.2A; Study M14-387 Interim CSR Table 14.3__2.3.1. Source datasets: ADSL and ADAE (VIALE-A); ADSL and ADAE (Study M14-358); ADSL (6-Month Follow-Up Analysis) and ADAE (6-Month Follow-Up Analysis) (VIALE-C); and ADSL and ADAE (Study M14-387).

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment based on the investigator's assessment of causality of death due to AE. In both the VIALE-A and VIALE-C study, no excess mortality within 30 days of initiation of treatment was observed with the addition of venetoclax to either backbone.

Serious Adverse Events

Data:
Serious AEs with ≥ 5% incidence in any study for patients receiving proposed doses of venetoclax in combination with HMAs or LDAC are presented in Table 38.

In VIALE-A, SAEs were experienced by 83.0% of patients treated with VEN 400 mg + AZA and 72.9% of patients treated with PBO + AZA. SAEs experienced by ≥ 5% of patients treated with VEN + AZA included febrile neutropenia (29.7%), pneumonia (16.6%), and sepsis (5.7%); SAEs experienced by ≥ 5% of patients treated with PBO + AZA included pneumonia (22.2%), febrile neutropenia (10.4%), and sepsis (8.3%).

In Study M14-358, SAEs were experienced by 77.4% of patients treated with VEN 400 mg + AZA. SAEs experienced by ≥ 5% of patients treated with VEN + AZA included febrile neutropenia (31.0%), pneumonia (26.2%), and multiple organ dysfunction syndrome (6.0%).

In Study M14-358, SAEs were experienced by 80.6% of patients treated with VEN 400 mg + DEC. SAEs experienced by ≥ 5% of patients who received VEN + DEC included febrile neutropenia (41.9%), bacteremia (16.1%), pneumonia (29.0%), sepsis (6.5%), malignant neoplasm progression (6.5%), and respiratory failure (6.5%).

In VIALE-C, SAEs were experienced by 66.9% of patients treated with VEN 600 mg + LDAC and 61.8% of patients treated with PBO + LDAC. SAEs experienced by ≥ 5% of patients treated with VEN + LDAC included febrile neutropenia (16.9%), pneumonia (14.1%), and sepsis (5.6%); SAEs experienced by ≥ 5% of patients treated with PBO + LDAC included febrile neutropenia (17.6%), pneumonia (10.3%), pyrexia (7.4%), sepsis (5.9%), and septic shock (5.9%).

In Study M14-387, SAEs were experienced by 91.5% of patients treated with VEN 600 mg + LDAC. SAEs experienced by ≥ 5% of patients treated with VEN + LDAC included febrile neutropenia (28.0%), pneumonia (12.2%), sepsis (8.5%), and malignant neoplasm progression (6.1%).

The Applicant's Position:
The incidence of SAEs was generally consistent across studies and are consistent with what would be expected in an AML population. The overall incidence of serious infections is comparable between the VEN and PBO arms of VIALE-C, and is higher in the VEN treatment arm of VIALE-A. The incidence of febrile neutropenia was higher in the VEN treatment arms of both randomized studies. The SAEs observed in these studies were not associated with a clinically significant increase in infectious deaths for patients treated with VEN. The most common SAEs

across all treatment arms were febrile neutropenia, pneumonia, and sepsis.

Table 40. Serious Adverse Events Reported for SOCs and for PTs with ≥ 5% of Patients Receiving Proposed Doses of Venetoclax in Combination with HMAs or LDAC

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO + AZA (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Any SAE	105 (72.9)	235 (83.0)	65 (77.4)	25 (80.6)	42 (61.8)	95 (66.9)	75 (91.5)
Blood and lymphatic system disorders	24 (16.7)	113 (39.9)	28 (33.3)	13 (41.9)	16 (23.5)	33 (23.2)	26 (31.7)
Febrile neutropenia	15 (10.4)	84 (29.7)	26 (31.0)	13 (41.9)	12 (17.6)	24 (16.9)	23 (28.0)
Cardiac disorders	14 (9.7)	38 (13.4)	6 (7.1)	2 (6.5)	5 (7.4)	9 (6.3)	7 (8.5)
Gastrointestinal disorders	14 (9.7)	32 (11.3)	13 (15.5)	3 (9.7)	1 (1.5)	10 (7.0)	8 (9.8)
General disorders and administration site conditions	17 (11.8)	31 (11.0)	13 (15.5)	2 (6.5)	8 (11.8)	6 (4.2)	13 (15.9)
Multiple organ dysfunction syndrome	1 (0.7)	2 (0.7)	5 (6.0)	0	1 (1.5)	1 (0.7)	0
Pyrexia	3 (2.1)	7 (2.5)	3 (3.6)	1 (3.2)	5 (7.4)	3 (2.1)	3 (3.7)
Infections and infestations	63 (43.8)	162 (57.2)	40 (47.6)	17 (54.8)	25 (36.8)	53 (37.3)	36 (43.9)
Bacteraemia	0	5 (1.8)	3 (3.6)	5 (16.1)	0	1 (0.7)	2 (2.4)
Pneumonia	32 (22.2)	47 (16.6)	22 (26.2)	9 (29.0)	7 (10.3)	20 (14.1)	10 (12.2)
Sepsis	12 (8.3)	16 (5.7)	3 (3.6)	2 (6.5)	4 (5.9)	8 (5.6)	7 (8.5)
Septic shock	1 (0.7)	7 (2.5)	1 (1.2)	1 (3.2)	4 (5.9)	5 (3.5)	0
Injury, poisoning and procedural complications	8 (5.6)	8 (2.8)	7 (8.3)	0	1 (1.5)	3 (2.1)	8 (9.8)
Metabolism and nutrition disorders	6 (4.2)	9 (3.2)	2 (2.4)	0	0	5 (3.5)	5 (6.1)
Musculoskeletal and connective tissue disorders	1 (0.7)	5 (1.8)	1 (1.2)	0	2 (2.9)	0	5 (6.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (4.9)	6 (2.1)	0	2 (6.5)	2 (2.9)	0	5 (6.1)
Malignant neoplasm progression	5 (3.5)	2 (0.7)	0	2 (6.5)	0	0	5 (6.1)
Nervous system disorders	6 (4.2)	21 (7.4)	5 (6.0)	3 (9.7)	3 (4.4)	9 (6.3)	11 (13.4)
Renal and urinary disorders	8 (5.6)	13 (4.6)	1 (1.2)	1 (3.2)	0	2 (1.4)	4 (4.9)
Respiratory, thoracic and mediastinal disorders	10 (6.9)	23 (8.1)	13 (15.5)	4 (12.9)	5 (7.4)	4 (2.8)	13 (15.9)
Respiratory failure	1 (0.7)	5 (1.8)	3 (3.6)	2 (6.5)	1 (1.5)	2 (1.4)	1 (1.2)

AZA = azacitidine; DEC = decitabine; HMA = hypomethylating agent; LDAC = low-dose cytarabine; MedDRA = Medical Dictionary for Regulatory Activities; N = sample size; n = number of patients; PBO = placebo; PT = preferred term; SAE = serious adverse event; SOC = system organ class; VEN = venetoclax

Sources: VIALE-A Interim CSR Table 14.3__2.1.3.1; Study M14-358 Interim CSR Table 14.3__2.1.2.1.1, Table 14.3__2.1.2.1.2; VIALE-C Interim CSR Table 14.3__2.1.3A; Study M14-387 Interim CSR Table 14.3__2.1.2.1. Source datasets: ADSL and ADAE (VIALE-A); ADSL and ADAE (Study M14-358); ADSL (6-Month Follow-Up Analysis) and ADAE (6-Month Follow-Up Analysis) (VIALE-C); and ADSL and ADAE (Study M14-387).

Regulatory Authorities' Assessment:

FDA performed an analysis of all-grade treatment-emergent SAEs, and events occurring in ≥5% are presented in the tables below for VIALE-A and VIALE-C. AEs regarding laboratory evaluation (e.g., neutropenia or neutrophil count decreased) are excluded here and evaluated in the laboratory section or AESI where relevant. Analysis of SAEs appears similar to the Applicant's analysis except with different grouped terms.

	VIALE-A	
	Placebo + Aza N=144	**Venetoclax + Aza N=283**
	(%)	**(%)**
Any SAE	73	83
Febrile neutropenia	10	30
Pneumonia*	26	22
Sepsis	8	6
Hemorrhage*	5	6
Atrial fibrillation	1	5
Source: FDA analysis using adae.xpt, adsl.xpt *Grouped term (see Appendix 19.5)		

	VIALE-C	
	Placebo + LDAC N=68	**Venetoclax + LDAC N=142**
	(%)	**(%)**
Any SAE	62	62
Pneumonia*	15	17
Febrile neutropenia	18	16
Sepsis	6	6
Source: FDA analysis using adae.xpt, adsl.xpt (15 Feb 2020) *Grouped term (see Appendix 19.5)		

In VIALE-A, SAEs of febrile neutropenia were more common in the venetoclax arm, but SAEs of infections do not appear to be significantly more common. In VIALE-C, SAEs of febrile neutropenia was balanced between arms, and there does not appear to be an excess of pneumonia and sepsis SAEs. See discussion of infections under AESI below.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 41. Summary of Reasons for VEN/PBO Treatment Discontinuation (Full Analysis Set)

Discontinuation Due to:	VIALE-A PBO + AZA (N = 145)	VIALE-A VEN (400 mg) + AZA (N = 286)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 143)	M14-387 VEN (600 mg) + LDAC (N = 82)
Treatment Discontinuation due to Primary Reasons	127 (87.6)	209 (73.1)	75 (89.3)	28 (90.3)	63 (92.6)	117 (81.8)	78 (95.1)
AEs – Related to Disease Progression	5 (3.4)	5 (1.7)	3 (3.6)	1 (3.2)	3 (4.4)	5 (3.5)	8 (9.8)
AEs – Not Related to Disease Progression	13 (9.0)	43 (15.0)	17 (20.2)	3 (9.7)	6 (8.8)	15 (10.5)	14 (17.1)
Withdrew Consent	22 (15.2)	26 (9.1)	2 (2.4)	1 (3.2)	8 (11.8)	8 (5.6)	7 (8.5)
Lost to Follow-up	0	1 (0.3)	0	0	0	0	0
Physician Decision	9 (6.2)	17 (5.9)	2 (2.4)	1 (3.2)	8 (11.8)	8 (5.6)	9 (11.0)
Non-compliance with Study Drug	1 (0.7)	0	0	0	0	0	0
Study Terminated by Sponsor	0	0	0	0	0	0	0
Progressive Disease	21 (14.5)	9 (3.1)	27 (32.1)	12 (38.7)	12 (17.6)	17 (11.9)	32 (39.0)
Morphologic Relapse[a]	15 (10.3)	64 (22.4)	0	0	3 (4.4)	23 (16.1)	0
Treatment Failure[a]	13 (9.0)	4 (1.4)	0	0	13 (19.1)	18 (12.6)	0
Death	23 (15.9)	39 (13.6)	0	0	8 (11.8)	18 (12.6)	0
Toxicity	0	0	1 (1.2)	0	0	0	0
Other	5 (3.4)	1 (0.3)	23 (27.4)	10 (32.3)	2 (2.9)	5 (3.5)	8 (9.8)

AE = adverse events; AZA = azacitidine; DEC = decitabine; LDAC = low-dose cytarabine; N = sample size; PBO = placebo; VEN = venetoclax

[a] Treatment Failure and Morphologic Relapse were not included as categories for discontinuation reasons in Study M14-358 and Study M14-387.

Note: Patients who discontinued VEN/PBO are counted under each reason given for discontinuation. Therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

Sources: VIALE-A Interim CSR Table 14.1__2.1.2; Study M14-358 Interim CSR Table 14.1__2.1.1, Table 14.1__2.1.2; VIALE-C Interim CSR Table 14.1__1.4.1A; Study M14-387 Interim CSR Table 14.1__2.1. Source datasets: ADSL (VIALE-A); ADSL (Study M14-358); ADSL (6-Month Follow-Up Analysis) (VIALE-C); and ADSL (Study M14-387).

Table 42. Adverse Events Leading to VEN/PBO Treatment Discontinuation Reported in ≥ 2% of Patients Receiving Proposed Doses of Venetoclax in Combination with HMAs or LDAC

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO + AZA (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Any AE	29 (20.1)	69 (24.4)	21 (25.0)	8 (25.8)	16 (23.5)	37 (26.1)	27 (32.9)
Blood and lymphatic system disorders	6 (4.2)	11 (3.9)	5 (6.0)	1 (3.2)	4 (5.9)	6 (4.2)	3 (3.7)
Febrile neutropenia	1 (0.7)	4 (1.4)	3 (3.6)	0	2 (2.9)	2 (1.4)	1 (1.2)
Thrombocytopenia	3 (2.1)	3 (1.1)	0	0	1 (1.5)	1 (0.7)	2 (2.4)
Cardiac disorders	2 (1.4)	7 (2.5)	0	0	2 (2.9)	3 (2.1)	1 (1.2)
Gastrointestinal disorders	1 (0.7)	4 (1.4)	2 (2.4)	0	0	2 (1.4)	0

SOC and PT, n (%) (MedDRA, v21.0)	**VIALE-A PBO + AZA (N = 144)**	**VIALE-A VEN (400 mg) + AZA (N = 283)**	**M14-358 VEN (400 mg) + AZA (N = 84)**	**M14-358 VEN (400 mg) + DEC (N = 31)**	**VIALE-C PBO + LDAC (N = 68)**	**VIALE-C VEN (600 mg) + LDAC (N = 142)**	**M14-387 VEN (600 mg) + LDAC (N = 82)**
General disorders and administration site conditions	4 (2.8)	7 (2.5)	3 (3.6)	0	1 (1.5)	3 (2.1)	3 (3.7)
Fatigue	2 (1.4)	0	1 (1.2)	0	0	1 (0.7)	0
Infections and infestations	10 (6.9)	25 (8.8)	6 (7.1)	3 (9.7)	6 (8.8)	17 (12.0)	6 (7.3)
Pneumonia	4 (2.8)	4 (1.4)	2 (2.4)	3 (9.7)	1 (1.5)	7 (4.9)	1 (1.2)
Sepsis	5 (3.5)	4 (1.4)	0	0	1 (1.5)	2 (1.4)	2 (2.4)
Investigations	0	1 (0.4)	1 (1.2)	0	1 (1.5)	0	3 (3.7)
WBC count increased	0	0	0	0	0	0	2 (2.4)
Metabolism and nutrition disorders	0	0	0	0	0	3 (2.1)	1 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.1)	6 (2.1)	0	1 (3.2)	2 (2.9)	0	2 (2.4)
Tumour-associated fever	0	0	0	0	2 (2.9)	0	0
Malignant neoplasm progression	3 (2.1)	3 (1.1)	0	1 (3.2)	0	0	2 (2.4)
Nervous system disorders	1 (0.7)	5 (1.8)	1 (1.2)	1 (3.2)	1 (1.5)	4 (2.8)	4 (4.9)
Haemorrhage intracranial	0	1 (0.4)	0		1 (1.5)	1 (0.7)	2 (2.4)
Embolic stroke	0	0	0	1 (3.2)	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (1.4)	4 (1.4)	2 (2.4)	2 (6.5)	1 (1.5)	1 (0.7)	1 (1.2)
Respiratory arrest	0	0	0	1 (3.2)	0	0	0
Respiratory failure	0	1 (0.4)	1 (1.2)	1 (3.2)	0	0	0

AE = adverse event; AZA = azacitidine; DEC = decitabine; HMA = hypomethylating agent; LDAC = low-dose cytarabine; MedDRA = Medical Dictionary for Regulatory Activities; N = sample size; n = number of patients; PBO = placebo; PT = preferred term; SOC = system organ class; VEN = venetoclax; WBC = white blood cell

Note: The sum of the total number of patients reporting each of the PTs should be greater than or equal to the SOC total. A patient who reports two or more different PTs which are in the same SOC is counted only once in the SOC total.

Sources: VIALE-A Interim CSR Table 14.3__1.6.1.1; Study M14-358 Interim CSR Table 14.3__2.2.4.1.1.1.1, Table 14.3__2.2.4.1.1.1.2; VIALE-C Interim CSR Table 14.3__1.6.1A; Study M14-387 Interim CSR Table 14.3__2.2.4.1.1. Source datasets: ADSL and ADAE (VIALE-A); ADSL and ADAE (Study M14-358); ADSL (6-Month Follow-Up Analysis) and ADAE (6-Month Follow-Up Analysis) (VIALE-C); and ADSL and ADAE (Study M14-387).

Per protocol (in all 4 studies), study treatment could be discontinued if patients experienced toxicities related to treatment requiring more than 4-weeks (1 cycle) of dose interruption of VEN combination (in the absence of clinical benefit), if a patient became pregnant while on study treatment, or if a patient requires any radiotherapy or chemotherapy agents during the study period (with the exception of hydroxyurea allowed during Cycle 1).

In VIALE-A, AEs leading to study treatment discontinuation were reported for 69 patients (24.4%) treated with VEN 400 mg + AZA and 29 patients (20.1%) treated with PBO + AZA. The most commonly reported AEs leading to VEN/PBO discontinuation in the VEN + AZA arm versus PBO + AZA arm were sepsis (1.4% vs. 3.5%) and pneumonia (1.4% vs. 2.8%), followed by neutropenia (1.4% vs. 1.4%), febrile neutropenia (1.4% vs. 0.7%), and thrombocytopenia (1.1% vs. 2.1%).

In Study M14-358, AEs leading to study treatment discontinuation were reported for 21 patients (25.0%) treated with VEN 400 mg + AZA. AEs that led to VEN discontinuation reported in > 1 patient included febrile neutropenia reported in 3 patients (3.6%) and pneumonia reported in 2 patients (2.4%).

In Study M14-358, AEs leading to study treatment discontinuation were reported for 8 patients (25.8%) treated with VEN 400 mg + DEC. Pneumonia (reported in 3 patients, 9.7%) was the only AE leading to VEN discontinuation reported in > 1 patient.

In VIALE-C, AEs leading to study treatment discontinuation were similar across treatment arms and reported for 37 patients (26.1%) treated with VEN 600 mg + LDAC and 16 patients (23.5%) treated with PBO + LDAC. AEs that led to VEN discontinuation, reported in > 1 patient (VEN + LDAC arm) included pneumonia (7 patients, 4.9%), febrile neutropenia, lung infection, sepsis, septic shock, and TLS (2 patients each, 1.4%). AEs leading to PBO discontinuation (PBO + LDAC arm) reported in > 1 patient included febrile neutropenia and tumor associated fever (2 patients each, 2.9%).

In Study M14-387, AEs leading to study treatment discontinuation were reported for 27 patients (32.9) treated with VEN 600 mg + LDAC. AEs that led to VEN discontinuation included thrombocytopenia, sepsis, WBC count increased, malignant neoplasm progression, and haemorrhage intracranial, reported in 2 patients each (2.4%).

Discontinuations in the SOC of Infections and Infestations

Across studies, Infections and Infestations was the SOC with the highest incidence of AEs leading to VEN or PBO discontinuation.

In VIALE-A, for patients treated with VEN 400 mg or PBO in combination with AZA, AEs in the SOC of Infections and Infestations that led to study treatment discontinuation were reported for 25 patients (8.8%) in the VEN + AZA arm versus 10 patients (6.9%) in PBO + AZA arm.

In Study M14-358, AEs in the SOC of Infections and Infestations that led to VEN discontinuation

were reported for 6 patients (7.1%) treated with VEN 400 mg + AZA.

In Study M14-358, AEs in the SOC of Infections and Infestations that led to venetoclax discontinuation were observed in 3 patients (9.7%) treated with VEN 400 mg + DEC.

In VIALE-C, for patients treated with VEN 600 mg or PBO in combination with LDAC, AEs in the SOC of Infections and Infestations that led to study treatment discontinuation were reported for 17 patients (12.0%) in the VEN + LDAC arm versus 6 patients (8.8%) in the PBO + LDAC arm.

In Study M14-387, AEs in the SOC of Infections and Infestations that led to VEN discontinuation were reported for 6 patients (7.3%) treated with VEN 600 mg + LDAC.

The Applicant's Position:
The incidence of AEs leading to discontinuation of study treatment was similar across the VEN and PBO treatment arms in both VIALE-A and VIALE-C. Venetoclax in combination with HMAs or LDAC was well tolerated in newly-diagnosed patients with AML who are ineligible for intensive chemotherapy; the data support VEN treatment in combination with currently available low-intensity therapies (HMAs or LDAC) without adding clinically significant toxicity.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. The Applicant reported in this section only AEs leading to discontinuation of venetoclax or placebo. Patients could continue backbone chemotherapy without venetoclax/placebo and less commonly continue venetoclax/placebo without backbone therapy. In VIALE-A, 20% of patients discontinued all protocol therapy due to an AE in the VEN/AZA arm compared to 14% in the PBO/AZA arm. In VIALE-C, 16% of patients discontinued all protocol therapy due to an AE in the VEN/LDAC arm compared to 15% in the PBO/LDAC arm. Particular AEs leading to discontinuation of all protocol therapy did not occur in more than 2% of patients across both randomized trials except for pneumonia in VIALE-C which lead to discontinuation in 5% in the VEN/LDAC arm compared to 3% in the PBO/LDAC arm.

Dose Interruption/Reduction Due to Adverse Effects

Dose Interruption
Data:

Table 43. Adverse Events Leading to VEN/PBO Dose Interruption Reported in ≥ 5% of Patients Receiving Proposed Doses of Venetoclax in Combination with HMAs or LDAC

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO + AZA (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Any AE	82 (56.9)	204 (72.1)	57 (67.9)	20 (64.5)	35 (51.5)	90 (63.4)	48 (58.5)
Blood and lymphatic system disorders	24 (16.7)	116 (41.0)	23 (27.4)	6 (19.4)	15 (22.1)	47 (33.1)	15 (18.3)
Febrile neutropenia	6 (4.2)	56 (19.8)	14 (16.7)	4 (12.9)	5 (7.4)	11 (7.7)	4 (4.9)
Neutropenia	15 (10.4)	55 (19.4)	11 (13.1)	2 (6.5)	4 (5.9)	28 (19.7)	9 (11.0)
Thrombocytopenia	6 (4.2)	27 (9.5)	4 (4.8)	0	6 (8.8)	22 (15.5)	11 (13.4)
Anaemia	3 (2.1)	9 (3.2)	0	1 (3.2)	2 (2.9)	8 (5.6)	1 (1.2)
Cardiac disorders	6 (4.2)	15 (5.3)	0	2 (6.5)	5 (7.4)	3 (2.1)	6 (7.3)
Gastrointestinal disorders	14 (9.7)	31 (11.0)	9 (10.7)	1 (3.2)	4 (5.9)	12 (8.5)	8 (9.8)
General disorders and administration site conditions	10 (6.9)	24 (8.5)	3 (3.6)	0	2 (2.9)	6 (4.2)	6 (7.3)
Infections and infestations	37 (25.7)	117 (41.3)	15 (17.9)	8 (25.8)	18 (26.5)	28 (19.7)	15 (18.3)
Pneumonia	18 (12.5)	27 (9.5)	8 (9.5)	5 (16.1)	5 (7.4)	8 (5.6)	4 (4.9)
Injury, poisoning and procedural complications	0	8 (2.8)	4 (4.8)	0	1 (1.5)	1 (0.7)	5 (6.1)
Investigations	7 (4.9)	16 (5.7)	25 (29.8)	11 (35.5)	0	12 (8.5)	4 (4.9)
Neutrophil count decreased	0	3 (1.1)	19 (22.6)	6 (19.4)	0	7 (4.9)	1 (1.2)
Platelet count decreased	0	2 (0.7)	0	2 (6.5)	0	0	1 (1.2)
WBC count decreased	0	2 (0.7)	5 (6.0)	7 (22.6)	0	2 (1.4)	1 (1.2)
Metabolism and nutrition disorders	3 (2.1)	14 (4.9)	1 (1.2)	0	1 (1.5)	12 (8.5)	3 (3.7)
Nervous system disorders	3 (2.1)	6 (2.1)	5 (6.0)	1 (3.2)	2 (2.9)	3 (2.1)	2 (2.4)
Renal and urinary disorders	2 (1.4)	13 (4.6)	2 (2.4)	2 (6.5)	1 (1.5)	3 (2.1)	3 (3.7)
Respiratory, thoracic and mediastinal disorders	6 (4.2)	10 (3.5)	5 (6.0)	0	3 (4.4)	1 (0.7)	1 (1.2)

AE = adverse event; AZA = azacitidine; DEC = decitabine; HMA = hypomethylating agent; LDAC = low-dose cytarabine; MedDRA = Medical Dictionary for Regulatory Activities; N = sample size; n = number of patients; PBO = placebo; PT = preferred term; SOC = system organ class; VEN = venetoclax; WBC = white blood cell

Note: The sum of the total number of patients reporting each of the PTs should be greater than or equal to the SOC total. A patient who reports two or more different PTs which are in the same SOC is counted only once in the SOC total.

Source: VIALE-A Interim CSR Table 14.3__1.8.2.1, Study M14-358 Interim CSR Table 14.3__2.2.4.2.2.1 and Table 14.3__2.2.4.2.2.2, VIALE-C Interim CSR Table 14.3__1.8.2A, and Study M14-387 Interim CSR Table 14.3__2.2.4.2.2. Source datasets: ADSL and ADAE (VIALE-A); ADSL and ADAE (Study M14-358); ADSL (6-Month Follow-Up Analysis) and ADAE (6-Month Follow-Up Analysis) (VIALE-C); and ADSL and ADAE (Study M14-387).

Table 44. Adverse Events Leading to VEN/PBO Dose Reduction Reported in ≥ 2% of Patients Receiving Proposed Doses of Venetoclax in Combination with HMAs or LDAC

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO + AZA (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Any AE	6 (4.2)	7 (2.5)	1 (1.2)	2 (6.5)	5 (7.4)	14 (9.9)	6 (7.3)
Blood and lymphatic system disorders	1 (0.7)	0	0	1 (3.2)	2 (2.9)	5 (3.5)	4 (4.9)
Thrombocytopenia	1 (0.7)	0	0	0	1 (1.5)	3 (2.1)	4 (4.9)
Neutropenia	0	0	0	1 (3.2)	1 (1.5)	0	0
Infections and infestations	3 (2.1)	5 (1.8)	0	0	3 (4.4)	3 (2.1)	1 (1.2)
Investigations	0	0	1 (1.2)	1 (3.2)	0	2 (1.4)	0
Neutrophil count decreased	0	0	1 (1.2)	1 (3.2)	0	0	0

AE = adverse event; AZA = azacitidine; DEC = decitabine; HMA = hypomethylating agent; LDAC = low-dose cytarabine; MedDRA = Medical Dictionary for Regulatory Activities; N = sample size; n = number of patients; PBO = placebo; PT = preferred term; SOC = system organ class; VEN = venetoclax

Note: The sum of the total number of patients reporting each of the PTs should be greater than or equal to the SOC total. A patient who reports two or more different PTs which are in the same SOC is counted only once in the SOC total.

Source: VIALE-A Interim CSR Table 14.3__1.8.3.1, Study M14-358 Interim CSR Table 14.3__2.2.4.2.3.1 and Table 14.3__2.2.4.2.3.2, VIALE-C Interim CSR Table 14.3__1.8.3A, and Study M14-387 Interim CSR Table 14.3__2.2.4.2.3. Source datasets: ADSL and ADAE (VIALE-A); ADSL and ADAE (Study M14-358); ADSL (6-Month Follow-Up Analysis) and ADAE (6-Month Follow-Up Analysis) (VIALE-C); and ADSL and ADAE (Study M14-387).

In VIALE-A, 72.1% of patients in the VEN + AZA arm reported AEs of any grade leading to study treatment interruption between treatment cycles compared to 56.9% in the PBO + AZA arm. The SOCs with the highest incidence of AEs leading to VEN/PBO dose interruption were Infections and Infestations (VEN: 41.3% vs. PBO: 25.7%) and Blood and Lymphatic Disorders (VEN: 41.0% vs. PBO: 16.7%); both of which had a higher incidence in the VEN + AZA arm versus the PBO + AZA arm. Febrile neutropenia, neutropenia, and pneumonia were the most commonly reported AEs (≥ 10% of patients) leading to VEN dose interruption, and were reported by 19.8%, 19.4%, and 9.5% of patients, respectively, in the VEN + AZA arm; these events were reported by 4.2%, 10.4%, and 12.5% of patients in the PBO + AZA arm.

In VIALE-A, 66.4% of patients in the VEN + AZA arm reported AEs leading to AZA interruption in the VEN + AZA arm compared to 46.5% in the PBO + AZA arm. For AEs leading to AZA dose interruption, the most common AEs overall (reported in ≥ 10% of patients) were neutropenia and febrile neutropenia.

In Study M14-358, AEs that led to VEN dose interruption were reported for 67.9% patients who received VEN 400 mg + AZA. Febrile neutropenia, neutropenia, and neutrophil count decreased were the only events that led to dose interruption reported for ≥ 10% of patients. AEs that led to AZA dose interruption were reported for 56.0% patients who received VEN + AZA. The most common AEs leading to AZA dose interruption (≥ 5% of patients) were febrile neutropenia, neutropenia, pneumonia, neutrophil count decreased, and WBC count decreased.

In Study M14-358, AEs that led to VEN dose interruption were reported for 64.5% patients who received VEN 400 mg + DEC. Febrile neutropenia, pneumonia, neutrophil count decreased, and WBC count decreased led to dose interruption reported for ≥ 10% of patients. AEs that led to DEC dose interruption were reported for 58.1% patients who received VEN + DEC. The most common AEs leading to DEC dose interruption (≥ 5% of patients) were febrile neutropenia, neutropenia, pneumonia, neutrophil count decreased, and WBC count decreased.

In VIALE-C, 63.4% of patients in the VEN + LDAC arm reported AEs leading to VEN/PBO interruption compared to 51.5% in the PBO + LDAC arm. Blood and Lymphatic System Disorders was the SOC with the highest incidence of AEs leading to VEN dose interruption and was higher in the VEN + LDAC arm compared to the PBO + LDAC arm (33.1% vs. 22.1%). A lower incidence of AEs leading to VEN/PBO dose interruption was observed in the VEN + LDAC arm vs PBO + LDAC arm in the Infections and Infestations SOC (19.7% vs. 26.5%) and Cardiac Disorders SOC (2.1% vs. 7.4%). For AEs leading to VEN dose interruption, the most common AEs (reported in ≥ 10% of patients) were neutropenia and thrombocytopenia; reported in 19.7% and 15.5% of patients in the VEN + LDAC arm; these events were reported by 5.9% and 8.8% of patients in the PBO + LDAC arm.

In VIALE-C, a higher percentage of patients in the VEN + LDAC arm reported AEs leading to LDAC interruption in the VEN + LDAC arm compared to the PBO + LDAC arm (57.7% vs. 47.1%). For AEs leading to LDAC dose interruption, the most common AEs (reported in ≥ 10% of patients overall) were neutropenia and thrombocytopenia.

In Study M14-387, 58.5% patients in the VEN 600 mg + LDAC arm reported AEs that led to VEN dose interruption. The AEs that led to VEN dose interruption experienced by ≥ 5% of patients included neutropenia and thrombocytopenia.

In Study M14-387, 50.0% patients in the VEN 600 mg + LDAC arm reported AEs that led to LDAC dose interruption. The AEs that led to LDAC dose interruption experienced by ≥ 5% of patients included neutropenia and thrombocytopenia.

Dose Reduction

Data:

In VIALE-A, the incidence of AEs leading to VEN/PBO dose reduction including reduction in duration within the scheduled treatment cycle of 28 days was generally low in both arms and was numerically lower in the VEN + AZA arm versus the PBO + AZA arm (2.5% vs 4.2%). Pneumonia was the only AE leading to dose reduction reported in more than 1 patient and was reported by 1 patient (0.4%) in the VEN + AZA arm and 2 patients (1.4%) in the PBO + AZA arm. There were 34 patients (12.0%) in the VEN + AZA arm and 2 patients (1.4%) in the PBO + AZA arm who reported AEs leading to AZA discontinuation.

In Study M14-358, for patients treated with VEN 400 mg + AZA, AEs that led to VEN dose reduction were reported for 1 patient (1.2%); this was an event of neutrophil count decreased. There were 4 patients (4.8%) with AEs leading to AZA dose reduction.

In Study M14-358, 2 patients (6.5%) in the VEN 400 mg + DEC arm reported AEs of neutropenia and neutrophil count decreased (1 event each) leading to VEN dose reduction. There were 2 patients (6.5%) with AEs leading to DEC dose reduction.

In VIALE-C, the incidence of AEs leading to VEN/PBO dose reduction was 9.9% in the VEN + LDAC arm versus 7.4% in the PBO + AZA arm. Thrombocytopenia and lung infection were the only AEs leading to dose reduction reported in more than 1 patient. These AEs were reported by 2 patients each (1.4%) in the VEN + LDAC arm. There were 4 patients (2.8%) in VEN + LDAC arm who reported AEs leading to LDAC discontinuation; no patients in the PBO + LDAC arm reported AEs leading to LDAC discontinuation.

In Study M14-387, AEs that led to VEN dose reduction were reported in 7.3% of patients in the VEN 600 mg + LDAC arm. Thrombocytopenia (4 patients [5.9%]) was the only AEs leading to VEN dose reduction reported in > 1 patient. There was 1 patient (1.2%) with an AE leading to LDAC dose reduction.

The Applicant's Position:

Dose interruption and/or dose reduction was permitted per protocol in these clinical studies consistent with standard clinical practice in AML to allow treatment interruption in patients with cytopenias who achieve morphological clearance of AML, in order to allow for peripheral blood count recovery. As such, dose interruption and/or reduction represent routine clinical

practice in the treatment of AML and are not necessarily indicators of treatment tolerability in these studies.

Across the 4 studies, febrile neutropenia was the primary AE leading to dose interruptions or dose reductions. Rates of VEN/PBO dose interruption or dose reduction due to febrile neutropenia or neutropenia were higher among patients who received VEN with AZA or LDAC compared to those who received PBO with AZA or LDAC. The higher incidence of dose interruptions in the VEN arm, driven mostly by infections, neutropenia, and febrile neutropenia allowed mitigation of the risks known to be associated with VEN treatment by following the currently implemented and proposed toxicity management. These dose interruptions allowed a relatively low incidence of treatment discontinuation and continued use of VEN combinations.

Regulatory Authorities' Assessment:
FDA analysis of AEs leading to dose modification (reduction or interruption) of venetoclax or placebo indicated 65% in the VEN/AZA arm and 47% in the PBO/AZA arm of VIALE-A. Similarly, in VIALE-C AEs leading to dose modification of venetoclax or placebo occurred in 61% in the VEN/LDAC arm and 46% in the PBO/LDAC arm. As noted above, the majority of dose modifications were interruptions while dose reductions were uncommon. This evaluation appears to be consistent with the dose intensity reported in Tables 23 and 24, respectively.

Significant Adverse Events

Across the 4 studies, the investigator rated the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 4.0). If a reported AE increased in severity, the initial AE was given a final outcome date, and a new AE was reported to reflect the change in severity. For AEs not captured by the CTCAE, the investigator used definitions as follows:

- Grade 1: The AE is transient and easily tolerated by the patient (mild).
- Grade 2: The AE causes the patient discomfort and interrupts the patient's usual activities (moderate).
- Grade 3: The AE causes considerable interference with the patient's usual activities and may be incapacitating (moderate to severe).
- Grade 4: The AE is life-threatening requiring urgent intervention (severe).
- Grade 5: The AE resulted in death of the patient (severe).

Data:
Grade ≥ 3 AEs reported in ≥ 10% of patients receiving VEN at the proposed doses, or PBO, in combination with HMAs or LDAC are summarized in Table 43.

In VIALE-A, Grade ≥ 3 AEs were reported for 279 patients (98.6%) receiving VEN 400 mg + AZA and for 139 patients (96.5%) receiving PBO + AZA. Among patients treated with VEN + AZA, the most common Grade ≥ 3 AEs (reported in ≥ 10% of patients) were thrombocytopenia, neutropenia, febrile neutropenia, anemia, leukopenia, pneumonia, and hypokalemia.

In VIALE-A, Grade ≥ 3 AEs for which there was a ≥ 2% difference between treatment arms and higher in VEN + AZA arm versus PBO + AZA arm were thrombocytopenia, neutropenia, febrile neutropenia, anemia, leukopenia, pancytopenia, atrial fibrillation, asthenia, lung infection, bacteremia, Escherichia bacteremia, Pseudomonas infection, platelet count decreased, WBC count decreased, neutrophil count decreased, decreased appetite and syncope.

In Study M14-358, Grade ≥ 3 AEs were reported for 82 patients (97.6%) receiving VEN 400 mg + AZA. The most common Grade ≥ 3 AEs (reported in ≥ 10% of patients) were febrile neutropenia, WBC count decreased, pneumonia, anemia, neutrophil count decreased, platelet count decreased, thrombocytopenia, neutropenia, and hypophosphatemia.
In Study M14-358, Grade ≥ 3 AEs were reported for 31 patients (100%) receiving VEN 400 mg + DEC. The most common Grade ≥ 3 AEs (reported in ≥ 10% of patients) were febrile neutropenia, platelet count decreased, WBC count decreased, pneumonia, neutrophil count decreased, anemia, thrombocytopenia, bacteremia, hypokalemia, and respiratory failure.

In VIALE-C, Grade ≥ 3 AEs were reported for 138 patients (97.2%) receiving VEN 600 mg + LDAC and for 65 patients (95.6%) receiving PBO + LDAC. Among patients treated with VEN + LDAC, the most common Grade ≥ 3 AEs (reported in ≥ 10% of patients) were neutropenia, thrombocytopenia, febrile neutropenia, anemia, pneumonia, and hypokalemia.

In VIALE-C, Grade ≥ 3 AEs for which there was a ≥ 2% difference between treatment arms and higher in the VEN + LDAC arm compared to PBO + LDAC were neutropenia, thrombocytopenia, febrile neutropenia, anemia, leukopenia, diarrhea, lung infection, urinary tract infection, neutropenic sepsis, neutrophil count decreased, WBC count decreased, blood bilirubin decreased, TLS, and syncope.

In Study M14-387, Grade ≥ 3 AEs were reported for 80 patients (97.6%) receiving VEN 600 mg + LDAC. The most common Grade ≥ 3 AEs (reported in ≥ 10% of patients) were febrile neutropenia, thrombocytopenia, WBC count decreased, anemia, neutropenia, platelet count decreased, lymphocyte count decreased, neutrophil count decreased, hypophosphatemia, hypokalemia, pneumonia, sepsis, and hypertension.

The Applicant's Position:
In the Phase 3 studies, the incidence of Grade ≥ 3 AEs was similar among patients treated with VEN in combination with AZA (98.6% of patients) or LDAC (97.2% of patients), and were comparable to rates reported in patients treated with PBO in combination with AZA (96.5%) or LDAC (95.6%). These results were consistent with events expected in this study population of AML patients.

Across trials and combinations, febrile neutropenia, neutropenia, thrombocytopenia, and infections (especially pulmonary infections) were the most frequently observed AEs. Similarly, Grade 3 to 5 AEs which were consistently observed at a higher incidence in the VEN arm were febrile neutropenia, neutropenia, thrombocytopenia, infections, and syncope in both VIALE-A and VIALE-C. These events are considered to be known risks associated with VEN treatment

and were the most common Grade ≥ 3 AEs reported by patients treated at the target doses of VEN.

Although Study M14-358 is not a randomized trial, certain Grade ≥ 3 AEs had a higher incidence in patients treated with VEN + DEC compared to patients treated with VEN + AZA in VIALE-A. Numerical differences are noted between VEN + AZA and VEN + DEC treatment arms in the incidence of some AEs. Whether these reflect differences in reporting practices between sites or statistical variation is not known.

Table 45. Treatment-Emergent Adverse Events with NCI CTCAE ≥ Grade 3 Reported in ≥ 10% of Patients Receiving Proposed Doses of Venetoclax in Combination with HMAs or LDAC

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO +Aza (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Any AE	139 (96.5)	279 (98.6)	82 (97.6)	31 (100)	65 (95.6)	138 (97.2)	80 (97.6)
Blood and lymphatic system disorders	98 (68.1)	233 (82.3)	59 (70.2)	24 (77.4)	50 (73.5)	111 (78.2)	66 (80.5)
Anaemia	29 (20.1)	74 (26.1)	25 (29.8)	8 (25.8)	15 (22.1)	38 (26.8)	24 (29.3)
Febrile neutropenia	27 (18.8)	118 (41.7)	33 (39.3)	20 (64.5)	20 (29.4)	46 (32.4)	35 (42.7)
Leukopenia	17 (11.8)	58 (20.5)	2 (2.4)	0	5 (7.4)	14 (9.9)	2 (2.4)
Neutropenia	41 (28.5)	119 (42.0)	17 (20.2)	3 (9.7)	12 (17.6)	69 (48.6)	23 (28.0)
Thrombocytopenia	55 (38.2)	126 (44.5)	21 (25.0)	7 (22.6)	26 (38.2)	65 (45.8)	32 (39.0)
Cardiac disorders	20 (13.9)	44 (15.5)	10 (11.9)	1 (3.2)	11 (16.2)	13 (9.2)	8 (9.8)
Gastrointestinal disorders	17 (11.8)	42 (14.8)	18 (21.4)	4 (12.9)	6 (8.8)	19 (13.4)	12 (14.6)
General disorders and administration site conditions	22 (15.3)	38 (13.4)	18 (21.4)	4 (12.9)	7 (10.3)	12 (8.5)	17 (20.7)
Infections and infestations	74 (51.4)	180 (63.6)	44 (52.4)	19 (61.3)	34 (50.0)	61 (43.0)	41 (50.0)
Bacteraemia	0	7 (2.5)	3 (3.6)	6 (19.4)	0	1 (0.7)	2 (2.4)
Pneumonia	36 (25.0)	56 (19.8)	27 (32.1)	10 (32.3)	11 (16.2)	25 (17.6)	11 (13.4)
Sepsis	13 (9.0)	17 (6.0)	3 (3.6)	3 (9.7)	4 (5.9)	8 (5.6)	9 (11.0)
Injury, poisoning and procedural complications	9 (6.3)	15 (5.3)	6 (7.1)	1 (3.2)	1 (1.5)	4 (2.8)	9 (11.0)
Investigations	13 (9.0)	58 (20.5)	50 (59.5)	19 (61.3)	10 (14.7)	27 (19.0)	39 (47.6)
Lymphocyte count decreased	1 (0.7)	1 (0.4)	0	1 (3.2)	1 (1.5)	1 (0.7)	15 (18.3)
Neutrophil count decreased	0	8 (2.8)	23 (27.4)	9 (29.0)	2 (2.9)	10 (7.0)	14 (17.1)
Platelet count decreased	0	9 (3.2)	23 (27.4)	14 (45.2)	4 (5.9)	8 (5.6)	20 (24.4)
White blood cell count decreased	1 (0.7)	9 (3.2)	28 (33.3)	14 (45.2)	3 (4.4)	10 (7.0)	28 (34.1)
Metabolism and nutrition disorders	39 (27.1)	78 (27.6)	28 (33.3)	10 (32.3)	22 (32.4)	40 (28.2)	29 (35.4)
Hypokalaemia	15 (10.4)	30 (10.6)	5 (6.0)	5 (16.1)	11 (16.2)	17 (12.0)	12 (14.6)
Hypophosphataemia	11 (7.6)	21 (7.4)	11 (13.1)	2 (6.5)	2 (2.9)	3 (2.1)	13 (15.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (5.6)	8 (2.8)	0	4 (12.9)	3 (4.4)	1 (0.7)	5 (6.1)
Nervous system disorders	8 (5.6)	31 (11.0)	10 (11.9)	4 (12.9)	3 (4.4)	8 (5.6)	13 (15.9)
Respiratory, thoracic and mediastinal disorders	15 (10.4)	44 (15.5)	17 (20.2)	7 (22.6)	11 (16.2)	12 (8.5)	13 (15.9)
Respiratory failure	1 (0.7)	7 (2.5)	3 (3.6)	4 (12.9)	1 (1.5)	2 (1.4)	2 (2.4)
Vascular disorders	12 (8.3)	36 (12.7)	12 (14.3)	3 (9.7)	7 (10.3)	17 (12.0)	15 (18.3)
Hypertension	6 (4.2)	17 (6.0)	7 (8.3)	3 (9.7)	4 (5.9)	8 (5.6)	9 (11.0)

AZA = azacitidine; DEC = decitabine; HMA = hypomethylating agent; LDAC = low-dose cytarabine; MedDRA = Medical Dictionary for Regulatory Activities; N = sample size; n = number of patients; PBO = placebo; PT = preferred term; SAE = serious adverse event; SOC = system organ class; VEN = venetoclax

Sources: VIALE-A Interim CSR Table 14.3__1.4.1.1; Study M14-358 Interim CSR Table 14.3__1.3.2.1.1, Table 14.3__1.3.2.1.2; VIALE-C Interim CSR Table 14.3__1.4.1A; Study M14-387 Interim CSR Table 14.3__1.3.2.1. Source datasets: ADSL and ADAE (VIALE-A); ADSL and ADAE (Study M14-358); ADSL (6-Month Follow-Up Analysis) and ADAE (6-Month Follow-Up Analysis) (VIALE-C); and ADSL and ADAE (Study M14-387).

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of grade ≥3 TEAEs. For purposes of labeling, the Agency reports all grade and grade 3-4 TEAEs instead of grade ≥3 as deaths due to AE are reported separately. The Agency's assessment uses grouped terms as listed in Appendix 19.5 and for VIALE-C was at the time of the final efficacy analysis (15 Feb 2019). However, the overall safety profile was similar to that reported above. See Table 48 and Table 49 for Grade 3-4 TEAEs in VIALE-A and VIALE-C, respectively.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-Emergent Adverse Events
A summary of treatment-emergent AEs for patients in VIALE-A (VEN+ AZA, PBO + AZA), VIALE-C (VEN + LDAC, PBO + LDAC), and Study M14-358 (VEN 400 mg + DEC) are presented in Table 44.

Adverse Drug Reactions – Venetoclax in combination with Azacitidine or LDAC
Adverse drug reactions in patients treated with VEN + AZA or VEN + LDAC were identified based on the primary data analysis from VIALE-A and the 6-month follow-up data analysis from VIALE-C, respectively. ADRs in patients treated with VEN + DEC were also identified based on the primary data analysis from Study M14-358 because no randomized data are available for VEN + DEC.

ADRs were based on the difference between the AE rates in the VEN treatment arms versus the PBO treatment arms in VIALE-A and VIALE-C. A difference of at least 5% in the incidence of AEs with a minimal overall incidence of 10% in the VEN combination arm or a difference of at least 2% in the incidence of Grade ≥ 3 AEs was required to meet the ADR criteria. AEs reported in ≥ 30% (all grades) in the VEN 400 mg + DEC treatment arm in Study M14-358 were also considered for ADRs. Additionally, medical judgment was used to identify ADRs based on existing clinical study data from VEN combination therapy, the mechanism of action of the drugs, nonclinical data, and a detailed medical review of cases for confounding factors and causal relationship with the study drug. Biologic plausibility and consistency between studies were also considered.

Data:
Blood and Lymphatic Disorders
The AEs of anemia, febrile neutropenia, neutropenia, and thrombocytopenia were among the most commonly reported AEs and Grade ≥ 3 AEs in all 4 studies. In VIALE-A and VIALE-C, all these events were reported with an incidence ≥ 5% higher in the VEN arm compared to the PBO arm or have an incidence of ≥ 2% higher for Grade ≥ 3 events. These events are considered to be ADRs.

Cardiac Disorders
In VIALE-C, the incidence of Cardiac Disorders was lower in the VEN arm versus the PBO arm (18.3% versus 23.5%, respectively), while in VIALE-A, the incidence was higher in the VEN arm versus the PBO arm (31.1% versus 25.7%, respectively). Increased duration of therapy may

have contributed to the imbalance in treatment arms in VIALE-A as incidence rates per 100 patient-years are 42.2% versus 48.6%, respectively. Within the SOC of Cardiac Disorders, the incidence of atrial fibrillation was reported in 5.6% versus 5.9% of patients treated with VEN + LDAC versus PBO + LDAC, respectively, in VIALE-C, and 11.7% versus 10.4% of patients treated with VEN + AZA versus PBO + AZA, respectively, in VIALE-A. Corresponding incidences for Grade ≥ 3 AEs of atrial fibrillation were 2.1% versus 4.4%, respectively, in VIALE-C, and 6.0% versus 2.1%, respectively, in VIALE-A. However, patients treated with VEN + AZA had a higher incidence of history of atrial fibrillation versus patients treated with the PBO + AZA (15.0% vs. 10.3%, respectively) in VIALE-A. Due to the lack of consistency between studies, atrial fibrillation is not considered to be an ADR.

Gastrointestinal disorders

Nausea, vomiting, and diarrhea were among the most commonly reported AEs with incidences ≥ 5% higher in the VEN arm compared to the PBO arm in both VIALE-A and VIALE-C. The incidences of stomatitis and abdominal pain were also ≥ 5% higher in the VEN arm compared to the PBO arm in VIALE-A and/or VIALE-C. These events are considered to be ADRs.

Constipation was also a commonly reported AE; however, the comparative incidences were not consistent: 42.8% versus 38.9% (VEN vs. PBO arms) in VIALE-A and 20.4% versus 32.4% (VEN vs. PBO arms) in VIALE-C. Therefore, constipation is not considered to be an ADR.

General Disorders and Administration Site Conditions

The incidences of fatigue were 20.8% versus 16.7% of patients treated with VEN + AZA versus PBO + AZA, respectively, in VIALE-A and 15.5% versus 14.7% of patients treated with VEN + LDAC versus PBO + LDAC, respectively, in VIALE-C. Respective incidences of Grade ≥ 3 fatigue were 2.8% versus 1.4%, respectively, in VIALE-A and 1.4% versus 0, respectively, in VIALE-C.

The incidences of asthenia were 15.5% versus 8.3% of patients treated with VEN + AZA versus PBO + AZA, respectively, in VIALE-A and 12.0% versus 11.8% of patients treated with VEN + LDAC versus PBO + LDAC, respectively, in VIALE-C. Respective incidences of Grade ≥ 3 asthenia were 3.9% versus 0.7%, respectively, in VIALE-A and 1.4% versus 0, respectively, in VIALE-C. These are related terms, and both are considered to be ADRs.

The incidences of peripheral edema were 24.4% versus 18.1% of patients treated with VEN + AZA versus PBO + AZA, respectively, in VIALE-A and 14.1% versus 20.6% of patients treated with VEN + LDAC versus PBO + LDAC, respectively, in VIALE-C. The longer exposure time of the VEN arm in VIALE-A may have been a factor in the higher incidence rate of peripheral edema and there is no biologic rationale for VEN to cause peripheral edema; therefore, peripheral edema is not considered to be an ADR.

Hepatobiliary Disorders

Hepatobiliary disorders were reported with similar incidences in both VIALE-A and VIALE-C. However, when the terms cholelithiasis, cholelithiasis acute, cholelithiasis chronic, and cholelithiasis are combined, an imbalance is noted: 4.2% versus 0.7% of patients treated with

VEN + AZA versus PBO + AZA, respectively, in VIALE-A and 2.1% versus 0 patients treated with VEN + LDAC versus PBO + LDAC, respectively, in VIALE-C. The respective incidences of Grade ≥ 3 events are 2.1% versus 0, respectively, in VIALE-A and 1.4% versus 0, respectively, in VIALE-C. The VEN arms also had an increased incidence of serum bilirubin elevations. The AEs and laboratory findings are consistent. The grouped term cholecystitis/cholelithiasis is considered to be an ADR.

Infections and Infestations

Infections are a known complication of AML but have also been seen in higher frequency with VEN versus comparator in non-AML studies. The incidence of infections and infestations was 84.5% versus 67.4% of patients treated with VEN + AZA versus PBO + AZA, respectively, in VIALE-A and 64.8% versus 60.3% of patients treated with VEN + LDAC versus PBO + LDAC, respectively, in VIALE-C. In general, the most commonly reported infections included pneumonia, sepsis, and urinary tract infection. In VIALE-A and/or VIALE-C, pneumonia and sepsis (group terms) were reported with an incidence ≥ 5% higher in the VEN arm compared to the PBO arm and/or had an incidence of ≥ 2% higher for Grade ≥ 3 events. The AE of urinary tract infection did not meet the minimum standards of the algorithm stated above; however, there is biologic plausibility. Therefore, pneumonia, sepsis, and urinary tract infection are considered ADRs.

Investigations/Metabolism and Nutrition Disorders

In VIALE-A and/or VIALE-C, decreased weight, decreased appetite, and hypokalemia were reported with an incidence ≥ 5% higher in the VEN arm compared to the PBO arm. All 3 events are considered to be ADRs.

Tumor lysis syndrome is considered to be an ADR. Results for TLS are presented in Section 8.2.5, under the subheading of “Tumor Lysis Syndrome”.

Musculoskeletal and Connective Tissue Disorders

The AE of arthralgia was reported with an incidence ≥ 5% higher in the VEN arm compared to the PBO arm in both VIALE-A and VIALE-C. Arthralgia is considered to be an ADR.

Nervous System Disorders

The AEs of dizziness (combined term) and headache were reported with an incidence ≥ 5% higher in the VEN arm compared to the PBO arm in VIALE-A and/or VIALE-C. Dizziness and headache are considered to be ADRs.

Respiratory, Thoracic, and Mediastinal Disorders

The AE of dyspnea was reported with an incidence ≥ 5% higher in the VEN arm compared to the PBO arm in VIALE-A. Dyspnea is considered to be an ADR.

Vascular Disorders
While the AE of hypotension did not meet the minimum standards of the algorithm stated above, the incidence of hypotension is consistently higher in the VEN arm compared to the PBO arm in both VIALE-A and VIALE-C; therefore, hypotension is considered an ADR. Hemorrhage is considered to be an ADR. Results for hemorrhages are presented in Section 8.2.5, under the subheading of "Hemorrhages".

Adverse Drug Reactions – Venetoclax in combination with Decitabine
AEs with a frequency ≥ 30% in patients treated with VEN 400 mg + DEC in Study M14-358 that have not already been identified as ADRs from VIALE-A and VIALE-C included constipation, cough, pyrexia, and peripheral edema. After considering consistency across VIALE-A and VIALE-C, these AEs are not likely to be actual ADRs. Therefore, no additional ADRs were identified based on the VEN 400 mg + DEC treatment arm.

The Applicant's Position:
Venetoclax can be combined with HMAs or LDAC without leading to clinically significant toxicity. Rates and types of AEs reported among patients with AML who received VEN in combination with either AZA or LDAC were similar to those reported among patients who received PBO in combination with AZA or LDAC. The overall safety profile observed in the Phase 3 studies was consistent with results of the Phase 1/2 studies in patients treated with VEN at the proposed doses in combination with either AZA or LDAC. Furthermore, the profile of VEN + AZA is similar to that of VEN + DEC.

Adverse events observed in patients receiving VEN in combination with HMAs or LDAC were not unexpected based on the patient population and mechanism of action of VEN. Nearly all patients (> 98%) in the AML studies reported AEs. Although there were numerical differences in PTs, the overall pattern of AEs is similar across treatment arms that received VEN in the 4 combination studies. Furthermore, the pattern of AEs is similar between patients who received PBO + AZA versus VEN 400 mg + AZA in VIALE-A, and between patients who received PBO + LDAC versus VEN 600 mg + LDAC in VIALE-C.

Overall, in the Phase 3 studies, AEs were most commonly reported in the SOCs of Blood and Lymphatic System Disorders, Gastrointestinal Disorders, and Infections and Infestations. AEs of anemia, neutropenia, febrile neutropenia and thrombocytopenia, nausea, vomiting, diarrhea, as well as infections and hemorrhages were higher in patients who received VEN in combination with AZA or LDAC, compared to those who received PBO in combination with AZA or LDAC. AEs were manageable following standard/routine medical practice guidelines and product labeling.

Table 46. Summary of Adverse Events in VIALE-A, VIALE-C, and for VEN + DEC in Study M14-358 (Safety Analysis Set)

	VIALE-A		VIALE-C		Study M14-358
Patients with:	PBO + AZA (N = 144)	VEN + AZA[a] (N = 283)	PBO + LDAC (N = 68)	VEN + LDAC[a] (N = 142)	VEN + DEC[a] (N = 31)
Any AE	144 (100)	283 (100)	67 (98.5)	141 (99.3)	31 (100)
Any AE with NCI-CTCAE toxicity Grade ≥ 3	139 (96.5)	279 (98.6)	65 (95.6)	138 (97.2)	31 (100)
Any AE with NCI-CTCAE toxicity Grade 3 or 4	136 (94.4)	276 (97.5)	63 (92.6)	135 (95.1)	31 (100)
Any AE with NCI-CTCAE toxicity Grade 3	120 (83.3)	264 (93.3)	60 (88.2)	124 (87.3)	NR
Any AE with NCI-CTCAE toxicity Grade 4	98 (68.1)	223 (78.8)	38 (55.9)	102 (71.8)	NR
Any reasonable possibility venetoclax/placebo-related AE[b]	96 (66.7)	241 (85.2)	47 (69.1)	106 (74.6)	25 (80.6)
Any reasonable possibility Aza/LDAC/Dec-related AE[b]	108 (75.0)	246 (86.9)	49 (72.1)	107 (75.4)	28 (90.3)
Any AE leading to venetoclax/placebo discontinuation	29 (20.1)	69 (24.4)	16 (23.5)	37 (26.1)	8 (25.8)
Any AE leading to Aza/LDAC/Dec discontinuation	29 (20.1)	68 (24.0)	16 (23.5)	37 (26.1)	4 (12.9)
Any AE leading to venetoclax/placebo interruption	82 (56.9)	204 (72.1)	35 (51.5)	90 (63.4)	20 (64.5)
Any AE leading to Aza/LDAC/Dec interruption	67 (46.5)	188 (66.4)	32 (47.1)	82 (57.7)	18 (58.1)
Any AE leading to venetoclax/placebo reduction	6 (4.2)	7 (2.5)	5 (7.4)	14 (9.9)	2 (6.5)
Any AE leading to Aza/LDAC/Dec reduction	2 (1.4)	34 (12.0)	0	4 (2.8)	2 (6.5)
Any AE leading to venetoclax/placebo interruption or reduction	84 (58.3)	204 (72.1)	36 (52.9)	92 (64.8)	20 (64.5)
Any AE leading to Aza/LDAC/Dec interruption or reduction	67 (46.5)	190 (67.1)	32 (47.1)	82 (57.7)	18 (58.1)
Fatal AE (AE leading to death)	29 (20.1)	64 (22.6)	14 (20.6)	33 (23.2)	6 (19.4)
All deaths[c]	109 (75.7)	159 (56.2)	54 (79.4)	99 (69.7)	25 (80.6)

AE = adverse event; Aza = azacitidine; Dec = decitabine; LDAC = low-dose cytarabine; N = sample size; n = number of patients; NR = not reported; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PBO = placebo; VEN = venetoclax

a. Venetoclax was provided at a dose of 400 mg in combination with azacitidine and decitabine. Venetoclax was provided at a dose of 600 mg in combination with LDAC.

b. As assessed by the Investigator.

c. Includes non-treatment-emergent deaths.

Note: Data included are subject to a cutoff date of 04 January 2020.

Sources: VIALE-A CSR Table 14.3__1.1.1, VIALE-C CSR Table 14.3__1.1.1A, and Study M14-358 CSR Table 14.3__1.1.1.2. Source datasets: ADSL and ADAE (VIALE-A); ADSL and ADAE (Study M14-358); and ADSL (6-Month Follow-Up Analysis) and ADAE (6-Month Follow-Up Analysis) (VIALE-C).

Table 47. Treatment-Emergent Adverse Events Reported in ≥ 20% of AML Patients Receiving Placebo or Venetoclax in Any Study Combination with HMAs or LDAC

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO +Aza (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Any AE	144 (100)	283 (100)	84 (100)	31 (100)	67 (98.5)	141 (99.3)	82 (100)
Blood and lymphatic system disorders	100 (69.4)	236 (83.4)	61 (72.6)	24 (77.4)	51 (75.0)	115 (81.0)	67 (81.7)
Anaemia	30 (20.8)	78 (27.6)	25 (29.8)	8 (25.8)	15 (22.1)	41 (28.9)	25 (30.5)
Febrile neutropenia	27 (18.8)	118 (41.7)	33 (39.3)	20 (64.5)	20 (29.4)	46 (32.4)	36 (43.9)

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO +Aza (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Leukopenia	20 (13.9)	58 (20.5)	2 (2.4)	0	5 (7.4)	14 (9.9)	2 (2.4)
Neutropenia	42 (29.2)	119 (42.0)	17 (20.2)	3 (9.7)	12 (17.6)	69 (48.6)	24 (29.3)
Thrombocytopenia	58 (40.3)	130 (45.9)	21 (25.0)	7 (22.6)	27 (39.7)	65 (45.8)	32 (39.0)
Cardiac disorders	37 (25.7)	88 (31.1)	34 (40.5)	10 (32.3)	16 (23.5)	26 (18.3)	31 (37.8)
Eye disorders	15 (10.4)	29 (10.2)	17 (20.2)	5 (16.1)	7 (10.3)	19 (13.4)	10 (12.2)
Gastrointestinal disorders	112 (77.8)	241 (85.2)	78 (92.9)	29 (93.5)	47 (69.1)	106 (74.6)	78 (95.1)
Abdominal pain	12 (8.3)	31 (11.0)	16 (19.0)	9 (29.0)	3 (4.4)	17 (12.0)	14 (17.1)
Constipation	56 (38.9)	121 (42.8)	42 (50.0)	16 (51.6)	22 (32.4)	29 (20.4)	30 (36.6)
Diarrhoea	48 (33.3)	117 (41.3)	51 (60.7)	14 (45.2)	12 (17.6)	47 (33.1)	41 (50.0)
Nausea	50 (34.7)	124 (43.8)	54 (64.3)	20 (64.5)	21 (30.9)	61 (43.0)	57 (69.5)
Vomiting	33 (22.9)	84 (29.7)	32 (38.1)	12 (38.7)	10 (14.7)	41 (28.9)	25 (30.5)
General disorders and administration site conditions	95 (66.0)	195 (68.9)	76 (90.5)	27 (87.1)	35 (51.5)	76 (53.5)	66 (80.5)
Fatigue	24 (16.7)	59 (20.8)	30 (35.7)	14 (45.2)	10 (14.7)	22 (15.5)	35 (42.7)
Oedema peripheral	26 (18.1)	69 (24.4)	34 (40.5)	10 (32.3)	14 (20.6)	20 (14.1)	15 (18.3)
Pyrexia	32 (22.2)	66 (23.3)	25 (29.8)	10 (32.3)	13 (19.1)	25 (17.6)	18 (22.0)
Infections and infestations	97 (67.4)	239 (84.5)	65 (77.4)	25 (80.6)	41 (60.3)	92 (64.8)	60 (73.2)
Bacteraemia	0	7 (2.5)	4 (4.8)	7 (22.6)	0	4 (2.8)	3 (3.7)
Pneumonia	39 (27.1)	65 (23.0)	27 (32.1)	12 (38.7)	11 (16.2)	31 (21.8)	13 (15.9)
Injury, poisoning and procedural complications	42 (29.2)	83 (29.3)	40 (47.6)	17 (54.8)	9 (13.2)	38 (26.8)	29 (35.4)
Contusion	12 (8.3)	10 (3.5)	12 (14.3)	7 (22.6)	2 (2.9)	4 (2.8)	2 (2.4)
Investigations	56 (38.9)	136 (48.1)	66 (78.6)	24 (77.4)	22 (32.4)	54 (38.0)	56 (68.3)
Blood bilirubin increased	5 (3.5)	21 (7.4)	8 (9.5)	4 (12.9)	1 (1.5)	16 (11.3)	19 (23.2)
Neutrophil count decreased	1 (0.7)	8 (2.8)	23 (27.4)	9 (29.0)	3 (4.4)	10 (7.0)	14 (17.1)
Platelet count decreased	1 (0.7)	13 (4.6)	25 (29.8)	15 (48.4)	4 (5.9)	8 (5.6)	21 (25.6)
White blood cell count decreased	2 (1.4)	11 (3.9)	28 (33.3)	14 (45.2)	4 (5.9)	10 (7.0)	28 (34.1)
Metabolism and nutrition disorders	79 (54.9)	175 (61.8)	68 (81.0)	25 (80.6)	40 (58.8)	87 (61.3)	68 (82.9)
Decreased appetite	25 (17.4)	72 (25.4)	25 (29.8)	10 (32.3)	13 (19.1)	31 (21.8)	30 (36.6)
Hypocalcaemia	8 (5.6)	17 (6.0)	7 (8.3)	2 (6.5)	8 (11.8)	13 (9.2)	23 (28.0)
Hypokalaemia	41 (28.5)	81 (28.6)	29 (34.5)	11 (35.5)	17 (25.0)	44 (31.0)	40 (48.8)
Hypomagnesaemia	5 (3.5)	21 (7.4)	12 (14.3)	8 (25.8)	6 (8.8)	13 (9.2)	28 (34.1)
Hyponatraemia	7 (4.9)	16 (5.7)	8 (9.5)	0	7 (10.3)	9 (6.3)	18 (22.0)
Hypophosphataemia	17 (11.8)	35 (12.4)	22 (26.2)	4 (12.9)	4 (5.9)	5 (3.5)	24 (29.3)
Musculoskeletal and connective tissue disorders	50 (34.7)	110 (38.9)	48 (57.1)	23 (74.2)	18 (26.5)	44 (31.0)	46 (56.1)
Back pain	13 (9.0)	24 (8.5)	13 (15.5)	6 (19.4)	5 (7.4)	9 (6.3)	17 (20.7)
Musculoskeletal pain	5 (3.5)	18 (6.4)	7 (8.3)	7 (22.6)	3 (4.4)	5 (3.5)	1 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (6.3)	18 (6.4)	1 (1.2)	8 (25.8)	4 (5.9)	6 (4.2)	6 (7.3)

SOC and PT, n (%) (MedDRA, v21.0)	**VIALE-A PBO +Aza (N = 144)**	**VIALE-A VEN (400 mg) + AZA (N = 283)**	**M14-358 VEN (400 mg) + AZA (N = 84)**	**M14-358 VEN (400 mg) + DEC (N = 31)**	**VIALE-C PBO + LDAC (N = 68)**	**VIALE-C VEN (600 mg) + LDAC (N = 142)**	**M14-387 VEN (600 mg) + LDAC (N = 82)**
Nervous system disorders	39 (27.1)	107 (37.8)	57 (67.9)	21 (67.7)	15 (22.1)	49 (34.5)	45 (54.9)
Dizziness	10 (6.9)	37 (13.1)	22 (26.2)	12 (38.7)	2 (2.9)	12 (8.5)	11 (13.4)
Headache	10 (6.9)	30 (10.6)	21 (25.0)	10 (32.3)	3 (4.4)	20 (14.1)	24 (29.3)
Psychiatric disorders	37 (25.7)	71 (25.1)	42 (50.0)	16 (51.6)	19 (27.9)	38 (26.8)	46 (56.1)
Insomnia	15 (10.4)	35 (12.4)	20 (23.8)	8 (25.8)	9 (13.2)	20 (14.1)	17 (20.7)
Renal and urinary disorders	33 (22.9)	71 (25.1)	30 (35.7)	10 (32.3)	11 (16.2)	23 (16.2)	24 (29.3)
Respiratory, thoracic and mediastinal disorders	60 (41.7)	138 (48.8)	67 (79.8)	25 (80.6)	25 (36.8)	54 (38.0)	54 (65.9)
Cough	20 (13.9)	35 (12.4)	17 (20.2)	10 (32.3)	6 (8.8)	14 (9.9)	20 (24.4)
Dyspnoea	11 (7.6)	37 (13.1)	25 (29.8)	5 (16.1)	5 (7.4)	11 (7.7)	23 (28.0)
Epistaxis	12 (8.3)	26 (9.2)	17 (20.2)	4 (12.9)	3 (4.4)	15 (10.6)	12 (14.6)
Oropharyngeal pain	6 (4.2)	25 (8.8)	9 (10.7)	8 (25.8)	3 (4.4)	6 (4.2)	8 (9.8)
Pleural effusion	8 (5.6)	28 (9.9)	17 (20.2)	4 (12.9)	5 (7.4)	5 (3.5)	11 (13.4)
Skin and subcutaneous tissue disorders	51 (35.4)	137 (48.4)	54 (64.3)	18 (58.1)	24 (35.3)	47 (33.1)	43 (52.4)
Vascular disorders	37 (25.7)	85 (30.0)	31 (36.9)	17 (54.8)	14 (20.6)	39 (27.5)	34 (41.5)
Hypotension	9 (6.3)	28 (9.9)	16 (19.0)	11 (35.5)	2 (2.9)	14 (9.9)	15 (18.3)

AML = acute myeloid leukemia; Aza = azacitidine; Dec = decitabine; HMA = hypomethylating agent; LDAC = low-dose cytarabine; MedDRA = Medical Dictionary for Regulatory Activities; N = sample size; n = number of patients; PBO = placebo; PT = preferred term; SAE = serious adverse event; SOC = system organ class; VEN = venetoclax

Sources: VIALE-A Interim CSR Table 14.3__1.2.1; Study M14-358 Interim CSR Table 14.3__1.2.1.1 , Table 14.3__1.2.1.2; VIALE-C Interim CSR Table 14.3__1.1.2A; Study M14-387 Interim CSR Table 14.3__1.2.1. Source datasets: ADSL and ADAE (VIALE-A); ADSL and ADAE (Study M14-358); ADSL (6-Month Follow-Up Analysis) and ADAE (6-Month Follow-Up Analysis) (VIALE-C); and ADSL and ADAE (Study M14-387).

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of all grade TEAEs. The Agency's assessment uses grouped terms as listed in Appendix 19.5 and for VIALE-C was at the time of the final efficacy analysis (15 Feb 2019). However, the overall safety profile was similar to that reported above.

(b) (4) The Agency will consider any TEAEs with ≥ 10% incidence and occurring ≥ 2% more frequent on the treatment arm an ADR. We do not agree with the Applicant's assessment (b) (4) In addition, because venetoclax is given in combination, TEAEs that occur due to the regimen, even if not reported at higher incidence with venetoclax, may be included in labeling to describe expected effects of the regimen.

Table 48 shows the TEAEs, all grade and grade 3-4, in VIALE-A and Table 49 shows TEAEs in VIALE-C. These tables exclude laboratory investigations which are generally underreported as AEs and will be reported separately in labeling. Items in bold are included in the comparative AE table in the prescribing information for TEAEs that occurred in ≥10% of patients who received VEN+AZA with a difference between arms of ≥ 5% for All Grades or ≥ 2% for Grade 3 or 4 compared with PBO+AZA.

Table 48: TEAEs in VIALE-A

	VEN+AZA Grade 1-5 N=283 %	VEN+AZA Grade 3-4 N=283 %	PBO+AZA Grade 1-5 N=144 %	PBO+AZA Grade 3-4 N=144 %
Any TEAE	100	76	100	76
Nausea	**44**	**1.8**	**34**	**0.7**
Diarrhea*	**43**	**4.9**	**33**	**2.8**
Constipation	43	0.7	39	1.4
Febrile neutropenia	**42**	**42**	**19**	**18**
Musculoskeletal Pain*	**36**	**2.5**	**28**	**1.4**
Pneumonia*	33	23	31	26
Fatigue*	**31**	**6**	**23**	**2.1**
Vomiting*	**30**	**2.5**	**23**	**0.7**
Hemorrhage*	**27**	**6**	**24**	**3.5**
Edema*	**27**	**0.4**	**19**	**0**
Decreased appetite	**25**	**4.2**	**17**	**0.7**
Rash*	**25**	**1.4**	**15**	**0**
Pyrexia*	23	1.8	22	1.4
Sepsis (excluding fungal)*	**22**	**22**	**16**	**14**
Dyspnea*	**18**	**4.2**	**10**	**2.1**

Stomatitis*	**18**	**1.1**	**13**	**0**
Abdominal Pain*	**18**	**0.4**	**12**	**0**
Dizziness*	**17**	**0.4**	**8**	**0.7**
Urinary Tract Infection*	**16**	**6**	**9**	**6**
Cough*	13	0	14	0
Weight decreased	13	1.4	10	1.4
Atrial fibrillation	12	5	10	2.1
Hypotension*	**12**	**4.9**	**8**	**2.1**
Acute Kidney Injury*	12	2.5	11	4.9
Insomnia	12	0	10	0
Headache*	11	0.4	7	0.7
Hypertension*	10	6	9	4.2
Pleural effusion	10	2.5	6	2.8
Fall	10	0.7	7	2.1
Source: FDA analysis using adae.xpt, adsl.xpt * Indicates grouped terms, see Appendix 19.5.				

Table 49: TEAEs in VIALE-C

	VEN+LDAC Grade 1-5 N=142 %	**VEN+LDAC Grade 3-4 N=142 %**	**PBO+LDAC Grade 1-5 N=68 %**	**PBO+LDAC Grade 3-4 N=68 %**
Any TEAE	99	76	99	76
Nausea	**42**	**1.4**	**31**	**0**
Febrile neutropenia	**32**	**32**	**29**	**29**
Pneumonia*	**28**	**17**	**21**	**21**
Diarrhea*	**28**	**2.8**	**16**	**0**
Hemorrhage*	**27**	**8**	**16**	**1.5**
Vomiting*	**25**	**0.7**	**13**	**0**
Musculoskeletal Pain*	**22**	**2.8**	**18**	**0**
Fatigue*	**22**	**2.1**	**21**	**0**
Decreased appetite	19	1.4	18	0
Constipation	18	0.7	31	0
Pyrexia*	17	2.8	16	4.4
Abdominal Pain*	**15**	**0.7**	**9**	**2.9**
Stomatitis*	**15**	**0.7**	**4.4**	**0**
Sepsis (excluding fungal)*	14	6	16	13
Edema*	14	0	22	0

Insomnia	13	0	12	1.5
Cough*	13	0	10	0
Rash*	12	0	13	1.5
Hypotension*	**11**	**4.9**	**4.4**	**1.5**
Headache*	**11**	**0**	**6**	**0**
Hypertension*	10	6	10	6
Dyspnea*	10	1.4	7	2.9
Source: FDA analysis using adae.xpt, adsl.xpt (15 Feb 2020) * Indicates grouped terms, see Appendix 19.5.				

Laboratory Findings

Data:
Shift tables were used to identify treatment-emergent laboratory abnormalities that were new or worsening from baseline. Common (≥ 10%) new or worsening laboratory abnormalities occurring at ≥ 5% (any grade) or ≥ 2% (Grade 3 or 4) higher incidence for VIALE-A and VIALE-C are presented in Table 46 and Table 47.

In VIALE-A, among patients treated with VEN or PBO in combination with AZA, no clinically important trends were observed for hematology or chemistry variables. Shifts in hematology values from Grades 0 to 2 to Grades 3 to 4, or from Grade 3 to Grade 4, at maximum CTCAE grade were observed in ≥ 50% of patients in each arm for low hemoglobin, low platelets, low leukocytes, and low neutrophils, and ≥ 40% of patients in each arm for low lymphocytes. In VIALE-A, more patients who received VEN versus PBO, in combination with AZA, had Grade 3 or 4 low hemoglobin (57.1% vs 52.1%), low platelets (87.5% vs 80.4%), low leukocytes (95.7% vs 67.7%), low neutrophils (97.6% vs 81.2%), and low lymphocytes (70.9% vs 39.4%).

A greater proportion of patients receiving VEN + AZA (vs. PBO + AZA) experienced increased bilirubin both overall (53.2% vs 39.6%) and Grade ≥ 3 (7.4% vs 4.2%). The laboratory findings are consistent with the reported AEs.

Laboratory findings in patients treated with VEN in combination with either AZA or DEC in Study M14-358 were consistent with the findings in VIALE-A. Likewise, laboratory findings in patients treated with VEN in combination with LDAC in Study M14-387 were consistent with the findings in VIALE-C.

In VIALE-C, among patients treated with either VEN or PBO in combination with LDAC, shifts from Grades 0 to 2 to Grades 3 to 4, or from Grade 3 to Grade 4, were observed for low potassium (16.9% vs. 17.6%) high glucose (13.4% vs. 10.2%), and low phosphate (11.9%, vs. 19.1%) in patients treated with VEN + LDAC versus PBO + LDAC, respectively. There were no clinically important trends for any of these parameters. Shifts in hematology values were observed in ≥ 50% of patients in each arm for low hemoglobin, low platelets, and low leukocytes, and in ≥ 40% of patients in each arm for low neutrophils; shifts were also observed for low lymphocytes (≥ 40% of patients receiving VEN + LDAC, ≥ 25% for patients receiving PBO

+ LDAC). More patients who received VEN versus PBO, in combination with LDAC, had Grade 3 or 4 low hemoglobin (57.0% vs. 54.4%), low platelets (94.7% vs. 91.8%), low leukocytes (90.0% vs. 65.0%), low neutrophils (92.3% vs. 73.7%), and low lymphocytes (70.9% vs. 27.3%).

In patients with AML, baseline neutrophil counts worsened in 95% to 100% of patients treated with VEN in combination with AZA, DEC, or LDAC.

Table 50. Common (≥ 10%) New or Worsening Laboratory Abnormalities Occurring at ≥ 5% (Any Grade) or ≥ 2% (Grade 3 or 4) Higher Incidence with VEN + AZA versus PBO + AZA

	VEN + AZA (N = 283)		PBO + AZA (N = 144)	
Laboratory Abnormality	**All Grades[a] (%)**	**Grade 3 or 4[b] (%)**	**All Grades[a] (%)**	**Grade 3 or 4[b] (%)**
Hematology				
Anemia	61.3	57.1	56.3	52.1
Thrombocytopenia	94.0	87.5	93.8	80.4
Leukopenia	97.6	95.7	81.2	67.7
Neutropenia	98.4	97.6	88.2	81.2
Lymphopenia	91.5	70.9	71.8	39.4
Chemistry				
Alkaline phosphatase increased	41.8	1.1	29.2	0.7
Hyperbilirubinemia	53.2	7.4	39.6	4.2
Blood bicarbonate decreased	31.3	0.8	25.2	0
Hypocalcemia	50.7	6.5	38.7	9.2
Hyponatremia	46.1	13.8	46.5	8.3

AZA = azacitidine; N = sample size; PBO = placebo; VEN = venetoclax

a. Includes shifts from Grade 0 (Normal) at baseline to Grade 1 to 4 postbaseline and worsening from an abnormal baseline value of at least one grade postbaseline.

b. Includes shifts from Grade 0 to 2 at baseline to Grade 3 or 4 post-baseline and from Grade 3 at baseline value to Grade 4 postbaseline.

Note: Grades are as defined by NCI common terminology criteria for adverse events version 4.03. N_obs indicates the number of patients with at least one postbaseline observed value for the respective parameter, excluding patients with a Grade 4 baseline value.

Note: A baseline grade of 0 (Normal) was imputed for all patients with at least one postbaseline value but missing a baseline value for the respective parameter.

Sources: VIALE-A CSR Tables 14.3__4.1.3 and 14.3__4.2.3. Source datasets: ADSL and ADLB.

Table 51. Common (≥ 10%) New or Worsening Laboratory Abnormalities Occurring at ≥ 5% (Any Grade) or ≥ 2% (Grade 3 or 4) Higher Incidence with VEN + LDAC versus PBO + LDAC

	VEN + LDAC (N = 142)		PBO + LDAC (N = 68)	
Laboratory Abnormality	**All Grades[a] (%)**	**Grade 3 or 4[b] (%)**	**All Grades[a] (%)**	**Grade 3 or 4[b] (%)**
Hematology				
Anemia	63.4	57.0	57.4	54.4
Leukopenia	95.4	90.0	75.0	65.0
Lymphopenia	92.2	70.9	65.2	27.3
Neutropenia	95.4	92.3	81.6	73.7
Thrombocytopenia	96.8	94.7	93.9	91.8
Chemistry				
Hypocalcemia	54.7	7.9	46.9	12.5
ALT/SGPT increased	32.4	4.2	26.5	1.5
AST/SGOT increased	38.0	5.6	36.8	1.5
Alkaline phosphatase increased	34.5	1.4	27.9	1.5
Hyperbilirubinemia	62.0	7.0	38.2	7.4
Hypokalemia	57.0	16.9	43.9	13.6
Hyperglycemia	52.1	13.4	58.8	10.3
Creatinine increased	33.1	4.9	35.3	2.9
Hypoalbuminemia	62.0	6.3	42.6	4.4
Hypernatremia	11.3	2.8	5.9	1.5

LDAC = low dose cytarabine; N = sample size; PBO = placebo; VEN = venetoclax

a. Includes shifts from Grade 0 (Normal) at baseline to Grade 1 to 4 postbaseline and worsening from an abnormal baseline value of at least one grade postbaseline.

b. Includes shifts from Grade 0 to 2 at baseline to Grade 3 or 4 post-baseline and from Grade 3 at baseline value to Grade 4 postbaseline.

Note: Grades are as defined by NCI common terminology criteria for adverse events version 4.03. N_obs indicates the number of patients with at least one postbaseline observed value for the respective parameter, excluding patients with a Grade 4 baseline value.

Note: A baseline grade of 0 (Normal) was imputed for all patients with at least one postbaseline value but missing a baseline value for the respective parameter.

Sources: VIALE-C CSR Tables 14.3__4.1.3A and 14.3__4.2.3A. Source datasets: ADSL and ADLB (6-month Follow-Up Analysis).

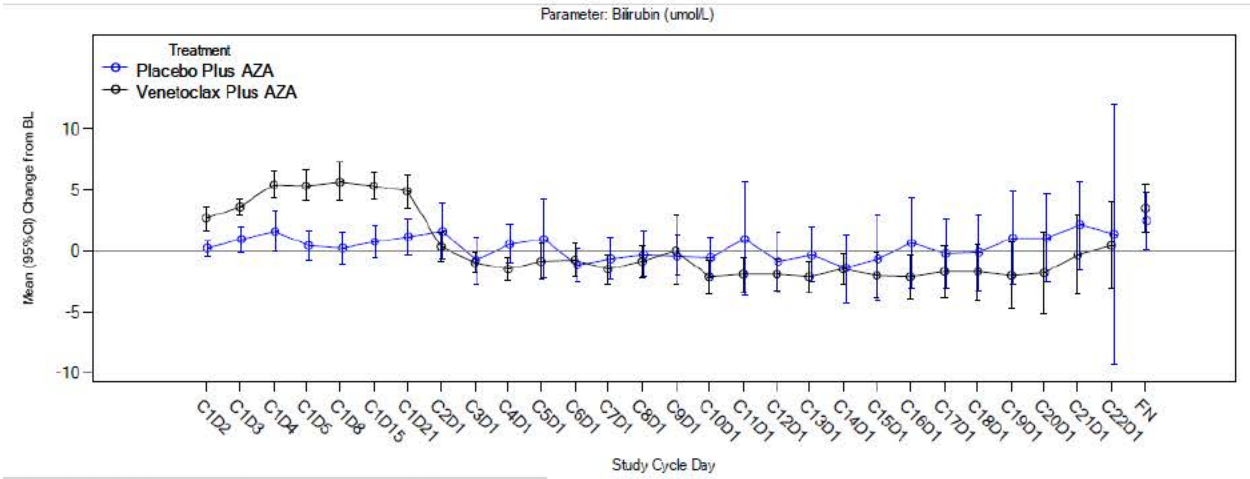
The Applicant's Position:

Changes from baseline in hematology and clinical chemistry laboratory values were analyzed over the length of each study. The data were reviewed, and laboratory changes were assessed for any clinically meaningful trends. No clinically meaningful trends over time were observed for clinical chemistry or hematology variables. The decreases in lymphocyte counts are consistent with the mechanism of action of VEN, HMAs, or LDAC. Decreases in other blood counts are consistent with the reported hematologic AEs and are part of the known AE profile of HMAs and LDAC. The elevations in serum bilirubin are consistent with reported AEs.

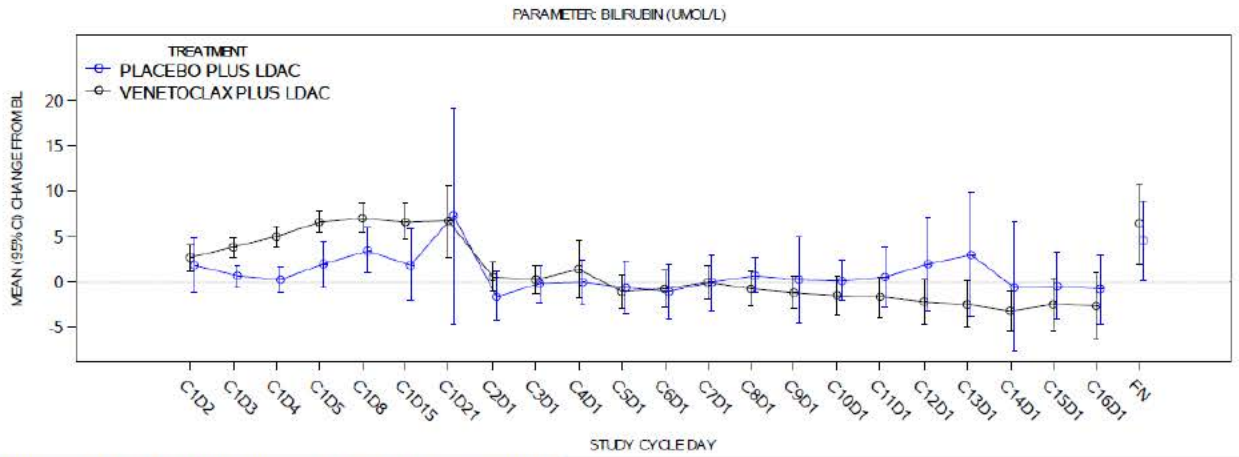
Regulatory Authorities' Assessment:

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). An evaluation of neutrophil counts over time is shown in Section 8.2.5. See also Section 8.2.5 for review of the consequences of cytopenias including infections and hemorrhage.

Non-hematologic laboratory evaluations over the course of the studies was similar between the venetoclax and placebo arms of both randomized studies with the exception of bilirubin. Bilirubin appeared increased in the venetoclax treatment arm compared to placebo in both studies as shown in the figures below for VIALE-A and VIALE-C, respectively. This finding was isolated to cycle 1, and the etiology is somewhat unclear. Labeling reflects the increased rate of bilirubin increase in the venetoclax arm.



Source: M15-656 interim CSR, Figure 14, page 287



Source: M16-043 CSR, Figure 14.3__1.2A, page 2443

Vital Signs

The Applicant's Position:
Across the studies, there were no clinically meaningful trends from baseline or differences between treatment arms in patient weight, blood pressure (including diastolic and systolic values), heart rate, or body temperature.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. No clinically significant changes from baseline in blood pressure, heart rate, weight, or temperature were observed in the venetoclax arm compared to the placebo arm.

Electrocardiograms (ECGs)

The Applicant's Position:
ECGs were conducted at baseline and as clinically indicated during the studies. No clinically significant ECGs were reported among patients treated with VEN or PBO in combination with AZA in VIALE-A. In Study M14-358, 3 patients who received VEN + AZA (N = 2) or VEN + DEC (N = 1) had clinically significant ECG abnormalities postbaseline, all of which were assessed by the investigator as not related to VEN or any other study drug.

There were no reports of ECG abnormalities among patients who received VEN + LDAC in VIALE-C; however, 1 patient in the PBO + LDAC arm had an AE of ECG abnormality that was assessed as not related to study drug. One patient who received VEN + LDAC in Study M14-387 had a clinically significant ECG abnormality, also assessed as not related to study drug. In all cases, patients had preexisting cardiac disease or other cardiac AEs that could reasonably account for ECG abnormalities.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment.

QT

The Applicant's Position:
No QT evaluations were performed as part of VIALE-A, VIALE-C, Study M14-358, or Study M14-387. One patient in VIALE-A was reported to have developed torsade de pointes. That patient had a history of long QT interval and developed torsade in the context of pneumonia and hypokalemia.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment. 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

The Applicant's Position:
No immunogenicity assessments were conducted as part of VIALE-A, VIALE-C, Study M14-358, or Study M14-387.

Regulatory Authorities' Assessment:
We agree with the Applicant's position.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:
Based on the accumulating experience with VEN combination therapy in numerous studies including VIALE-A and VIALE-C, the following events are considered of particular interest to patients with AML receiving VEN: neutropenia, anemia, thrombocytopenia, infections, hemorrhage, TLS, and DILI. For analysis of selected AEs across studies, the search criteria used is described in Section 8.2.3.

8.2.5.1 Neutropenia

Data:
Neutropenia is a common manifestation of AML; due to an increased incidence when VEN was added to an HMA or LDAC, it is considered an identified risk of venetoclax. Neutropenia and/or febrile neutropenia were observed in approximately half of patients treated with VEN in combination with HMAs or LDAC; febrile neutropenia was a primary AE leading to non-per-protocol dose interruptions and/or reductions. Since the majority of patients had Grade ≥ 3 events of neutropenia, anemia, and thrombocytopenia, reported AEs were also Grade ≥ 3. In these studies, to manage neutropenia in patients who achieved a response of MLFS or CRi, a delay in subsequent cycle of study treatment was implemented to allow for recovery of neutrophil counts.

In VIALE-A, 71.0% patients receiving VEN + AZA versus 44.4% patients receiving PBO + AZA reported AEs in the neutropenia search (subset for selected AEs). The most commonly

reported AE in the neutropenia search was the event of neutropenia reported by 42.0% patients in the VEN arm versus 29.2% patients in the PBO arm. Febrile neutropenia (41.7% vs. 18.8%) and neutrophil count decreased (2.8% vs. 0.7%) were also reported in more patients in the VEN arm versus the PBO arm. Neutropenic infection (0.7% patients) and neutropenic sepsis (0.4% patients) were also reported in the VEN arm (versus 0 patients each in the PBO arm). Agranulocytosis was not reported for any patient in either treatment arm. With the exception of the events of neutropenic infection, all events were Grade ≥ 3.

In Study M14-358, incidence of neutropenia was assessed using the combined PTs of febrile neutropenia, neutropenia, neutropenic sepsis, and neutrophil count decreased. Patients treated with VEN + AZA reported 67.9% incidence of PTs, all of which were Grade ≥ 3. Neutropenia as a single PT was reported for 20.2% patients and febrile neutropenia as a single PT was reported for 39.3% patients treated with VEN + AZA.

In Study M14-358, patients treated with VEN + DEC reported 71.0% incidence of PTs, all of which were Grade ≥ 3. Neutropenia as a single PT was reported for 9.7% patients and febrile neutropenia as a single PT was reported for 64.5% patients treated with VEN + DEC.

In VIALE-C, 68.3% patients receiving VEN + LDAC versus 45.6% patients receiving PBO + LDAC reported AEs in the neutropenia search (subset for selected AEs). The most commonly reported AE in the neutropenia search was the event of neutropenia reported by 48.6% patients in the VEN arm versus 17.6% patients in the PBO arm. Febrile neutropenia (32.4% vs. 29.4%) and neutrophil count decreased (7.0% vs. 4.4%) were reported in similar numbers of patients in the VEN arm versus the PBO arm. Neutropenic sepsis was reported for 3 patients in the VEN arm, and agranulocytosis was reported for 1 patient in the PBO arm. All events were Grade ≥ 3.

In Study M14-387, incidence of neutropenia was assessed using the combined PTs of febrile neutropenia, neutropenia, neutropenic sepsis, and neutrophil count decreased. Incidence of the combined PTs was 70.7% among patients treated with VEN 600 mg + LDAC. With the exception of 1 event of neutropenia, all events were Grade ≥ 3.

Serious AEs of Neutropenia

In VIALE-A, incidence of SAEs within the neutropenia search (subset for selected AEs) was higher among patients in the VEN + AZA arm compared to the PBO + AZA arm (33.6% and 11.8%, respectively). Febrile neutropenia was the most common SAE in the neutropenia search in both treatment arms and was reported by 29.7% patients in the VEN arm versus 10.4% patients in the PBO arm. Serious events of neutropenia were reported by 4.6% patients in VEN arm versus 2.1% patients in the PBO arm. Serious events of neutropenic sepsis and neutrophil count decreased were reported for 1 patient each in the VEN arm only.

In VIALE-C, incidence of SAEs within the neutropenia search (subset for selected AEs) was similar between the VEN + LDAC and PBO + LDAC arms (19.7% and 17.6%, respectively). Febrile neutropenia was the most common SAE in the neutropenia search in both treatment arms and

was reported by 16.9% patients in the VEN arm versus 17.6% patients in the PBO arm. Serious events of neutropenia (2.8%), neutropenic sepsis (2.1%), and neutrophil count decreased (0.7%) were reported in the VEN + LDAC arm but not in the PBO + LDAC arm.

AEs of Neutropenia Leading to VEN Discontinuation, Dose Interruption, or Dose Reduction

In VIALE-A, rates of VEN discontinuation in VEN + AZA due to febrile neutropenia or neutropenia were low (VEN: 1.4% febrile neutropenia, 1.4% neutropenia; PBO: 0.7% febrile neutropenia, 1.4% neutropenia). Rates of VEN or PBO dose interruption or dose reduction due to febrile neutropenia or neutropenia were higher among patients who received VEN + AZA compared to those who received PBO + AZA (VEN: 19.8% febrile neutropenia, 19.4% neutropenia PBO: 4.2% febrile neutropenia, 10.4% neutropenia).

In VIALE-C, rates of VEN or PBO discontinuation due to febrile neutropenia or neutropenia were numerically low (VEN: 1.4% febrile neutropenia, 0.7% neutropenia; PBO: 2.9% febrile neutropenia, 0% neutropenia). Rates of VEN or PBO dose interruption or dose reduction due to febrile neutropenia or neutropenia were also low, but somewhat higher in the VEN arm versus the PBO arm (VEN: 7.7% febrile neutropenia, 19.7% neutropenia; PBO: 7.4% febrile neutropenia, 7.4% neutropenia).

The Applicant's Position:

While the addition of VEN to an HMA or LDAC increased the incidence of hematologic AEs compared to patients who received an HMA or LDAC monotherapy, these events were tolerated and were not associated with substantive differences in clinical consequences between the treatment groups. Effective management of febrile neutropenia and neutropenia during the Phase 3 studies (VIALE-A and VIALE-C), including dose modification for hematologic toxicities, and prophylactic anti-infectives, mitigated clinical effects from the increase in high grade hematologic AEs, which did not lead to increased incidence of clinically consequential serious infections or deaths due to serious infections.

The events of neutropenia/febrile neutropenia, which were observed with VEN in combination with HMAs or LDAC were in the range expected for these agents and in this population.

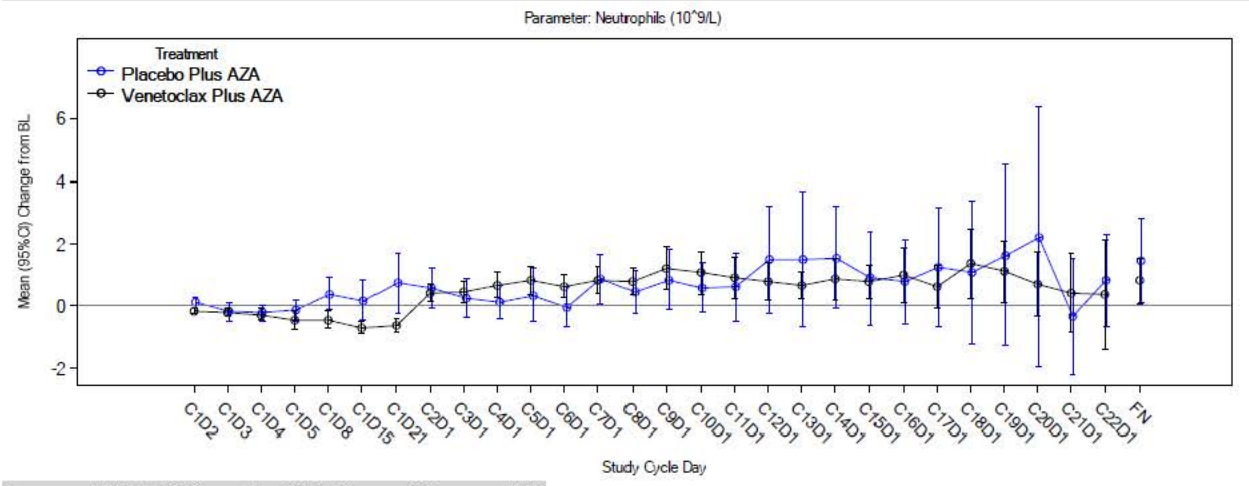
Regulatory Authorities' Assessment:

Neutropenia is an expected component of AML due to marrow involvement of malignant cells, and grade 3-4 neutropenia frequently occurs with the use of azacitidine and LDAC. Neutropenia is also an on-target effect of venetoclax and is listed as a Warning and Precaution in the current venetoclax USPI.

By laboratory evaluation, in both randomized clinical studies, grade 3-4 neutropenia that was new or worsening from baseline occurred in ≥95% of patients. Evaluation by AE tends to underreport the occurrence of hematologic laboratory abnormalities. 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

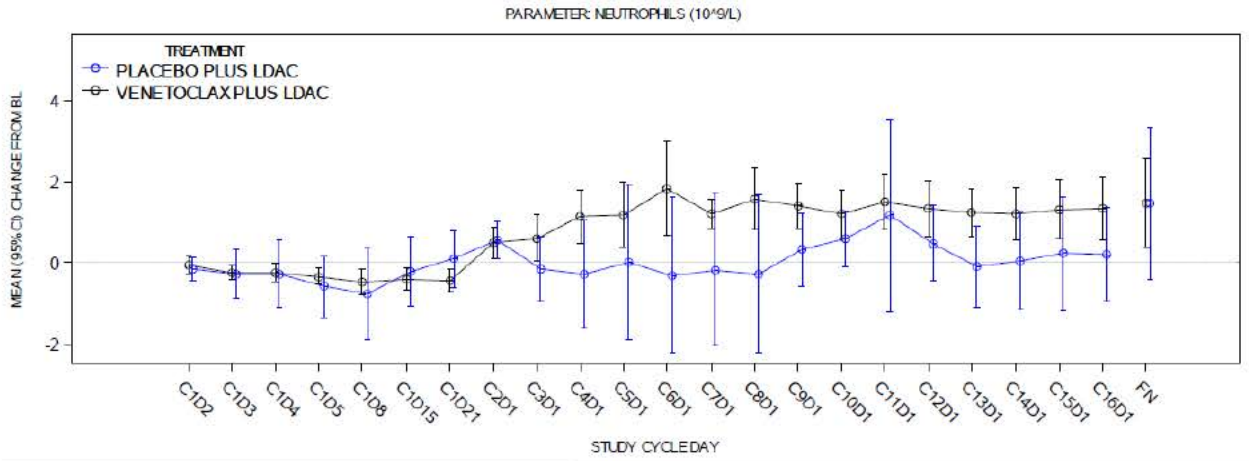
managed by dose interruption and/or dose delay for neutropenia >7 days and G-CSF if indicated.

An analysis of the neutrophil count change from baseline was performed by the Applicant and is shown in the Figure below for VIALE-A.



Source: M15-656 interim CSR, Figure 13, page 282

A similar analysis of the neutrophil count change from baseline was performed for VIALE-C, shown in the Figure below.



Source: M16-043 CSR, Figure 14.3__1.1A, page 2432

As anticipated, the neutrophil recovery appeared delayed with venetoclax treatment which is more easily visualized in the VIALE-A study. This reflects on-target neutropenia with venetoclax treatment. In subsequent cycles, neutrophil count change from baseline was similar between arms, likely reflecting ongoing responses.

8.2.5.2 Anemia

Data:
Anemia was evaluated using the combined PTs of "anaemia" and "haemoglobin decreased."

In VIALE-A, 27.6% patients receiving VEN + AZA versus 20.8% receiving PBO + AZA reported anemia as defined by these PTs. One event of hemoglobin decreased was identified in the VEN arm. Grade ≥ 3 AEs for "anaemia" were reported by 26.1% patients in the VEN arm versus 20.1% patients in the PBO arm. Events of anemia were considered SAEs in 4.9% vs. 4.2% of patients in the VEN arm versus PBO arm, respectively.

In Study M14-358, 29.8% patients receiving VEN + AZA reported anemia (as a single PT). No events of "hemoglobin decreased" were identified. All events were Grade ≥ 3.

In Study M14-358, 25.8% patients receiving VEN + DEC reported anemia (as a single PT). No events of "hemoglobin decreased" were identified. All events were Grade ≥ 3.

In VIALE-C, 28.9% patients receiving VEN + LDAC versus 22.1% patients receiving PBO + LDAC reported anemia (as a single PT). No events of hemoglobin decreased were identified in either treatment arm. Most events of anemia were assessed as Grade ≥ 3 (26.8% in VEN + LDAC vs. 22.1% in PBO + LDAC). These events were considered SAEs in 2.8% patients in VEN + LDAC versus 0% patients in PBO + LDAC.

In Study M14-387, 31.7% patients receiving VEN + LDAC reported anemia defined by the combined PTs; 1 event of "hemoglobin decreased" was included. Anemia (as a single PT) was reported as an AE for 30.5% of patients receiving VEN + LDAC. All events, except 1 event of anemia, were Grade ≥ 3.

The Applicant's Position:
No clinically meaningful worsening of anemia was observed when patients were treated with VEN in combination with HMAs or LDAC.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment based on reported AEs. Refer to the laboratory abnormality section for further evaluation as AEs tend to underreport hematologic laboratory abnormalities. Anemia can be present at baseline in patients with AML and is common with treatment with azacitidine or LDAC. With the addition of venetoclax to backbone therapy, anemia trended somewhat more common in the venetoclax arm by reported AE. Evaluation of the change from baseline in hemoglobin over time did not show significant differences between venetoclax and placebo arms in either study.

8.2.5.3 Thrombocytopenia

Data:

Thrombocytopenia was evaluated using the combined PTs of "thrombocytopenia" and "platelet count decreased."

In VIALE-A, 50.5% patients receiving VEN + AZA versus 41.0% receiving PBO + AZA reported thrombocytopenia as defined by the combined PTs. Thrombocytopenia (as a single PT) was reported for 45.9% patients in the VEN arm versus 40.3% patients in the PBO arm. Thrombocytopenia and platelet count decreased were assessed as Grade ≥ 3 for 47.7% patients in VEN + AZA and 38.2% patients in PBO + AZA. These events were considered SAEs in 4.6% in VEN arm versus 1.4% in PBO arm.

In Study M14-358, 53.6% patients receiving VEN + AZA reported thrombocytopenia as defined by the combined PTs. The majority of events were Grade ≥ 3. Thrombocytopenia (as a single PT) was reported for 25.0% patients in VEN + AZA. All events of thrombocytopenia were assessed as Grade ≥ 3.

In Study M14-358, 71.0% patients receiving VEN + DEC reported thrombocytopenia as defined by the combined PTs. The majority of events were Grade ≥ 3. Thrombocytopenia (as a single PT) was reported for 22.6% patients in VEN + DEC. All events of thrombocytopenia were assessed as Grade ≥ 3.

In VIALE-C, 50.0% patients receiving VEN + LDAC versus 45.6% of patients receiving PBO + LDAC reported thrombocytopenia as defined by the combined PTs. Thrombocytopenia and platelet count decreased were assessed as Grade ≥ 3 for 50.0% patients in VEN arm and 44.1% patients in PBO arm. These events were considered SAEs for 4.9% patients in VEN arm and 4.4% patients in PBO arm.

In Study M14-387, 61.0% patients receiving VEN + LDAC reported thrombocytopenia as defined by the combined PTs. All events, except 1 event of platelet count decreased, were Grade ≥ 3. Thrombocytopenia (as a single PT) was reported for 39.0% patients in VEN + LDAC. All events of thrombocytopenia were assessed as Grade ≥ 3.

The Applicant's Position:
Although an increase in thrombocytopenia incidence was observed during treatment with VEN in combination with HMAs or LDAC, the worsening was not clinically significant.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment based on reported AEs. Refer to the laboratory abnormality section for further evaluation as AEs tend to underreport hematologic laboratory abnormalities. Thrombocytopenia can be present at baseline in patients with AML and is common with treatment with azacitidine or LDAC. The addition of venetoclax to backbone therapy resulted in increased reporting of AEs of thrombocytopenia. Evaluation of the change from baseline in platelet count over time did not show significant differences between venetoclax and placebo arms in either study. Refer also to analyses of hemorrhage.

8.2.5.4 Infections

Data:
Infections are a common complication in patients with AML and are an expected feature of the disease. AEs within the SOC of Infections and Infestations were reported for approximately 60% to 70% of patients treated with PBO in combination with HMAs and LDAC and for approximately 65% to 85% of patients treated with VEN in combination with HMAs or LDAC.

In VIALE-A, AEs within the SOC of Infections and Infestations were observed in 84.5% of patients treated with VEN + AZA and 67.4% of patients treated with PBO + AZA. In Study M14-358, AEs within this SOC were observed in 77.4% of patients treated with VEN + AZA and in 80.6% of patients treated with VEN + DEC.

In VIALE-C, AEs within the SOC of Infections and Infestations were observed in 64.8% of patients treated with VEN + LDAC and 60.3% of patients treated with PBO + LDAC. In Study M14-387, AEs within this SOC were observed in 73.2% of patients treated with VEN + LDAC.

Grade ≥ 3 AEs within the SOC of Infections and Infestations were similar across treatment arms, reported for 63.6% and 43.0% of patients who received VEN + AZA or VEN + LDAC compared to 51.4% and 50.0% of patients who received PBO + AZA or PBO + LDAC in VIALE-A and VIALE-C, respectively. Similar results were observed in the Phase 1 studies: Grade ≥ 3 AEs of infection were reported in 52.4% and 61.3% of patients treated with VEN + AZA or VEN + DEC in Study M14-358, and in 50.0% of patients treated with VEN + LDAC in Study M14-387. Pneumonia was the most common Grade ≥ 3 infection for all treatment arms.

In VIALE-A, SAEs in the SOC of Infections and Infestations were reported for 57.2% of patients receiving VEN + AZA, compared with 43.8% of patients receiving PBO + AZA. In Study M14-358, SAEs in this SOC were reported for 47.6% of patients receiving VEN + AZA and 54.8% of patients receiving VEN + DEC. In VIALE-C, SAEs in the SOC of Infections and Infestations were reported for 37.3% of patients treated with VEN + LDAC and 36.8% of patients treated with PBO + LDAC. In Study M14-387, SAEs in this SOC were reported for 43.9% of patients in the VEN + LDAC arm.

In VIALE-A, AEs within the SOC of Infections and Infestations that led to death were observed in 9.2% patients in VEN + AZA and 7.6% patients in PBO + AZA. In Study M14-358, AEs leading to death in this SOC were reported for 6.0% patients receiving VEN + AZA and 6.5% patients receiving VEN + DEC. In VIALE-C, AEs in the SOC of Infections and Infestations that led to death were reported for 14.8% patients treated with VEN + LDAC and 10.3% patients treated with PBO + LDAC. In Study M14-387, AEs leading to death in this SOC were reported for 7.3% patients in the VEN + LDAC arm.

The Applicant's Position:
In VIALE-A, there was a higher incidence of serious, all grade, and Grade ≥ 3 infections in the VEN + AZA arm compared to the PBO + AZA arm. The incidence of dose interruptions for infections (and neutropenia) was also higher in the VEN arm versus the PBO arm. However,

discontinuations due to infections and fatal infective events were balanced across arms.

These findings confirm that VEN is associated with the occurrence of serious and severe infections, but the current guidance implemented in both VIALE-A and VIALE-C, as well as in the proposed label are appropriate and adequate to mitigate the risk of fatal infections and ensure continued use of VEN combinations (standard treatment practices, e.g., prophylactic treatment with anti-infective agents [including antifungals] and effective management of febrile neutropenia and neutropenia, including treatment interruptions, dosing, and schedule modifications). There were no clinically significant increases in fatal infections.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of infections. Overall, infections appear to occur more often in patients treated with venetoclax, particularly in the azacitidine combination, compared to placebo. This includes a trend towards increase in an increase in fatal infections. Prophylaxis and management of infections and neutropenia is standard practice in the treatment of AML.

8.2.5.5 Hemorrhage

Data:
AEs of any grade defined by the Haemorrhages SMQ were reported for approximately 38% to 62% of patients.

In VIALE-A, 37.8% patients receiving VEN + AZA versus 36.8% patients receiving PBO + AZA reported AEs in this SMQ. The most common terms identified in > 5% of patients in either treatment arm included contusion, epistaxis, petechiae, and hematoma. Grade ≥ 3 AEs were reported for 10.2% patients in VEN arm and 6.3% patients in the PBO arm; SAEs were reported by 8.8% patients in VEN arm and 5.6% patients in PBO arm.

In Study M14-358, 58.3% patients receiving VEN + AZA and 51.6% of patients receiving VEN + DEC had AEs in this SMQ. AEs identified in ≥ 5% of patients in either treatment arm included contusion, epistaxis, petechiae, ecchymosis, hematuria, and hematoma. SAEs in this SMQ were reported for 4.8% patients treated with VEN + AZA and no patients treated with VEN + DEC. No SAEs were reported for ≥ 2 patients.

In VIALE-C, 41.5% patients receiving VEN + LDAC versus 30.9% patients receiving PBO + LDAC had AEs in this SMQ. Terms identified in > 5% of patients were epistaxis (10.6%) in the VEN arm and haematochezia (5.9%) in the PBO arm. Grade ≥ 3 AEs were reported for 11.3% patients in VEN arm and 7.4% patients in the PBO arm; SAEs were reported for 8.5% patients in VEN + LDAC versus 5.9% patients in PBO + LDAC. SAEs reported for ≥ 2 patients included upper gastrointestinal haemorrhage (in the VEN arm).

In Study M14-387, 62.2% of patients who received VEN + LDAC had AEs in this SMQ. Adverse events identified in ≥ 5% of patients in this treatment arm included epistaxis, mouth

haemorrhage, petechiae, and haematuria. SAEs were reported for 15.9% patients in VEN + LDAC. SAEs reported for ≥ 2 patients included haemorrhage intracranial, haematuria, and epistaxis.

AEs of Hemorrhage Leading to Discontinuation

Preferred terms suggestive of haemorrhage were reported as leading to VEN discontinuation in patients who received VEN 400 mg in combination with AZA or DEC. In VIALE-A, in the VEN + AZA arm, these PTs included 1 event each of gastritis hemorrhagic, intestinal hemorrhage, soft tissue hemorrhage, cerebral hematoma, intracranial hemorrhage, and hemorrhagic stroke; in the PBO + AZA arm, no events suggestive of hemorrhage led to treatment discontinuation. In Study M14-358, no AEs suggestive of haemorrhage led to VEN discontinuation in patients treated with VEN in combination with either AZA or DEC.

Preferred terms suggestive of haemorrhage were also reported as leading to VEN discontinuation in patients who received VEN 600 mg + LDAC. In VIALE-C, these PTs included 1 event each of cerebral haemorrhage and haemorrhage intracranial; 1 event of haemorrhage intracranial also led to discontinuation in a patient treated with PBO + LDAC. In Study M14-387, 5 events of haemorrhage led to discontinuation among patients receiving VEN + LDAC; these events included 2 AEs of haemorrhage intracranial and 1 AE each of subdural haemorrhage, cerebral haemorrhage, and pulmonary alveolar haemorrhage.

AEs of Hemorrhage Leading to Death

Overall, among 622 patients treated at the proposed doses of venetoclax in these 4 studies, 13 haemorrhage-related AEs that led to death were identified in patients receiving the proposed dose of VEN in combination with either AZA or LDAC. Five hemorrhage-related AEs leading to death were identified in 212 patients receiving PBO with either AZA (4 patients) or LDAC (1 patient).

In VIALE-A, for patients treated with VEN + AZA, 3 events of intracranial hemorrhage, as well as 1 event each of gastritis hemorrhagic, intestinal hemorrhage, cerebral hematoma, cerebral hemorrhage, and hemorrhagic stroke leading to death were reported. For patients in the PBO + AZA arm, AEs of catheter site hemorrhage, subdural hematoma, cerebral hemorrhage, and hemoptysis leading to death were reported for 1 patient each. In Study M14-358, no AEs of hemorrhage leading to death were reported among patients receiving VEN 400 mg in combination with AZA or DEC.

In VIALE-C, 1 event each of cerebral haemorrhage and pulmonary alveolar haemorrhage were reported in VEN + LDAC leading to death; the AE of pulmonary alveolar haemorrhage was assessed as possibly related to study treatment. Among patients in the PBO arm, an AE of haemorrhage intracranial leading to death was reported for 1 patient (assessed as possibly related to treatment). In Study M14-387, 3 AEs of haemorrhage leading to death were reported in patients receiving VEN 600 mg + LDAC, including 2 events of haemorrhage intracranial and 1 event of cerebral haemorrhage; both events were assessed as not related to venetoclax.

The Applicant's Position:

AEs of any grade defined by a Haemorrhages SMQ were reported for 37% to 62% of patients. However, Grade ≥ 3 bleeding events were reported for only 10.2% and 11.3% of patients treated at the proposed VEN doses in combination with AZA or LDAC, and serious events of haemorrhage were reported for < 10% of patients in VIALE-A and VIALE-C (higher in Study M14-387). No hemorrhage-related AEs leading to death were reported for patients treated with VEN + DEC. The majority of bleeding events were manageable using standard monitoring, prophylactic and therapeutic measures.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment of hemorrhage. Overall, hemorrhages appear to occur more often in patients treated with venetoclax, particularly in the LDAC combination, compared to placebo. Hemorrhages lead to discontinuation in some patients but did not appear to lead death more commonly in patients treated with venetoclax. Prophylaxis and management of thrombocytopenia and hemorrhage is standard practice in the treatment of AML.

8.2.5.6 Tumor Lysis Syndrome

Data:
There is a potential risk for TLS in patients with AML, especially in those with elevated leukocyte count, circulating blasts, elevated pretreatment lactate dehydrogenase (LDH) levels, renal dysfunction, and dehydration. In addition, the on-target effect of venetoclax could lead to rapid cell death and pose a risk of TLS. Data from the 4 studies suggest that the rate of TLS was approximately 1 to 2% for patients receiving VEN in combination with HMAs (AZA or DEC), compared with approximately 5% for patients receiving VEN in combination with LDAC.

In VIALE-A, among patients who received VEN 400 mg or PBO, respectively, in combination with AZA, 3 (1.1%) and 1 patient (0.7%) reported events of TLS, all of which occurred during ramp up and within the 7 days of study drug administration in Cycle 1. (The 1 event of TLS in the PBO + AZA arm was reported on Day 68, which was after VEN ramp-up). One of these events was reported as being due to clinical abnormalities, but there were no reported AEs that would qualify this event as clinical TLS. Two of the 3 events in the VEN + AZA arm were reported as Grade ≥ 3 TLS; all 3 events resolved with medical intervention.

In Study M14-358, there were no reported AEs of TLS among patients who received VEN 400 mg in combination with AZA or DEC.

In VIALE-C, no events of TLS were reported among patients who received PBO + LDAC; 8 AEs of TLS (5.6%) were reported among patients treated with VEN 600 mg + LDAC, of which 4 cases were clinical TLS and 4 cases were laboratory TLS. Of these events, 7/8 events were reported as Grade ≥ 3 and led to death in 2/8 patients. Both of these patients were considered of high risk.

In Study M14-387, 2 AEs of TLS (2.4%) were reported among patients treated with VEN 600 mg + LDAC; these patients had laboratory TLS during VEN ramp-up, which was managed using routine clinical measures.

In VIALE-A, laboratory abnormalities at any time during study treatment meeting the Howard criteria for laboratory TLS were experienced by 7 patients (2.5%) in VEN + AZA arm and 3 patients (2.1%) in PBO + AZA arm. In Study M14-358, 2 patients (2.4%) receiving VEN 400 mg + AZA experienced laboratory abnormalities meeting the Howard criteria for laboratory TLS; these abnormalities were not reported as AEs of TLS by the investigators as the chemistry lab abnormalities were transient or present at baseline prior to dosing.

In VIALE-C, laboratory abnormalities at any time during study treatment meeting the Howard criteria for laboratory TLS were experienced by 9 patients (6.3%) in the VEN + LDAC arm and 1 patient (1.5%) in the PBO + AZA arm. In the VEN + LDAC arm, 2 patients with reported TLS did not meet Howard criteria but were reported as TLS by the investigator because of kidney injury. In Study M14-387, 2 patients (2.4%) receiving VEN 600 mg + LDAC reported events for TLS; both patients met the Howard criteria for TLS.

The Applicant's Position:
These results suggest that risk of TLS risk can be mitigated with prophylaxis and ramp-up dosing of venetoclax, and with a controlled WBC < 25,000/µL prior to initiation of therapy.

Regulatory Authorities' Assessment:
We agree with the Applicant's presentation of TLS in the randomized studies. In VIALE-A, the rate of TLS either by AE reporting or by Howard criteria were balanced between the venetoclax arm (2.5% by Howard criteria) and the placebo arm (2.1% by Howard criteria).

However, in VIALE-C, the rate of TLS was somewhat higher than expected, and higher than reported in the VEN/LDAC single arm study. No patients in the placebo arm had TLS reported as an AE and 1 patient by Howard criteria. In the venetoclax arm, there were 8 patients who had TLS reported as an AE, 4 were laboratory TLS and 4 had associated clinical events. Of those events, 2/8 were fatal. Both fatal events were considered to be in high-risk patients by the Applicant; however, only one patient clearly was high risk due to renal insufficiency prior to treatment (subject (b) (6)). Subject (b) (6) was determined to be high risk because he had an unplanned hospitalization prior to initiating therapy. The narrative for subject (b) (6) does not describe the reason for hospitalization, but states that it was due to a non-protocol related SAE. Both patients received anti-hyperuricemic treatment and hydration for TLS prophylaxis.

Overall, the rate of TLS remains relatively low in patients with AML treated with venetoclax. TLS can be mitigated by the venetoclax dose ramp up, TLS prophylaxis, monitoring, and appropriate clinical management.

8.2.5.7 Drug-Induced Liver Injury

Data:
In VIALE-A, 6 patients (2.1%) treated with VEN + AZA and 3 patients (2.1%) treated with PBO + AZA and had liver enzyme values meeting the criteria for potential DILI (ALT > 3 × upper limit of normal [ULN] or AST > 3 × ULN and total bilirubin 2 × ULN within 72 hours of each other). All cases were confounded by medical history or current illness. In the VEN + AZA arm, 3 patients had sepsis, 2 patients had cholecystitis, and 1 patient had transient liver toxicity from levofloxacin.

In Study M14-358, 4 patients (4.8%) treated with VEN + AZA had liver enzyme values meeting the criteria for potential DILI. All patients had alternative causality for the laboratory values. In Study M14-358, 1 patient (3.2%) treated with VEN + DEC had liver enzyme values meeting the criteria for potential DILI. There were alternative etiologies for laboratory values in these cases.

In VIALE-C, 3 patients (2.1%) receiving VEN + LDAC and no patients receiving PBO + LDAC had liver enzyme values meeting the criteria for potential DILI. All cases were confounded by medical history or current illness. Two of the 3 patients had alternative causality for the laboratory values, including elevated serum albumin aminotransferase and bilirubin in conjunction with fatal psoas abscess and elevated transaminases and bilirubin in the context of heart failure. One patient developed acute cholecystitis thought to be possibly related to venetoclax; this patient resumed study treatment with a reduced dose of venetoclax but discontinued soon thereafter due to abdominal discomfort.

In Study M14-387, 2 patients (2.4%) treated with VEN 600 mg + LDAC had liver enzyme values meeting the criteria for potential DILI.

The Applicant's Position:
Few patients in the Phase 3 studies reported DILI or liver enzyme values compatible with DILI. Overall, DILI does not appear to be an issue in the clinical studies conducted with VEN in combination with HMAs or LDAC in patients with AML.

Regulatory Authorities' Assessment:
We agree with the Applicants presentation of potential Hy's law cases. FDA reviewed narratives for all of the potential Hy's law cases on the venetoclax treatment arms (6 with VEN/AZA and 3 with VEN/LDAC) and ruled out drug-induced liver injury based on plausible alternative causes, including sepsis (n=3), cholestasis (n=2), transient toxicity due to levofloxacin (n=1), fatal psoas abscess (n=1), acute cholecystitis (n=1), and heart failure with disease progression (n=1).

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:
VIALE-A showed that the within-group mean change from baseline in the PROMIS Cancer Fatigue SF-7a scores was greater in the VEN + AZA arm compared to the PBO + AZA arm on Day 1 of Cycles 5, 7, 9, 11, and 13 (–3.036 vs. –0.796, –2.263 vs. –1.976, –3.377 vs. –0.990,

–2.209 vs. –1.745, and –1.644 vs. –1.453). A greater mean change from baseline in EORTC QLQ-C30 GHS/QoL scores was observed in the VEN + AZA arm compared to the PBO + AZA arm on Day 1 of all cycles, except Cycle 19. The between-group differences favored VEN + AZA at each treatment cycle and the mean score change differences were at or greater than EORTC-QLQ-C30 MID at Cycles 5 and 21. However, there were no clinically meaningful differences in mean change from baseline in the PROMIS Cancer Fatigue SF-7a and EORTC-QLQ-C30 GHS/QoL scores for VEN + AZA compared to PBO + AZA.

Time to deterioration (TTD) of quality of life is defined as the first event of worsening of at least 10 in the EORTC-QLQ-C30 Global Health Status score. TTD was assessed based on a deterioration of the within-group estimate of at least the meaningful change threshold (MCT) of 10 points. The median TTD of quality of life in the VEN + AZA arm was longer (16.5 months; 95% CI: 9.76, not estimated) compared to the PBO + AZA arm (9.3 months; 95% CI: 4.67, 16.6), with nominal p-value = 0.066.

VIALE-C showed that the within-group mean change from baseline in the PROMIS Cancer Fatigue SF-7a and EORTC-QLQ-C30 GHS/QoL were consistently greater for VEN + LDAC versus PBO + LDAC. The between-group differences favored VEN + LDAC at each treatment cycle and the mean score change differences were at or greater for the PROMIS Cancer Fatigue SF-7a MID of 3 points at Cycles 3 and 5 and the EORTC-QLQ-C30 MID of 5 points at Cycles 5, 7, and 9. However, these differences were not clinically meaningful differences between the groups.

The Applicant's Position:
Significant differences were not observed between the 2 treatment arms in either VIALE-A or VIALE-C (VEN vs. PBO) on measures of health-related quality of life in mean score change from baseline in the PROMIS Fatigue assessment and EORTC-QLQ-C30 GHS/QoL. Patients in VEN + AZA experienced longer time to deterioration in quality of life compared to patients in PBO + AZA as determined by the EORTC QLQ-C30 GHS/QoL assessment. Thus, the statistically significantly improved OS in VIALE-A and clinically meaningful improvement in OS in VIALE-C were achieved with VEN combination treatment and without any depreciation to patients' quality of life over and above that due to AZA or LDAC monotherapy, respectively.

Regulatory Authorities' Assessment:
COA measurements were conducted using the EORTC-QLQ-C30 Global Health Status score and PROMIS Cancer Fatigue SF-7a in both studies and were included in the statistical hierarchy for efficacy evaluation. In VIALE-A, OS in the FLT3 population was not significant and formal testing in the hierarchy was stopped, so COA measurements were not assessed for efficacy. In VIALE-C, the primary endpoint did not reach significance, so formal testing of the COA measurements was also not assessed for efficacy. Evaluation provided by the Applicant was not confirmed by the Agency but appears to show no difference in the venetoclax arm compared to the placebo arm in either study indicating no decrement on QOL or fatigue assessments with the addition of venetoclax.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:
The safety of the VEN in combination with AZA, DEC, or LDAC was investigated according to age, sex, race, geographic region, and organ (hepatic or renal) impairment. The safety profile was consistent with the overall safety profile in all subgroups analyzed, with no major differences between treatment arms. No specific pattern of AEs by SOC was identified and no clinically meaningful differences were observed.

Regulatory Authorities' Assessment:
Agree with Applicant's assessment. See Section 6 for discussion of organ impairment and race. Although patients were not restricted to 60 and older in the randomized studies as they were in the single arm studies, the majority of patients enrolled were 60 and older, so adequate evaluation by >65 years vs. <65 years could not be performed.

8.2.8. Specific Safety Studies/Clinical Trials

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

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Data:
There is evidence that adult patients with AML are at a significantly higher risk of secondary malignancies, which depends on the age of the patient and the latency period.[23] There are several reasons for the higher risk of secondary malignancies in patients with AML; chemotherapy is a well-known reason. Underlying immune impairment might also be implicated.[8,24] In order to capture any potential malignancies, the SMQs for malignant tumors and MDS were used.

In VIALE-A, the incidence of events in either the SMQ for malignancy or the SMQ for MDS was 3.9% in the VEN + AZA arm compared with 1.4% in the PBO + AZA arm. Gastric adenocarcinoma and neuroendocrine carcinoma of the skin, both in the VEN + AZA arm, led to discontinuation of venetoclax; neither led to death. A similar percentage of patients in the VEN + AZA and PBO + AZA arm reported Grade ≥ 3 terms for the SMQs of malignant tumors and MDS (1.1% and 1.4%, respectively). Likewise, the incidence of SAEs of within these SMQs was similar between the VEN + AZA and PBO + AZA arms (1.1% and 1.4%, respectively). All Grade ≥ 3 and SAEs of secondary primary malignancy were reported in single patients in either treatment arm.

In Study M14-358, 2 patients in the VEN 400 mg + DEC treatment arm died due to the AE of malignant neoplasm progression.

In VIALE-C, at the 6-month follow-up analysis, an event squamous cell carcinoma of the skin was reported in the VEN + LDAC arm which did not lead to discontinuation or death.

In Study M14-387, 3 patients died due to the AE of malignant neoplasm progression.

The Applicant's Position:
Taken together, there is insufficient evidence to suggest increased risk of malignancy with VEN in combination with HMAs or LDAC, considering the underlying risk of malignancy in the elderly patients with AML.

Regulatory Authorities' Assessment:
We agree with the Applicant's assessment.

Human Reproduction and Pregnancy
The Applicant's Position:
No pregnancies were reported.

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

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

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

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

Regulatory Authorities' Assessment:
We confirm the Applicant's position. 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
The Applicant's Position:
There were no new safety concerns for VEN combination therapy in terms of AEs. Updates to toxicity management guidelines have been made in response to interactions with prescribers.

Regulatory Authorities' Assessment:

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

The Applicant's Position:

Not applicable; there is considerable postmarket experience with VEN, AZA, DEC, and LDAC already available.

Regulatory Authorities' Assessment:

We agree with the Applicant's position. 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

The Applicant's Position:

This integrated analysis is done with emphasis on the randomized studies VIALE-A and VIALE-C. Except as noted, VIALE-A and VIALE-C confirmed and refined with greater robustness the safety profile previously observed in Study M14-358 and Study M14-387.

The safety profile of VEN in combination with an HMA (AZA or DEC) or LDAC is acceptable and tolerable; VEN can be combined with an HMA or LDAC without adding clinically significant toxicity. The overall safety profile observed in the Phase 3 studies was consistent with results of the Phase 1/2 studies in patients treated with VEN at the proposed doses in combination with either AZA, DEC, or LDAC.

The safety profile of VEN in combination with an HMA or LDAC was consistent with the natural history of AML and not unexpected based on the mechanism of action of VEN, AZA, DEC, and LDAC, and the study patient population of AML. The most common AEs occurring in ≥ 30% of patients treated with VEN in combination with AZA or LDAC in VIALE-A and/or VIALE-C were febrile neutropenia, neutropenia, thrombocytopenia, diarrhea, and nausea. Each of these events, as well as anemia, abdominal pain, vomiting, dizziness, headache, and hypotension, occurred more often in the VEN + AZA or VEN + LDAC arms compared to the PBO + AZA or PBO + LDAC arms. In most patients, GI events were Grade 1 or 2. The safety events were manageable using standard clinical practice guidelines. Venetoclax in combination with LDAC may be associated with a higher incidence of TLS while VEN combination with an HMA (AZA or DEC) may be associated with a higher incidence of infections.

Although a lower number of patients have been treated with VEN (400 mg) in combination with DEC, confidence in the safety profile is strengthened based on the safety data from the AZA combination therapy and the consistency with the safety profile observed in historical DEC monotherapy data.[18]

The events anemia, febrile neutropenia, neutropenia, and thrombocytopenia were among the most commonly reported AEs and Grade ≥ 3 AEs reported across all 4 studies; these events are

considered to be ADRs. While the addition of VEN to an HMA or LDAC increased the incidence of hematologic AEs compared to patients who received an HMA or LDAC monotherapy, these events were tolerated and were not associated with substantive differences in clinical consequences between the treatment groups. Effective management of febrile neutropenia and neutropenia, including dose interruption, dose reduction, and the use of prophylactic anti-infectives, mitigated the increase in high-grade hematologic AEs which did not lead to an increased incidence of clinically consequential serious infections or deaths due to serious infections.

The risk of bleeding events was comparable for patients treated with VEN in combination with AZA compared to AZA monotherapy in VIALE-A; the risk was similar whether VEN was combined with AZA or DEC in Study M14-358. The risk of bleeding events was higher for patients treated with VEN in combination with LDAC compared to LDAC monotherapy (VIALE-C and Study M14-387). However, the incidence of Grade ≥ 3 AEs and SAEs of hemorrhage remained low across all 4 studies. The majority of bleeding events were manageable using standard monitoring, prophylactic, and therapeutic measures and there were no increases in death due to hemorrhage in patients treated with VEN combination therapy. Hemorrhage and hypotension are considered to be ADRs.

Infections are expected features of the AML disease process and are common in AML patient populations. Venetoclax in combination with an HMA or LDAC increased the rate of serious infections compared to AZA or LDAC alone; however, these events were manageable with standard medical practice and did not result in adverse clinical outcomes. Prophylactic treatment with anti-infective agents and effective management of febrile neutropenia and neutropenia mitigated the rate of serious, severe, and fatal infections. There were no clinically significant increases in fatal infections across treatment arms. Pneumonia was the most common Grade ≥ 3 AE and SAE of infection for all treatment groups; pneumonia, sepsis, and urinary tract infection are considered ADRs.

The overall risk of TLS was low among AML patients treated with VEN in combination with an HMA or LDAC, and all events of TLS occurred during ramp-up. A higher incidence of TLS was observed in patients treated with VEN in combination with AZA or LDAC compared to patients treated with PBO in combination with AZA or LDAC, respectively. TLS is a risk for any highly effective treatment for patients with acute leukemia. Although the incidence of TLS was greater with VEN in combination with AZA or LDAC compared to PBO treatment arms, the incidence was lower than those reported with intensive chemotherapy.[21] The risk of TLS can be mitigated with prophylaxis, ramp-up dosing of venetoclax, a controlled WBC < 25×10^9/L prior to initiation of therapy, and monitoring of TLS blood chemistries (predose and 6 to 8 hours postdose after each new dose during ramp-up and 24 hours after reaching the final dose). Tumor lysis syndrome is considered an ADR.

Early mortality (30-day and 60-day) was not increased with the addition of VEN to an HMA or LDAC, compared to HMA or LDAC alone. These rates were comparable with those of patients who received PBO in combination with AZA or LDAC and historical DEC monotherapy[18] and

suggest that patients treated with VEN in combination with HMA or LDAC are not at increased risk of early mortality.

In summary, the available safety data for venetoclax in combination with an HMA or LDAC demonstrates a predictable and acceptable safety profile for patients with newly diagnosed AML who are ineligible for intensive chemotherapy. Risks were manageable following standard/routine medical practice guidelines and proposed product labeling.

Table 52. Safety Summary of VIALE-A and VIALE-C

Safety parameter n (%)	VIALE-A		VIALE-C	
	VEN + AZA N = 283	PBO + AZA N = 144	VEN + LDAC N = 142	PBO + LDAC N = 68
Total deaths	159 (56.2)	109 (75.7)	99 (69.7)	54 (79.4)
30-day mortality[1]	21 (7.4)	9 (6.3)	18 (12.7)	11 (16.2)
60-day mortality[2]	43 (15.2)	24 (16.7)	29 (20.4)	21 (30.9)
On-treatment deaths[3]	81 (28.6)	43 (29.9)	48 (33.8)	28 (41.2)
Fatal TEARs	11 (3.9)	2 (1.4)	8 (5.6)	5 (7.4)
All-grade TEARs	241 (85.2)	96 (66.7)	106 (74.6)	47 (69.1)
Grade ≥3 TEARs	216 (76.3)	71 (49.3)	90 (63.4)	37 (54.4)
TESARs	128 (45.2)	35 (24.3)	40 (28.2)	14 (20.6)
All-cause discontinuation[4]	209/286 (73.1)	127/145 (87.6)	117/143 (81.8)	63/68 (92.6)
TEAR with discontinuation	23 (8.1)	6 (4.2)	14 (9.9)	6 (8.8)

AR = adverse reactions; AZA = azacitidine; LDAC = low-dose cytarabine; N = sample size; n = number of patients; PBO = placebo; TEAR = treatment-emergent adverse reaction; TESARs = treatment-emergent serious adverse reactions; VEN = venetoclax

[1] Within 30 days following the first dose of study drug

[2] Within 60 days following the first dose of study drug

[3] On or within 30 days after the last dose of study drug

[4] Data values are provided for the Efficacy Analysis Set (N = 431) for VIALE-A and Full Analysis Set (N = 211) for VIALE-C. Therefore, the N values (denominator) used to calculate percentages are different for this row.

Note: Adverse reactions are those events considered by the Investigator to be reasonably possibly related to venetoclax/placebo.

Sources: VIALE-A Interim CSR Table 14.3__2.6.1.1, Table 14.3__2.5.7, Table 14.3__1.1.1, Table 14.3__1.4.2, Table 14.3__2.2.1, Table 14.1__2.1.2, and AAid Ad Hoc Table 14.3__T1; VIALE-C Interim CSR (6-month follow-up analysis) Table 14.3__2.6.1A, Table 14.3__2.5.3A, Table 14.3__1.3.1A, Table 14.3__1.4.2A, Table 14.3__2.2.1A, Table 14.1__1.4.1A, and AAid Ad Hoc Table 14.3__1.1. Source datasets: DM, DD, ADSL and ADAE (VIALE-A); DM (6-Month Follow-Up Analysis), DD (6-Month Follow-Up Analysis), ADSL (6-Month Follow-Up Analysis) and ADAE (6-Month Follow-Up Analysis) (VIALE-C).

Regulatory Authorities' Assessment:

Overall safety summary performed by the Agency differed from the summary provided by the Applicant in Table 37. The Agency analysis below is based on all reported adverse events without consideration of adverse reactions as defined by the Applicant above to provide an overall assessment of AEs that occurred on study.

Table 53: Safety summary, VIALE-A and VIALE-C

	VIALE-A		VIALE-C	
	Venetoclax + AZA N=283	**Placebo + AZA N=144**	**Venetoclax + LDAC N=142**	**Placebo + LDAC N=68**
Total deaths	159 (56%)	109 (76%)	99 (70%)	54 (79%)
All grade TEAE	283 (100%)	144 (100%)	141 (99%)	67 (99%)
Grade ≥ 3 TEAE	279 (99%)	139 (97%)	138 (97%)	65 (96%)
Serious AE	235 (83%)	105 (73%)	95 (67%)	42 (62%)
AE leading to death	64 (23%)	29 (20%)	33 (23%)	14 (21%)
TEAE with discontinuation	58 (20%)	20 (14%)	26 (18%)	11 (16%)
TEAE with ven/pbo modification	183 (65%)	67 (47%)	87 (61%)	31 (46%)
Source: FDA analysis using adae.xpt, adsl.xpt for each study				

In the FDA 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 VIALE-A, VIALE-C, M14-358, and M14-387. Overall, the safety analysis demonstrated the already known safety profile of venetoclax in combination with azacitidine, decitabine, or LDAC in this population.

In the azacitidine combination, the most common TEAEs not related to a laboratory evaluation that occurred in >40% were nausea, diarrhea, constipation, and febrile neutropenia. The most common grade 3-4 TEAEs (>5%) were febrile neutropenia, pneumonia, fatigue, hemorrhage, urinary tract infection, and hypertension. The most common serious AEs (>5%) were febrile neutropenia, pneumonia, sepsis, and hemorrhage. A similar pattern was observed in the single-arm study of venetoclax with azacitidine.

In the LDAC combination, the most common TEAEs not related to a laboratory evaluation that occurred in >25% were nausea, febrile neutropenia, pneumonia, diarrhea, and vomiting. The most common grade 3-4 TEAEs (>10%) were febrile neutropenia and pneumonia. The most common serious AEs (>5%) were pneumonia, febrile neutropenia, and sepsis. A similar pattern was observed in the single-arm study of venetoclax with LDAC.

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.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

Regulatory Authorities' Assessment:

There were four major studies (VIALE-A, M14-358, VIALE-C, M14-387) supporting the efficacy of venetoclax in combination with azacytidine, decitabine, and low-dose cytarabine. The statistical design of the Phase 2 single arm trials (M14-358 and M14-387) and Phase 3 pivotal trials (VIALE-A and VILAE-C) supporting this supplemental labeling were previously discussed and agreed.

VIALE-A: No major statistical issues were identified during the statistical evaluation of efficacy of VEN+AZA in comparison with PBO+AZA. The analysis of the primary endpoint OS showed numerically higher survival times for VEN+AZA arm as compared to PBO+AZA (HR=0.66 95% CI (0.52, 0.85); p-value<0.001). The OS endpoint appeared to be robust with respect to censoring, and no outliers were observed. The statistical review team agrees that the data support inclusion of the OS results in labeling.

M14-358: No major statistical issues were identified during the statistical evaluation of efficacy of VEN+AZA and VEN+DEC in this Phase 2 study. Both trials VIALE-A and M14-358 clearly provide statistical evidence of efficacy for VEN+AZA combination. However, because of the limited data, there is currently no comparative evidence regarding the efficacy of the VEN+DEC combination. The CR rate for VEN+AZA was 43.3% and the CR+CRh rate was 61.2%. For VEN+DEC, the CR rate was 54% and CR+CRh rate was 61.5%.

VIALE-C: The primary endpoint OS was numerically longer in the VEN+LDAC vs. PBO+LDAC. However, this finding did not reach statistical significance (HR=0.749 95% CI (0.52,1.07); p-value=0.114). Failure to achieve statistical significance at the time of the primary analysis may be due to an underpowered study design. The additional 6 months of follow-up showed a similar treatment effect on OS with HR = 0.70 (95% CI: 0.50, 0.99). (b) (4)

We further investigated the impact of treatment arms on the OS of patients by borrowing treatment effect (VEN+LDAC) from the phase 2 study (M14-387) using a Bayesian approach. The results showed that the OS was consistent across Phase 2 (M14-387) and Phase 3 (VIALE-C) trials. Additional analyses performed with more diffuse priors yielded similar results.

The CR rate in the VEN+LDAC arm was 27% (95% CI; 20, 35) with a median DOCR of 11.1 months (95% CI: 5.9, NE), and the CR rate in the PBO+LDAC arm was 7.4% (95% CI; 2.4, 16) with a median DOCR of 8.3 months (95% CI: 3.1, 8.3). The CR+CRh rate in the VEN+LDAC arm was 47% (95% CI; 39, 55) and in the PBO+LDAC arm was 15% (95% CI; 7.3, 25) with a median

DOCR+CRh of 11.1 months with VEN+LDAC treatment and 6.2 months with PBO+LDAC treatment.

M14-387: No major statistical issues were identified during the statistical evaluation of efficacy of VEN+LDAC in this Phase 2 study. Both trials VIALE-C and M14-387 clearly provide statistical evidence of efficacy for VEN+LDAC combination. The CR rate was 21% and CR+CRh rate was 43% for VEN+LDAC combination.

8.4. Conclusions and Recommendations

Regulatory Authorities' Assessment:
The review team was able to verify or clarify the efficacy and safety endpoints as provided by the Applicant. The review team recommends approval of the NDA.

X	X
Sarabdeep Singh, PhD Primary Statistical Reviewer OB/DBIX	Jonathon Vallejo, PhD Statistical Team Leader OB/DBIX
X	X
Lori Ehrlich, MD, PhD Primary Clinical Reviewer OOD/DHM1	Kelly Norsworthy, MD Clinical Team Leader OOD/DHM1

9 Advisory Committee Meeting and Other External Consultations

Regulatory Authorities' Assessment:
This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

10 Pediatrics

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

Regulatory Authorities' Assessment:
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).

11 Labeling Recommendations

The table below summarizes changes to the proposed prescribing information made by applicant and FDA. See the final approved prescribing information for VENCLEXTA (venetoclax) accompanying the approval letter for more information.

Section	Applicant Proposed Labeling	FDA Proposed Labeling
General	…	Proposed several formatting changes to comply with the format elements listed in the Selected Requirement of Prescribing Information (SRPI), which is collated from the regulations 21 CFR 201.56 and 21 CFR 201.57 and guidances.
1.2 Indications and Usage, AML	Removed (b) (4) statement (b) (4)	Agreed with removal of statement (b) (4)
2.1 Recommended Dosage, AML	Included dosing information for VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine. *(See Section 6.2.1 of the present document)*	Agreed with addition of dosing regimens. Reorganized DOSAGE AND ADMINISTRATION, including creation of new subsections to house important safety information and the recommended dosage for each indication based on recommendations found in the **Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products.** Revised the subsection title (b) (4) to include all information relevant to administration of venetoclax for both indications.

2.3 Dosage Modifications Based on Toxicities, AML	Updated to include recommendation for bone marrow assessment as needed. Updated the tabular presentation of the dosage modification and interruption recommendations for Grade 4 cytopenias for clarity.	Agreed to include recommendation for a bone marrow evaluation as a footnote in the table describing dosage modifications for adverse reactions in AML. Retained table found in approved labeling and added dosage modifications for non-hematologic adverse reactions. Removed (b) (4) and modified subsection title for consistency with recently approved labeling.
5.1 Warnings and Precautions, TLS 5.2 Warnings and Precautions, Neutropenia	Updated to include rates from Studies M15-656 (VIALE A) and M16-043 (VIALE C). *(See Section 8.2.4 and 8.2.5 of the present document)*	Agreed to include safety information from VIALE A and VIALE C in subsections 5.1 and 5.2. In subsection 5.1, added a phrase that deaths and renal failure occurred in patients who received venetoclax with low-dose cytarabine to specify severity. Revised the description of the drug interaction with P-gp inhibitors or strong or moderate CYP3A inhibitors for additional clarity.
6.2 Adverse Reactions, Clinical Trial Experience with AML	Included information from Studies VIALE A and VIALE C. Streamlined and updated information from studies M14-358 and M14-387 with longer follow up data. *(See Section 8.2 of the present document)*	Agreed with inclusion of information from VIALE A and VIALE C. Modified the summary of the trial to include the dosing regimen and relevant eligibility criteria. Removed information (b) (4)

		Added summary of fatal adverse reactions and the most frequent adverse reactions leading to dosage modifications. Modified to the tabular summary of adverse reactions to used grouped terms and omit (b) (4) ; order body systems such that the body systems are listed in decreasing order based on the highest rate for an individual reaction within the system; and include a footnote for each composite term. Modified the tabular summary of the laboratory adverse reactions to ensure the rates were determined based on number of patients with a baseline and at least one post baseline laboratory value; reordered lab terms to listed in decreasing order [21 CFR 201.57(c)(7)(ii)]. Agreed with removal (b) (4) but added a brief description of the trial to support the new statement about the safety profile consistent with that of VIALE C. Added the most common statements found in the HIGHLIGHTS, because the HIGHLIGHTS should be a concise summary of the information

		found in the FULL PRESCRIBING INFORMATION.
8.4 Pediatric Use	Editorial update.	Changed (b) (4) to 'of VENCLEXTA' because the proper name is used here as recommended in the guidance: **Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling.**
8.5 Geriatric Use	Modified language to incorporate outcomes from Studies VIALE-A and VIALE-C. *(See Section 8.1.2 and 8.1.4 of the present document)*	Agreed to revise the percentage of patients exposed to venetoclax in VIALE-A, Study M14-358 and VIALE-C. Revised regulatory statement, because an insufficient number of younger adults were included in these trials to determine if patients 65 years and older respond differently from young patients.
8.6 Renal Impairment 12.3 Pharmacokinetics	Updated to include information from VIALE-A in patients with severe renal impairment. (*See Section 8.2.2 of the present document*)	In subsection 8.6, further revised the dosing information for patients with renal impairment to state no dose adjustment is recommended for patients with severe renal impairment. In subsection 12.3, added a statement summarizing the pharmacokinetics of venetoclax in White, Black and Asian patients in United States and Asian patients from Asian countries.
14. 2 Clinical Studies, AML	Included information from Studies VIALE-A and VIALE-C. Streamlined and updated information from studies M14-358 and M14-387 with longer follow up data. *(See Section 8.1 of the present document)*	Agreed with inclusion of efficacy information from VIALE-A and VIALE-C. In VIALE-A, removed (b) (4)

		(b) (4) Summarized transfusions in text below efficacy table. For Study M14-358, retained summary of study population in tabular format. For VIALE-C, added a statement that efficacy was based on rate of CR and duration of CR with additional supportive evidence. Summarized transfusion independence based on those transfusion dependent at baseline and those who were not. Removed (b) (4)
17 Patient Counseling Information, Neutropenia	Updated (b) (4)	Removed as this subsection typically focuses how the patient may mitigate or manage an adverse reaction; this added information is a step taken by a healthcare provider.
Medication Guide	Updated to reflect changes in the USPI for dose interruptions and ADRs.	Revised the bulleted list of the most common side effects for consistency with HIGHLIGHTS of the prescribing information. Additional changes made to support additional labeling changes made to product labeling as described below.

<u>The Applicant's Position:</u>
The results presented in the dossier from studies VIALE-A and VIALE-C, supported by longer term follow up data from studies M14-358 and M14-387, provide meaningful information regarding the use 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 Applicant believes the magnitude of clinical benefit and acceptable safety profile seen in both randomized studies, confirm the positive benefit-risk balance of treatment in this patient population in clinical practice. As such, the Applicant recommends that the Accelerated

Approval be converted to a full approval for venetoclax in combination with azacitidine or decitabine or low-dose cytarabine.

Regulatory Authorities' Assessment:

The approved labeling document was also reviewed to help ensure that product information:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[2] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations).
[2] See *PLR Requirements for PI* website for PLR labeling guidances.

12 Risk Evaluation and Mitigation Strategies (REMS)

Regulatory Authorities' Assessment:
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 Postmarketing Requirements and Commitment

Regulatory Authorities' Assessment:
No postmarketing requirements or commitments will be issued.

14 Division Director (DHOT) (NME ONLY)

X

Not Applicable

15 Division Director (OCP)

X

Brian Booth, PhD
Division Director
OCP/DCPI

16 Division Director (OB)

X

Thomas Gwise, PhD
Division Director
OB/DBIX

17 Division Director (Clinical)

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

X

R. Angelo de Claro, MD
Acting Division Director
OOD/DHM1

18 Appendices

18.1. References

The Applicant's References:

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2. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukaemia: rationale and important changes. Blood. 2009;114(5):937-51.
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Regulatory Authorities' References:
None

18.2. Financial Disclosure

The Applicant's Position:
See Sections 8.1.2 and 8.1.4 for Financial Disclosure information from the Applicant.

Regulatory Authorities' Assessment:
We agree with the Applicants presentation of financial disclosure information. VIALE-A and VIALE-C were covered studies.

Covered Clinical Studies (VIALE-A and VIALE-C):*

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1911		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 11 individuals (4 of whom participated in both VIALE-A and VIALE-C)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 11 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial	Yes ☒	No ☐ (Request details from Applicant)

interests/arrangements:		
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) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above was filled by the applicant, and confirmed/edited by the FDA.

18.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
Not applicable to this submission.

Regulatory Authorities' Assessment:
No nonclinical evaluations were submitted with this application.

18.4. OCP Appendices (Technical documents supporting OCP recommendations)

Regulatory Authorities' Assessment:

18.4.1. Summary of Applicant's Population PK Analysis

The Applicant's population PK analysis for venetoclax was conducted based on 4575 plasma venetoclax concentrations in 771 patients with AML at venetoclax doses ranging from a ramp-up dose of 10 mg to a target dose of 1200 mg from 5 trials M14-212, M14-358, M14-387, M15-656 and M16-043. Summary statistics of key demographics and covariates that were evaluated in the population PK analysis are shown in Table 49. The patients had a median (range) age of 75 (19, 93) years, and were primarily White (78.9%), with 16.0% Asian, 2.7% Black, 1.0% others, and 1.6% missing reported race. There were 224 (29.1%), 321 (41.6%), 219 (28.4%), and 6 (0.8%) patients with normal renal function, mild, moderate and severe renal impairment respectively, according to their creatinine clearance (CRCL) calculated using the Cockcroft-Gault formula. There were 583 (75.6%), 149 (19.3%), 32 (4.2%) and 2 (0.3%) patients with normal hepatic function, mild, moderate, and severe hepatic impairment, respectively, based on NCI-ODWG criteria. There were 418 (54.2%), 228 (29.6%) and 110 (14.3%) patients on mild, moderate and strong (9.1% posaconazole and 5.2% non-posaconazole) CYP3A inhibitors, respectively. A total of 66 (8.6%) patients received P-gp inhibitors.

Table 54 Demographic and Other Covariates Data Summary for Subjects Included in the Population PK Analysis

Characteristic	Study M14-212 (N = 32)	Study M14-358 (N = 212)	Study M14-387 (N = 92)	Study M15-656 (N = 293)	Study M16-043 (N = 142)	Total (N = 771)
Designated VEN Cohort Dose, N (%)						
400 mg		127 (59.9%)		293 (100%)		420 (54.5%)
600 mg			82 (89.1%)		142 (100%)	224 (29.1%)
800 mg	32 (100%)	74 (34.9%)	10.0 (10.9%)			116 (15.1%)
1200 mg		11 (5.2%)				11 (1.4%)
Age (yrs)						
Mean (SD)	65.9 (14.8)	74.6 (5.64)	74.9 (5.47)	75.3 (6.24)	75.0 (8.05)	74.6 (7.15)
Median (range)	70.5 (19, 84)	74.0 (61, 90)	74.5 (63, 90)	76.0 (49, 91)	76.0 (36, 93)	75.0 (19, 93)
Age Group (yrs)						
18 - 64	13 (40.6%)	3 (1.4%)	2 (2.2%)	13 (4.4%)	11 (7.8%)	42 (5.5%)
65 - 74	11 (34.4%)	109 (51.4%)	44 (47.8%)	106 (36.2%)	50 (35.2%)	320 (41.5%)
≥ 75	8 (25.0%)	100 (47.2%)	46 (50.0%)	174 (59.4%)	81 (57.0%)	409 (53.1%)
Body Weight (kg)						
Mean (SD)	77.0 (18.3)	80.3 (16.7)	78.9 (15.5)	73.1 (18.1)	71.5 (17.5)	75.7 (17.6)
Median (range)	72.9 (46.8, 126)	78.9 (49.7, 136)	79.2 (35.0, 125)	71.1 (34.0, 168)	68.0 (32.6, 125)	74.5 (32.6, 168)
Race, N (%)						
White	25 (78.1%)	182 (85.9%)	85 (92.4%)	215 (73.4%)	101 (71.1%)	608 (78.9%)
Black	4 (12.5%)	10 (4.7%)	2 (2.2%)	3 (1.0%)	2 (1.4%)	21 (2.7%)
American Indian/ Alaska native		2 (0.9%)				2 (0.3%)
Asian	3 (9.4%)	4 (1.9%)	2 (2.2%)	75 (25.6%)	39 (27.5%)	123 (16.0%)
Native Hawaiian or Pacific Islander		3 (1.4%)				3 (0.4%)
Multiple		2 (0.9%)				2 (0.3%)
Missing		9 (4.3%)	3 (3.3%)			12 (1.6%)

Characteristic	Study M14-212 (N = 32)	Study M14-358 (N = 212)	Study M14-387 (N = 92)	Study M15-656 (N = 293)	Study M16-043 (N = 142)	Total (N = 771)
Grouped Race						
non-Asian	29 (90.6%)	199 (93.9%)	87 (94.6%)	218 (74.4%)	103 (72.5%)	636 (82.5%)
Asian	3 (9.4%)	4 (1.9%)	2 (2.2%)	75 (25.6%)	39 (27.5%)	123 (16.0%)
Missing		9 (4.3%)	3 (3.3%)			12 (1.6%)
Country						
Japan				24 (8.2%)	18 (12.7%)	42.0 (5.5%)
China				34 (11.6%)	9 (6.3%)	43.0 (5.6%)
Rest of World	32 (100%)	212 (100%)	92 (100%)	235 (80.2%)	115 (81.0%)	686 (89.0%)
Sex, N (%)						
Male	16 (50.0%)	120 (56.6%)	60 (65.2%)	177 (60.4%)	78 (54.9%)	451 (58.5%)
Female	16 (50.0%)	92.0 (43.4%)	32 (34.8%)	116 (39.6%)	64 (45.1%)	320 (41.5%)
Albumin (g/dL)						
Mean (SD)	29.9 (4.47)	33.0 (4.79)	31.1 (4.51)	34.2 (5.61)	38.6 (34.0)	34.1 (15.5)
Median (range)	30.0 (19.0, 40.0)	33.0 (20.0, 51.0)	31.0 (20.0, 45.2)	34.3 (18.0, 48.0)	35.0 (18.0, 346)	33.8 (18.0, 346)
ALT (U/L)						
Mean (SD)	51.7 (41.7)	22.1 (14.8)	22.6 (20.0)	19.9 (13.7)	23.3 (21.5)	22.8 (19.3)
Median (range)	35.0 (10.0, 179)	18.0 (4.00, 90.0)	15.0 (5.00, 120)	16.0 (1.00, 84.0)	18.0 (4.00, 165)	17.0 (1.00, 179)
AST (U/L)						
Mean (SD)	34.3 (27.1)	23.1 (12.3)	21.3 (12.4)	20.9 (10.4)	25.0 (20.4)	22.9 (14.6)
Median (range)	25.0 (10.0, 131)	20.0 (8.00, 85.0)	18.0 (7.00, 72.0)	18.0 (8.00, 76.0)	19.2 (4.00, 177)	19.0 (4.00, 177)
Bilirubin (mg/dL)						
Mean (SD)	0.68 (0.34)	0.77 (0.46)	0.73 (0.35)	0.74 (0.44)	0.71 (0.40)	0.74 (0.43)
Median (range)	0.60 (0.20, 1.40)	0.62 (0.07, 2.70)	0.70 (0.05, 1.90)	0.64 (0.16, 4.50)	0.60 (0.20, 2.81)	0.63 (0.05, 4.50)

Characteristic	Study M14-212 (N = 32)	Study M14-358 (N = 212)	Study M14-387 (N = 92)	Study M15-656 (N = 293)	Study M16-043 (N = 142)	Total (N = 771)
Creatinine Clearance (mL/min)						
Mean (SD)	84.3 (37.6)	83.4 (25.2)	85.2 (23.0)	72.9 (27.7)	68.6 (27.5)	77.0 (27.6)
Median (range)	76.9 (45.5, 230)	82.0 (17.0, 161)	82.3 (41.1, 156)	69.0 (29.8, 205)	63.9 (18.3, 185)	74.0 (17.0, 230)
Renal Function, N (%)						
Normal	11 (34.4%)	78 (36.8%)	36 (39.1%)	69 (23.6%)	30 (21.1%)	224 (29.1%)
Mild Impairment	14 (43.8%)	98 (46.2%)	44 (47.8%)	116 (39.6%)	49 (34.5%)	321 (41.6%)
Moderate Impairment	7 (21.9%)	34 (16.0%)	12 (13.0%)	107 (36.5%)	59 (41.6)	219 (28.4%)
Severe Impairment		2 (0.9%)		1 (0.3%)	3 (2.1%)	6 (0.8%)
Missing					1 (0.7%)	1 (0.1%)
Hepatic Function, N (%)						
Normal	18 (56.3%)	158 (74.5%)	69.0 (75.0%)	234 (79.9%)	104 (73.2%)	583 (75.6%)
Mild Impairment	13 (40.6%)	40 (18.9%)	20 (21.7%)	46 (15.7%)	30 (21.1%)	149 (19.3%)
Moderate Impairment		13 (6.1%)	3 (3.3%)	9 (3.1%)	7 (4.9%)	32 (4.2%)
Severe Impairment				2 (0.7%)		2 (0.3%)
Missing	1 (3.1%)	1 (0.5%)		2 (0.7%)	1 (0.7%)	5 (0.7%)
Maximum CYP3A Inhibitors, N (%)						
None		2 (0.9%)		12 (4.1%)	1 (0.7%)	15 (2.0%)
Mild	16 (50.0%)	116 (54.7%)	45 (48.9%)	144 (49.2%)	97 (68.3%)	418 (54.2%)
Moderate	16 (50.0%)	62 (29.3%)	41 (44.6%)	77 (26.3%)	32 (22.5%)	228 (29.6%)
Strong		32 (15.1%)	6 (6.5%)	60 (20.5%)	12 (8.5%)	110 (14.3%)
P-gp Inhibitors, N (%)						
No	29 (90.6%)	194 (91.5%)	82 (89.1%)	266 (90.8%)	134 (94.4%)	705 (91.4%)
Yes	3 (9.4%)	18 (8.5%)	10 (10.9%)	27 (9.2%)	8 (5.6%)	66 (8.6%)

Characteristic	Study M14-212 (N = 32)	Study M14-358 (N = 212)	Study M14-387 (N = 92)	Study M15-656 (N = 293)	Study M16-043 (N = 142)	Total (N = 771)
Posaconazole, N (%)						
No	32 (100%)	185 (87.3%)	89 (96.7%)	260 (88.7%)	135 (95.1%)	701 (90.9%)
Yes		27 (12.7%)	3 (3.3%)	33 (11.3%)	7 (4.9%)	70 (9.1%)
Azacitidine, N (%)						
No	32 (100%)	85 (40.1%)	92 (100%)	1 (0.3%)	142 (100%)	352 (45.7%)
Yes		127 (59.9%)		292 (99.7%)		419 (54.4%)
Decitabine, N (%)						
No	32 (100%)	127 (59.9%)	92 (100%)	293 (100%)	142 (100%)	686 (89.0%)
Yes		85 (40.1%)				85.0 (11.0%)
Cytarabine, N (%)						
No	32 (100%)	212 (100%)		293 (100%)	2 (1.4%)	539 (69.9%)
Yes			92 (100%)		140 (98.6%)	232 (30.1%)

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CYP = cytochrome P450; P-gp = P-glycoprotein; SD = standard deviation

Note: Due to rounding, some percentages do not add up to 100%.

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 5.

The previously developed two-compartment population PK model of venetoclax with first-order absorption and elimination in patients with relapsed/refractory CLL, SLL, or NHL and healthy subjects was used as a starting point for the population PK analysis in patients with AML. The final model was identical to the previously developed model in both the fixed and random (inter-individual variability and residual-error) components, with two additional covariates: race (Asian vs. non-Asian) on venetoclax relative bioavailability (F1) and azacitidine on venetoclax apparent volume of distribution (V^2/F). The final PK model parameter estimates and the corresponding estimates of precision (95% CI) are presented in Table 50.

Table 55 Key Parameter Estimates and Variability for Final Venetoclax Population PK Model

Parameter	Estimate	%RSE[a]	95% Confidence Interval[b]	Population Estimate in the Legacy Model
	Population Value (θ)			
CL/F (L/day)	452	3.10	425, 479	447
$\theta_{CL/F,moderateCYP3Ainhibitor}$	0.814	2.38	0.776, 0.852	0.842
$\theta_{CL/F,strongCYP3Ainhibitor}$	0.175	3.59	0.163, 0.187	0.184
$\theta_{CL/F,OATPinhibitor}$	0.853 (fixed)	--	--	0.853
V_2/F (L)	110	12.2	83.7, 136	118
$\theta_{V2/F,Sex}$[c]	0.721	4.06	0.664, 0.778	0.680
$\theta_{V2/F,patient}$[d]	1.93	10.3	1.54, 2.32	1.71
$\theta_{V2/F,AZA}$	1.24	4.21	1.14, 1.34	NA
K_a (1/day)	3.66	3.25	3.43, 3.89	3.72
Q/F (L/day)	93.1	5.16	83.7, 103	97.2
V_3/F (L)	115	3.85	106, 124	119
F1[e]	1 (fixed)	--	--	1
Dose nonlinearity (exponential)[f]	–0.217	1.86	–0.225, –0.209	–0.180
$\theta_{F1,Asian}$	1.67	4.95	1.51, 1.83	NA
$\theta_{F1,fed}$[g]	1.25	3.35	1.17, 1.33	1.23
	Inter-Individual Variability (ω^2)			
CL/F (L/day) (Variance and %CV[h])	0.179 (44.3%)	6.54	0.156, 0.202	0.153 (40.7%)
V_2/F (L) (Variance and %CV[h])	0.234 (51.3%)	5.26	0.210, 0.258	0.205 (47.7%)
F1 (Variance and %CV[h])	0.0986 (32.2%)	9.42	0.0804, 0.117	0.0972 (32.0%)
	Residual Variability (σ^2)			
σ_1^2 (Proportional)	0.220	1.34	0.214, 0.226	0.223
σ_2^2 (Additive)	3.06×10^{-7}	38.9	7.28×10^{-8}, 5.39×10^{-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; F1 = relative bioavailability; V_3/F = Apparent volume of distribution of the peripheral compartment

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.

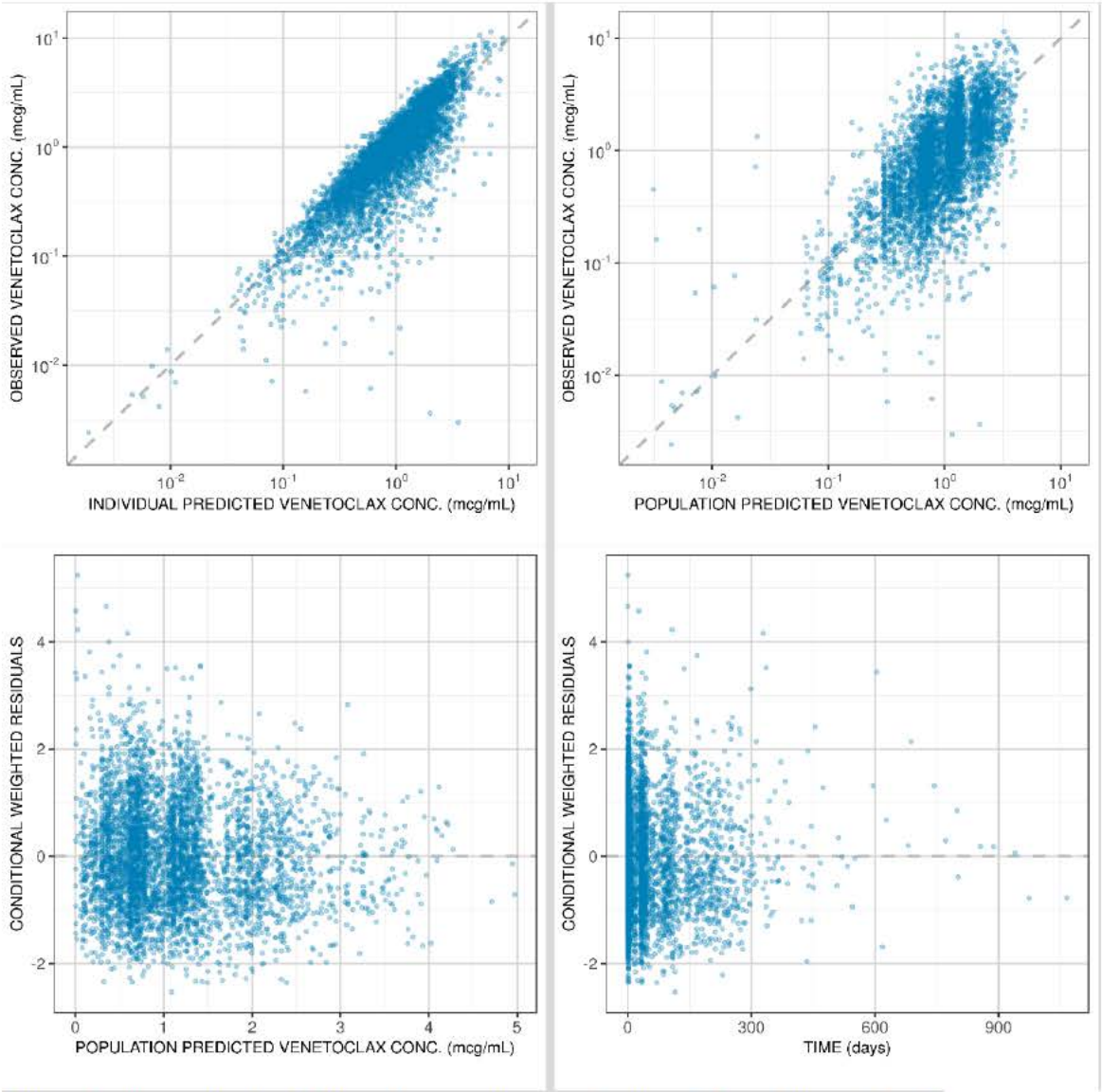
g. Relative bioavailability under fed conditions without specification of fat-content.

h. Percent coefficient of variation (%CV) was approximated as $\sqrt{e^{\omega^2} - 1} \times 100\%$.

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 7.

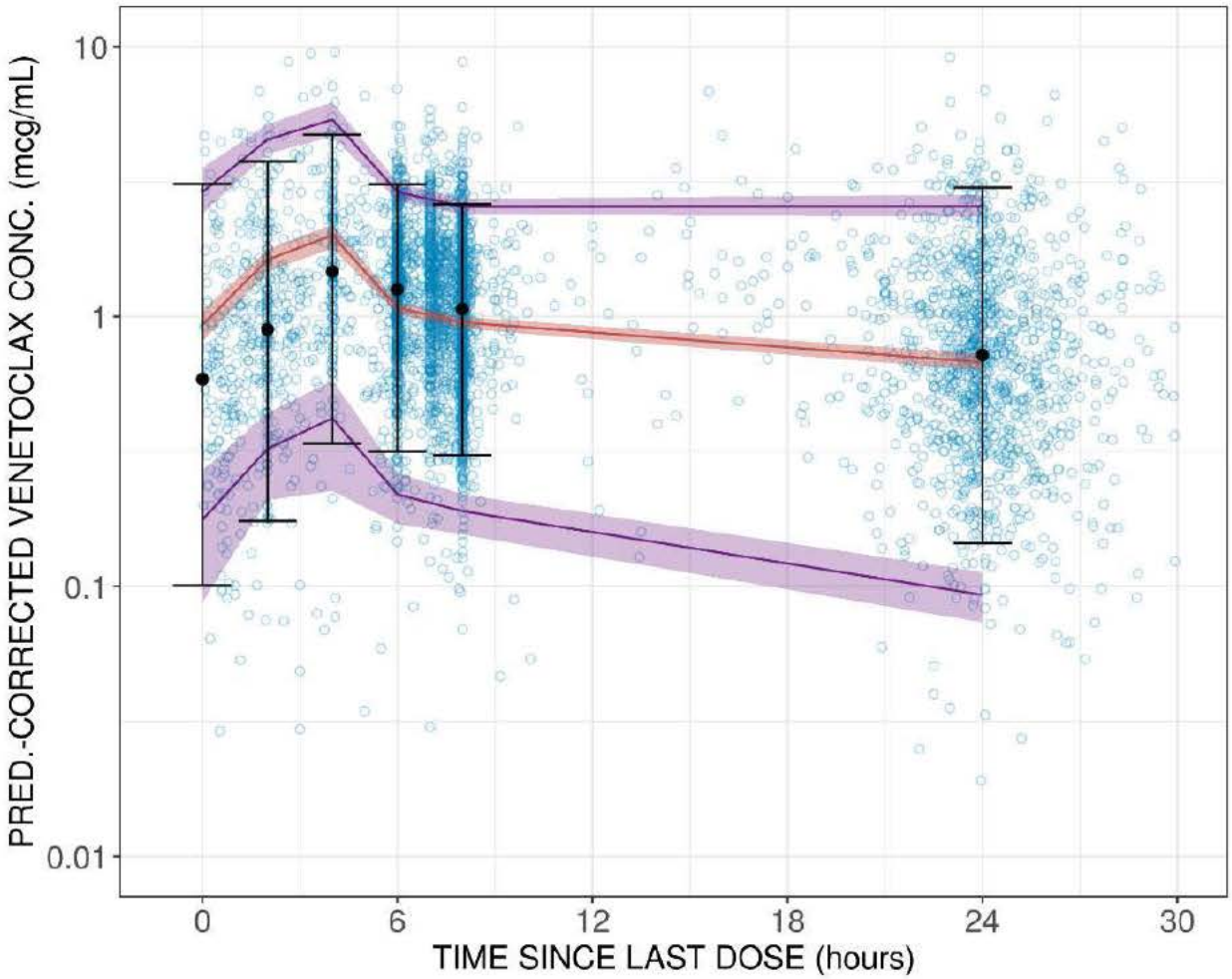
The goodness-of-fit plots (Figure 13) and prediction-corrected visual predictive check (pcVPC) plots (Figure 14) indicated that the final population PK model generally well described the venetoclax PK profiles.

Figure 11 Goodness-of-fit Plots for the Final Venetoclax PK Model



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figures 2 and 3.

Figure 12 Prediction-Corrected Visual Predictive Checks for Venetoclax Concentration Versus Time After Last Dose

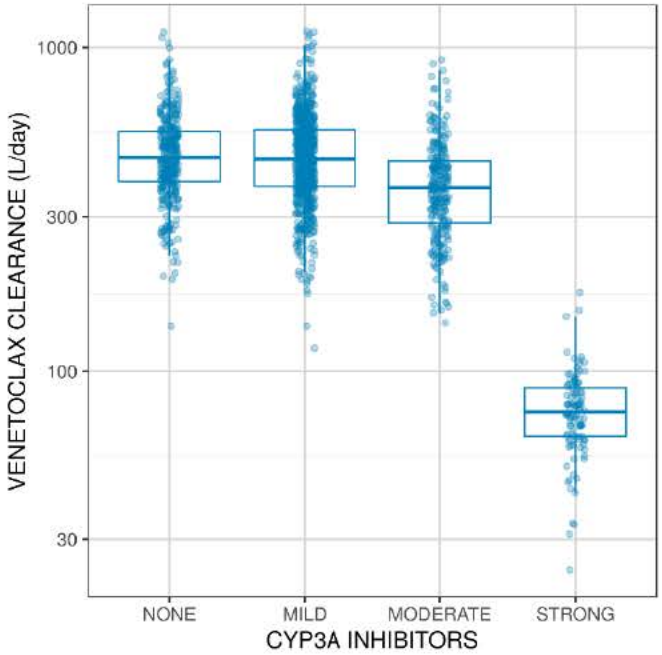


Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 4.

There was no relationship between venetoclax total exposure and body weight, age, sex, mild to moderate hepatic impairment, mild to severe renal impairment, and co-administration of weak CYP3A or P-gp inhibitors. In addition, there was no relationship between venetoclax total exposure and co-administration of AZA, DEC, or LDAC, although co-administration of AZA did increase venetoclax apparent volume of distribution by 24%.

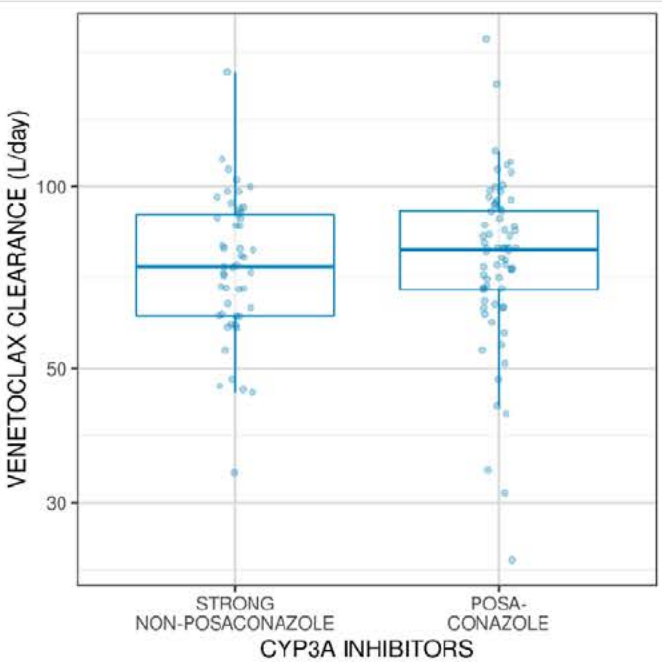
In agreement with the previous model, strong and moderate CYP3A inhibitors reduced the apparent clearance of venetoclax by 81% (95% CI: [78%, 85%]) and 19% (95% CI: [16%, 19%]), respectively, of that without any CYP3A inhibitors (Figure 15). Post-hoc empirical Bayes estimates showed generally comparable effects of posaconazole vs. other strong CYP3A inhibitors on venetoclax CL/F (Figure 16).

Figure 13 Boxplot of the Post Hoc CL/F by Co-administration of CYP3A Inhibitor Categories



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 7.

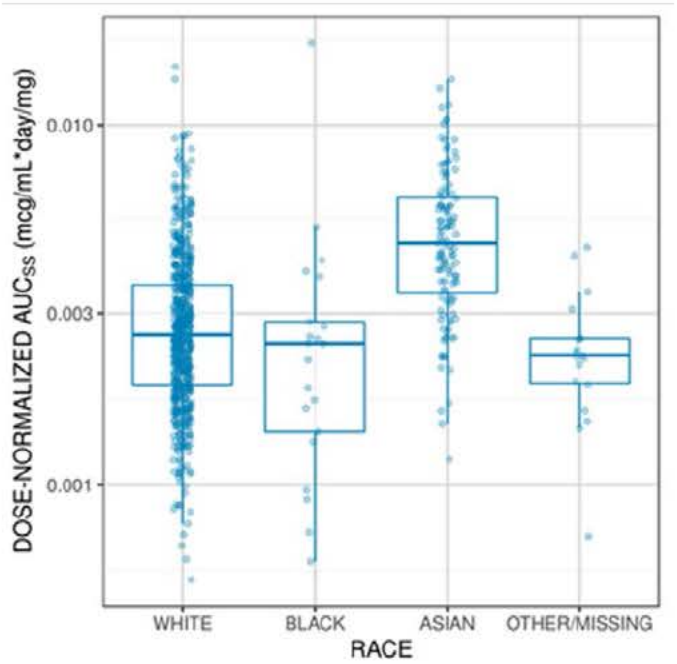
Figure 14 Boxplot of the Post Hoc CL/F by Co-administration of Strong CYP3A Inhibitors



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 8.

The covariate analysis identified that Asian subjects had 67% higher relative bioavailability, however, while the mean change was higher, the range of individual venetoclax exposures in Asian subjects were generally comparable to the range of individual exposures in non-Asian subjects (Figure 17).

Figure 15 Boxplot of the Post Hoc Dose-Normalized AUCss by Race



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 6.

The FDA's Assessment:

The Applicant's final population PK model was able to reasonably describe the observed venetoclax PK profiles following the administration of venetoclax ranged from 10 to 1200 mg in patients with AML. Therefore, the final PK model is generally acceptable to generate post-hoc exposure metrics, e.g., AUC_{SS} for E-R analyses of efficacy and safety measurements.

The 19 PK concentrations collected from 6 patients with severe renal impairment generally fell within the range of PK profiles in patients with normal renal function, mild to moderate renal impairment (Figure 1). The covariate analysis also suggested severe renal impairment was not a significant covariate on venetoclax clearance (Figure 2), which is consistent with that kidney contributes negligible clearance to the total clearance of venetoclax in humans. Therefore, the population PK analysis supports the FDA's recommendation of no dose adjustment for patients with severe renal impairment.

In 5 venetoclax AML studies, most of the Asian patients (n = 105) enrolled were from Asian countries (Japan, China, South Korea, and Taiwan). There were only 11, 3 and 1 Asian patients from the US, Canada, and Australia, respectively. Using the Applicant's updated population PK model, reviewers found no clinically significant differences in venetoclax PK among White,

Black, and Asian patients from the United States (Figure 4). Of 771 patients with AML, Asian patients from Asian countries [China (5.6%), Japan (5.5%), South Korea (2.1%), and Taiwan (0.91%)] had 63% higher venetoclax exposure than non-Asian populations.

18.4.2. Summary of Applicant's Exposure-Response Analysis

A total of 575 patients (431 patients with VEN + HMA and 144 with PBO + HMA) were included in the exposure-efficacy and exposure- safety analysis for VEN + HMA. A total of 279 patients (211 with VEN + LDAC and 68 with PBO + LDAC) were included in the exposure-efficacy analysis for VEN + LDAC. Patient characteristics from all patients included in the exposure-response analyses by population are shown in Table 51.

Table 56 Demographic and Other Covariates Data Summary for Patients Included in the Exposure-Response Analyses

Characteristics	VEN/PBO + HMA (N = 575)	VEN/PBO + LDAC (N = 279)	All Subjects (N = 854)
Designated Cohort Dose, N (%)			
Placebo	144 (25.0%)	68 (24.4%)	212 (24.8%)
400 mg	379 (65.9%)		379 (44.4%)
600 mg		203 (72.8%)	203 (23.8%)
800 mg	45 (7.8%)	8 (2.9%)	53 (6.2%)
1200 mg	7 (1.2%)		7 (0.8%)
Age (yrs)			
Mean (SD)	75.6 (5.97)	75.1 (7.70)	75.4 (6.58)
Median	76.0	76.0	76.0
Min, max	49, 91	36, 93	36, 93

Characteristics	VEN/PBO + HMA (N = 575)	VEN/PBO + LDAC (N = 279)	All Subjects (N = 854)
Age Group (yrs), N (%)			
18 - 64	22 (3.8%)	22 (7.89%)	44 (5.2%)
65 - 74	194 (33.7%)	90 (32.3%)	284 (33.3%)
≥ 75	359 (62.4%)	167 (59.9%)	526 (61.6%)
Body Weight (kg),			
Mean (SD)	75.2 (18.4)	72.9 (17.2)	74.5 (18.0)
Median	73.9	71.0	73.2
Min, max	28.9, 168	27.1, 125	27.1, 168
Sex, N (%)			
Male	340 (59.1%)	167 (59.9%)	507 (59.4%)
Female	235 (40.9%)	112 (40.1%)	347 (40.6%)
Race, N (%)			
White	442 (76.9%)	212 (76.0%)	654 (76.6%)
Black	11 (1.9%)	4 (1.4%)	15 (1.8%)
American Indian/Alaska	Native	2 (0.4%)	2 (0.2%)
Asian	111 (19.3%)	60 (21.5%)	171 (20.0%)
Native Hawaiian or	Pacific Islander	3 (0.5%)	3 (0.4%)
Multiple	1 (0.2%)		1 (0.1%)
Missing	5 (0.9%)	3 (1.1%)	8 (0.9%)
Grouped Race, N (%)			
non-Asian	459 (79.8%)	216 (77.4%)	675 (79.0%)
Asian	111 (19.3%)	60 (21.5%)	171 (20.2%)
Missing	5 (0.9%)	3 (1.1%)	8 (0.9%)
Country, N (%)			
Japan	37 (6.4%)	27 (9.7%)	64 (7.5%)
China	47 (8.2%)	15 (5.4%)	62 (7.3%)
Rest of world	491 (85.4%)	237 (85.0%)	728 (85.3%)

Characteristics	VEN/PBO + HMA (N = 575)	VEN/PBO + LDAC (N = 279)	All Subjects (N = 854)
Hepatic Function, N (%)			
Normal	434 (75.5%)	203 (72.8%)	637 (74.6%)
Mild impairment	107 (18.6%)	57 (20.4%)	164 (19.2%)
Moderate impairment	26 (4.5%)	17 (6.1%)	43 (5.0%)
Severe Impairment	3 (0.5%)	1 (0.4%)	4 (0.5%)
Missing	5 (0.9%)	1 (0.4%)	6 (0.7%)
Renal Function, N (%)			
Normal	149 (25.9%)	70 (25.1%)	219 (25.6%)
Mild impairment	236 (41.0%)	107 (38.4%)	343 (40.2%)
Moderate impairment	186 (32.4%)	97 (34.8%)	283 (33.1%)
Severe impairment	4 (0.7%)	4 (1.4%)	8 (0.9%)
Missing	0 (0%)	1 (0.4%)	1 (0.1%)
CYP3A/P-gp Inhibitor for ≥ 7 Consecutive Days, N (%)			
No	304 (52.9%)	185 (66.3%)	489 (57.3%)
Yes	271 (47.1%)	94 (33.7%)	365 (42.7%)
Use of Azacitidine, N (%)			
No	45 (7.8%)	279 (100%)	324 (37.9%)
Yes	530 (92.2%)		530 (62.1%)
Use of Decitabine, N (%)			
No	530 (92.2%)	279 (100%)	809 (94.7%)
Yes	45 (7.8%)		45 (5.3%)
FLT3 Mutation, N (%)			
Not detected	336 (58.4%)	179 (64.2%)	515 (60.3%)
Detected	71 (12.4%)	41 (14.7%)	112 (13.1%)
Missing	168 (29.2%)	59 (21.2%)	227 (26.6%)
Baseline ECOG Performance Status, N (%)			
0 - 1	332 (57.7%)	153 (54.8%)	485 (56.8%)
≥ 2	243 (42.3%)	126 (45.2%)	369 (43.2%)

Characteristics	VEN/PBO + HMA (N = 575)	VEN/PBO + LDAC (N = 279)	All Subjects (N = 854)
Prior HMA,[a] N (%)			
No		218 (78.1%)	218 (25.5%)
Yes		61 (21.9%)	61 (7.1%)
Not Applicable	575 (100%)		575 (67.3%)
Baseline Cytogenetic Risk, N (%)			
Poor	222 (38.6%)	91 (32.6%)	313 (36.7%)
Intermediate	352 (61.2%)	173 (62.0%)	525 (61.5%)
Favorable[a]		4 (1.4%)	4 (0.5%)
Missing	1 (0.2%)	11 (3.9%)	12 (1.4%)
IDH1/2 Mutation, N (%)			
Not detected	356 (61.9%)	172 (61.7%)	528 (61.8%)
Detected	108 (18.8%)	48 (17.2%)	156 (18.3%)
Missing	111 (19.3%)	59 (21.2%)	170 (19.9%)
NPM1 Mutation, N (%)			
Not detected	280 (48.7%)	189 (67.7%)	469 (54.9%)
Detected	63 (11.0%)	31 (11.1%)	94 (11.0%)
Missing	232 (40.4%)	59 (21.2%)	291 (34.1%)
TP53 Mutation, N (%)			
Not detected	270 (47.0%)	184 (66.0%)	454 (53.2%)
Detected	73 (12.7%)	36 (12.9%)	109 (12.8%)
Missing	232 (40.4%)	59 (21.2%)	291 (34.1%)
AML-MRC Flag, N (%)			
No	298 (51.8%)	126 (45.2%)	424 (49.7%)
Yes	139 (24.2%)	84 (30.1%)	223 (26.1%)
Missing	138 (24.0%)	69 (24.7%)	207 (24.2%)
AML Type, N (%)			
De novo AML	329 (57.2%)	129 (46.2%)	458 (53.6%)
Secondary AML	108 (18.8%)	81 (29.0%)	189 (22.1%)
Missing	138 (24.0%)	69 (24.7%)	207 (24.2%)
Secondary AML Type, N (%)			
Therapy Related to AML	36 (33.3%)	10 (12.4%)	46 (24.3%)
Post MDS/CMML	72 (66.7%)	71 (87.7%)	143 (75.7%)

Characteristics	VEN/PBO + HMA (N = 575)	VEN/PBO + LDAC (N = 279)	All Subjects (N = 854)
Baseline Transfusion Independence for RBC, N (%)			
No	310 (53.9%)	205 (73.5%)	515 (60.3%)
Yes	265 (46.1%)	74 (26.5%)	339 (39.7%)
Baseline Transfusion Independence for Platelets, N (%)			
No	156 (27.1%)	96 (34.4%)	252 (29.5%)
Yes	419 (72.9%)	183 (65.6%)	602 (70.5%)
Baseline Bone Marrow Blast Count (%)			
Mean (SD)	49.6 (24.0)	47.9 (24.3)	49.1 (24.1)
Median	45.7	44.0	45.0
Min, max	4.00, 100	4.80, 99.4	4.00, 100
Baseline Platelet Count ($\times 10^9$/L)			
Mean (SD)	67.2 (67.3)	60.5 (57.1)	65.1 (64.2)
Median	43.0	41.0	41.5
Min, max	3.00, 606	4.00, 356	3.00, 606
Baseline Neutrophil Count ($\times 10^9$/L)			
Mean (SD)	1.30 (2.73)	1.33 (2.46)	1.31 (2.64)
Median	0.50	0.45	0.50
Min, max	0.00, 39.6	0.00, 20.4	0.00, 39.6

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 6.

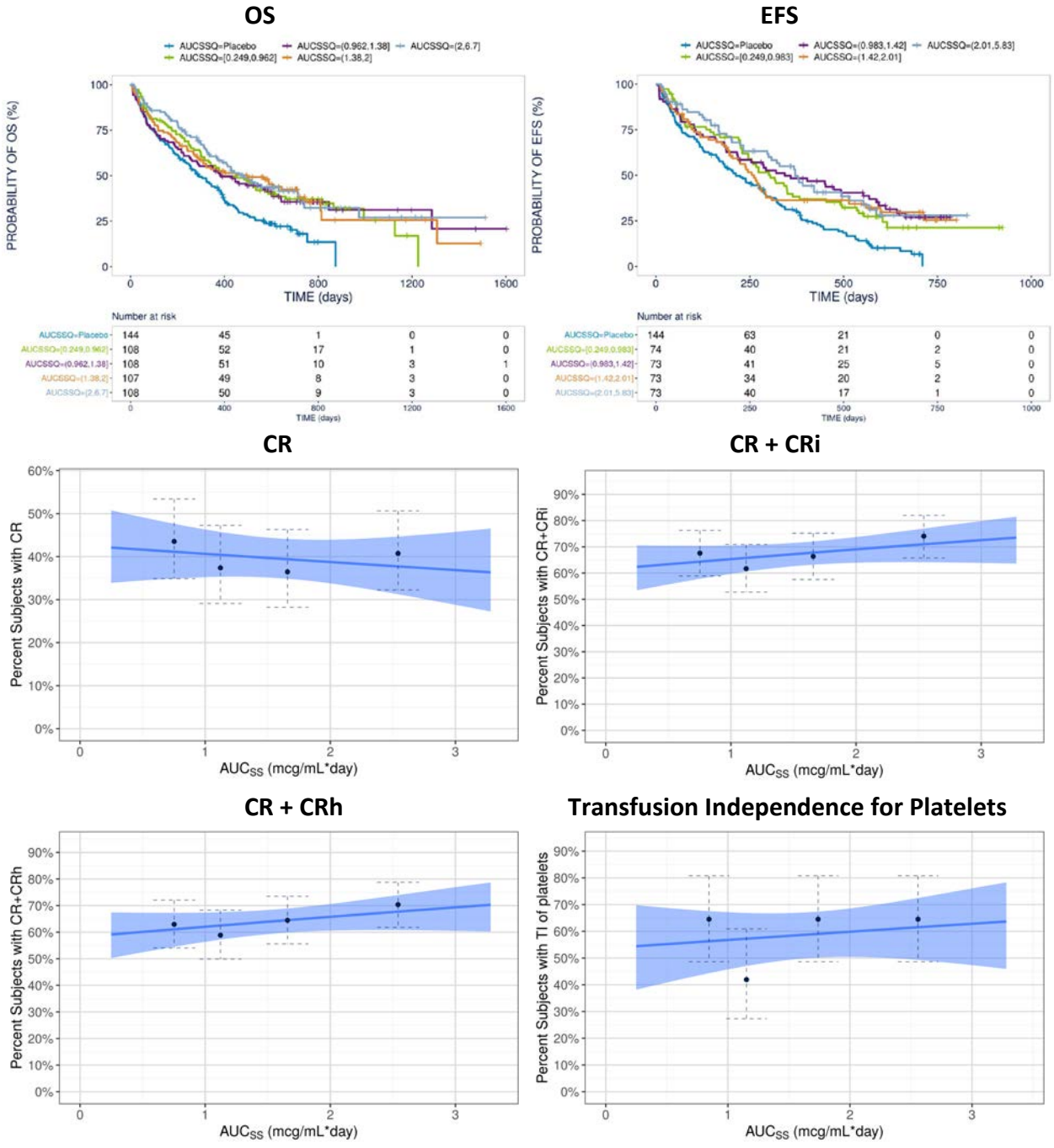
The Applicant conducted exposure-response analyses based on data from all patients in active treatment arms and placebo arms, and based on data from patients in active treatment arms, separately. Only the analysis results based on data from patients in active treatment arms are summarized below.

18.4.2.1. Exposure-Efficacy Analysis

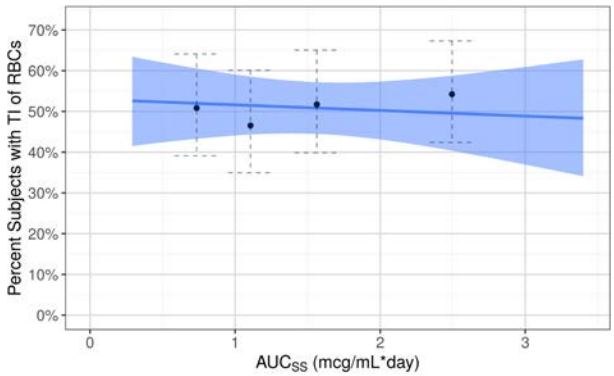
Venetoclax in Combination with HMA

The Applicant's exposure-efficacy analysis showed no significant relationship for venetoclax exposure vs. OS (P = 0.46), EFS (P = 0.44), CR (P = 0.48), CR + CRi (P = 0.16) , CR + CRh (P = 0.17), transfusion independence for platelets (P = 0.53) or RBCs (P = 0.71) in the studied dose range of 400 mg to 1200 mg in combination with HMA (Figure 18), indicating that the beneficial effect of venetoclax is maximized at 400 mg.

Figure 16 Exposure-Efficacy Analyses in Patients with AML who Received Venetoclax in Combination with HMA



Transfusion Independence for RBCs



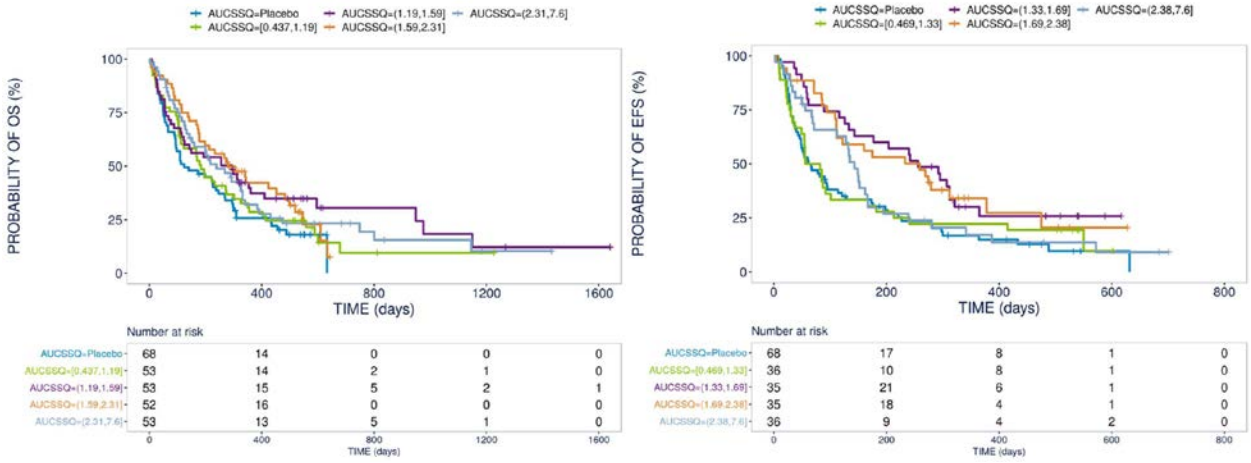
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figures 13, 12.4_3.2 and 12.4_3.3.

Venetoclax in Combination with Low-Dose Cytarabine

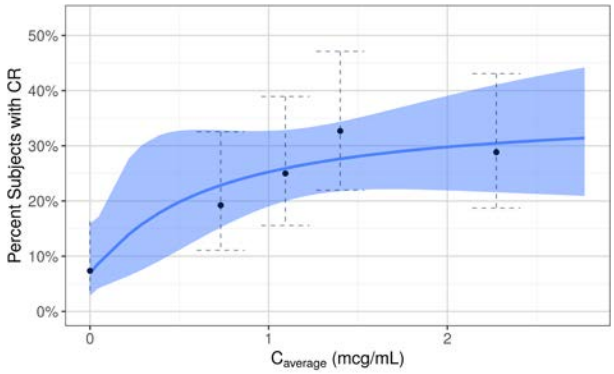
The Applicant's exposure-efficacy analysis showed no significant relationships for venetoclax exposure vs. OS (P = 0.66), EFS (P = 0.55), CR (P = 0.92), CR + CRi (P = 0.87) , CR + CRh (P = 0.43), transfusion independence for platelets (P = 0.62) and RBCs (P = 0.12) in the studied dose range of 600 mg to 800 mg in combination with LDAC (Figure 19), indicating that the maximum beneficial effect of venetoclax is reached by the 600 mg dose, with no apparent additional benefit at higher doses.

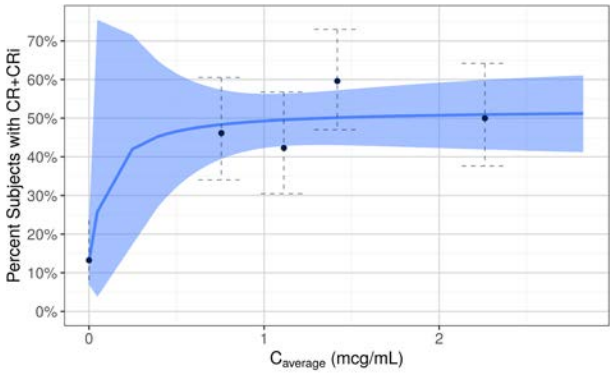
Figure 17 Exposure-Efficacy Analyses in Patients with AML who Received Venetoclax in Combination with LDAC

OS **EFS**

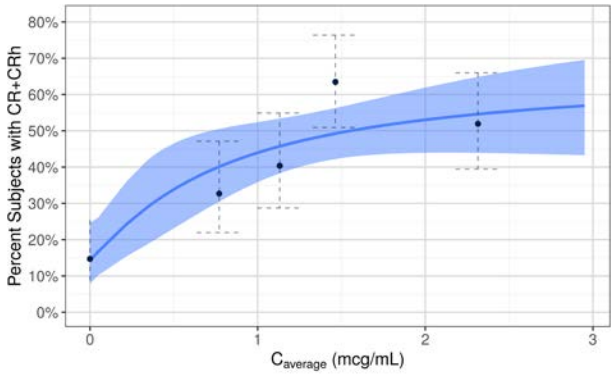


CR **CR + CRi**

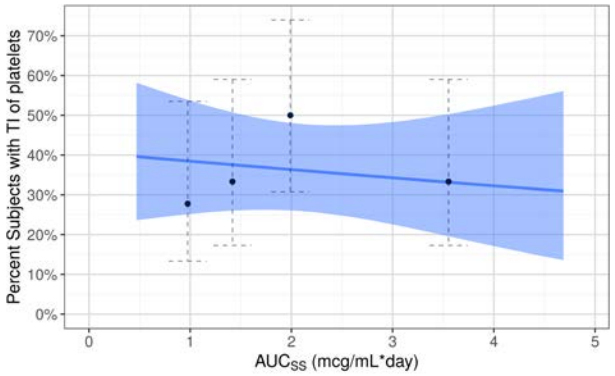




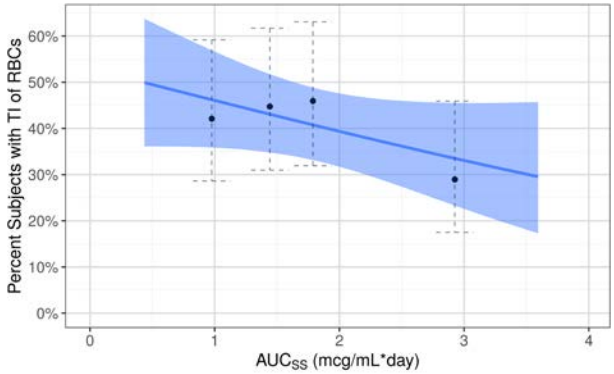
CR + CRh



Transfusion Independence for Platelets



Transfusion Independence for RBCs

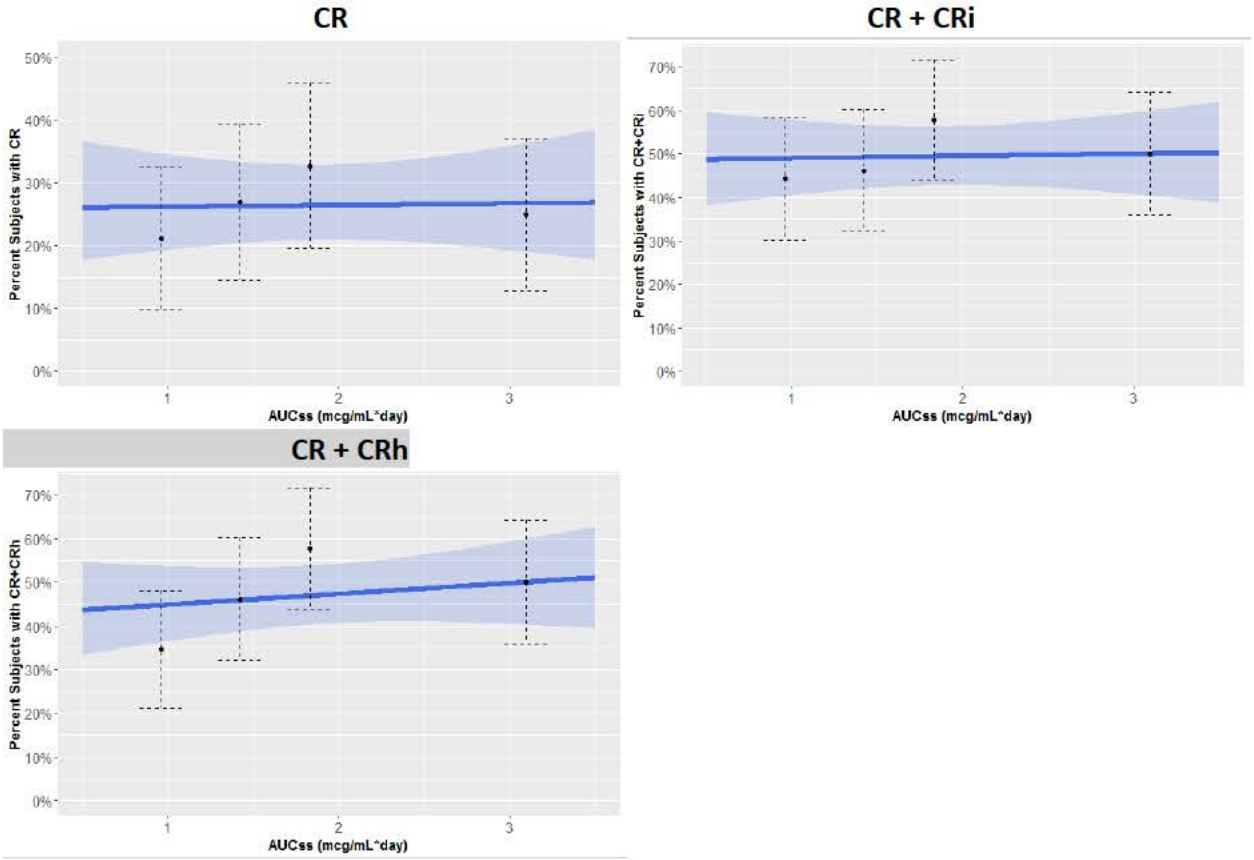


Source: Applicant's Population PK and Exposure-Response Analyses Report, Figures 22, 12.5_3.3 and 12.5_3.4.

The FDA's Assessment:

The Applicant's exposure-efficacy analyses are generally acceptable. The Applicant did not provide the correct figures for the relationships between venetoclax AUC_{SS} and CR, CR + CRi, as well as CR + CRh (figures with $C_{average}$ instead, in Figure 19) in patients with AML who received venetoclax in combination with LDAC. The reviewer's independent analysis confirmed no exposure-response relationships for CR, CR + CRi, and CR + CRh in patients on venetoclax and LDAC (Figure 20).

Figure 18 FDA's Exposure-Efficacy Analyses for CR, CR + CRi, and CR + CRh in Patients with AML who Received Venetoclax in Combination with LDAC



Source: Reviewer's analysis.

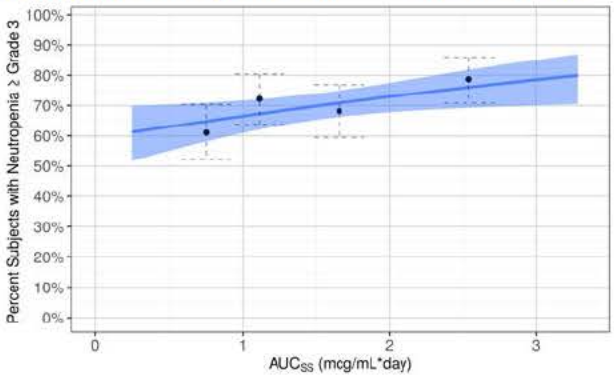
18.4.2.2. Exposure-Safety Analysis

Venetoclax in Combination with HMA

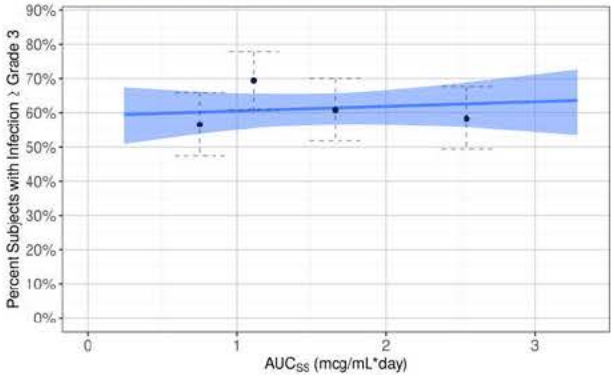
The Applicant's exposure-safety analysis showed a shallow positive exposure-response relationship for treatment-emergent Grade ≥ 3 neutropenia (P = 0.02), but no significant relationship for treatment-emergent Grade ≥ 3 infections (P = 0.62), or treatment-emergent Grade ≥ 3 thrombocytopenia (P = 0.71) in the studied venetoclax dose range of 400 mg to 1200 mg in combination with HMA (Figure 21).

Figure 19 Exposure-Safety Analyses in Patients with AML who Received Venetoclax in Combination with HMA

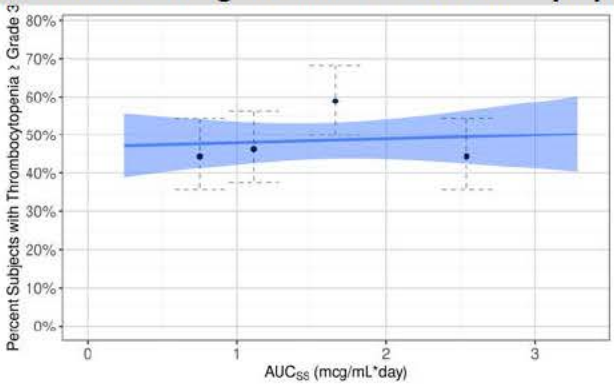
Treatment-emergent Grade ≥ 3 neutropenia



Treatment-emergent Grade ≥ 3 infections



Treatment-emergent Grade ≥ 3 thrombocytopenia



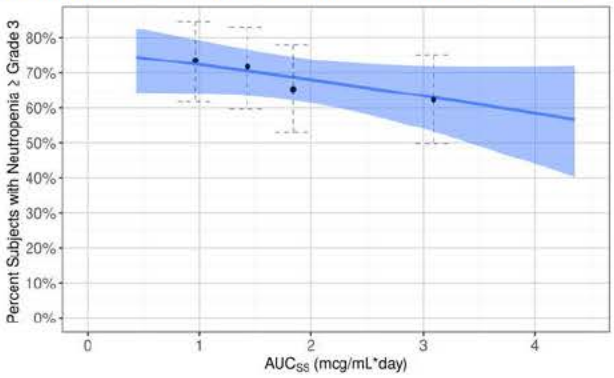
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 12.4__8.1.

Venetoclax in Combination with Low-Dose Cytarabine

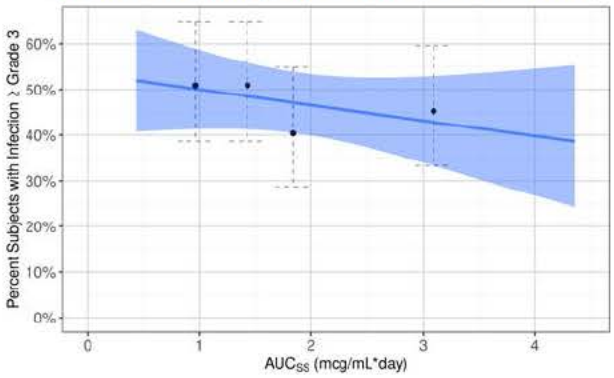
The Applicant's exposure-safety analysis showed no significant relationship for treatment-emergent Grade ≥ 3 neutropenia (P = 0.11), treatment-emergent Grade ≥ 3 infections (P = 0.28), or treatment-emergent Grade ≥ 3 thrombocytopenia (P = 0.42) in the studied venetoclax dose range of 600 mg to 800 mg in combination with LDAC (Figure 22).

Figure 20 Exposure-Safety Analyses in Patients with AML who Received Venetoclax in Combination with LDAC

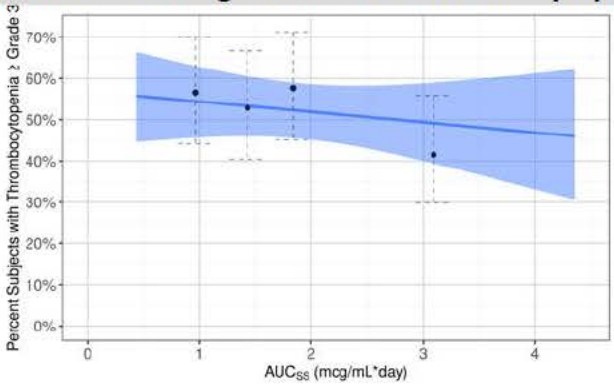
Treatment-emergent Grade ≥ 3 neutropenia



Treatment-emergent Grade ≥ 3 infections



Treatment-emergent Grade ≥ 3 thrombocytopenia



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 12.5__8.3.

The FDA's Assessment:

The Applicant's exposure-safety analyses are acceptable.

18.5. Additional Safety Analyses Conducted by FDA

Regulatory Authorities' Assessment:
Grouped preferred terms are displayed in the Table below.

Grouped term	Preferred terms
Abdominal Pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort
Acute Kidney Injury	Acute kidney injury, Anuria, Azotaemia, Glomerular filtration rate decreased, Oliguria, Renal failure, Renal impairment, Renal injury
Arrhythmia	Atrioventricular block, Bundle branch block left, Electrocardiogram QT prolonged, Nodal arrhythmia, Sinus bradycardia
Cough	Cough, Productive cough, Upper-airway cough syndrome
Diarrhea	Colitis, Diarrhoea
Dizziness	Dizziness, Vertigo
Dysgeusia	Ageusia, Dysgeusia, Hypogeusia
Dyspnea	Dyspnoea, Dyspnoea at rest, Dyspnoea exertional
Fatigue	Asthenia, Fatigue
Hemorrhage	Adrenal haemorrhage, Anal haemorrhage, Arterial haemorrhage, Catheter site haemorrhage, Cerebral haemorrhage, Conjunctival haemorrhage, Epistaxis, Eye haemorrhage, Gastric haemorrhage, Gastritis haemorrhagic, Gastrointestinal haemorrhage, Gingival bleeding, Haematuria, Haemoptysis, Haemorrhage, Haemorrhage intracranial, Haemorrhage subcutaneous, Haemorrhage urinary tract, Haemorrhagic diathesis, Haemorrhagic stroke, Haemorrhagic vasculitis, Haemorrhoidal haemorrhage, Lip haemorrhage, Lower gastrointestinal haemorrhage, Mouth haemorrhage, Mucosal haemorrhage, Muscle haemorrhage, Naevus haemorrhage, Penile haemorrhage, Pharyngeal haemorrhage, Post procedural haemorrhage, Pulmonary alveolar haemorrhage, Pulmonary haemorrhage, Rectal haemorrhage, Retinal haemorrhage, Shock haemorrhagic, Skin haemorrhage, Soft tissue haemorrhage, Subdural haemorrhage, Tongue haemorrhage, Tooth pulp haemorrhage, Upper gastrointestinal haemorrhage, Urethral haemorrhage, Uterine haemorrhage, Vaginal haemorrhage, Vascular access site haemorrhage, Vessel puncture site haemorrhage, Vitreous haemorrhage, Wound haemorrhage
Headache	Headache, Migraine, Tension headache
Hypertension	Blood pressure increased, Hypertension, Hypertensive crisis

Hypotension	Hypotension, Orthostatic hypotension
Musculoskeletal Pain	Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, Spinal pain
Neuropathy Peripheral	Dysaesthesia, Hypoaesthesia, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral motor neuropathy, Peripheral sensory neuropathy, Polyneuropathy
Edema	Eye oedema, Eyelid oedema, Face oedema, Generalised oedema, Localised oedema, Oedema, Oedema peripheral, Penile oedema, Periorbital oedema, Swelling
Pneumonia	Atypical pneumonia, Enterobacter pneumonia, Lower respiratory tract infection, Lower respiratory tract infection fungal, Lung infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia cytomegaloviral, Pneumonia fungal, Pneumonia haemophilus, Pneumonia klebsiella, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia staphylococcal, Pneumonia viral
Pneumonitis	Interstitial lung disease, Organising pneumonia, Pneumonitis
Pyrexia	Body temperature increased, Pyrexia
Rash	Dermatitis, Dermatitis acneiform, Dermatitis bullous, Drug eruption, Eczema, Eczema asteatotic, Erythema multiforme, Exfoliative rash, Lichen planus, Perivascular dermatitis, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash morbilliform, Rash popular, Rash pruritic, Rash pustular
Sepsis (excluding fungal)	Bacteraemia, Bacterial sepsis, Enterococcal bacteraemia, Escherichia bacteraemia, Escherichia sepsis, Klebsiella bacteraemia, Klebsiella sepsis, Neutropenic sepsis, Pseudomonal sepsis, Sepsis, Septic shock, Staphylococcal bacteraemia, Streptococcal bacteraemia
Stomatitis	Aphthous ulcer, Cheilitis, Glossitis, Mouth ulceration, Mucosal inflammation, Stomatitis, Tongue ulceration
Urinary Tract Infection	Cystitis, Escherichia urinary tract infection, Pyelonephritis acute, Urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal, Urinary tract infection pseudomonal, Urinary tract infection staphylococcal
Vomiting	Haematemesis, Vomiting

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ramadevi Gudi, PhD	CDER/DHOT	Sections: 5	Select one: ☑ Authored ☐ Approved
	Signature: Ramadevi Gudi -S Digitally signed by Ramadevi Gudi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ramadevi Gudi -S, 0.9.2342.19200300.100.1.1=2000462985 Date: 2020.10.15 09:04:53 -04'00'			
Acting Nonclinical Team Leader	Brenda Gehrke, PhD	CDER/DHOT	Sections: 5	Select one: ☐ Authored ☑ Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brenda Gehrke -S, 0.9.2342.19200300.100.1.1=0012062023 Date: 2020.10.15 10:12:13 -04'00'			
Clinical Pharmacology Reviewer	Hisham Qosa, PhD	OCP/DCPII	Sections: 6	Select one: ☑ Authored ☐ Approved
	Signature: Hisham Qosa -S (Affiliate) Digitally signed by Hisham Qosa -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001883898, cn=Hisham Qosa -S (Affiliate) Date: 2020.10.15 10:21:48 -04'00'			
Clinical Pharmacology Team Leader	Ruby Leong, PharmD	OCP/DCPI	Sections: 6	Select one: ☐ Authored ☑ Approved
	Signature: Ruby Leong -S3 Digitally signed by Ruby Leong -S3 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruby Leong -S3, 0.9.2342.19200300.100.1.1=2000548953 Date: 2020.10.15 10:31:35 -04'00'			
Pharmacometrics Reviewer	Liang Li, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Liang Li -S Digitally signed by Liang Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liang Li -S, 0.9.2342.19200300.100.1.1=2001459144 Date: 2020.10.15 10:42:46 -04'00'			
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☐ Authored ☑ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15, 19.4	Select one: ___ Authored ✓ Approved
	Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brian P. Booth -S, 0.9.2342.19200300.100.1.1=1300137436 Date: 2020.10.15 10:47:42 -04'00'			
Clinical Reviewer	Lori Ehrlich, MD, PhD	CDER/OOD/DHMI	Sections: 2, 4, 7, 8, 9, 10, 11, 12, 13, 19	Select one: ✓ Authored ___ Approved
	Signature: Lori Ehrlich -S Digitally signed by Lori Ehrlich -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lori Ehrlich -S, 0.9.2342.19200300.100.1.1=2001528093 Date: 2020.10.15 11:27:40 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Sarabdeep Singh, PhD	OB/DBIX	Sections: 8	Select one: ✓ Authored ___ Approved
	Signature: Sarabdeep Singh -S			
Acting Statistical Team Leader	Jonathon Vallejo, PhD	OB/DBIX	Sections: 8	Select one: ___ Authored ✓ Approved
	Signature: Jonathon J. Vallejo -S Digitally signed by Jonathon J Vallejo S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 2002146299 cn Jonathon J Vallejo S Date: 2020 10 15 11:11:11 04 00			
Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections: 8, 16	Select one: ___ Authored ✓ Approved
	Signature: Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369224, cn=Thomas E. Gwise -S Date: 2020.10.15 11:20:43 -04'00'			
Associate Director for Labeling (ADL)	Stacy Shord, PharmD	OOD/DHMI	Sections: 11	Select one: ✓ Authored ___ Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Stacy Shord S 0 9 2342 19200300 100 1 1=2000356537 Date: 2020 10 15 11:48:08 04'00'			

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/s/

SURIA YESMIN
10/16/2020 01:29:03 AM

KELLY J NORSWORTHY
10/16/2020 09:28:45 AM

ROMEO A DE CLARO
10/16/2020 10:24:11 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s020, s021

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA-208573-SUPPL-20**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PAS	5/22/2020	5/22/2020	5/28/2020	11/22/2020	6/25/2020

3. **Proposed Changes**:

This PAS efficacy supplement provides for clinical data to fulfill PMR 3545-1 and PMR 3545-2 and to support the full approval of venetoclax in combination with azacitidine, or decitabine, or LDAC for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

4. **Review #**: 1

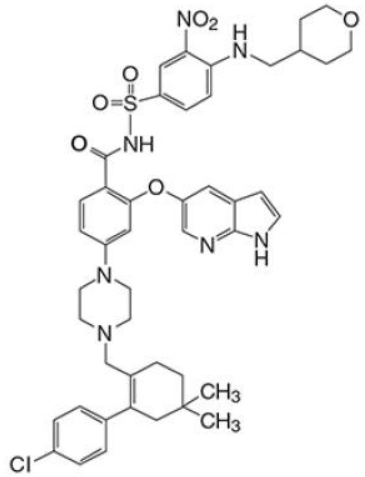
5. **Clinical Review Division**: OND/OOD/DHM2

6. **Name and Address of Applicant**:
   AbbVie, Inc.
   1 N. Waukegan Road
   Dept. PA77/Bldg. AP30
   North Chicago, IL 60064
   Attn: Allan Bonsol,
   Associate Director, Regulatory Affairs
   Tel: (847)935-6723
   Fax: (847)935-5344
   Email**:** allan.bonsol@abbvie.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength (mg)	Route of Administration	Rx or OTC	Special Product
VENCLEXTA® (venetoclax tablets)	Tablets	10, 50, 100	Oral	Rx	15-5068

8. Chemical Name and Structure of Drug Substance:

	**USAN:** Venetoclax **Chemical Name:** 4-(4-{[2-(4-chlorophenyl)-4,4dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide) **Molecular Formula:** $C_{45}H_{50}ClN_7O_7S$ **Molecular Weight:** 868.44

9. Indication:
Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

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.

10. Supporting/Relating Documents: N/A.

11. Consults: N/A

12. Executive Summary:

Background and Proposed Changes: VENCLEXTA® (venetoclax tablets) was granted accelerated approval on 11/21/2018 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, in combination with azacitidine, or decitabine, or low-dose cytarabine.

This PAS efficacy supplement provides for clinical data to fulfill PMR 3545-1 and PMR 3545-2 and to support the full approval of the aforementioned indication.

The supplement was submitted under the Agency's Real-Time Oncology Review (RTOR) pilot program to NDA 208573.

1.12.14. Environmental Analysis:
There are no proposed CMC changes except for the EA categorical exclusion request.

The applicant claims a categorical exclusion from the requirements to prepare an environmental assessment or an environmental impact statement in accordance with 21 CFR 25.31(b) because an estimate of the expected introduction concentration (EIC) of venetoclax at the point of entry into the aquatic environment is (b) (4) ppb, well below 1 ppb. The applicant also claims that no extraordinary

circumstances, as referenced in 21 CFR 25.21, exist relative to this action. As such, the categorical exclusion request may be granted.

13. Conclusions & Recommendations:

This PAS efficacy supplement is recommended for approval from a CMC perspective.

14. Comments/Deficiencies to be Conveyed to Applicant: N/A

15. Primary Reviewer:

Wei-Hua Emily Wu, Ph.D., CMC reviewer, Branch 1, DPMA I, OLDP, OPQ

16. Secondary Reviewer:

Ramesh Raghavachari, Ph.D., Branch Chief, Branch 1, DPMA I, OLDP, OPQ

Wei-Hua Emily Wu

Digitally signed by Wei-Hua Emily Wu
Date: 6/25/2020 10:52:28AM
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Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 6/25/2020 12:27:01PM
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/s/

WEI-HUA E WU
06/25/2020 12:45:45 PM

RAMESH RAGHAVACHARI
06/25/2020 01:18:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s020, s021

OTHER REVIEW(S)

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:	October 1, 2020
To:	Suria Yesmin Senior Regulatory Project Manager **Division of Hematologic Malignancies (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **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-020
Applicant:	AbbVie, Inc.

1 INTRODUCTION

On May 22, 2020, AbbVie, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 208573/S-020 for VENCLEXTA (venetoclax tablets) for oral use. With this supplement, the Applicant proposes the following changes for venetoclax: conversion from accelerated approval to full approval for venetoclax in combination with azacitidine, or decitabine, or low-dose cytarabine (LDAC) for the treatment of newly-diagnosed AML who are age 75 years or older, who have comorbidities that preclude use of intensive induction chemotherapy.

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 Hematologic Malignancies (DHM1) on July 2, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VENCLEXTA (venetoclaxtablets).

2 MATERIAL REVIEWED

- Draft VENCLEXTA (venetoclax tablets) MG received on May 22, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 23, 2020.
- Draft VENCLEXTA (venetoclax tablets) Prescribing Information (PI) received on May 22, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 23, 2020.
- Approved VENCLEXTA (venetoclax tablets) labeling dated June 12, 2020.

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.

7 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SUSAN W REDWOOD
10/01/2020 09:56:38 AM

NISHA PATEL
10/01/2020 10:07:36 AM

SHAWNA L HUTCHINS
10/01/2020 10:23:38 AM

LASHAWN M GRIFFITHS
10/01/2020 11:42:43 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 1, 2020

To: Suria Yesmin, Regulatory Project Manager
Division of Hematologic Malignancies 1 (DHM1)

Stacy Shord, Associate Director for Labeling, DHM1

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, Team Leader, OPDP

Subject: OPDP Labeling Comments for VENCLEXTA® (venetoclax tablets), for oral use

NDA: 208573/S-020 and S-021

In response to DHM1's consult request dated July 2, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for VENCLEXTA® (venetoclax tablets), for oral use. These supplements (S-020 and S-021) provide for:

- S-020: Verification of clinical benefit for venetoclax in combination with azacitidine or decitabine, for the treatment of newly-diagnosed AML who are age 75 years or older, who have comorbidities that preclude use of intensive induction chemotherapy. S-020 also fulfills the requirements for Study M15-656 (VIALE-A) as postmarketing requirement PMR 3542-2 under 21 CFR 314 Subpart H upon approval.

- S-021: Verification of clinical benefit for venetoclax in combination with LDAC for the treatment of newly-diagnosed AML who are age 75 years or older, who have comorbidities that preclude use of intensive induction chemotherapy. S-021 also fulfills the requirements for M16-043 (VIALE-C) as postmarketing requirement PMR 3542-1 under 21 CFR 314 Subpart H upon approval.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DHM1 on September 23, 2020, and are provided below.

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 October 1, 2020.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

Product Labeling

Section	Statement from draft	Comment
14 Clinical Studies, 14.2 Acute Myeloid Leukemia	(b) (4)	This statement is promotional in tone. Is this statement needed since OS results are presented in Table 25 of the full PI?

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/s/

NISHA PATEL
10/01/2020 10:11:17 PM