22 April 2021
EMA/280804/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Venclyxto

International non-proprietary name: venetoclax

Procedure No. EMEA/H/C/004106/II/0030

Marketing authorisation holder (MAH) AbbVie Deutschland GmbH & Co. KG

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADD	Average daily dose
ADR	Adverse drug reaction
ADME	Adsorption, distribution, metabolism, and excretion
AE	Adverse event
BCL	B-cell lymphoma
BCR	B-cell receptor
BCRP	Breast cancer resistance protein
CCDS	Company Core Data Sheet
CI	Confidence interval
Cmax	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CR	Complete remission
Cri	Complete remission with incomplete blood count recovery
CrCl	Creatinine clearance
CSR	Clinical Study Report
CT	Computed tomography
CYP	Cytochrome P450
DOR	Duration of response
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FISH	Fluorescence in situ hybridization
HCT	Hematopoietic stem cell transplantation
HMA	Hypomethylating agent
HRQoL	Health-related quality of life
IRC	Independent review committee
LDAC	Low-dose cytarabine
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NDAML	Newly diagnosed AML
NOAEL	No-observed-adverse-effect-level
ORR	Objective response rate or overall response rate
OS	Overall survival

PASS	Post Authorization Safety Study
PFS	Progression-free survival
PR	Partial remission
PT	Preferred term
PTD	Patient treatment days
PTY	Patient treatment years
PY	Patient-year
QD	Once a day
QTc	Corrected QT interval
RMP	Risk Management Plan
RPTD	Recommended Phase 2 dose
R/R	Relapsed/refractory
SEER	Surveillance, Epidemiology, and End Results
SMQ	Standardised MedDRA Query
SmPC	Summary of Product Characteristics
SOC	System Organ Class
tAML	Therapy-related AML
TLS	Tumor lysis syndrome
TTNT	Time to next anti-CLL treatment
TTP	Time to tumor progression
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 23 June 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication for Venclyxto (venetoclax) in combination with Hypomethylating Agents (HMAs) or Low Dose Cytarabine (LDAC) for the treatment of adult patients with newly-diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. As a consequence, sections 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet and RMP version 6.1 are also updated accordingly.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0246/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0246/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 23 June 2016 (EMA/CHMP/SAWP/422430/2016). The Scientific Advice pertained to clinical aspects of the dossier.

EMA/CHMP/SAWP/422430/2016 is a protocol assistance on clinical development of venetoclax and azacitidine (study M15-656) in newly-diagnosed AML patients ineligible for intensive chemotherapy (regarding subject eligibility criteria, choice of comparator/backbone therapy, dosing regimen, endpoint selection, and various statistical aspects)

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	23 June 2020
Start of procedure:	18 July 2020
CHMP Co-Rapporteur Assessment Report	11 September 2020
CHMP Rapporteur Assessment Report	14 September 2020
PRAC Rapporteur Assessment Report	17 September 2020
PRAC members comments	23 September 2020
PRAC Outcome	1 October 2020
CHMP members comments	5 October 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 October 2020
1st Request for supplementary information (RSI)	15 October 2020
CHMP Rapporteur Assessment Report	4 January 2021
PRAC Rapporteur Assessment Report	5 January 2021
PRAC members comments	6 January 2021
PRAC Outcome	14 January 2021
CHMP members comments	18 January 2021
Updated CHMP Rapporteur Assessment Report	21 January 2021
2nd Request for supplementary information (RSI)	28 January 2021
SAG experts meeting to address questions raised by the CHMP	30 March 2021
CHMP Rapporteur Assessment Report	1 April 2021
PRAC Rapporteur Assessment Report	6 April 2021
PRAC members comments	12 April 2021
Updated PRAC Rapporteur Assessment Report	13 April 2021
PRAC Outcome	8 April 2021
CHMP members comments	13 April 2021
Updated CHMP Rapporteur Assessment Report	16 April 2021
CHMP Opinion	22 April 2021
The CHMP adopted a report on similarity comparing already authorised orphan medicinal product(s) (Dacogen, Rydapt, Mylotarg, Vyxeos liposomal,	22 April 2021

Timetable	Actual dates
Xospata, Daurismo) (Appendix 1)	
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Venclyxto in comparison with existing therapies (Appendix 2)	22 April 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Acute myeloid leukemia (AML) is an aggressive hematologic stem-cell malignancy characterised by the clonal expansion of myeloblasts in the bone marrow, peripheral blood and occasionally extramedullary tissues, disrupting normal hematopoiesis.

Noteworthy, more than 50% of AML patients are considered ineligible for intensive chemotherapy regimens due to age, performance status and/or comorbid conditions.

Claimed therapeutic indication

Venclyxto (venetoclax) in combination with hypomethylating agents or low-dose cytarabine is indicated for the treatment of adult patients with newly-diagnosed acute myeloid leukaemia (NDAML) who are ineligible for intensive chemotherapy.

Epidemiology

The median age at diagnosis of AML is 68 years of age. The incidence is increasing as the population ages. In Europe, the annual incidence is 5-8 per 100,000 in adults, which triples to 15-25 per 100,000 in those over 70 years of age.

Biologic features

Less than 10% of patients > 65 are alive 5 years after the diagnosis, while the life expectancy in a normal population is 15 to 20 additional years. The reasons for such poor outcomes can be attributed to patient- and disease-related features. Older age usually is associated with lower performance status, frailty (a syndrome of unintentional weight loss, exhaustion, weakness and decreased physical activity), comorbidities and organ impairment leading to more severe toxicities (e.g. severe infections) of intensive, remission-oriented, regimens.

The biological and cytogenetic profile of elderly AML patients do differ from those of younger patients, due to a higher incidence of unfavourable cytogenetics (lower frequency of 'favourable' NPM1 and FLT3 mutations, increase of p53 gene mutations, the presence of complex and/or monosomal caryotypes),

secondary AML after previous disorders such as myelodysplastic syndrome and myeloproliferative neoplasms or following radio-chemotherapy (known as therapy-related AML).

Indeed, AML in older patients appears to be a biologically and clinically distinct disease with a diminished response to induction chemotherapy, lower remission rates, shorter disease-free survival and overall survival than observed with younger patients: the 5-year survival rate for patients less than age 65 years at diagnosis is 47.5%, while for patients age 65 years and older at diagnosis is approximately 8%.

Management

In the 1970s, the '7+3' regimen (7 days of cytarabine and 3 days of anthracycline) became available and remains the mainstay of curative-intent standard of care for NDAML. In the last twenty years, new drugs such as hypomethylating agents (azacitidine, decitabine) have been introduced in the therapeutic arsenal for patients considered unfit for standard chemotherapy.

After a stagnation of decades in the treatment of AML, the recent years witnessed a wave of approvals and applications in the US and EU, mostly addressing specific mutations (e.g FLT3 with midostaurin, quizartinib, , gilteritinib;, improved formulations of 'old' drugs (Vyxeos, liposomal cytarabine and daunorubicine at a 5:1 molar ratio), products targeting tumoral antigens (anti-CD33 gemtuzumab ozogamicin) or specific pathways (HH/GLI inhibitor glasdegib).Nevertheless, for NDAML patients with or without actionable mutations and deemed unfit for intensive chemotherapy or for those who refuse it despite being eligible, HMAs or LDAC monotherapy are the mainstay of therapy. The prognosis remains poor. In this population, the reported median OS was 7.7 months for patients receiving decitabine, 10.4 months for azacitidine, and 5 months for LDAC, when given as single agents.

A substantial unmet need exists for 'middle-ground' therapies that can provide clinical efficacy translated into survival benefits at lower toxicities than standard chemotherapy.

ESMO 2020

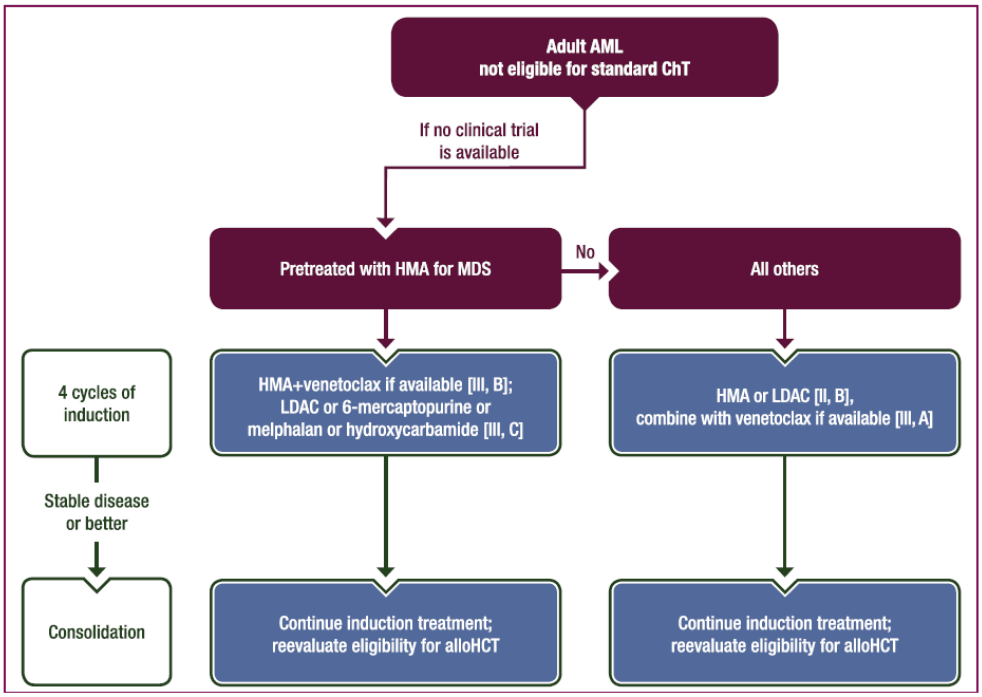
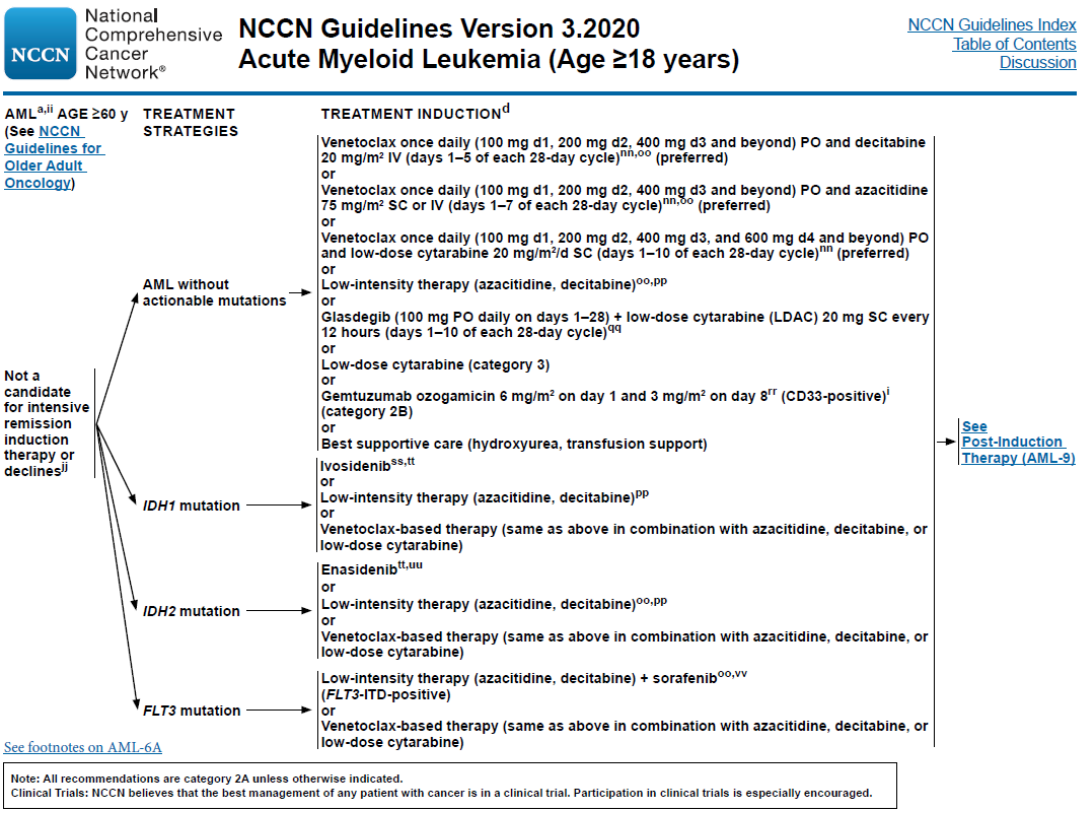


Figure 2. Treatment algorithm for first-line treatment in newly diagnosed AML patients not eligible for standard induction and consolidation treatment.
alloHCT, allogeneic haematopoietic cell transplantation; AML, acute myeloid leukaemia; ChT, chemotherapy; HMA, hypomethylating agent; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome.

NCCN 2020



2.1.2. About the product

B-cell leukemia/lymphoma-2 (BCL2) family members, including BCL2, BCL-X_L and MCL1, mediate cancer survival by sequestering pro-apoptotic proteins and BCL2 activity promotes chemotherapy resistance and enhances the survival of leukemic progenitor and blast cells. Venetoclax is a potent, highly selective, orally bioavailable, small-molecule BCL2 inhibitor. Resistance to venetoclax may be mediated by other pro-survival proteins such as BCL-X_L and MCL1, that sequester endogenous BH3-only activity proteins released by venetoclax upon BCL2 binding. Cytotoxic drugs, including cytarabine, synergize with venetoclax by enhancing BH3-only activity and/or suppressing MCL1 to promote apoptosis in preclinical models of AML.

Approved indications for venetoclax:

Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL.

Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

Venclyxto monotherapy is indicated for the treatment of CLL:

in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor,

or

in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

See section 1 (scientific advice).

2.1.4. General comments on compliance with GLP, GCP

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1b Efficacy, PK, and safety	M14-358	5.3.5.2	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	Dose escalation and Dose expansion, Non-randomized, Combination	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	212 N = 127 venetoclax in combination with azacitidine; N = 73 venetoclax in combination with decitabine; N = 12 DDI substudy	Newly diagnosed elderly (≥ 60 years) subjects with AML who are not eligible for standard induction therapy	Venetoclax + azacitidine = 5.5 months (median) Venetoclax + decitabine = 6.7 months (median) DDI substudy = 2.2 months (median)	Enrollment complete, follow-up ongoing; Full interim

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1/2 Efficacy, PK, and safety	M14-387	5.3.5.2	Characterize PK and safety, determine MTD/RPTD, and evaluate efficacy	Dose escalation, Non-randomized, Safety expansion	Venetoclax: 600 mg or 800 mg, orally, QD, 28-day cycles Cytarabine: 20 mg/m^2, SC Days 1 – 10 for each 28-day cycle	92 N = 82 venetoclax (600 mg) in combination with LDAC N = 10 venetoclax (800 mg) in combination with LDAC	Treatment naïve subjects with AML who are ≥ 60 years of age and who are not eligible for standard anthracycline-based induction therapy	4.1 – 4.4 months (median)	Enrollment complete, follow-up ongoing; Full interim
Phase 2 Efficacy, PK, and safety	M14-212	5.3.5.2	Characterize PK and safety, evaluate efficacy	Non-randomized, Single-agent	Venetoclax 800 mg or 1200 mg, orally, QD	32 N = 30 R/R N = 2 Frontline	Adults with R/R AML or untreated AML unfit for intensive therapy	62 days (median)	Complete; Full final

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy, PK, and safety	M15-656	5.3.5.1	Evaluate if venetoclax in combination with azacitidine improved overall survival (OS) and composite complete remission rate (complete remission [CR] + complete remission with incomplete marrow recovery [CRi]) versus placebo in combination with azacitidine, in treatment-naïve subjects with acute myeloid leukemia (AML).	Double-blind, randomized, placebo-controlled	Venetoclax or Placebo tablet; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3 (ramp-up); oral; 400 mg/day thereafter, oral 28-day cycles Azacitidine 75 mg/m^2 SC or IV (per local label) is administered daily for 7 days beginning on Day 1 of each 28-day cycle	427 N = 282 venetoclax in combination with azacitidine; N = 143 placebo in combination with azacitidine	Treatment-naïve subjects with acute myeloid leukemia (AML) who are ≥ 18 years of age and not eligible for standard induction therapy due to age or comorbidities	Venetoclax + azacitidine: 7.6 months (median) Placebo + azacitidine: 4.3 months (median)	Enrollment complete; Follow up ongoing; Full interim

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy, PK, and safety	M16-043	5.3.5.1	Evaluate if venetoclax when co administered with LDAC improves overall survival (OS) versus LDAC and placebo, in treatment-naïve subjects with AML	Double-blind, randomized, placebo-controlled	Venetoclax or Placebo 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, 600 mg Day 4 (ramp-up); oral; 600 mg/day thereafter, oral, 28-day cycles LDAC 20 mg/m^2 SC is administered daily for Day 1 – 10 each 28-day cycle	210 N = 142 venetoclax (600 mg) in combination with LDAC N = 68 placebo in combination with LDAC	Treatment naïve subjects with AML who are ≥ 18 years of age and who are ineligible for intensive chemotherapy	Venetoclax + LDAC: 4.1 months (median) Placebo + LDAC: 1.7 months (median)	Enrollment complete; Follow up ongoing; Full interim

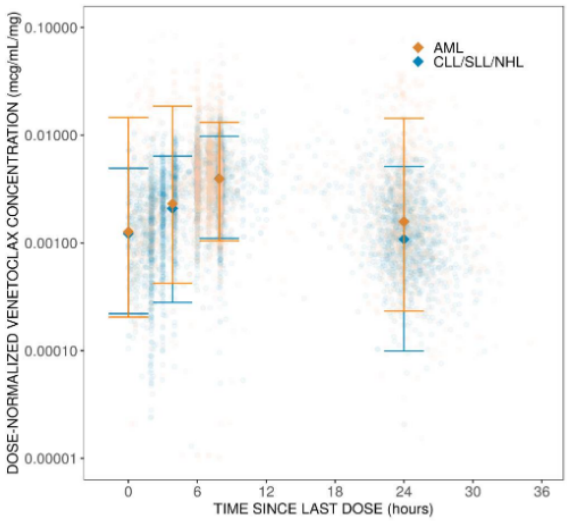
AML = acute myeloid leukemia; DDI = drug drug interaction: venetoclax 400 mg + decitabline + posaconzaole; IV = intravenous; LDAC = low-dose cytarabine; MTD = maximum-tolerated dose; OS = overall survival; PK = pharmacokinetics; QD = once daily; R/R = relapsed or refractory; RPTD = recommended Phase 2 dose; SC = subcutaneous

2.3.2. Pharmacokinetics

The pharmacokinetic data were analysed using population pharmacokinetic (popPK) modelling approach. The objectives were to evaluate whether a previously developed popPK model is able to describe venetoclax PK in AML subjects and to evaluate the relationship between venetoclax exposures and clinical

response (efficacy and safety) in subjects with AML, with separate analyses for venetoclax in combination with hypomethylating agents (HMA) (VEN + HMA) and for venetoclax in combination with low-dose cytarabine (LDAC) (VEN + LDAC), see 5.3.4. PK/PD modelling.

Figure 1. Observed Dose-Normalized Venetoclax Concentrations Versus Binned Time Since Last Dose



Orange circles represent observed venetoclax concentrations (normalized by the most recent prior dose) from AML Studies M14-212, M14-358, M14-387, M15-656 and M16-043. Blue open circles represent observed venetoclax concentrations (normalized by the most recent prior dose) from CLL, SLL and NHL subjects from studies included in the previous population PK model (R&D/15/0256). Closed diamonds and error bars represent median and 5th and 95th percentiles for the binned observed data.

Analytical Methods

Bioanalysis

Details of specific and sensitive LC-MS/MS bioanalytical methods developed and validated for the quantitation of venetoclax in human plasma were provided in the original application. A list of the validation reports and analytical method reports for the AML clinical studies are provided in Table 1. All validations were conducted in compliance with internal standard operating procedures of the respective laboratories that performed the method validation. During sample analysis, the assay reproducibility was demonstrated at least once per assay using an incurred sample reanalysis (ISR) approach (Table 2). There was no change in analytical methods for venetoclax assays that was provided in the original application.

Table 1. Summary of Validated Analytical Method Reports

Compound(s)	Validation Report	Report Site	Studies	Bioanalytical Study Report
Venetoclax (A-1195425)	c-da-rd140548-val-lcms-plasma c-da-rd150131-update-lcms-plasma c-da-rd170857-update-lcms-plasma	AbbVie	M14-212 M14-358 M14-387 M15-656 M16-043	m14212-analytical-plasma m14358-analytical-plasma m14387-analytical-plasma-final m15656-analytical-plasma m16043-analytical-plasma-final
	c-da-17bas0234-val-lcms-pla	WuXi	M15-656 M16-043	m15656-analytical-plasma-wuxi-global-interim m16043-analytical-plasma-wuxi
	c-da-rd180140-xval-lcms-human-pla	AbbVie/WuXi	Cross validation	N/A
Azacitidine	c-da-p1040-val-lcms-pla-azacitidine	PPD	M14-358 M15-656	m14358-analytical-plasma-azacitidine m15656-analytical-plasma-azacitidine-interim
Cytarabine	c-da-145096akso-val-lcms-pla-cytarabine-update	inVentiv	M14-387 M16-043	m14387-analytical-plasma-cytarabine m16043-analytical-plasma-cytarabine-final
Decitabine	c-da-p1276-val-lcms-pla-decitabine	PPD	M14-358	m14358-analytical-plasma-decitabine

N/A = not applicable

Table 2. Summary of Analytical Methods

Compound	Validation Report	Method	LLOQ	Linear Range	Inter-Run Accuracy %Bias[a]	Inter-Run Precision %CV[a]	Long Term Stability	ISR
Venetoclax	c-da-rd140548-val-lcms-plasma c-da-rd150131-update-lcms-plasma c-da-rd170857-update-lcms-plasma	LC-MS/MS (plasma)	2.11 ng/mL	2.11 to 2030 ng/mL	–1.6 to 0.0	1.6 to 5.5	1500 d (–20°C)	Yes
	c-da-17bas0234-val-lcms-pla		2.00 ng/mL	2.00 to 2000 ng/mL	–5.0 to –0.6	3.2 to 13.5	92 d (–20°C) 210 d (–80°C)	Yes
Azacitidine	c-da-p1040-val-lcms-pla-azacitidine	LC-MS/MS (plasma)	1.00 ng/mL	1.00 to 2000 ng/mL	–5.24 to 3.64	3.43 to 8.05	14 d (–20°C) 627 d (–70°C)	Yes
Cytarabine	c-da-145096akso-val-lcms-pla-cytarabine-update	LC-MS/MS (plasma)	250.00 pg/mL	250.00 to 250000.00 pg/mL	–4.63 to –1.03	2.63 to 9.36	366 d (–20°C and –80°C)	Yes
Decitabine	c-da-p1276-val-lcms-pla-decitabine	LC-MS/MS (plasma)	0.500 ng/mL	0.500 to 250 ng/mL	1.27 to 5.53	3.43 to 8.19	229 d (–20°C) 631 d (–70°C)	Yes

CV = coefficient of variation; ISR = incurred sample reanalysis; LLOQ = lower limit of quantitation

a. Inter-run precision %bias and inter-run precision %CV were statistics from runs designated for precision and accuracy in validation.

Population PK analysis

Data from the 5 clinical studies in AML patients were included in the analysis (M14-358, M14-212, M14-387, M15-656, M16-043).

A previously developed non-linear mixed-effects population PK model of venetoclax in relapsed/refractory Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Lymphoma (SLL), and Non-Hodgkin's Lymphoma (NHL) subjects and healthy subjects was used as a starting point for the current analysis. The population parameter estimates, and the variance-covariance matrix were used as informative priors for the analysis presented in this report. The magnitudes of the covariate effects were re-estimated. In addition, the effects of race (Asian vs. non-Asian), azacitidine (AZA), decitabine (DEC) and LDAC on venetoclax apparent clearance (CL/F), apparent volume of distribution of the central compartment (V2/F), and relative bioavailability (F1) were tested as covariates.

Results

In total, the population PK analysis included 4,575 plasma venetoclax observations from 771 subjects at venetoclax doses ranging from a ramp-up dose of 10 mg to a target dose of 1200 mg (Table 3). Twenty-seven (0.6%) concentration records > LLOQ were excluded from analysis.

Table 3. 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)
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%)

Table 4. Demographic and Other Covariates Data Summary for Subjects Included in the Population PK Analysis (cont.)

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%)
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%)
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%)

Co-administration of HMAs (AZA or DEC) and LDAC as well as race (Asian vs. non-Asian) were tested as covariates (without any priors) on venetoclax apparent clearance, apparent central volume of distribution, and relative bioavailability. The final model included race (Asian vs. non-Asian) as a statistically significant covariate on venetoclax relative bioavailability, with Asian subjects having 67% higher relative bioavailability, and co-administration of AZA as a statistically significant covariate on venetoclax apparent volume of distribution, increasing venetoclax apparent volume of distribution by 24% (Table 5). All pharmacokinetic parameters in the model were estimated precisely (RSE < 15%). Shrinkage of the inter-individual random effects was moderate (23 to 35%).

The goodness-of-fit plots do not indicate systematic bias in the observed vs. individual and population predicted concentrations for the final model. Most values lay near the line of identity. The distributions of the conditional weighted residuals (CWRES) with population predicted concentrations and time also do not indicate systematic model misspecifications.

The pcVPC plots of the simulated percentiles overlaid with the observed data showed that the model was able to adequately capture the variability of the data (Figure 4). A tendency to under-predict the 5th percentile was noted; this was also seen in the previous analysis (R&D/15/0256). However, the central tendency and range of observed data was described adequately.

Table 5. Key Parameter Estimates and Variability for Venetoclax Pharmacokinetics: Final Model

Parameter	Estimate	%RSE[a]	95% Confidence Interval[b]	Population Estimate in the Legacy Model
	Population Value (θ)			
CL/F (L/day)	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.

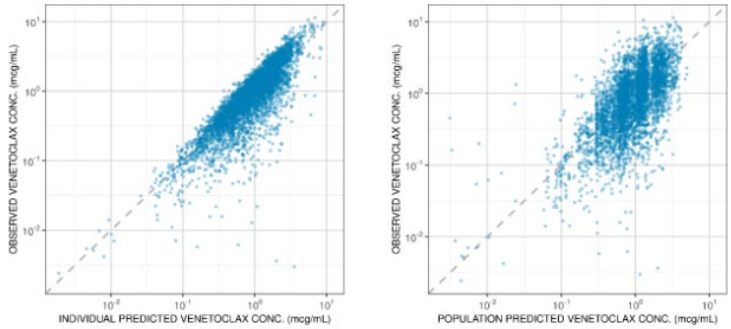
f. Reference 400 mg.

g. Relative bioavailability under fed conditions without specification of fat-content.

h. Percent coefficient of variation (%CV) was approximated as $\sqrt{e^{\omega^2} - 1} \times 100\%$.

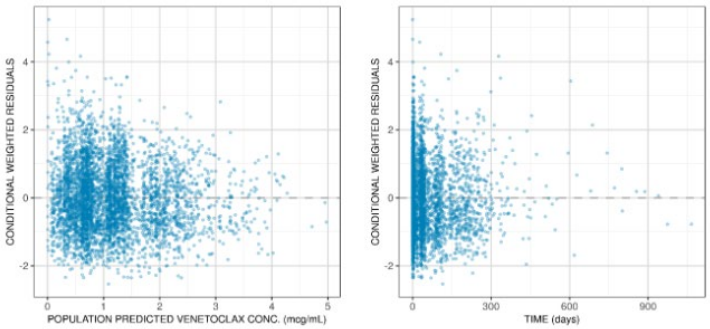
Note: Only parameter estimates relevant to the current analysis are being shown.

Figure 2. Goodness-of-Fit Plots of Final PK Model



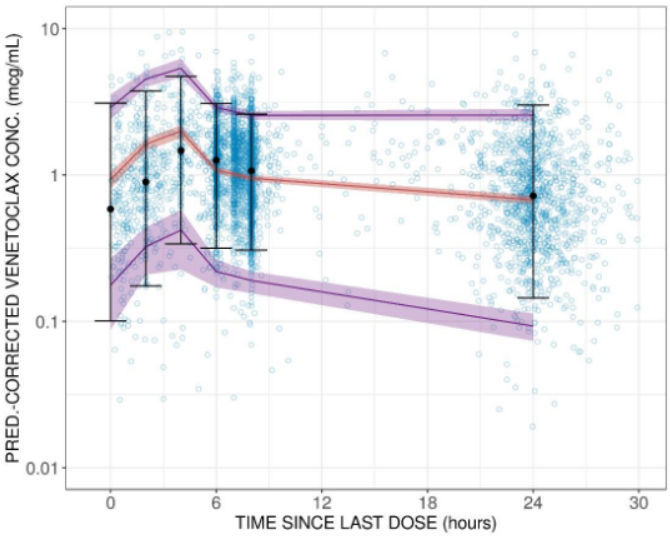
Note: Below the lower limit of quantitation (BLQ) observations not pictured. Dashed lines represent the line of unity.

Figure 3. CWRES Versus Population Predicted Concentration and Time (Final Model)



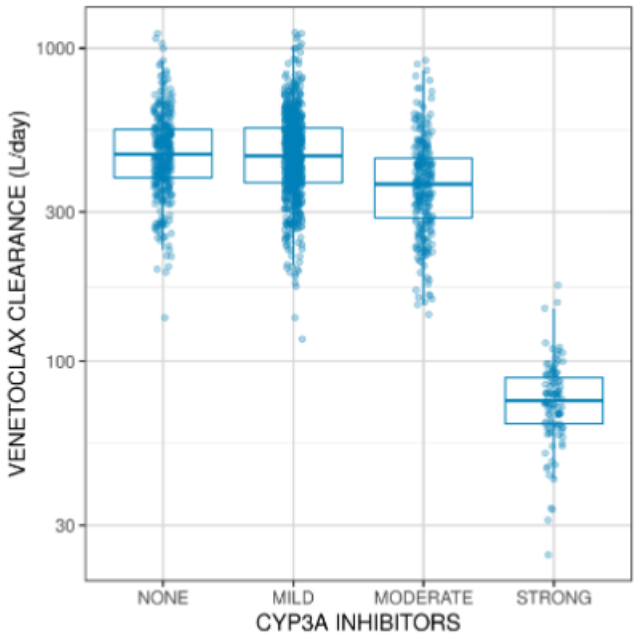
CWRES = conditional weighted residuals

Figure 4. Prediction-Corrected Visual Predictive Checks for Venetoclax Concentration Versus Time After Last Dose (Log-Linear Scale)



The shaded areas represent the prediction interval of the 5th (purple), 50th (red) and 95th (purple) percentiles of prediction corrected simulated venetoclax concentrations shown as solid line. Black points and error bars represent median and 5th and 95th percentiles for the prediction-corrected binned observed venetoclax concentrations. Blue circles represent prediction corrected observed venetoclax concentrations.

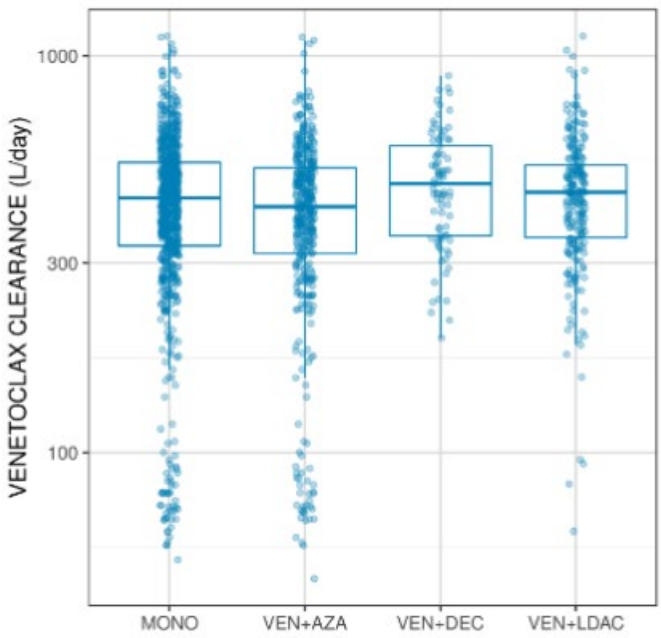
Figure 5. Boxplot of the Post Hoc CL/F by Co-administration of CYP3A Inhibitor Categories



CL/F = apparent clearance; CYP3A = cytochrome P450 3A

Note: Subjects may appear in more than one category if co-administration of CYP3A inhibitors changed during treatment.

Figure 6. Boxplot of the Post Hoc CL/F by Co-administration of AZA, DEC, and LDAC



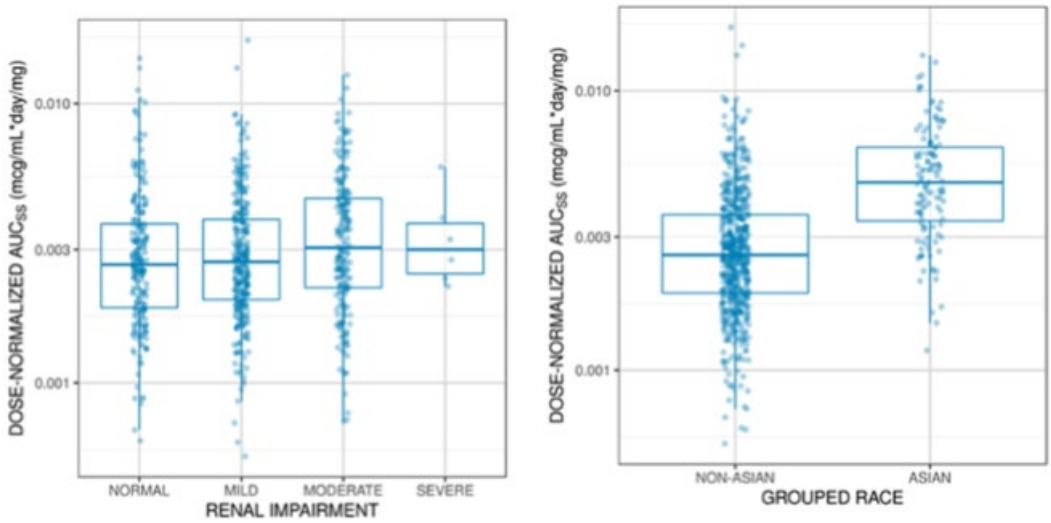
AZA = azacitidine; DEC = decitabine; CL/F = apparent clearance; LDAC = low-dose cytarabine

Note: Subjects on venetoclax in combination with AZA, DEC, or LDAC may also appear in venetoclax alone (MONO) if pharmacokinetic data were collected while on venetoclax alone.

Special populations

Covariate analysis with respect to age, race, weight, renal and hepatic impairment was conducted during the population PK analysis (see section above or Discussion on Clinical Pharmacology).

Figure 7. Boxplots of the Post Hoc Dose-Normalized AUCss by Categorical Covariates of interest



Pharmacokinetic interaction studies

Study M14-358 enrolled 12 subjects in Arm C as part of a drug-drug interaction (DDI) evaluation at a single site to assess the safety and PK of venetoclax when co-administered with posaconazole, a strong cytochrome P450 (CYP)3A inhibitor (Table 6). Azole antifungals, such as posaconazole, are widely used as prophylaxis in AML patients.

Compared to venetoclax 400 mg administered alone, co-administration of posaconazole with venetoclax 50 and 100 mg resulted in 61% and 86% higher venetoclax Cmax, respectively. The venetoclax AUC24 was 90% and 144% higher, respectively (Table 7).

Table 6. Pharmacokinetic Parameter of Venetoclax Alone and in Combination with Posaconazole – Arm C

		Mean ± Standard Deviation (Geometric Mean, %CV)				
					Dose Normalized	
Venetoclax Dose (mg)	N	T_{max}[a] (h)	C_{max} (µg/mL)	AUC_{24} (µg•h/mL)	C_{max} (ng/mL)/mg	AUC_{24} (ng•h/mL)/mg
Cycle 1 Day 20 - Venetoclax Alone						
300	1	6.0	1.67	35.4	5.57	118
400	11	8.0 (4.0 - 24.0)	2.34 ± 1.95 (1.72, 84)	38.5 ± 37.4 (26.4, 97)	5.84 ± 4.88 (4.30, 84)	96.3 ± 93.4 (66.1, 97)
All	12	--	--	--	5.82 ± 4.65 (4.39, 80)	98.1 ± 89.3 (69.4, 91)
Cycle 1 Day 28 - Venetoclax with Posaconazole						
50	5	8.0 (4.0 - 24.0)	2.78 ± 1.96 (2.32, 70)	47.2 ± 27.3 (41.9, 58)	55.6 ± 39.1 (46.4, 70)	943 ± 546 (838, 58)
100	6	7.0 (4.0 - 8.0)	3.74 ± 0.578 (3.70, 15)	76.0 ± 13.1 (75.1, 17)	37.4 ± 5.78 (37.0, 15)	760 ± 131 (751, 17)
All	11	--	--	--	45.7 ± 26.8 (41.0, 59)	843 ± 370 (789, 44)

CV = coefficient of variation

a. T_{max} presented as median (range).

Cross reference: Tables 14.2__7.1.3.1 through 14.2__7.1.4.3

Table 7. Effects of Co-Administration of Posaconazole on the Exposures of Venetoclax (Study M14-358)

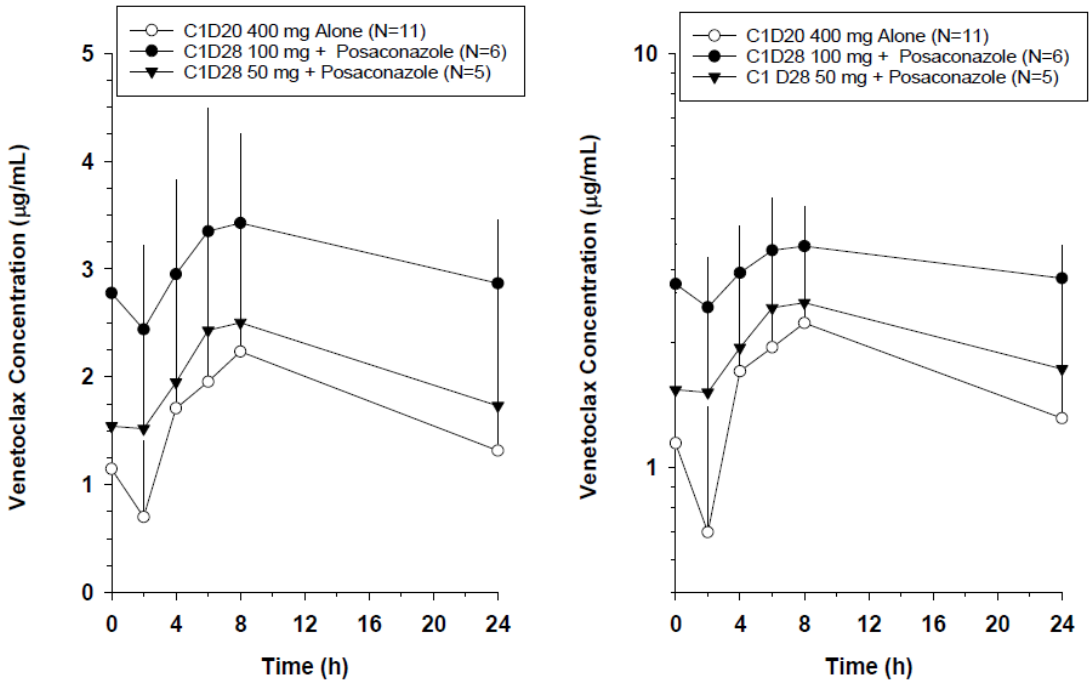
				Ratio of Central Values[a]	
Regimens Test versus Reference	Pharmacokinetic Parameter (units)	Central Value		Point Estimate	90% Confidence Interval
		Test	Reference		
Venetoclax 100 mg w/Posaconazole (Cycle 1 Day 28) versus Venetoclax 400 mg Alone (Cycle 1 Day 20)	C_{max} (µg/mL)	3.699	1.989	1.859	(1.214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

AUC_{24} = area under the plasma concentration-time curve from time 0 to 24 hours; C_{max} = maximum observed plasma concentration

a. Cycle 1 Day 28 (venetoclax w/posaconazole)/Cycle 1 Day 20 (venetoclax alone).

Source: Study M14-358 3rd Interim CSR Appendix 16.1 9.2.2.1, Appendix 16.1 9.2.2.2

Figure 8. Mean +SD Venetoclax Plasma concentration-time profiles Alone and in Combination with Posaconazole (Arm C), Linear and Log-Linear scales



2.3.3. Pharmacodynamics

2.3.4. PK/PD modelling

The objective of the PKPD modelling analysis was to evaluate the relationship between venetoclax exposures and clinical response (efficacy and safety) in subjects with AML, with separate analyses for venetoclax in combination with hypomethylating agents (HMA) (VEN + HMA) and for venetoclax in combination with low-dose cytarabine (LDAC) (VEN + LDAC), Table 8:

- To determine the relationship(s) between venetoclax exposure and best response of complete remission (CR), CR + CR with incomplete hematologic recovery (CRi), and CR + CR with partial hematologic recovery (CRh)
- To determine the relationship(s) between venetoclax exposure and overall survival (OS) and event-free survival (EFS)
- To determine the relationship(s) between venetoclax exposure and conversion to post baseline platelet transfusion independence and conversion to post baseline red blood cell (RBC) transfusion independence
- To determine the relationship(s) between venetoclax exposure and treatment-emergent adverse events (TEAEs) of Grade ≥ 3 neutropenia, Grade ≥ 3 infections, and Grade ≥ 3 thrombocytopenia

Table 8. Dose and combination treatment information for Subjects 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%)

For the exposure-efficacy and exposure-safety analyses, the predictor variable was venetoclax exposure expressed as the steady-state area under the plasma concentration-time curve (AUCss). AUCssfor each subject was calculated using the designated cohort dose as well as the individual apparent clearance (CL/F) and relative bioavailability (F1) of venetoclax estimated using the final population PK model. Data from subjects taking placebo were included in exposure-response analyses to inform the intercept (i.e., at zero concentrations of venetoclax). The relationships between venetoclax exposures and each of the response variables for efficacy or safety were evaluated graphically by quartile plots or Kaplan-Meier plots. Cox proportional hazards (CPH) and logistic regression analyses were performed using efficacy and safety data from Studies M14-358 and M15-656 (VEN/PBO + HMA) or Studies M14-387 and M16-043 (VEN/PBO + LDAC). Separate exposure-response (ER) analyses were conducted for VEN + HMA (StudiesM14-358 and M15-656) and VEN + LDAC (Studies M14-387 and M16-043). Covariate selection was performed using step-wise forward addition and backward elimination procedure with significance levels of $\alpha = 0.01$ and $\alpha = 0.001$, respectively. The covariates tested for influence on exposure-efficacy and exposure-safety relationships included the following:

- Sex (Male, Female)
- Age (18 – 64 years, 65 – 74 years, ≥ 75 years)
- Race (Asian vs. non-Asian)
- ≥ 7 consecutive days of moderate/strong CYP3A or P-gp inhibitors (Yes, No)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (0 - 1, ≥ 2)
- Subjects who received prior HMA for myelodysplastic syndrome (MDS) (Yes, No)
- Cytogenetic risk categorization (Favorable, Intermediate, Poor, Missing)
- Molecular markers (fms-like tyrosine kinase 3 (FLT3), isocitrate dehydrogenase 1/2 (IDH1/2), tumor protein p53 (TP53), nucleophosmin 1 (NPM1); Not detected, Detected, Missing)
- AML with myelodysplasia related changes (AML-MRC; Yes, No, Missing)
- AML Type (De Novo, Secondary)

Additionally, the following covariate was tested for VEN + HMA:

- Impact of individual HMAs (AZA vs. DEC)

In the exposure-safety analyses, the following covariates were also tested:

- Baseline platelet count for treatment-emergent Grade ≥ 3 thrombocytopenia

- Baseline neutrophil count for treatment- emergent Grade ≥ 3 neutropenia

Covariates were only assessed if > 50% of all subjects included in the exposure-response (ER) analyses had non-missing values.

Venetoclax in Combination with Hypomethylating Agents

A total of 575 subjects (431 subjects with VEN + HMA and 144 with PBO + HMA) were included in the exposure-efficacy and exposure-safety analyses for VEN + HMA. A total of 437 subjects (293 subjects with VEN + HMA and 144 with PBO + HMA) from the Phase 3 Study M15-656 were included in the analysis of EFS (event-free survival). A total of 156 and 310 subjects who were transfusion dependent at baseline were included in the analyses of conversion to post baseline transfusion independence for platelets and RBCs, respectively.

Exposure-efficacy (VEN+HMA)

Response rates from combination therapy (VEN + HMA) were compared to those of the PBO + HMA arm from Study M15-656 (i.e., at zero concentrations of venetoclax). Results of the logistic regression analysis are illustrated in Figure 9 for the exposure metric AUCss, showing that there is a statistically significant exposure-response relationship ($P < 0.01$) between venetoclax exposure and the probability of response of CR + CRi and CR + CRh. The parameters of the logistic regression model are presented in Table 9. Although the data for achieving CR appear to follow the same trend, the Emax model did not converge with stable parameter estimates and the linear model did not adequately capture the trend of the data. Covariate analysis identified that subjects with intermediate cytogenetic risk had a higher probability of achieving CR + CRi than those subjects with poor risk regardless of venetoclax exposures.

Table 9. Parameter Estimates of the Logistic Regression Model of Best Response for Venetoclax in Combination with HMA

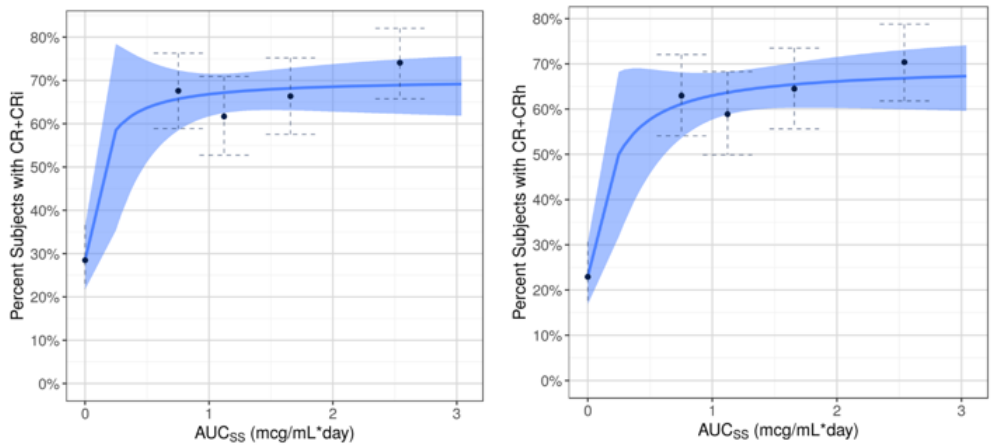
Parameter	Response	Estimate	95% Confidence Interval	P-value
α_1	CR + CRi	−1.38	−1.82, −0.934	< 0.001
$\theta_{\alpha 1,\text{intermediatecytogeneticrisk}}$	CR + CRi	0.711	0.345, 1.08	< 0.001
E_{max}	CR + CRi	1.82	1.20, 2.44	< 0.001
EC_{50} (µg/mL•day)	CR + CRi	0.0922	0.00239, 3.56	0.201
α_2	CR + CRh	−1.22	−1.61, −0.828	< 0.001
E_{max}	CR + CRh	1.39	0.803, 1.97	< 0.001
$\theta_{\text{Emax,intermediatecytogeneticrisk}}$	CR + CRh	0.835	0.377, 1.29	< 0.001
EC_{50} (µg/mL•day)	CR + CRh	0.0479	1.65×10^{-4}, 13.9	0.294

CR = complete remission; CRi = CR with incomplete hematologic recovery; CRh = CR with partial hematologic recovery

The parameters α_1 and α_2 denote the intercepts. E_{max} represents the maximal effect estimate and EC_{50} the concentration at which half the maximal effect is achieved. A negative estimate denotes less probability of response.

Cross reference: Table 12.4__4.5

Figure 9. Probability of Achieving CR + CRi and CR + CRh Versus AUCss for Venetoclax in Combination with HMA (Results from Logistic Regression Base Model)



AUC_{ss} = area under the plasma concentration-time curve at steady state; CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete blood count recovery

Shaded regions indicate the predicted 95% confidence interval (CI), and points with vertical bars indicate the observed proportions with 95% binomial CI at the observed concentration quartile.

Note: One subject with response before the first dose of study drug was excluded from the analysis.

Source: R&D/19/0625 Figure 12

A clear trend for increased survival in subjects taking venetoclax was observed compared to those taking placebo, but within the venetoclax exposure quartiles, no clear exposure-response trend was observed. Results from the CPH model identified statistically significant (P < 0.01) exposure-response relationships between higher venetoclax exposures and better survival outcomes for OS and EFS (Table 10).

Table 10. Parameter Estimates of the Cox Proportional Hazards Models for Venetoclax in Combination with HMA

Model	Predictor	Hazard Ratio[a] (95% CI)	P-value
Overall Survival	AUC_{ss} (µg/mL•day)	0.828 (0.741, 0.936)	< 0.001
	Intermediate Cytogenetic Risk[b]	0.559 (0.449, 0.696)	< 0.001
	TP53 mutations	2.10 (1.55, 2.85)	< 0.001
Event-Free Survival	AUCss (µg/mL•day)	0.803 (0.710, 0.907)	< 0.001
	Intermediate Cytogenetic Risk[b]	0.522 (0.416, 0.653)	< 0.001

AUC_{SS} = area under the plasma concentration-time curve at steady state; TP53 = Tumor protein p53; CI = confidence interval

a. Hazard ratio presented here represents the exponential of the estimated slope from the CPH model, or the hazard ratio when the predictor variable = 1.

b. Reference = poor cytogenetic risk.

Cross reference: Table 12.4__6.4

A trend for higher rates of conversion to post baseline platelet and RBC transfusion independence for subjects on VEN + HMA was observed as compared to those subjects on PBO + HMA. Both Emax and linear regression models were fit to the data, but the Emax model did not converge with stable parameter estimates and the linear model did not adequately capture the trend of the data. Analyses excluding the placebo subjects showed no significant exposure-response relationship between venetoclax exposures and probability of conversion to transfusion independence (P = 0.53 and P = 0.71 for platelets and RBCs, respectively).

Exposure-safety (VEN+HMA)

The parameters of the logistic regression model (rates of occurrence of treatment-emergent Grade≥ 3 neutropenia in combination therapy (VEN + HMA) were compared to those of the PBO + HMA arm from Study M15-656), showing a statistically significant exposure-response relationship (P < 0.01), for the analyses of treatment-emergent Grade ≥ 3 neutropenia are presented in Table 11. Covariate analysis identified that Asian subjects were more likely to have treatment-emergent Grade ≥ 3 neutropenia, including subjects taking PBO + HMA. The magnitude of venetoclax effect was however similar in Asian and non-Asian subjects. Model predicted incidence shows that subjects taking VEN + HMA had approximately 20 - 25% higher probability of treatment-emergent Grade ≥ 3 neutropenia compared to subjects taking PBO + HMA for both Asian and non-Asian subjects, further indicating that this is an effect that is not specific to venetoclax treatment

No apparent relationship between venetoclax exposure and occurrence of treatment-emergent Grade ≥ 3 infections was observed. Both Emax and linear regression models were fit to the data, but the Emax model did not converge with stable parameter estimates and the linear model did not adequately capture the trend of the data. Rates of occurrence of treatment-emergent Grade ≥ 3 infections vs Cavg quartiles also showed no apparent relationship.

No apparent relationship between venetoclax exposure and occurrence of treatment-emergent Grade ≥ 3 thrombocytopenia was observed. Both Emax and linear regression models were fit to the data, but the Emax model did not converge with stable parameter estimates and the linear model did not adequately capture the trend of the data. Rates of occurrence of treatment-emergent Grade ≥ 3 thrombocytopenia vs Cavg quartiles also showed no apparent relationship.

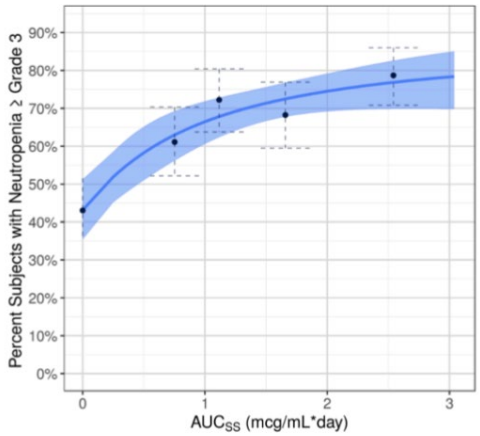
Table 11. Parameters of the Logistic Regression Models for Analyses of Neutropenia (Grade ≥ 3) for Venetoclax in Combination with HMA

Parameter	Estimate	95% Confidence Interval	P-value
α	–0.559	–0.919, –.200	< 0.01
$\theta_{\alpha,Asian}$	1.15	0.607, 1.69	< 0.001
EC_{50} (µg/mL•day)	0.420	0.0503, 3.51	0.423
E_{max}	1.39	0.591, 2.19	< 0.001
$\theta_{Emax,BaselineNeutrophils}$	0.866	0.247, 1.52	< 0.01

The parameter α denotes the intercept. E_{max} represents the maximal effect estimate and EC_{50} the concentration at which half the maximal effect is achieved. A negative estimate denotes less probability of event.

Cross reference: Table 12.4__9.3

Figure 10. Probability of Treatment-Emergent Grade 3 or Worse Neutropenia for Venetoclax in Combination with HMA (Results from Logistic Regression Base Model)



AUC_{SS} = area under the plasma concentration-time curve at steady state; CI = confidence interval; HMA = hypomethylating agent

Shaded regions indicate the predicted 95% CI and points with vertical bars indicate the observed proportions with 95% binomial CI at the observed concentration quartile

Venetoclax in Combination with Low-Dose Cytarabine

A total of 279 subjects (211 with VEN + LDAC and 68 with PBO + LDAC) were included in the exposure-efficacy and exposure-safety analyses for VEN + LDAC. A total of 210 subjects (142 subjects with VEN + LDAC and 68 subjects with PBO + LDAC) from the Phase 3 Study M16-043 were included in the analysis of EFS. A total of 96 and 205 subjects who were transfusion dependent at baseline were included in the analyses of conversion to post baseline transfusion independence for platelets and RBCs, respectively. Venetoclax target doses of 600mg and 800 mg were evaluated in this population.

Exposure-Efficacy (VEN+LDAC)

Results of the logistic regression of CR, CR+ CRi, and CR + CRh analysis are illustrated in Figure 11 for the exposure metric AUCss, showing that there is a statistically significant exposure-response relationship ($P < 0.01$) between venetoclax exposure and the probability of response. The parameters of the final logistic regression models are presented in Table 12. NPM1 mutations significantly associated with an increased probability of all responses tested (CR, CR + CRi, and CR + CRh) while TP53 mutations significantly associated with a decreased probability of response for CR + CRi and CR + CRh.

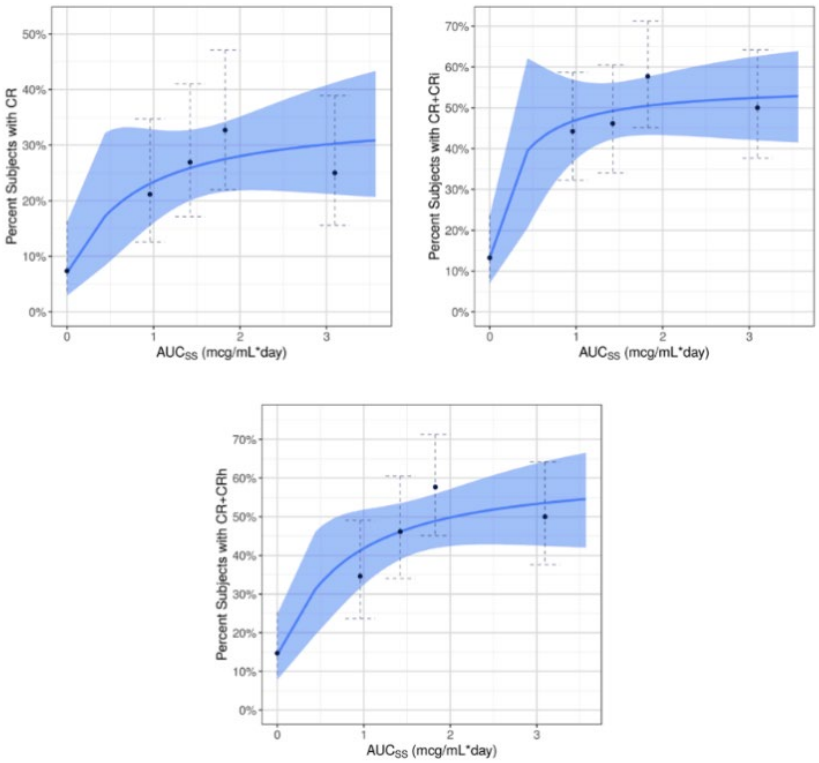
Table 12. Parameter Estimates of the Logistic Regression Model of Best Response for Venetoclax in Combination with LDAC

Parameter[a]	Response	Estimate	95% Confidence Interval	P-value
α_1	CR	−3.06	−4.08, −2.05	< 0.001
$\theta_{\alpha 1,NPM1mutation}$	CR	1.96	1.10, 2.82	< 0.001
E_{max}	CR	2.23	0.704, 3.76	< 0.01
EC_{50} (µg/mL•day)	CR	0.512	0.0429, 6.12	0.597
α_2	CR + CRi	−2.08	−2.89, −1.28	< 0.001
$\theta_{\alpha 2,NPM1mutation}$	CR + CRi	1.89	0.878, 2.91	< 0.001
$\theta_{\alpha 2,TP53mutation}$	CR + CRi	−1.60	−2.63, −0.573	< 0.01
E_{max}	CR + CRi	2.53	1.33, 3.73	< 0.001
EC_{50} (µg/mL•day)	CR + CRi	0.322	0.0368, 2.82	0.306
α_3	CR + CRh	−2.02	−2.81, −1.23	< 0.001
$\theta_{\alpha 3,NPM1mutation}$	CR + CRh	1.96	0.958, 2.95	< 0.001
$\theta_{\alpha 3,TP53mutation}$	CR + CRh	−1.82	−2.94, −0.693	< 0.01
E_{max}	CR + CRh	2.86	1.33, 4.38	< 0.001
EC_{50} (µg/mL•day)	CR + CRh	0.779	0.149, 4.08	0.767

CR = complete remission; CRi = CR with incomplete hematologic recovery; CRh = CR with partial hematologic recovery; NPM1 = Nucleophosmin 1; TP53 = tumor protein p53

a. The parameters α_1, α_2, and α_3 denote the intercepts. E_{max} represents the maximal effect estimate and EC_{50} the concentration at which half the maximal effect is achieved. A negative estimate denotes less probability of response.

Figure 11. Probability of Achieving CR, CR + CRi, and CR + CRhVersus AUCss for Venetoclax in Combination with LDAC (Results from Logistic Regression Base Model)



AUC_{SS} = area under the plasma concentration-time curve at steady state; CI = confidence interval; CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete hematologic recovery; LDAC = low-dose cytarabine

Shaded regions indicate the predicted 95% CI and points with vertical bars indicate the observed proportions with 95% binomial CI at the observed concentration quartile median.

Note: Three subjects with response before first dose of study drug excluded from analysis.

The CPH model to assess relationship between exposure and survival showed a trend for better survival outcomes in VEN + LDAC (P = 0.02 for both OS and EFS), although no significant exposure-response relationship was identified. Covariate analysis identified TP53 mutations as a negative predictor of both survival outcomes (OS and EFS) and that subjects with ECOG scores ≥ 2 had worse OS.

Table 13. Parameter Estimates of the Cox Proportional Hazards Models for Venetoclax in Combination with LDAC

Model	Predictor	Hazard Ratio[a] (95% CI)	P-value
Overall Survival	AUC_{ss} (µg/mL•day)	0.868 (0.770, 0.979)	< 0.05
	TP53 mutations	4.01 (2.68, 6.01)	< 0.001
	ECOG score ≥ 2	1.68 (1.27, 2.22)	< 0.001
Event-Free Survival	AUC_{ss} (µg/mL•day)	0.857 (0.752, 0.978)	< 0.05
	TP53 mutations	2.77 (1.82, 4.22)	< 0.001

AUC_{ss} = area under the plasma concentration-time curve at steady state; CI = confidence interval; TP53 = tumor protein p53; ECOG = Eastern Cooperative Oncology Group

a. Hazard ratio presented here represents the exponential of the estimated slope from the CPH model, or the hazard ratio when the predictor variable = 1.

Rates of conversion to post baseline transfusion independence in combination therapy (VEN + LDAC) were compared to rates in subjects receiving PBO + LDAC in Study M16-043. Both Emax and linear regression models were fit to the data, but the Emax model did not converge with stable parameter estimates and the linear model did not adequately capture the trend of the data for rate of conversion to RBC transfusion independence. An Emax logistic regression model best described the data for rate of conversion to platelet transfusion independence, and although there was a trend for higher probability of conversion in VEN + LDAC, there was no significant exposure-response relationship identified. Additionally, this analysis indicated that subjects with NPM1 mutations had higher probability of achieving conversion to platelet transfusion independence than those without NPM1 mutations. For both parameters, there was no significant exposure-response relationship when tested without subjects in the placebo group.

Exposure-Safety (VEN+LDAC)

No apparent relationship between venetoclax exposures and occurrence of treatment-emergent Grade ≥ 3 neutropenia was observed, although subjects taking VEN + LDAC had higher rates on average than subjects taking PBO + LDAC. Both Emax and linear regression models were fit to the data, but the Emax model did not converge with stable parameter estimates and the linear model did not adequately capture the trend of the data.

No apparent relationship between venetoclax exposures and occurrence of treatment-emergent Grade ≥ 3 infections was observed. A logistic regression model using AUCss as exposure metric was fit to the data and indicated no statistically significant exposure-response relationship.

No apparent relationship between venetoclax exposures and occurrence of treatment-emergent Grade ≥ 3 thrombocytopenia was observed. A logistic regression model using AUCss as exposure metric was fit to the data and indicated no statistically significant exposure-response relationship (Table 14).

Table 14. Parameters of the Logistic Regression Models for Analyses of Thrombocytopenia (Grade ≥ 3) for Venetoclax in Combination with LDAC

Parameter	Estimate	95% Confidence Interval	P-value
α	−0.186	−0.563, 0.191	0.333
$\theta_{\alpha,BaselinePlatelets}$	0.0097	0.00466, 0.0147	< 0.001
β	0.0173	−0.176, 0.211	0.861

LDAC = low-dose cytarabine

The parameters α, and β denote the intercept and the slope of the exposure metric AUC_{ss}, respectively. A positive estimate denotes higher probability of the adverse event.

2.3.5. Discussion on clinical pharmacology

The bioanalysis method for Venetoclax at AbbVie were not changed since the original application and have not been reassessed. In studies M15-656 and M16-043, bioanalysis of Venetoclax for subjects enrolled in China was performed at CRO WuXi (Shanghai, China) according to validation report 17BAS0234. A cross-validation was performed which showed that the results from the two methods were comparable (AbbVie/WuXi Report R&D/18/0140).

The pharmacokinetic data were analysed using population pharmacokinetic (popPK) modelling approach. The objectives were to evaluate whether a previously developed popPK model is able to describe venetoclax PK in AML subjects and to evaluate the relationship between venetoclax exposures and clinical response (efficacy and safety) in subjects with AML, with separate analyses for venetoclax in combination with hypomethylating agents (HMA) (VEN + HMA) and for venetoclax in combination with low-dose cytarabine (LDAC) (VEN + LDAC). In addition, the applicant conducted a drug-drug interaction (DDI) substudy in 12 subjects who were given venetoclax with and without posaconazole, to assess the interaction.

The approach to use the previously developed model, with previously estimated parameters as priors is considered acceptable. The plot of dose normalized observed concentration indicate that the exposure is similar in the AML population compared to other populations (CLL, SLL and NHL). It seems that the pcVPC indicates model misspecification in the absorption phase and that the model does not capture Cmax. A similar model misspecification was observed in the original application as well; this issue is not further pursued, and the model is in this applicant considered adequate for its purpose as the elimination phase appears to be sufficiently well captured. It is recommended that the model should not be used for simulation in the future without correction of the misspecification.

The popPK model could well describe the individual concentration profiles of the 5 subjects with severe renal impairment with PK data available, supporting that there is no greater differences in exposure in subjects with severe renal impairment as compared to subjects with normal, mild and moderate renal impairment/function. This support the claims in 4.2 and 5.2 in the SmPC that no dose adjustment is needed in patients with severe (CrCl ≥15 ml/min and <90 ml/min) renal impairment.

The covariate **"**Asian" was identified as significant on the parameter 'relative bioavailability' with this dataset. The applicant provided data that indicated a little to no additional risk of treatment-emergent AEs (TEAEs) at higher exposures of venetoclax in the dose range studied. Since the individual exposure in Asian subjects are within the same range as non-Asian subjects, and that there seems not to be any significantly increased risk of TEAEs at higher exposure, no dose adjustment in Asian subjects is needed.

The results from the DDI study of venetoclax alone (400 mg) compared to a dose of 100 mg venetoclax+posaconazole results in an, on average, 2.4-fold higher AUC24. A dose of 50 mg venetoclax results in an, on average, 1.9-fold higher AUC24 compared with 400 mg venetoclax given alone.

The proposed venetoclax dose reduction to 100 mg or less for all strong CYP3A inhibitors corresponds to a dose reduction of 75% for the 400 mg venetoclax dose in combination with azacitidine or decitabine, or 83.3% for the 600 mg venetoclax dose in combination with LDAC. This is consistent with the approved dose reduction for the CLL indication, where the dose is reduced by at least 75% of the original dose. This is also in the line with the results from the popPK analysis, which showed that strong CYP3A inhibitors decreased venetoclax apparent clearance by 82.5%.

To further support the proposed dosing regimen of venetoclax in combination with a CYP3A inhibitor, the applicant provided concentration data from 53 subjects from studies M14-358, M14-387, M15-656, and M16-043 during co-administration with posaconazole at venetoclax doses ranging from 10 to 600 mg. During ramp-up in which subjects received mostly up to 50 mg venetoclax in combination with the strong CYP3A4 inhibitor, venetoclax concentrations were in the range of subjects receiving no or a mild CYP3A4 inhibitor. During steady state, in which subjects received mostly 50-100 mg venetocloax in combination with the strong CYP3A4 inhibitor, venetoclax concentrations were in the range of subjects receiving no or a mild CYP3A4 inhibitor. Furthermore, patients experiencing persistent drug-related adverse events, such as neutropenia, infections, or thrombocytopenia can have further venetoclax dose modifications. In summary, the data provided support the proposed dosing regimens during ramp-up and at steady state during co-administration with a CYP3A inhibitor. These recommendations (dose reductions and monitoring) are adequately reflected in the SmPC (see sections 4.2 and 4.5).

It is noted that strong CYP3A inhibitors are contraindicated (see SmPC section 4.3) during the titration phase in the CLL indication, but not in the proposed AML indication, which is considered acceptable as the indications and risk of side effects differ. In all patients, if a CYP3A inhibitor must be used, follow the recommendations for managing drug-drug interactions (see SmPC section 4.2).

The exposure-response analysis was done separately for the venetoclax arm with different combination treatment (VEN+HMA or VEN+LDAC). The majority of subjects in the VEN+HMA treatment received 400 mg (66%, n=379) venetoclax, while 25% (n=144) received placebo and only 8% (n=45) and 1% (n=7) received 800 mg and 1200 mg respectively. In the VEN+LDAC analysis 73% (n=203) received 600 mg venetoclax, 25% (n=68) received placebo and 3% (n=8) received venetoclax 800 mg. No subject received 1200 mg in that combination treatment group. The consequence and limitation of this is that very few subjects are informing the exposure response at higher doses than the proposed.

Exposure-response VEN+HMA

The logistic regression analysis results for AUCss showed that there is a statistically significant exposure-response relationship ($P < 0.01$) between venetoclax exposure and the probability of response of CR + CRi and CR + CRh, however, the Emax model for CR did not converge with stable parameter estimates. The EC50 CI is wide in both models. The results need to be interpreted with caution. There is an indication towards a flat exposure-response relationship. The typical exposure range with a dose of 400 mg VEN+HMA was not marked in the plots, and the distribution of subjects across the exposure range is unclear; the models for conversion to post baseline platelet and RBC transfusion independence did not converge..

For all efficacy variables evaluated, venetoclax AUCss quartile plots showed a clear trend of higher efficacy with VEN + HMA than PBO + AZA. Within subjects receiving VEN + HMA, there were no apparent exposure-response relationships. Model-based analyses, excluding the PBO + AZA data, confirmed this lack of significant exposure-response relationships in the dose range studied (400 to 1200 mg).

There is a statistically significant relationship between neutropenia in combination therapy (VEN + HMA) compared the PBO + HMA arm from study M15-656. Covariate analysis identified that Asian subjects in general were more likely to have treatment-emergent Grade $\geq$ 3 neutropenia. The magnitude of

venetoclax effect was however similar in Asian and non-Asian subjects. No apparent relationship between venetoclax exposure and occurrence of treatment-emergent Grade ≥ 3 infections or treatment-emergent Grade ≥ 3 thrombocytopenia was observed.

Exposure-response VEN+LDAC

Results of the logistic regression of CR, CR+ CRi, and CR + CRh analysis versus the exposure metric AUCss, showed that there is a statistically significant exposure-response relationship ($P < 0.01$) between venetoclax exposure and the probability of response. Few subjects given a dose other than 600 mg were included in the analysis, which limits the conclusions that can be made. NPM1 mutations were found to be significantly associated with an increased probability of all responses tested (CR, CR + CRi, and CR + CRh) while TP53 mutations were found to be significantly associated with a decreased probability of response for CR + CRi and CR + CRh. The confidence interval of both EC50 and Emax are wide. The typical exposure range with a dose of 600 mg VEN+LDAC was not marked in the plots, and the distribution of subjects across the exposure range is unclear. Rates of conversion to post baseline transfusion independence in combination therapy (VEN + LDAC) were best described with an Emax logistic regression model however, although there was a trend for higher probability of conversion in VEN + LDAC, there are limitation to the analysis and no significant exposure-response relationship identified.

No apparent relationship between venetoclax exposures and occurrence of treatment-emergent Grade ≥ 3 neutropenia, infections or thrombocytopenia was observed; however, close monitoring of blood counts is recommended throughout the treatment (see also discussion of Clinical Safety and SmPC section 4.4.).

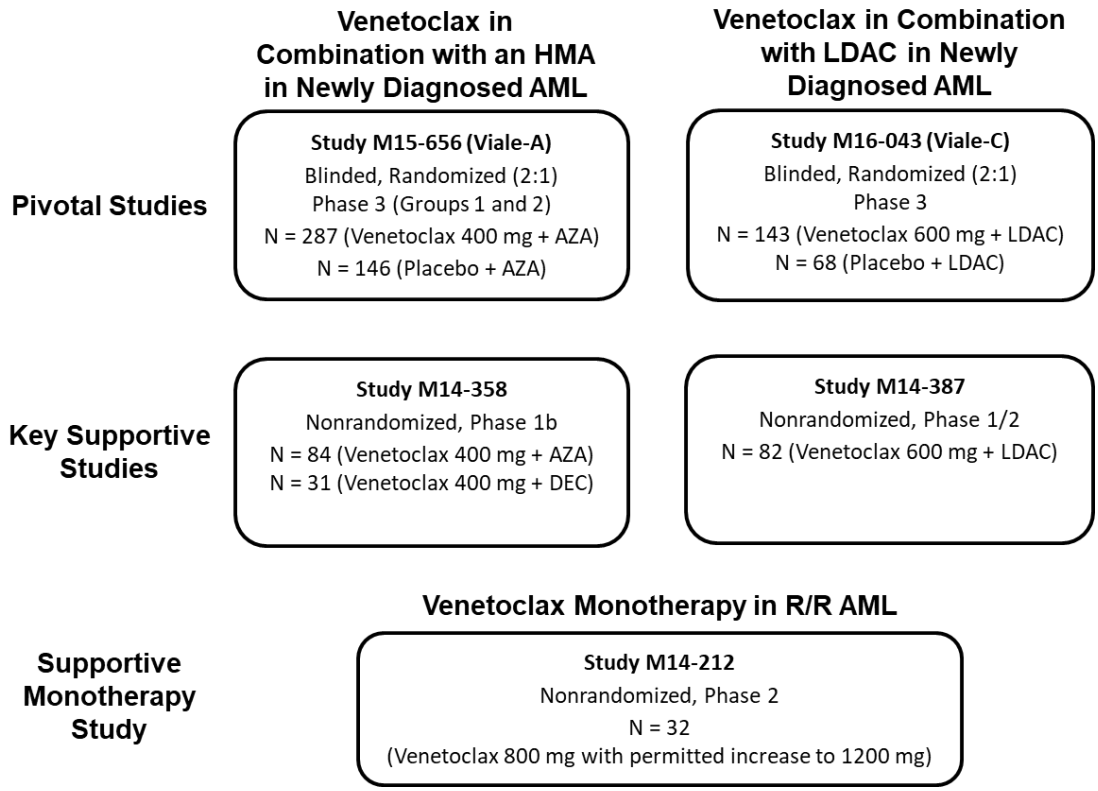
Evaluation of BCL2 expression is still ongoing and the Applicant is encouraged to submit these data when available.

2.3.6. Conclusions on clinical pharmacology

Clinical pharmacology data of venetoclax in the AML population was adequate and support relevant recommendations in the SmPC regarding special populations and drug-drug interaction with strong CYP3A inhibitors.

2.4. Clinical efficacy

The current marketing application includes the following phase 1 to phase 3 studies for newly-diagnosed AML patients ineligible for intensive chemotherapy:



With the exception of M14-212 (completed), all studies are ongoing at the time of the application.

2.4.1. Dose response studies

Studies M14-358 and M14-387 in relation with the pivotal studies M15-656 and M16-043, respectively provided information on dose – response.

2.4.2. Main studies

Study M15-656

A randomized, double-blind, placebo-controlled phase 3 study of venetoclax in combination with azacitidine versus azacitidine in treatment naïve subjects with acute myeloid leukemia who are ineligible for standard induction therapy.

First subject first visit: February 2017.

Study participants

Treatment-naïve subjects with AML ≥ 18 years of age and not eligible for standard induction therapy due to age or comorbidities were eligible for this study. Subjects must have received no prior treatment for AML, with the exception of hydroxyurea. Subjects must have ECOG of 0 to 2 (if ≥75 years of age) or 0 to 3 if (≥ 18 to 74 years of age), adequate renal function, and adequate liver function. Patients with previous HMA therapy or chemotherapy for MDS were excluded, as well as those with favourable cytogenetic risk.

Treatments

Subjects were randomized to one of the two treatment arms in a 2:1 ratio, both of which had treatment cycles of 28 days:

- Ven + Aza: Venetoclax 400 mg orally once a day (QD) on Days 1 – 28 plus azacitidine 75 mg/m^2 sc or iv (per local label) QD for 7 days
- Placebo + Aza: Placebo orally QD on Days 1 – 28 plus azacitidine 75 mg/m^2 sc or iv (per local label) QD for 7 days

Venetoclax or placebo was administered with a 3-day ramp up beginning with 100 mg dose on day 1 to reach the final dose of 400 mg venetoclax on day 3 of cycle 1. Venetoclax was to be continued at 400 mg daily thereafter. Subjects were to receive azacitidine for 7days of each cycle, beginning on day 1 of each cycle. Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a complete remission or a complete remission with incomplete hematologic recovery. Patients continued to receive treatment until disease progression or unacceptable toxic effects, until they withdrew consent, or until they met any protocol-defined criteria.

Except for patients who withdrew consent, all patients who discontinued a trial regimen were followed for survival.

Survival information and post-treatment follow-up (i.e., the date and cause of death, all post treatment cancer therapies including stem cell transplantation, regimens, dates of initiation and completion, etc.) were to be collected every 2 months after the last study visit for a period of approximately 2 years after the last subject had been enrolled into the study.

Outcomes/endpoints

Primary endpoint: OS AND composite complete remission rate (CR+CRi). For US, the primary endpoint was OS.

Secondary endpoints:

- Rate of CR
- Rate of CR and CRh
- Proportion of patients achieving composite complete remission (CR or CRi) by initiation of cycle 2
- DOR
- Transfusion independence rate
- MRD response rate
- Fatigue improvement and PRO assessments
- EFS

Exploratory endpoints:

- Biomarkers predictive of venetoclax activity and DOR

Response criteria definition

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.
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.
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 subjects surviving at least 7 days following completion of Cycle 1 treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.
MR:	Reappearance of ≥ 5% blasts after CR/CRi in peripheral blood or bone marrow or development of extramedullary disease.
PD:*	• 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 (WBC × % blasts) to > 25 × 10^9/L (> 25,000/µL); or • New extramedullary disease

ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; MLFS = morphologic leukemia-free state; MR = morphologic relapse; PD = progressive disease; PR = partial remission; RBC = red blood cell; RD = resistant disease; WBC = white blood cell

* PD is defined by ELN criteria.[17]

In addition, each subject was evaluated for transfusion independence based on the red blood cell (RBC) and platelet transfusion requirements, as well as 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.

* Subject must have platelet transfusion independence for ≥ 7 days prior to the hematology lab results.

Stratification factors: age, region and cytogenetics.

Randomisation

Study participants were randomised 2:1 in the Ven : Aza arms respectively.

Blinding

This was a double-blind study.

Sample size

The study includes dual-primary endpoints of CR + CRi rate and OS. The sample size calculation is based on the following assumptions:

- The significance level (two-sided 0.05) is split to give a 0.01 significance level to the CR + CRi rate analysis and a 0.04 significance level to the OS analysis
- CR + CRi rate of 28% for placebo + Aza arm
- CR + CRi rate of 55% for Ven + Aza arm
- Median OS of 10.4 months for placebo + Aza arm
- Median OS of 14.9 months for Ven + Aza arm (HR of 0.7)
- Interim analysis of OS at 75% of death events with O'Brien-Fleming (OBF) boundary; the interim data cutoff date for this analysis is determined when the 270th subject death is observed
- 2:1 randomization ratio to Ven + Aza and placebo + Aza arms

With the above assumptions, a total of 225 subjects (150 subjects in the Ven + Aza arm and 75 subjects in the placebo + Aza arm) provides 88% power to detect statistically significant differences in the CR + CRi rate between treatment arms at two-sided alpha levels of 0.01; a total of 360 death events will provide 86.7% power to detect statistically significant difference in OS between treatment arms at two-sided alpha level of 0.04.

Statistical methods

The primary analysis for CR + CRi was to occur 6 months after the first 225 subjects were randomized. A significance level of 0.01 out of 0.05 (two-sided) was to be allocated for this analysis.

There were 3 planned analyses for the primary endpoint of OS.

1. IA1: at the same time as the primary CR + CRi analysis. An administrative spending of 0.0001 (one-sided) significance level were allocated to this analysis)
2. IA2: at the time of approximately 270 OS events (75% of the total 360 events). (March 2020).
3. Final analysis at the time of approximately 360 OS events.

Analysis sets

Efficacy analyses were performed on the Efficacy Analysis Set (also called Full Analysis Set), defined as all randomized subjects in Group 2. This group consisted of subjects randomized under Protocol Amendment 1 and later versions. The safety analyses were performed on the Safety Analysis Set, defined as all subjects who received at least 1 dose of study drug (venetoclax or placebo, in combination with azacitidine).

Statistical method

All efficacy analyses were analyzed by treatment arm and strata assigned at time of randomization, based on IVRS/IWRS, age (18 to < 75, ≥ 75) and cytogenetic risk (intermediate, poor). For the primary OS

endpoint, the stratified log-rank test was used for the comparison of OS distributions between two arms. In addition, the stratified hazard ratio (HR) and corresponding 95% confidence interval (CI) were estimated from stratified Cox proportional hazard model. The CR + Cri rate and secondary endpoints were compared between two arms using stratified Cochran-Mantel-Haenszel (CMH) test.

Intercurrent events - OS censoring

If a subject has not died, then the data was censored at the date the subject was last known to be alive on or before the cutoff date. The date of the last known alive was determined by selecting the last available date of the following study procedures for a subject: adverse event start date, bone marrow collection, disease assessment, vital signs assessment, clinical laboratory collection, study drug administration, concomitant medicine start date, biospecimen sample collection, transfusion, survival follow-up, quality of life assessments, and performance status.

Alternative censoring rules applied as a sensitivity analysis were censoring OS and DoR at the start of post-study treatment (e.g., intensive chemotherapy) if occurred prior to an event.

Multiplicity

The alpha split, recycling, Lan DeMets alpha spending function and hierarchical testing strategies were used to control the familywise error rate (FWER) at interim and final analyses. For 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 overall survival to ensure the control of the FWER. If statistical test is significant for CR + CRi rate, the significance level 0.01 allocated to CR + CRi rate analysis is recycled to overall survival analysis.

If statistical test is significant for the primary efficacy endpoint of OS, then the fixed sequence testing procedure was performed with a significance level of 0.05 for key secondary efficacy endpoints sequentially. If statistical test is not significant for the primary efficacy endpoint of OS, then statistical significance cannot be declared for any of the secondary efficacy endpoints. The hierarchical ranking and alpha spending for each primary and key secondary endpoint at IA1, IA2 and FA is presented below.

Table 15 ***Alpha-spending boundary (one-sided p-value) for each ranked endpoint for EU and EU reference countries.***

<table>
<tr><td colspan="2" rowspan="2">Endpoint</td><td colspan="3">Timing of Analysis</td></tr>
<tr><td>IA1</td><td>IA2</td><td>FA</td></tr>
<tr><td>1</td><td>CR + CRi rate</td><td>0.005</td><td>No test</td><td>No test</td></tr>
<tr><td>1</td><td>OS</td><td>0.0001</td><td colspan="2">0.02 allocated at start for OS, actual boundary depends on possible recycling and information fraction (IF)</td></tr>
<tr><td>2</td><td>CR + CRi rate by the initiation of Cycle 2</td><td>No test</td><td rowspan="5">Calculated with IF if OS and higher ranked EP declared significant</td><td rowspan="5">Calculated with IF if OS and higher ranked EP declared significant</td></tr>
<tr><td>3</td><td>Post-baseline RBC transfusion independence</td><td>No test</td></tr>
<tr><td>4</td><td>CR + CRi rate in IDH1/2 subgroup</td><td>No test</td></tr>
<tr><td>5</td><td>CR rate</td><td>No test</td></tr>
<tr><td>6</td><td>CR + CRi rate in FLT3 subgroup</td><td>No test</td></tr>
</table>

7	Post-baseline platelet transfusion independence	No test		
8	EFS	No test		
9	CR + CRi MRD response rate	No test		
10	OS in IDH1/2 subgroup	No test	0.0001	0.025 if CR + CRi is rejected; 0.02 otherwise
11	OS in FLT3 subgroup	No test	0.0001	0.025 if CR + CRi is rejected; 0.02 otherwise
12	EORTC QLQ-C30 GHS/QoL	No test	0.0001	0.025 if CR + CRi is rejected; 0.02 otherwise
13	PROMIS Cancer Fatigue SF 7a	No test	0.0001	0.025 if CR + CRi is rejected; 0.02 otherwise

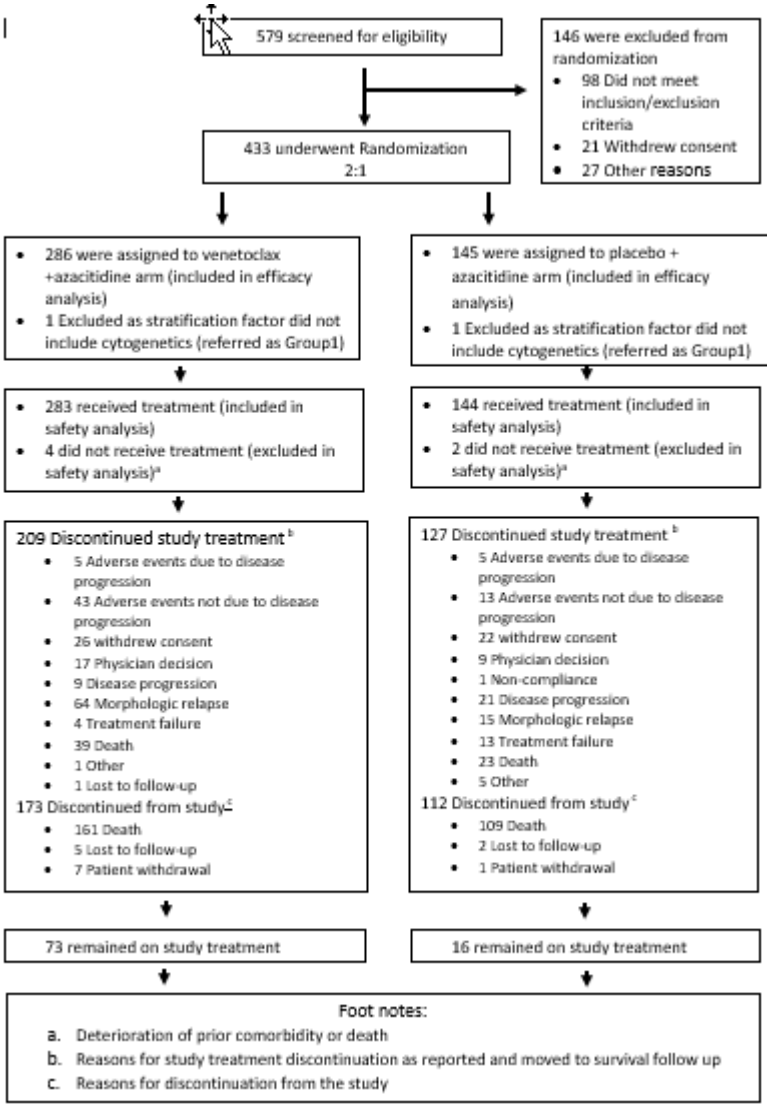
Efficacy Subgroup Analyses

To evaluate the impact of demographic and baseline characteristics on efficacy, subgroup analyses will be performed for CR rate, CR + CRi rate, CR + CRh rate, CR + CRi rate by the initiation of Cycle 2, CR + CRh rate by the initiation of Cycle 2, and overall survival for the full analysis set. The subgroups defined below, not limited to, will be used for these analyses:

- Gender (Male, Female)
- Age (18 - < 65 years, 65 - < 75 years, ≥ 75 years)
- Region (US, EU, China, JP, Asian, ROW)
- Baseline ECOG (Grade < 2, ≥ 2)
- Type of AML (De Novo, Secondary and therapy-related AML)
- Cytogenetic risk (Intermediate, Poor)
- Molecular marker by central lab (FLT3, IDH1/2, TP53, NPM1)
- Antecedent hematologic history of MDS (Yes, No)
- AML with Myelodysplasia related changes (AML-MRC)
- Post-study treatment (Yes, No).

Results

Participant flow



Conduct of the study

IA1 data cutoff date: 01 October 2018; IA2 data cutoff date: 04 January 2020

The IDMC recommended that the study be unblinded on 16 March 2020, based on the data at IA2 and guided by the prespecified OBF boundary.

Amendments to the original protocol

- Amendment 1 (December 2016; 2 subjects globally) NOTE: these two patients are denominated Group 1 by Abbvie; all consecutive patients are Group 2, with cytogenetics added to age and region as a stratification factor): to lower the age limit for study eligibility and enrol AML subjects ≥ 18 years of age who are ineligible for standard induction therapies due to comorbidities instead of ≥ 60 years of age.
- Amendment 2 (February 2017; 47 subjects globally): to clarify the definitions for PD and EFS. To support venetoclax dose reductions during the ramp-up when co-administered with strong cytochrome P450 3A (CYP3A) inhibitors exposure-response analysis from a Phase 1b study of venetoclax with HMAs (Study M14-358) was included. Subject stratification groups were updated

to include cytogenetic risk to evaluate the differences in biology of disease in younger AML patients.

- Amendment 3 (May 2017; 295 subjects globally): in response to a request during Voluntary Harmonisation Procedure to clarify that sponsor approval is not necessary for the investigator prior to unblinding a subject and to provide additional clarification of subjects with or without a BCR-ABL mutation within the eligibility criteria of the study.
- Amendment 4 (March 2018; 48 subjects globally): 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.
- Amendment 5 (August 2018; 30 subjects globally): 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 and US reference countries. 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 thresholds of $< 10^{-3}$), CRh, transfusion independence, and molecular markers.
- Amendment 6 (May 2019; 0 subjects globally): to update the total number of OS events (as enrolment in 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 subjects.
- Amendment 7 (August 2019; 0 subjects globally): 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.

Amendments to SAP

Several amendments to the SAP were performed to reflect the updates to the study protocol. SAP version 4 change the rationale for sample size and increased the power of the study.

- SAP version 4, dated 30 May 2019: described the full efficacy and safety statistical analyses for Protocol Amendment 6, dated 15 May 2019. 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%). This proposed change in OS events was discussed with the FDA via teleconference meeting on 10 May 2019 with their agreement. In addition, confirmed and un-confirmed PD were added. Unconfirmed PD was defined as a PD followed by non-PD/Non-MR prior to post-treatment therapy.

Protocol deviations

- Subject entered study and did not satisfy eligibility criteria: 8 in 8 subjects.
- Subject received wrong treatment or incorrect dose: 127 in 99 subjects.
- Subject received excluded concomitant medications: 9 in 9 subjects.
- Protocol Compliance – Study Procedures: 79 in 79 subjects.
- Protocol Compliance – Subject Dosing Compliance: 14 in 10 subjects
- Investigational Product (IP) – Dispensation/Administration: 9 in 8 subjects.

Baseline data

Demographics: predominantly male (259 subjects [60.1%]) and White (326 subjects [75.6%]). The median age was 76 years (range: 49 to 91 years). The majority of subjects (60.6%) were ≥ 75 years of age.

Table 16 Summary of baseline characteristics

Variable	Pbo + Aza (N = 145)	Ven 400 mg QD + Aza (N = 286)	Total (N = 431)
ECOG performance status - n (%)			
0	23 (15.9)	37 (12.9)	60 (13.9)
1	58 (40.0)	120 (42.0)	178 (41.3)
2	59 (40.7)	113 (39.5)	172 (39.9)
3	5 (3.4)	16 (5.6)	21 (4.9)
Cytogenetics (reported from EDC) - n (%)			
Intermediate	89 (61.4)	182 (63.6)	271 (62.9)
Poor	56 (38.6)	104 (36.4)	160 (37.1)
Cytogenetics (reported from IVRS/IWRS) - n (%)			
Intermediate	92 (63.4)	186 (65.0)	278 (64.5)
Poor	53 (36.6)	100 (35.0)	153 (35.5)
Bone marrow blast count - n (%)			
< 30%	41 (28.3)	85 (29.7)	126 (29.2)
≥ 30% to < 50%	33 (22.8)	61 (21.3)	94 (21.8)
≥ 50%	71 (49.0)	140 (49.0)	211 (49.0)
Bone marrow blast count (%)			
n	145	286	431
Mean (SD)	50.4 (24.12)	49.6 (24.41)	49.8 (24.29)
Median	47.0	47.0	47.0
Min, Max	11.0, 99.0	4.4, 100.0	4.4, 100.0
CTC grade of neutropenia - n (%)			
0	29 (20.1)	53 (18.5)	82 (19.1)
1	11 (7.6)	7 (2.4)	18 (4.2)
2	14 (9.7)	20 (7.0)	34 (7.9)
3	30 (20.8)	48 (16.8)	78 (18.1)
4	60 (41.7)	158 (55.2)	218 (50.7)
Missing[a]	1	0	1
CTC grade of anemia - n (%)			
0	2 (1.4)	2 (0.7)	4 (0.9)
1	17 (11.7)	39 (13.6)	56 (13.0)
2	74 (51.0)	157 (54.9)	231 (53.6)
3	52 (35.9)	88 (30.8)	140 (32.5)
4	0	0	0
CTC grade of thrombocytopenia - n (%)			
0	19 (13.1)	36 (12.6)	55 (12.8)
1	28 (19.3)	61 (21.3)	89 (20.6)
2	25 (17.2)	44 (15.4)	69 (16.0)
3	42 (29.0)	78 (27.3)	120 (27.8)
4	31 (21.4)	67 (23.4)	98 (22.7)
Type of AML - n (%)			
De Novo AML	110 (75.9)	214 (74.8)	324 (75.2)
Secondary AML	35 (24.1)	72 (25.2)	107 (24.8)
Type of secondary AML (reported from EDC) - n (%)			
Therapy-related AML	9 (25.7)	26 (36.1)	35 (32.7)
Post MDS/CMML	26 (74.3)	46 (63.9)	72 (67.3)
AML-MRC - n (%)			
Yes	49 (33.8)	92 (32.2)	141 (32.7)
No	96 (66.2)	194 (67.8)	290 (67.3)

IDH1 or IDH2 mutation from CDx - n (%)[d]			
IDH1	11 (8.7)	23 (9.4)	34 (9.1)
IDH2	18 (14.2)	40 (16.3)	58 (15.6)
Subtotal (IDH1 or IDH2)[e]	28 (22.0)	61 (24.9)	89 (23.9)
No Mutation Detected	99 (78.0)	184 (75.1)	283 (76.1)
Undetermined	0	5	5
Missing	18	36	54
FLT3 mutation from CDx - n (%)[d]			
ITD	13 (12.0)	23 (11.2)	36 (11.5)
TKD	10 (9.3)	7 (3.4)	17 (5.4)
ITD and/or TKD[f]	22 (20.4)	29 (14.1)	51 (16.2)
Not Detected	86 (79.6)	177 (85.9)	263 (83.8)
Undetermined	19	42	61
Missing	18	38	56
FLT3-ITD allelic ratio - n (%)			
≥ 0.5	5 (38.5)	8 (34.8)	13 (36.1)
< 0.5	8 (61.5)	15 (65.2)	23 (63.9)
NPM1 mutation from MyAML - n (%)[d]			
Detected	17 (19.8)	27 (16.6)	44 (17.7)
Not Detected	69 (80.2)	136 (83.4)	205 (82.3)
Undetermined	41	85	126
Missing	18	38	56
TP53 mutation from MyAML - n (%)[d]			
Detected	14 (16.3)	38 (23.3)	52 (20.9)
Not Detected	72 (83.7)	125 (76.7)	197 (79.1)
Undetermined	41	85	126
Missing	18	38	56
Baseline hepatic impairment - n (%)			
Yes	40 (28.0)	60 (21.0)	100 (23.3)
No	103 (72.0)	226 (79.0)	329 (76.7)
Missing	2	0	2
Baseline renal impairment - n (%)			
Yes	104 (71.7)	225 (78.7)	329 (76.3)
No	41 (28.3)	61 (21.3)	102 (23.7)

AML = acute myeloid leukemia; ANC = absolute neutrophil count; Aza = azacitidine; CDx = companion diagnostic; CMML = chronic myelomonocytic leukemia; CTC = Common Toxicity Criteria; DLCO = diffusing capacity of the lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; FEV1 = forced expiratory volume in 1 second; FLT3 = FMS-like tyrosine kinase 3; IDH = isocitrate dehydrogenase; ITD = internal tandem duplication; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; Max = maximum; MDS = myelodysplastic syndrome; Min = minimum; MRC = myelodysplasia-related changes; N = sample size; n = number of subjects; NPM1 = nucleophosmin 1; Pbo = placebo; QD = once daily; RBC = red blood cell; SD = standard deviation; TKD = tyrosine kinase domain; TP53 = tumor protein p53; ULN = upper limit of normal; Ven = venetoclax; WBC = white blood cell

a. WBC is too low to perform differential counts and report ANC for Subject 93601.

b. A subject can report more than one reason. Therefore, the sum of the counts for the reasons may be greater than the overall.

c. Within 8 weeks prior to the first dose of study drug or randomization for non-treated.

d. Percentages were calculated using the total number of subjects with results (Detected or Not Detected) as the denominator of the sample size. Non-evaluable subjects (undetermined or missing values) were not included in the denominator.

e. A subject can have both IDH1 and IDH2 mutations.

f. A subject can have both FLT3-ITD and FLT3-TKD mutations.

Extent of exposure

The median duration of exposure in the Ven + Aza arm was 7.6 months (range: 0.1-30.7) and in the Pbo + Aza arm was 4.3 months (range: 0.1-24). Subjects received venetoclax for a median of 7 cycles (range: 1-30) versus 4.5 cycles (range: 1-26) in the comparator arm.

In the Ven + Aza arm, 267 subjects (94.3%) had at least 1 dose interruption for any reason (including interruption during cycles, between 28-day cycles, and duration reduction): 17.7% had 1 interruption, 11.7% had 2 interruptions, and 65% had > 2 interruptions. In the comparator arm, 112 subjects (77.8%) had at least 1 dose interruption for any reason: 23.6% had 1 interruption, 20% had 2 interruptions, and 34% had > 2 interruptions.

The median duration of study follow-up was 20.5 months: 20.7 months (95% CI: 20.1, 22 months) for subjects in the Ven + Aza arm and 20.2 months (95% CI: 19.6, 22.4 months) for the comparator.

Outcomes and estimation

Unless otherwise specified, the primary analysis of all response-related endpoints is based on the investigator assessment. The analyses for the secondary endpoints are presented for the 431 subjects in

Group 2. Due to the small number of subjects in Group 1 (n=2), no formal statistical analyses were performed for these subjects.

IDMC performed 2 planned interim efficacy analyses, one for the primary CR+ CRi rate analysis with a data cutoff date of 01 October 2018 and a second interim analysis for the OS endpoint, with a data cutoff date of 04 January 2020, when 270 (75% of 360) OS events were observed.

Primary endpoint:

Composite complete remission rate (CR+CRi): primary analysis, cutoff date 1 October 2018 (IA1)

Table 7. Analysis of Best Response of CR + CRi Based on Investigators' Assessment (Efficacy Analysis Set, Group 2 - Including the First 226 Subjects for CR + CRi Interim Analysis Using IA1 Data)

	Pbo + Aza (N = 79)	Ven 400 mg QD + Aza (N = 147)	p-value[a]
CR + CRi Rate (as best response) - n (%) [95% CI][b]	20 (25.3) [16.2, 36.4]	96 (65.3) [57.0, 73.0]	< 0.001***

Aza = azacitidine; CI = confidence interval; CR + CRi = composite complete remission; IA1 = Interim Analysis 1; IVRS = Interactive Voice Response System; N = sample size; n = number of subjects; Pbo = placebo; QD = once daily; 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.

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

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

Data included are subject to a cutoff date of 01 October 2018.

Cross reference: Table 14.2__1A

Composite complete remission rate (CR+CRi): ITT, IA2 (cutoff date January 2020)

Table 8. Analysis of Best Response of CR + CRi and Best IWG Response Based on Investigators' Assessment (Efficacy Analysis Set; Group 2)

	Pbo + Aza (N = 145)	Ven 400 mg QD + Aza (N = 286)	p-value[a]
CR + CRi 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***
CRi	15 (10.3) [5.9, 16.5]	85 (29.7) [24.5, 35.4]	
CR + CRi	41 (28.3) [21.1, 36.3]	190 (66.4) [60.6, 71.9]	< 0.001***
Subjects with Best Response of CR + CRi - Mean (SD) Median [range]			
Time to First Response (months)			
CR + CRi	3.3 (2.61) 2.8 [0.8 - 13.2]	2.1 (1.82) 1.3 [0.6 - 9.9]	
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]	
CRi	3.5 (2.77) 3.4 [0.8 - 11.2]	2.4 (2.03) 1.3 [0.6 - 8.8]	
CR + CRi	4.2 (2.89) 3.7 [0.8 - 13.2]	3.6 (3.66) 2.3 [0.6 - 24.5]	
Best IWG Response - n (%)			
Complete Remission (CR)	26 (17.9)	105 (36.7)	
Complete Remission with Incomplete Blood Count Recovery (CRi)	15 (10.3)	85 (29.7)	
Partial Remission (PR)	3 (2.1)	3 (1.0)	
Morphologic Leukemia-Free State (MLFS)	6 (4.1)	24 (8.4)	
Resistant Disease (RD)	69 (47.6)	36 (12.6)	
Confirmed Morphologic Relapse (MR)	0	0	
Disease Progression (PD)	6 (4.1)	3 (1.0)	
Discontinued with No Response Data (DS)	20 (13.8)	30 (10.5)	
No Response Data but Still Active (NR)	0	0	
CR + CRi 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]	
CRi	8 (5.5) [2.4, 10.6]	87 (30.4) [25.1, 36.1]	
CR + CRi	11 (7.6) [3.8, 13.2]	124 (43.4) [37.5, 49.3]	< 0.001***

Aza = azacitidine; CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; IVRS = Interactive Voice Response System; IWG = International Working Group; IWRS = Interactive Web Response System; N = sample size; n = number of subjects; 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.

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

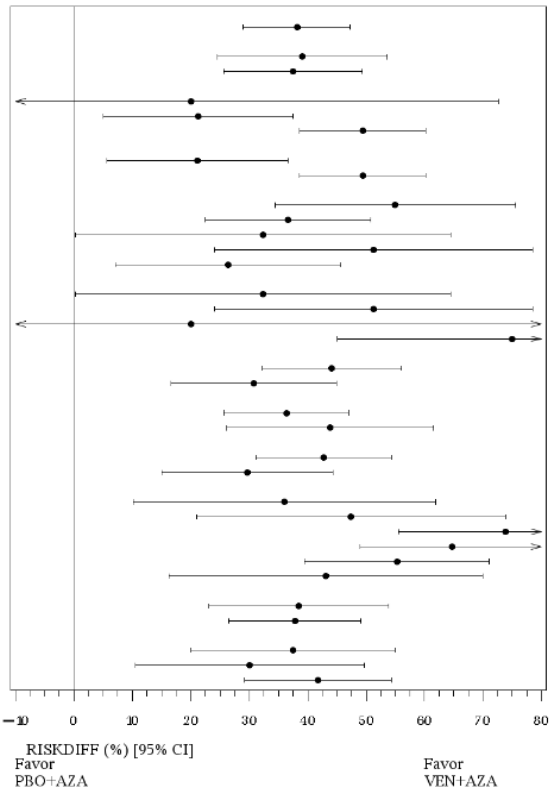
Sensitivity Analysis of Best Response of CR+CRi Based on Investigators' Assessment - Stratified by Stratification Factors (Age and Cytogenetics) Collected in EDC (Full Analysis Set Group 2)

	Placebo + Azacitidine (N=145)	Venetoclax 400 mg QD + Azacitidine (N=286)	P-value@	P-value$
CR+CRi Rate (as best response) - n (%) [95% CI]#				
CR	26 (17.9) [12.1, 25.2]	105 (36.7) [31.1, 42.6]	<0.001***	<0.001***
CRi	15 (10.3) [5.9, 16.5]	85 (29.7) [24.5, 35.4]		
CR+CRi	41 (28.3) [21.1, 36.3]	190 (66.4) [60.6, 71.9]	<0.001***	<0.001***
Subjects with Best Response of CR+CRi - Mean(SD) Median [range]				
Time to First Response (months)				
CR+CRi	3.3 (2.61) 2.8 [0.8-13.2]	2.1 (1.82) 1.3 [0.6-9.9]		
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]		
CRi	3.5 (2.77) 3.4 [0.8-11.2]	2.4 (2.03) 1.3 [0.6-8.8]		
CR+CRi	4.2 (2.89) 3.7 [0.8-13.2]	3.6 (3.66) 2.3 [0.6-24.5]		

Group 2: Enrolled not under original protocol.

CR+CRi Rate Based on Investigators' Assessment by Subgroup
(Full Analysis Set Group 2)

	PBO + AZA n/N (%)	VEN + AZA n/N (%)	RISKDIFF (%) [95% CI] VEN + AZA vs. PBO + AZA
All Subjects	41/145 (28.3)	190/286 (66.4)	38.16 [29.0 ,47.3]
Gender			
Female	17/ 58 (29.3)	78/114 (68.4)	39.11 [24.6 ,53.6]
Male	24/ 87 (27.6)	112/172 (65.1)	37.53 [25.7 ,49.3]
EDC Age (Years)			
18 - < 65	2/ 5 (40.0)	6/ 10 (60.0)	20.00 [-32.6 ,72.6]
65 - < 75	22/ 53 (41.5)	64/102 (62.7)	21.24 [5.0 ,37.5]
>= 75	17/ 87 (19.5)	120/174 (69.0)	49.43 [38.6 ,60.2]
EDC Age (Years)			
< 75	24/ 58 (41.4)	70/112 (62.5)	21.12 [5.6 ,36.6]
>= 75	17/ 87 (19.5)	120/174 (69.0)	49.43 [38.6 ,60.2]
Region			
US	6/ 24 (25.0)	40/ 50 (80.0)	55.00 [34.4 ,75.6]
EU	15/ 59 (25.4)	72/116 (62.1)	36.65 [22.5 ,50.8]
China	5/ 13 (38.5)	17/ 24 (70.8)	32.37 [0.3 ,64.5]
Japan	2/ 13 (15.4)	16/ 24 (66.7)	51.28 [24.1 ,78.5]
Rest of World	13/ 36 (36.1)	45/ 72 (62.5)	26.39 [7.1 ,45.7]
Asian Country			
China	5/ 13 (38.5)	17/ 24 (70.8)	32.37 [0.3 ,64.5]
Japan	2/ 13 (15.4)	16/ 24 (66.7)	51.28 [24.1 ,78.5]
Taiwan	2/ 5 (40.0)	3/ 5 (60.0)	20.00 [-40.7 ,80.7]
Korean	0/ 1	6/ 8 (75.0)	75.00 [45.0 ,100.0]
Baseline ECOG			
Grade < 2	20/ 81 (24.7)	108/157 (68.8)	44.10 [32.2 ,56.0]
Grade >= 2	21/ 64 (32.8)	82/129 (63.6)	30.75 [16.6 ,44.9]
Type of AML			
De Novo	33/110 (30.0)	142/214 (66.4)	36.36 [25.7 ,47.0]
Secondary	8/ 35 (22.9)	48/ 72 (66.7)	43.81 [26.1 ,61.5]
EDC - Cytogenetic Risk			
Intermediate	28/ 89 (31.5)	135/182 (74.2)	42.72 [31.2 ,54.3]
Poor	13/ 56 (23.2)	55/104 (52.9)	29.67 [15.0 ,44.3]
Molecular Marker by Central Lab			
FLT3	8/ 22 (36.4)	21/ 29 (72.4)	36.05 [10.2 ,61.9]
IDH1	1/ 11 (9.1)	13/ 23 (56.5)	47.43 [21.0 ,73.9]
IDH2	2/ 18 (11.1)	34/ 40 (85.0)	73.89 [55.6 ,92.1]
IDH1/2	3/ 28 (10.7)	46/ 61 (75.4)	64.70 [48.9 ,80.4]
TP53	0/ 14	21/ 38 (55.3)	55.26 [39.5 ,71.1]
NPM1	4/ 17 (23.5)	18/ 27 (66.7)	43.14 [16.3 ,70.0]
AML with Myelodysplasia Related Changes (AML-MRC)			
Yes	11/ 49 (22.4)	56/ 92 (60.9)	38.42 [23.1 ,53.8]
No	30/ 96 (31.3)	134/194 (69.1)	37.82 [26.5 ,49.1]
Bone Marrow Blast Count			
< 30%	16/ 41 (39.0)	65/ 85 (76.5)	37.45 [20.0 ,54.9]
30 -< 50%	9/ 33 (27.3)	35/ 61 (57.4)	30.10 [10.5 ,49.7]
>= 50%	16/ 71 (22.5)	90/140 (64.3)	41.75 [29.2 ,54.3]



Group 2: Enrolled not under original protocol.
AZA = Azacitidine. PBO = Placebo. VEN = Venetoclax. RISKDIFF = Risk Difference.
95% CI is exact unconditional confidence limits.
Arrow indicates confidence interval extended more than current range.
TP53 and NPM1 data are from the central lab using MyAML panel. IDH1/2 and FLT3 data are by CDX method.
Note: Data included are subject to a cutoff date of 04JAN2020.
Program Source Code: /prod6/SDA/ABT-196/AML/CSR/M15-656/X/14.2/PCMS_RUN/m15656-creu1x.sas

OS

Table 9. 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)	-
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:		**Ven + Aza vs. Pbo + Aza**
Stratified[a]		*p-value*[a]
p-value from Log-rank Test		< 0.001***
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)		0.662 (0.518, 0.845)
p-value		< 0.001***

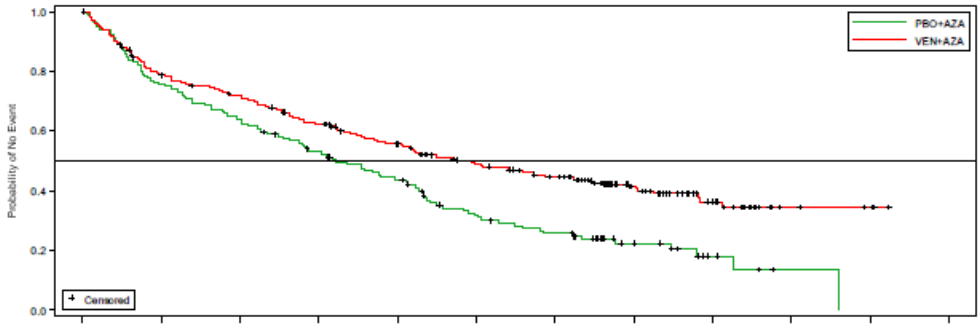
Aza = azacitidine; CI = confidence interval; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; N = sample size; n = number of subjects; Pbo = placebo; QD = once daily; Ven = venetoclax

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

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

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

Figure 2. 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; CI = confidence interval; HR = hazard ratio; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; N = sample size; PBO = placebo; PH = proportional hazard; VEN = venetoclax

$ Stratified by age (18 to < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk) from IVRS/IWRS. Data included are subject to a cutoff date of 04 January 2020.

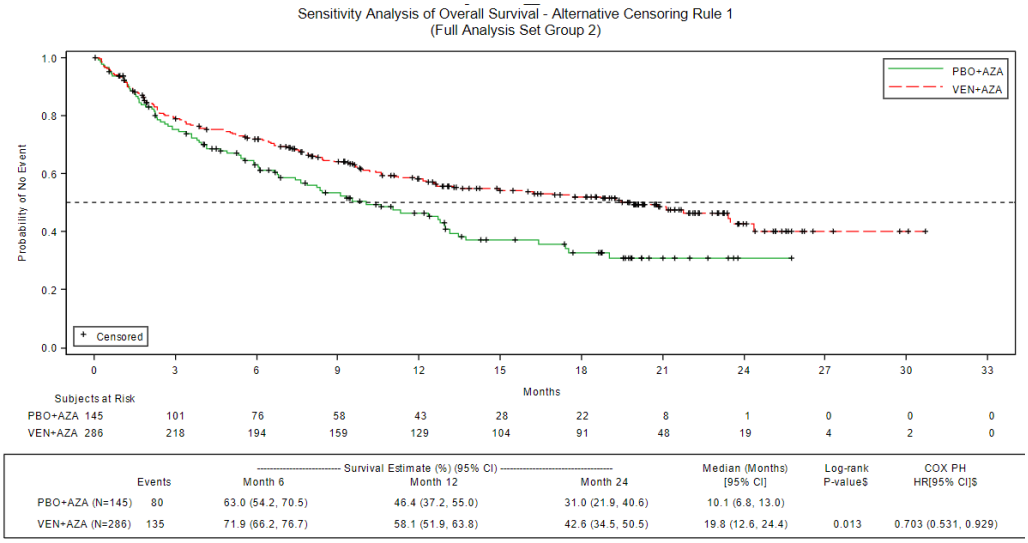
Sensitivity Analysis of Overall Survival - Including All Data in the Extracted Database
(Full Analysis Set Group 2)

	Placebo + Azacitidine (N=145)	Venetoclax 400 mg QD + Azacitidine (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)	- (27.4, -)
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:		VEN + AZA vs. PBO + AZA
Unstratified		P-value
P-value from Log-rank Test		<0.001***
P-value from Wilcoxon Test		0.006**
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)		0.627 (0.493, 0.797)
P-value		<0.001***
Stratified @		P-value @
P-value from Log-rank Test		<0.001***
P-value from Wilcoxon Test		0.002**
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)		0.653 (0.513, 0.832)
P-value		<0.001***

AZA = Azacitidine, PBO = Placebo, VEN = Venetoclax.

Sensitivity Analysis of Overall Survival - Alternative Censoring Rule 1
(Full Analysis Set Group 2)

	Placebo + Azacitidine (N=145)	Venetoclax 400 mg QD + Azacitidine (N=286)
Events (deaths) - n (%)	80 (55.2%)	135 (47.2%)
Duration of Overall Survival (months)		
25th (95% CI)	3.1 (2.1, 4.7)	4.8 (2.8, 6.6)
Median (95% CI)	10.1 (6.8, 13.0)	19.8 (12.6, 24.4)
75th (95% CI)	- (17.5, -)	-
6-Month Survival Estimate (95% CI)	63.0% (54.2%, 70.5%)	71.9% (66.2%, 76.7%)
12-Month Survival Estimate (95% CI)	46.4% (37.2%, 55.0%)	58.1% (51.9%, 63.8%)
24-Month Survival Estimate (95% CI)	31.0% (21.9%, 40.6%)	42.6% (34.5%, 50.5%)
Treatment Comparison:		VEN + AZA vs. PBO + AZA
Unstratified		P-value
P-value from Log-rank Test		0.006**
P-value from Wilcoxon Test		0.026*
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)		0.679 (0.514, 0.897)
P-value		0.006**
Stratified @		P-value @
P-value from Log-rank Test		0.013*
P-value from Wilcoxon Test		0.011*
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)		0.703 (0.531, 0.929)
P-value		0.013*

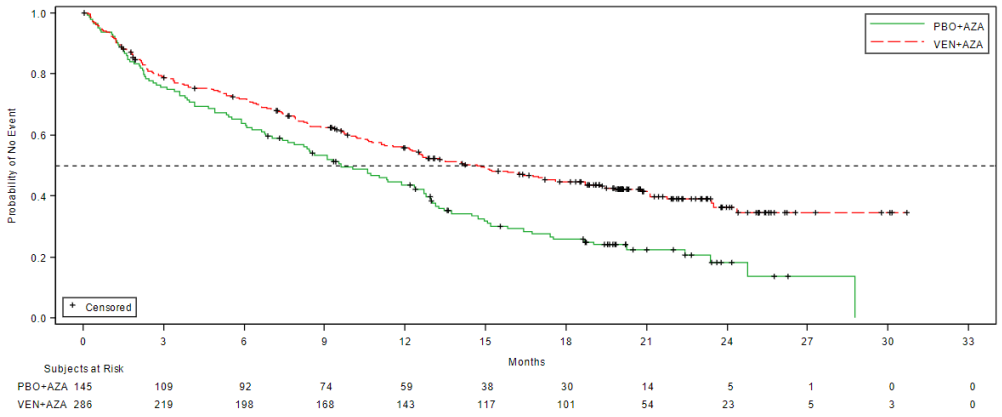


	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	Log-rank P-value$	COX PH HR[95% CI]$
PBO+AZA (N=145)	80	63.0 (54.2, 70.5)	46.4 (37.2, 55.0)	31.0 (21.9, 40.6)	10.1 (6.8, 13.0)		
VEN+AZA (N=286)	135	71.9 (66.2, 76.7)	58.1 (51.9, 63.8)	42.6 (34.5, 50.5)	19.8 (12.6, 24.4)	0.013	0.703 (0.531, 0.929)

Sensitivity Analysis of Overall Survival - Stratified by Stratification Factors (Age and Cytogenetics) Collected in EDC
(Full Analysis Set Group 2)

	Placebo + Azacitidine (N=145)	Venetoclax 400 mg QD + Azacitidine (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)	-
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:		VEN + AZA vs. PBO + AZA
Unstratified		P-value
P-value from Log-rank Test		<0.001***
P-value from Wilcoxon Test		0.008**
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)		0.641 (0.502, 0.819)
P-value		<0.001***
Stratified @		P-value @
P-value from Log-rank Test		<0.001***
P-value from Wilcoxon Test		0.003**
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)		0.662 (0.519, 0.846)
P-value		<0.001***

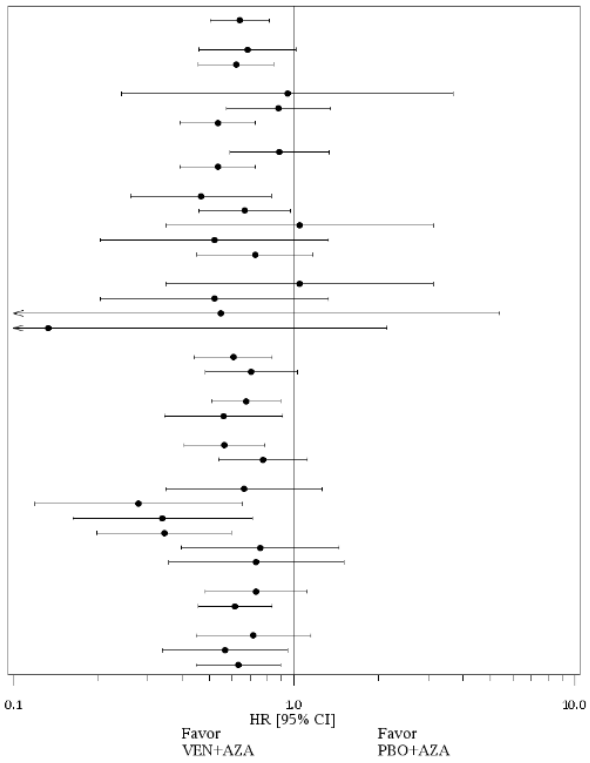
Sensitivity Analysis of Overall Survival - Stratified by Stratification Factors (Age and Cytogenetics) Collected in EDC
(Full Analysis Set Group 2)



	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 (0.519, 0.846)

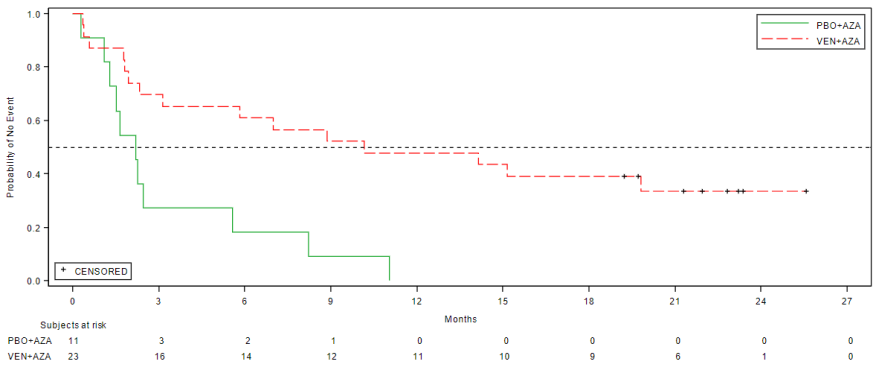
Overall Survival by Subgroup
(Full Analysis Set Group 2)

	PBO + AZA n/N (%)	VEN + AZA n/N (%)	HR [95% CI] VEN + AZA vs. PBO + AZA
All Subjects	109/145 (75.2)	161/286 (56.3)	0.641 (0.502, 0.819)
Gender			
Female	41/ 58 (70.7)	61/114 (53.5)	0.684 (0.460, 1.017)
Male	68/ 87 (78.2)	100/172 (58.1)	0.621 (0.455, 0.847)
EDC Age (Years)			
18 - < 65	3/ 5 (60.0)	7/ 10 (70.0)	0.947 (0.243, 3.691)
65 - < 75	33/ 53 (62.3)	59/102 (57.8)	0.880 (0.574, 1.348)
>= 75	73/ 87 (83.9)	95/174 (54.6)	0.535 (0.394, 0.727)
EDC Age (Years)			
< 75	36/ 58 (62.1)	66/112 (58.9)	0.888 (0.591, 1.333)
>= 75	73/ 87 (83.9)	95/174 (54.6)	0.535 (0.394, 0.727)
Region			
US	21/ 24 (87.5)	27/ 50 (54.0)	0.466 (0.262, 0.832)
EU	46/ 59 (78.0)	70/116 (60.3)	0.666 (0.458, 0.969)
China	5/ 13 (38.5)	9/ 24 (37.5)	1.048 (0.351, 3.133)
Japan	9/ 13 (69.2)	10/ 24 (41.7)	0.521 (0.204, 1.326)
Rest of World	28/ 36 (77.8)	45/ 72 (62.5)	0.726 (0.452, 1.168)
Asian Country			
China	5/ 13 (38.5)	9/ 24 (37.5)	1.048 (0.351, 3.133)
Japan	9/ 13 (69.2)	10/ 24 (41.7)	0.521 (0.204, 1.326)
Taiwan	3/ 5 (60.0)	1/ 5 (20.0)	0.550 (0.056, 5.396)
Korean	1/ 1 (100.0)	4/ 8 (50.0)	0.134 (0.008, 2.140)
Baseline ECOG			
Grade < 2	65/ 81 (80.2)	89/157 (56.7)	0.607 (0.440, 0.838)
Grade >= 2	44/ 64 (68.8)	72/129 (55.8)	0.704 (0.483, 1.027)
Type of AML			
De Novo	80/110 (72.7)	120/214 (56.1)	0.674 (0.508, 0.895)
Secondary	29/ 35 (82.9)	41/ 72 (56.9)	0.561 (0.346, 0.910)
EDC - Cytogenetic Risk			
Intermediate	62/ 89 (69.7)	84/182 (46.2)	0.566 (0.407, 0.786)
Poor	47/ 56 (83.9)	77/104 (74.0)	0.775 (0.538, 1.117)
Molecular Marker by Central Lab			
FLT3	19/ 22 (86.4)	19/ 29 (65.5)	0.664 (0.351, 1.257)
IDH1	11/ 11 (100.0)	15/ 23 (65.2)	0.280 (0.120, 0.655)
IDH2	14/ 18 (77.8)	15/ 40 (37.5)	0.340 (0.163, 0.711)
IDH1/2	24/ 28 (85.7)	29/ 61 (47.5)	0.345 (0.199, 0.598)
TP53	13/ 14 (92.9)	34/ 38 (89.5)	0.760 (0.398, 1.450)
NPM1	14/ 17 (82.4)	16/ 27 (59.3)	0.734 (0.357, 1.505)
AML with Myelodysplasia Related Changes (AML-MRC)			
Yes	38/ 49 (77.6)	56/ 92 (60.9)	0.732 (0.484, 1.107)
No	71/ 96 (74.0)	105/194 (54.1)	0.616 (0.455, 0.834)
Bone Marrow Blast Count			
< 30%	28/ 41 (68.3)	46/ 85 (54.1)	0.716 (0.447, 1.148)
30 -< 50%	26/ 33 (78.8)	36/ 61 (59.0)	0.567 (0.339, 0.949)
>= 50%	55/ 71 (77.5)	79/140 (56.4)	0.633 (0.448, 0.893)



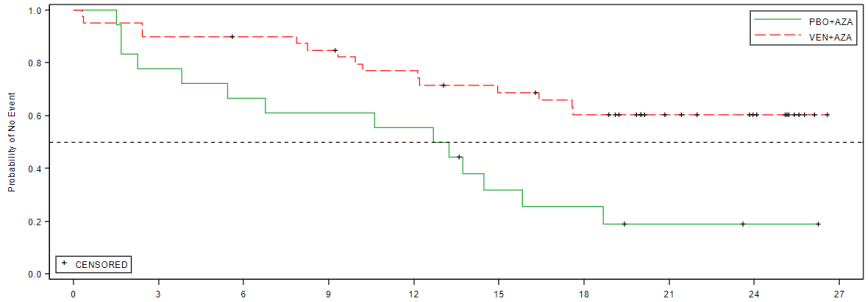
Group 2: Enrolled not under original protocol. AZA = Azacitidine. PBO = Placebo. VEN = Venetoclax.
HR is from unstratified Cox proportional hazards model.
Arrow indicates confidence interval extended more than current range.
Note: Data included are subject to a cutoff date of 04JAN2020.
TP53 and NPM1 data are from the central lab using MyAML panel. IDH1/2 and FLT3 data are by CDX method.
Program Source Code: /prod/SDA/ABT-396/AML/CSR/M15-656/X14.3/PGMS_RUN/m15696-os-subgs

Overall Survival by Molecular Marker IDH1
(Full Analysis Set Group 2)



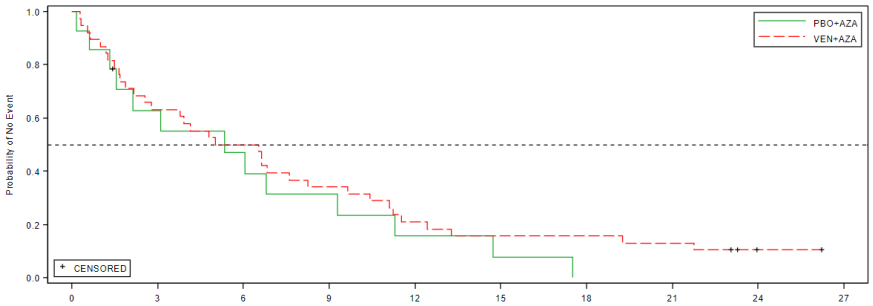
	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	Log-Rank P-value$	COX PH HR[95% CI]$
PBO+AZA (N=11)	11	18.2 (2.9, 44.2)	NA	NA	2.2 (1.1, 5.6)		
VEN+AZA (N=23)	15	60.9 (38.3, 77.4)	47.8 (26.8, 66.1)	33.5 (15.3, 53.0)	10.2 (2.3, -)	0.002	0.280 (0.120, 0.655)

Overall Survival by Molecular Marker IDH2
(Full Analysis Set Group 2)



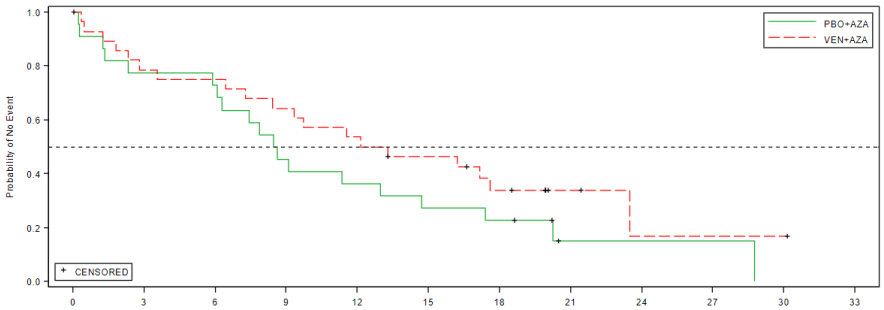
	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	Log-Rank P-value$	COX PH HR[95% CI]$
PBO+AZA (N=18)	14	66.7 (40.4, 83.4)	55.6 (30.5, 74.8)	19.0 (4.8, 40.3)	13.0 (3.8, 15.8)		
VEN+AZA (N=40)	15	90.0 (75.5, 96.1)	76.9 (60.3, 87.3)	60.2 (42.8, 73.9)	- (16.4, -)	0.003	0.340 (0.163, 0.711)

Overall Survival by Molecular Marker TP53
(Full Analysis Set Group 2)



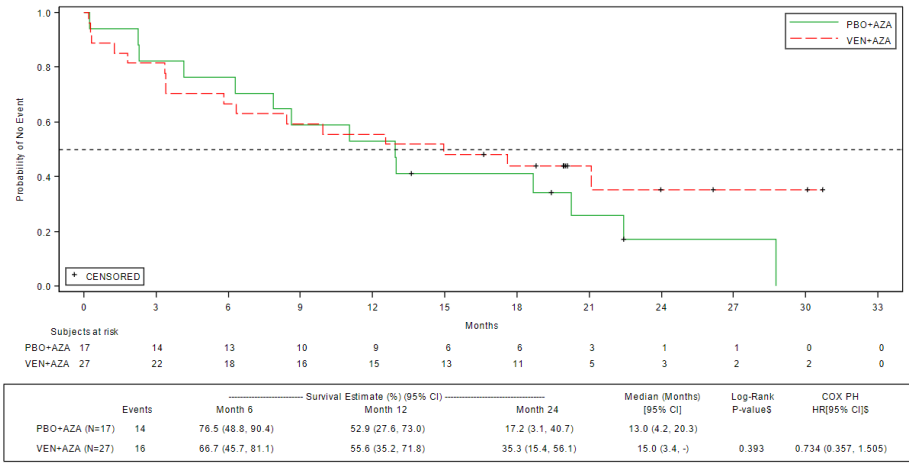
	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	Log-Rank P-value$	COX PH HR[95% CI]$
PBO+AZA (N=14)	13	47.1 (19.9, 70.5)	15.7 (2.5, 39.4)	NA	5.4 (1.3, 9.3)		
VEN+AZA (N=38)	34	50.0 (33.4, 64.5)	21.1 (9.9, 35.0)	10.5 (3.3, 22.5)	5.8 (2.6, 8.3)	0.401	0.760 (0.398, 1.450)

Overall Survival by Molecular Marker FLT3
(Full Analysis Set Group 2)



	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)

Overall Survival by Molecular Marker NPM1
(Full Analysis Set Group 2)

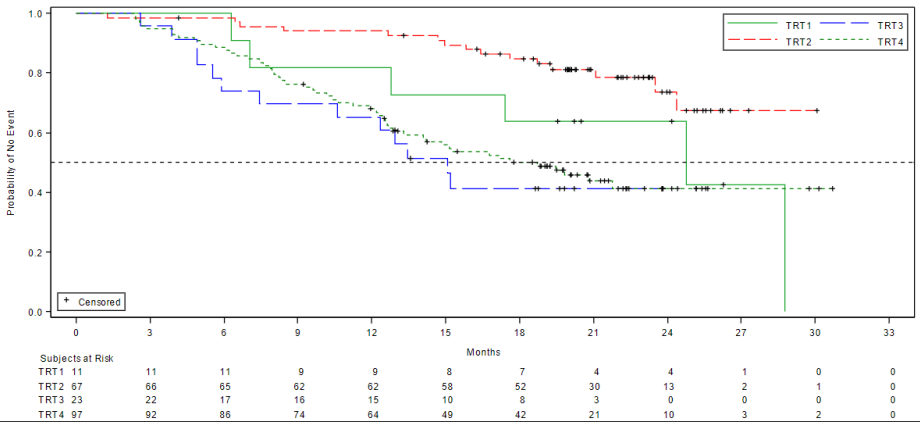


Subjects at risk

PBO+AZA	17	14	13	10	9	6	6	3	1	1	0	0
VEN+AZA	27	22	18	16	15	13	11	5	3	2	2	0

	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=17)	14	76.5 (48.8, 90.4)	52.9 (27.6, 73.0)	17.2 (3.1, 40.7)	13.0 (4.2, 20.3)		
VEN+AZA (N=27)	16	66.7 (45.7, 81.1)	55.6 (35.2, 71.8)	35.3 (15.4, 56.1)	15.0 (3.4, -)	0.393	0.734 (0.357, 1.505)

Overall Survival by Best Post-Baseline MRD Value (<10E-3 Vs >=10E-3) and Treatment Group
(Full Analysis Set Group 2 - Subjects Achieving CR+CRi Based on Investigators' Assessment)

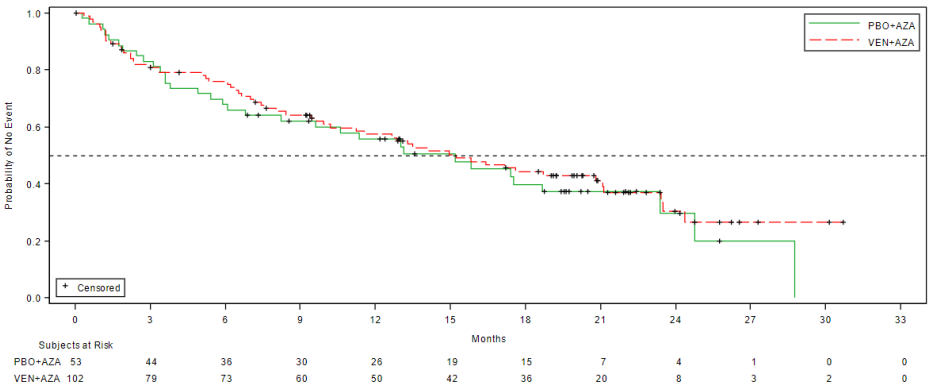


Subjects at Risk

TRT1	11	11	11	9	9	8	7	4	4	1	0	0
TRT2	67	66	65	62	62	58	52	30	13	2	1	0
TRT3	23	22	17	16	15	10	8	3	0	0	0	0
TRT4	97	92	86	74	64	49	42	21	10	3	2	0

	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]
TRT1 (N=11)	6	100.0 (100.0, 100.0)	81.8 (44.7, 95.1)	63.6 (29.7, 84.5)	24.8 (7.0, 28.8)
TRT2 (N=67)	15	98.5 (89.9, 99.8)	94.0 (84.7, 97.7)	73.6 (57.0, 84.6)	- (24.4, -)
TRT3 (N=23)	13	73.9 (50.9, 87.3)	65.2 (42.3, 80.8)	NA	15.1 (7.4, -)
TRT4 (N=97)	52	88.7 (80.5, 93.6)	67.9 (57.6, 76.2)	41.4 (30.2, 52.2)	18.7 (12.9, -)

Overall Survival - 65-<75 Age Group from EDC
(Full Analysis Set Group 2)

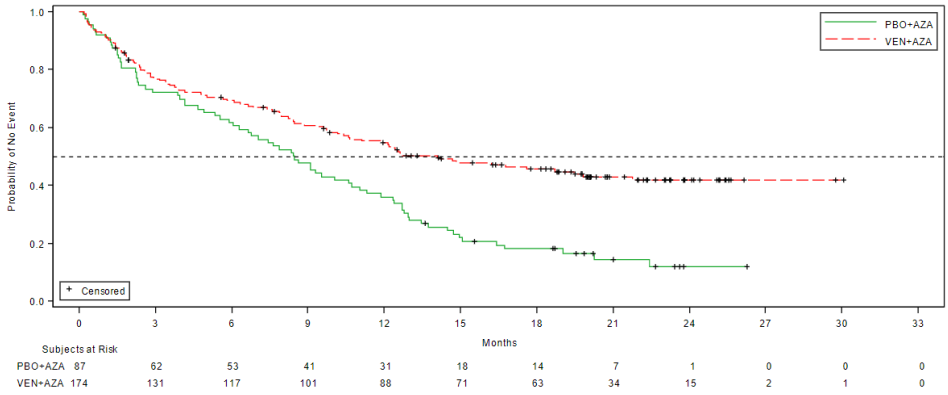


Subjects at Risk

PBO+AZA	53	44	36	30	26	19	15	7	4	1	0	0
VEN+AZA	102	79	73	60	50	42	36	20	8	3	2	0

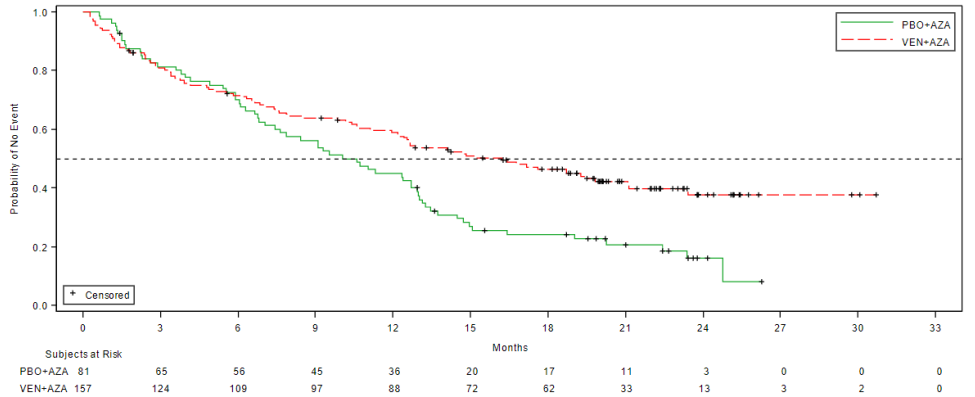
	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	COX PH HR[95% CI]$
PBO+AZA (N=53)	33	67.9 (53.6, 78.7)	55.7 (41.1, 68.0)	29.9 (14.1, 47.5)	15.2 (6.8, 23.4)	
VEN+AZA (N=102)	59	75.9 (66.2, 83.1)	57.5 (46.9, 66.7)	30.3 (18.7, 42.7)	15.2 (10.2, 21.1)	0.880 (0.574, 1.348)

Overall Survival - >=75 Age Group from EDC
(Full Analysis Set Group 2)



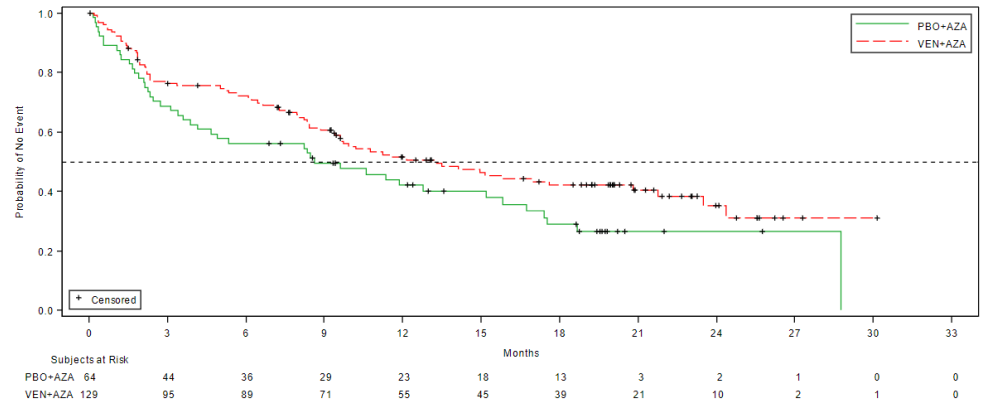
	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	COX PH HR[95% CI]$
PBO+AZA (N=87)	73	61.7 (50.6, 71.1)	36.1 (26.1, 46.2)	12.1 (5.6, 21.3)	8.5 (6.0, 10.7)	
VEN+AZA (N=174)	95	69.2 (61.7, 75.5)	54.7 (46.9, 61.9)	41.8 (33.9, 49.6)	14.1 (10.4, 21.8)	0.535 (0.394, 0.727)

Overall Survival - Baseline ECOG <2
(Full Analysis Set Group 2)

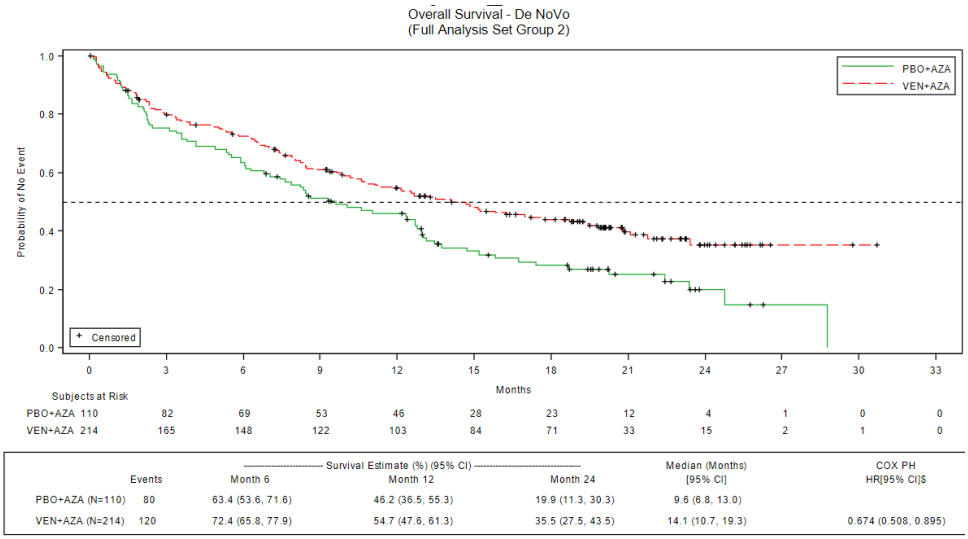


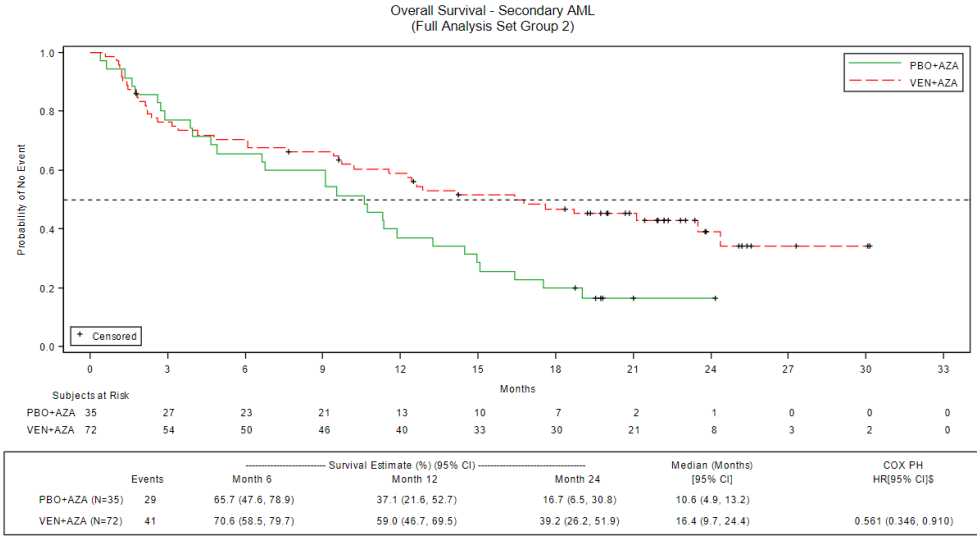
	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	COX PH HR[95% CI]$
PBO+AZA (N=81)	65	70.1 (58.8, 78.8)	45.0 (33.9, 55.5)	16.0 (8.1, 26.3)	10.6 (7.0, 13.0)	
VEN+AZA (N=157)	89	71.6 (63.8, 78.1)	59.1 (50.8, 66.4)	37.6 (28.7, 46.4)	16.2 (12.3, 21.1)	0.607 (0.440, 0.838)

Overall Survival - Baseline ECOG >=2
(Full Analysis Set Group 2)



	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) [95% CI]	COX PH HR[95% CI]$
PBO+AZA (N=64)	44	56.3 (43.3, 67.4)	42.2 (29.7, 54.2)	26.6 (15.5, 39.1)	8.6 (3.9, 15.8)	
VEN+AZA (N=129)	72	72.3 (63.6, 79.3)	51.5 (42.2, 60.1)	35.1 (24.6, 45.9)	13.3 (9.4, 20.8)	0.704 (0.483, 1.027)





Secondary endpoints:

CR+CRi rate by initiation of cycle 2

There were 124 subjects (43.4%) in the Ven + Aza arm versus 11 subjects (7.6%) in the Pbo + Aza arm who achieved CR + CRi by the initiation of Cycle 2. Among subjects in the Ven + Aza arm who achieved a best response of CR + CRi, median time to first response was 1.3 months (range: 0.6 to 9.9 months) compared to 2.8 months (range: 0.8 to 13.2 months) in the comparator arm. The median time to best response of CR + CRi was 2.3 months in the Ven + Aza arm and 3.7 months in the Pbo + Aza arm.

CR+CRh

Table 11. Analysis of Best Response of CR + CRh (Efficacy Analysis Set, Group 2)

	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***
Subjects 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 subjects; 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.

Notes: ***, **, * at p = 0.001, 0.01, 0.05 levels, respectively.
Data included are subject to a cutoff date of 04 January 2020.

DOR

- Duration of CR

The median duration of response for CR was 17.5 months (95% CI: 15.3, - months) in the Ven + Aza arm (N = 105) and 13.3 months (95% CI: 8.5, 17.6 months) in the comparator arm (N = 26). The number of subjects with events of MR, PD or death due to disease progression were 39/105 subjects (37.1%) in the Ven + Aza arm vs 13/26 subjects (50%).

- Duration of CR+CRi

The median duration of response for CR + CRi was 17.5 months (95% CI: 13.6, - months) in the Ven + Aza arm (N = 190) and 13.4 months (95% CI: 5.8, 15.5 months) in the comparator arm (N = 41). The number of subjects with events of MR, PD or death due to disease progression were 84/190 subjects (44.2%) in the Ven + Aza arm vs 23/41 subjects (56.1%).

- Duration of CR+CRh

The median duration of response for CR + CRh was 17.8 months (95% CI: 15.3, - months) in the Ven + Aza arm (N = 185) and 13.9 months (95% CI: 10.4, 15.7 months) in the comparator arm (N = 33). The number of subjects with events of MR, PD or death due to disease progression were 79/185 subjects (42.7%) in the Ven + Aza arm vs 17/33 subjects (51.5%).

Transfusion independence rate

Transfusion dependence at baseline was defined as having received RBCs and/or having received platelets within 8 weeks prior to study treatment (or prior to randomization if not dosed). Transfusion independence, defined as a 56-day or greater RBC and platelet transfusion-free period while on study therapy (subjects who did not receive study drug were considered transfusion dependent during the study), was evaluated for both groups.

RBC

In the Ven + Aza arm, 171 subjects (59.8%) achieved RBC transfusion independence compared to 51 subjects (35.2%) in the Pbo + Aza arm. The median duration of RBC transfusion independence after

receiving first dose of study treatment was 199 days for Ven + Aza (range: 57 to 933 days), and 193 days for Pbo + Aza (range: 56 to 727 days). The median time to first postbaseline RBC transfusion independence was 29 days for Ven + Aza arm and 51 days for Pbo + Aza arm.

Platelets

In the Ven + Aza arm, 196 subjects (68.5%) achieved platelet transfusion independence compared to 72 subjects (49.7%) in the Pbo + Aza arm. The median duration of platelet transfusion independence after receiving first dose of study treatment was 210 days for Ven + Aza (range: 56 to 933 days), and 227.5 days for Pbo + Aza (range: 58, 730 days). The median time to first postbaseline platelet transfusion independence was 7 days for Ven + Aza arm and 1 day for Pbo + Aza arm.

MRD

MRD at 10^{-3} level was assessed by centralized multicolour flow cytometry. Note: this was not a formal test of the secondary endpoint for the US marketing application (MRD negativity rate).

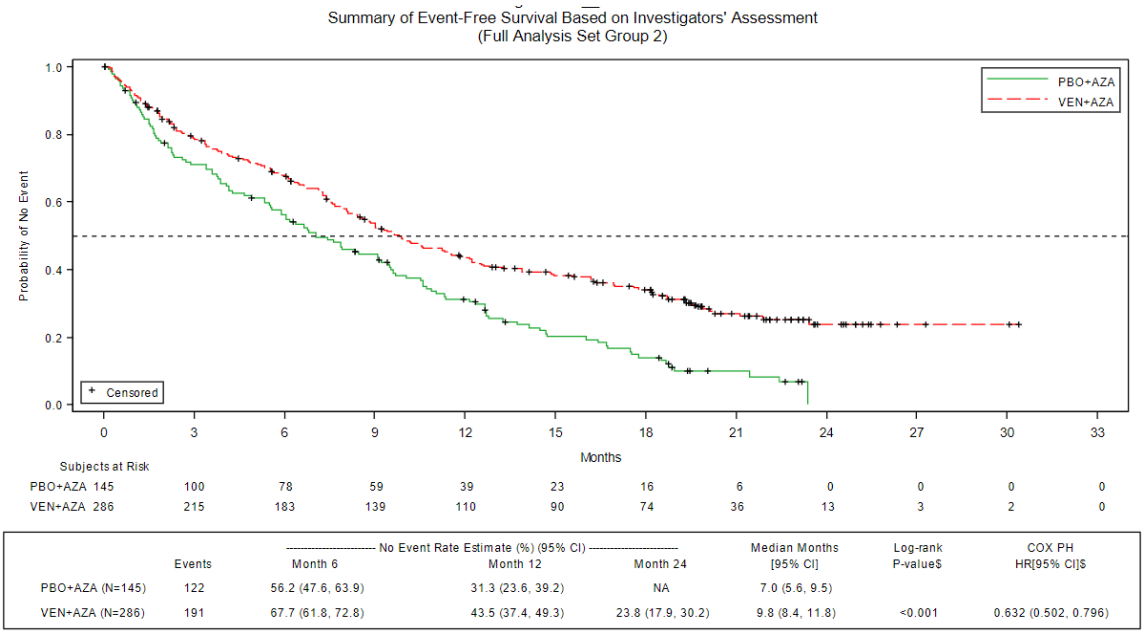
At the time of the data cutoff date (04 January 2020), 216/286 subjects in the Ven + Aza arm and 104/145 subjects in the Pbo + Aza arm had an MRD assessment. The median MRD value for all subjects was lower in the Ven + Aza arm compared with the Pbo + Aza arm (0.18 and 1.60, respectively). Among subjects in the Ven + Aza arm, 67/286 subjects (23.4%) achieved CR + CRi responses and MRD < 10^{-3} vs 11/145 subjects (7.6%) in the comparator arm. OS: for the CR + CRi and MRD < $10^{-3,}$ the median time was not reached in the Ven + Aza arm (N = 67) and was 24.8 months in the Pbo + Aza arm (N = 11).

EFS

EFS was defined as the number of days from randomization to the date of PD, confirmed MR from CR or CRi, treatment failure defined as failure to achieve CR, CRi, or MLFS after at least 6 cycles of study treatment collected on study drug completion eCRF, or death from any cause. A total of 313/360 EFS events were observed in IA2 and information fraction in IA2 is 87%. The two-sided alpha for EFS analysis at IA2 is 0.032.

Table 14. Summary of Event-Free Survival Based on Investigators' Assessment (Efficacy Analysis Set)

	Pbo + Aza (N = 145)	**Ven 400 mg QD + Aza (N = 286)**
Number of Subjects with Events - n (%)	122 (84.1%)	191 (66.8%)
Confirmed Morphologic Relapse/Confirmed Disease Progression	35/122 (28.7%)	83/191 (43.5%)
Treatment Failure	12/122 (9.8%)	4/191 (2.1%)
Death	75/122 (61.5%)	104/191 (54.5%)
Number of Subjects Without an Event – n (%)	23 (15.9%)	95 (33.2%)
Duration of Event-Free Survival (months)		
25th (95% CI)	2.3 (1.6, 3.8)	3.9 (2.8, 5.4)
Median (95% CI)	7.0 (5.6, 9.5)	9.8 (8.4, 11.8)
75th (95% CI)	13.2 (11.3, 16.7)	23.4 (19.3, -)
6-Month Event-Free Survival Estimate (95% CI)	56.2% (47.6%, 63.9%)	67.7% (61.8%, 72.8%)
12-Month Event-Free Survival Estimate (95% CI)	31.3% (23.6%, 39.2%)	43.5% (37.4%, 49.3%)
24-Month Event-Free Survival Estimate (95% CI)	NA	23.8% (17.9%, 30.2%)
Treatment Comparison:		**Ven + Aza vs. Pbo + Aza**
Stratified[a]		*p-value*[a]
p-value from Log-rank Test		< 0.001***
Cox Proportional Hazard Model		
Hazard Ratio (95% CI)		0.632 (0.502, 0.796)
p-value		< 0.001***



	Events	No Event Rate 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)	122	56.2 (47.6, 63.9)	31.3 (23.6, 39.2)	NA	7.0 (5.6, 9.5)		
VEN+AZA (N=286)	191	67.7 (61.8, 72.8)	43.5 (37.4, 49.3)	23.8 (17.9, 30.2)	9.8 (8.4, 11.8)	<0.001	0.632 (0.502, 0.796)

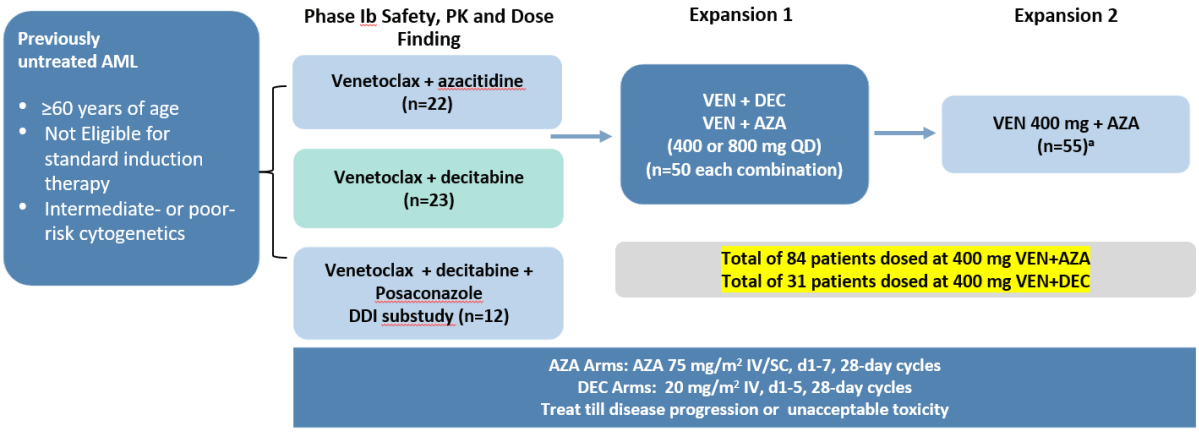
Patient reported outcomes

There were no differences in terms of fatigue and other PROs between arms.

Supportive studies

Study M14-358

This is a phase 1b study of ABT-199 (GDC-0199) in combination with azacitidine or decitabine in treatment-naïve subjects with AML who are ≥ 60 yo and who are not eligible for standard induction therapy



Key Eligibility Criteria
• 1L AML (WHO criteria) ≥60 years of age
• Ineligible for treatment with standard induction regimen
• ECOG PS 0–3
• Intermediate or poor risk cytogenetics
• No APL, no CNS involvement

Endpoints	
Primary (dose escalation):	Safety, PK, dose finding
Primary (expansion):	CR, CRh, CRi, OS
Key Secondary Exploratory	ORR, DOR, transfusion independence, MRD

a=The 55 subjects in expansion 2 were ≥60 years old and fulfilled the objectively defined medical criteria' AZA=azacitidine; DEC=decitabine; VEN=venetoclax; CR: complete remission; CRi=complete remission with incomplete blood count recovery; OS: overall survival; MRD: minimal residual disease; DoR : duration of response; APL, acute promyelocytic leukemia; CNS : Central nervous system

Methods

Phase 1b, open-label, non-randomized, multicenter study. First subject first dose: November 2014. Study ongoing. Data cutoff for the IA: August 2019.

Study participants

Inclusion criteria:

- ≥ 75 years of age

OR

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

- ECOG performance status of 2 or 3
- cardiac history of congestive heart failure requiring treatment or ejection fraction ≤ 50% or chronic stable angina
- diffusing capacity of the lungs for carbon monoxide ≤ 65% or forced expiratory volume in the first second of expiration ≤ 65%
- creatinine clearance ≥ 30 mL/minute to < 45 mL/minute
- moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN
- any other comorbidity that the physician judges to be incompatible with intensive chemotherapy

Baseline data

Parameters	Venetoclax (400 mg) + Azacitidine N=84 n (%)	Venetoclax (400 mg) + Decitabine N=31 n (%)
Sex, Male	51 (60.7)	15 (48.4)
Age, median (range)	74.5 (61 - 90)	72.0 (65 – 86)
Cytogenetic Risk*		
Intermediate	50 (59.5)	16 (51.6)
Poor	33 (39.3)	15 (48.4)
Subjects with secondary AML	21 (25.0)	9 (29.0)
ECOG performance status		
0	14 (16.7)	7 (22.6)
1	44 (52.4)	20 (64.5)
2	24 (28.6)	4 (12.9)
3	2 (2.4)	-
Bone marrow blast		
< 30%	24 (28.6)	7 (18.9)
≥ 30% to < 50%	28 (33.3)	14 (45.2)
≥ 50%	31 (36.9)	10 (32.3)

Of the 212 patients treated with any dose of venetoclax in combination with either of the HMAs, 195 (92%) had discontinued venetoclax treatment by the safety data cutoff date of 30 August 2019. The most common primary reasons for discontinuation (≥ 10% of subjects) of any dose of venetoclax with azacitidine were disease progression in 40 subjects (31.5%); AEs not related to progression (24, 18.9%); and other, 36 (28.3%). The most common primary reasons for discontinuation (≥ 10%) of any dose of venetoclax with decitabine were: disease progression in 30 subjects (41.1%); AEs not related to progression in 10 subjects (13.7%); and other in 20 subjects (27.4%).

The median duration of venetoclax exposure among subjects receiving 400 mg venetoclax in combination with azacitidine (n=84) was 6.4 months (range, 0.1 to 38.1 months). Approximately half of subjects in this group (45 subjects, 53.6%) received venetoclax for > 5 cycles, with a median of 6 cycles.

For subjects receiving 400 mg venetoclax in combination with decitabine (n=31), the median duration of venetoclax exposure was 5.7 months (range, 0.5 to 41.8 months). Approximately half of subjects in this group (16 subjects, 51.6%) received venetoclax for > 5 cycles, with a median of 6 cycles.

Outcomes and estimation

Table 6. Summary of Investigator-Assessed Best IWG Response (Full Analysis Set)

	All Doses Of Venetoclax + Azacitidine (N = 127)	400 mg Venetoclax + Azacitidine (N = 84)	All Doses Of Venetoclax + Decitabine (N = 73)	400 mg Venetoclax + Decitabine (N = 31)
Subject best IWG response – n (%)				
Complete remission (CR)	53 (41.7%)	37 (44.0%)	37 (50.7%)	17 (54.8%)
Complete remission with incomplete blood count recovery (CRi)	31 (24.4%)	23 (27.4%)	16 (21.9%)	6 (19.4%)
Partial remission (PR)	1 (0.8%)	0	1 (1.4%)	0
Morphologically leukemia-free state (MLFS)	16 (12.6%)	6 (7.1%)	7 (9.6%)	2 (6.5%)
Resistant disease (RD)	20 (15.7%)	14 (16.7%)	6 (8.2%)	3 (9.7%)
Disease progression (PD)	2 (1.6%)	2 (2.4%)	0	0
Discontinued with no response data (DS)	4 (3.1%)	2 (2.4%)	6 (8.2%)	3 (9.7%)
Non-response but still active (NR)	0	0	0	0
Objective response rate (CR + CRi + PR) n (%) [95% CI][#]	85 (66.9%) [58.0%, 75.0%]	60 (71.4%) [60.5%, 80.8%]	54 (74.0%) [62.4%, 83.5%]	23 (74.2%) [55.4%, 88.1%]
Leukemia response rate (CR + CRi + PR + MLFS) n (%) [95% CI][#]	101 (79.5%) [71.5%, 86.2%]	66 (78.6) [68.3%, 86.8%]	61 (83.6%) [73.0%, 91.2%]	25 (80.6%) [62.5%, 92.5%]
Duration of study (month) median [range]	35.2 [24.9 – 55.4]	28.1 [24.9 – 55.4]	40.0 [37.7 – 56.1]	39.5 [37.2 – 56.1]
Duration of study follow up (month) median [range]	34.3 [0.4 – 52.2]	28.9 [0.4 – 42.0]	40.4 [0.2 – 52.7]	40.4 [0.7 – 42.7]

95% confidence interval is from the exact binomial distribution.

Study duration is defined as cutoff date - first dose of study drug + 1.

Duration of study follow up is defined as time from first dose of study drug to date of death, last known alive date, or cutoff date whichever is earlier.

Table 10. Summary of Clinical Outcomes in Subjects Treated with Venetoclax 400 mg in Combination with Decitabine Who Achieved a CR or CRh

	Venetoclax (400 mg) + Decitabine				
	CR	CRh	CR + CRh	Non-CR + CRh	Overall
Parameters	N = 17	N = 5	N = 22	N = 9	N = 31
Duration of response, median; months (95% CI) (Number of subjects with events)	21.3 (6.9, -) (N = 8)	7.2 (2.4, 15.3) (N = 5)	15.3 (7.2, 30.2) (N = 13)	NA	NA
No event rate estimate at 12 months, % (95% CI)	69.6% (37.8%, 87.4%)	20.0% (0.8%, 58.2%)	56.9% (31.8%, 75.7%)	NA	NA
Overall survival, median; months (95% CI)	NP	NP	NP	NP	16.2 (9.1, 27.8)
No event rate estimate at 12 months, % (95% CI)	NP	NP	NP	NP	61.3% (42.0%, 75.8%)
			n (%)		
Post-baseline RBC & platelet transfusion independence	15 (88.2%)	3 (60.0%)	18 (81.8%)	1 (11.1%)	19 (61.3%)
Post-baseline RBC transfusion independence	15 (88.2%)	3 (60.0%)	18 (81.8%)	1 (11.1%)	19 (61.3%)
Post-baseline Platelet transfusion independence	17 (100.0%)	5 (100.0%)	22 (100.0%)	5 (55.6%)	27 (87.1%)
Duration of post-baseline RBC & platelet transfusion independence	259.0 (57 to 1178)	85.0 (64 to 279)	184.5 (57 to 1178)	63.0 (63 to 63)	110.0 (57 to 1178)
Duration of post-baseline RBC transfusion independence	289.0 (69 to 1178)	86.0 (64 to 342)	274.0 (64 to 1178)	63.0 (63 to 63)	259.0 (63 to 1178)
Duration of post-baseline platelet transfusion independence	261.0 (75 to 1181)	127.0 (67 to 279)	192.0 (67 to 1181)	96.0 (57 to 111)	127.0 (57 to 1181)

Table 12. Summary of Important Clinical Benefits in Subjects Treated with Venetoclax 400 mg in Combination with Decitabine Who Achieved a CR or CRh

	Venetoclax (400 mg) + Decitabine			
	CR	CRh	CR + CRh	Non-CR + CRh
Parameters	N = 17	N = 5	N = 22	N = 9
	Median: months [95% confidence interval]			
Time to First Transfusion after First Dose				
RBC transfusion	0.1 [0.1, 0.2]	NP	0.1 [0.1, 0.2]	0.1 [0.1, 0.2]
Platelet transfusion	6.5 [0.4, --]	NP	0.8 [0.4, --]	3.6 [0.1, --]
Time to First Transfusion after Response				
RBC transfusion	-- [6.7, --]	1.6 [0.0, --]	2.3 [0.8, --]	NP
Platelet transfusion	22.0 [2.9, --]	-- [1.9, --]	22.2 [2.9, --]	NP
Time to First Recurrence from First Transfusion after Response				
RBC transfusion	1.0 [0.6, --]	1.3 [0.1, --]	1.0 [0.1, 1.4]	0.1 [0.1, 0.5]
Platelet transfusion	2.4 [0.1, --]	0.6 [0.1, 1.1]	1.1 [0.1, 1.6]	0.2 [0.1, --]
	Event-Free Rate (6-Month): % [95% confidence interval]			
First Grade ≥ 3 Event After First Dose				
Hemorrhage	100 [100, 100]	NP	100 [100, 100]	100 [100, 100]
Infection or Infestation	48.5 [22.1, 70.7]	NP	52.1 [28.8, 71.0]	25.0 [1.4, 63.9]
First Grade ≥ 3 Event After Response				
Hemorrhage	100 [100, 100]	100 [100, 100]	100 [100, 100]	NP
Infection or Infestation	76.6 [43.3, 91.9]	80.0 [20.4, 96.9]	69.8 [44.5, 85.2]	NP

The rate of transfusion independence for RBC and platelets was 61.3%, with a duration of transfusion independence of 110 days for both RBC and platelets.

Study 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 ineligible for intensive chemotherapy.

First Subject First Visit: 24 May 2017

Last Subject Last Visit: not yet occurred, data cut-off for the primary analysis was 15 February 2019, and 15 August 2019 for the post-hoc the 6-month follow-up analysis.

Study participants

Subjects must have had histological confirmation of AML by WHO criteria, been ineligible for intensive induction chemotherapy, and either been:

- ≥ 75 years of age

OR

- ≥ 18 to 74 years of age and fulfil at least one criteria associated with lack of fitness for intensive induction chemotherapy:○ ECOG 2–3; history of CHF requiring treatment or EF ≤ 50% or chronic stable angina; DLCO ≤ 65% or FEV1 ≤ 65%; creatinine clearance ≥ 30 mL/min to < 45 ml/min; moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN

Patients with secondary AML with or without prior treatment with HMAs for myelodysplastic syndrome were included; those with secondary AML from underlying myeloproliferative neoplasms were not. Exclusion criteria included prior therapy for AML (except hydroxyurea before or during the first cycle of study treatment) and any previous exposure to cytarabine for any indication.

Treatments

Cycles of 28 days:

- Arm A (VEN + LDAC arm): Venetoclax 600 mg orally once daily on days 1 - 28 plus LDAC 20 mg/m^2 sc days 1 – 10
- Arm B (PBO + LDAC arm): Placebo 600 mg orally days 1 – 28 plus LDAC 20mg/m^2 sc d 1 – 10

Patients are treated until DP or unacceptable toxicity. FU every 2 months for 2 years after last subject is enrolled in the trial.

Response assessments were performed after cycle 1 (patients with resistant disease after cycle 1 had repeat assessments after cycle 2 or 3 to assess initial CR/CRi response) and every 3 cycles thereafter (starting at the end of cycle 4 and continuing until disease progression) until 2 consecutive samples confirmed stable achievement of CR or CRi. Assessments were also performed if there was suspected relapse and/or at the final study visit. Clinical responses were defined according to modified International Working Group response criteria for AML. Progressive disease was defined per European LeukemiaNet recommendations. Treatment failure was defined as failure to achieve morphologic leukemia-free state or higher response (CR, CRi, partial remission) after at least 6 cycles of treatment. EFS was defined as the number of days from randomization to disease progression, confirmed relapse, treatment failure, or death.

Outcomes/endpoints

Primary endpoint: OS

Secondary endpoints:

- Composite complete remission rate (CR+CRi)
- CR+CRh
- Proportion of patients achieving CR+CRi by initiation of cycle 2
- Proportion of patients achieving CR+CRh by initiation of cycle 2
- CR
- Transfusion independence rate
- MRD
- EFS
- Response in molecular subgroups
- Fatigue and other PROs

Exploratory endpoints:

- Biomarkers predictive of V activity and DOR

Sample size

The primary endpoint of the study is overall survival and sample size calculation is based on the following assumptions:

- Median OS of 6 months for placebo plus LDAC arm
- Median OS of 11 months for venetoclax plus LDAC arm (hazard ratio of 0.545)
- Interim analysis of OS at 75% of death events with O'Brien-Fleming boundary
- 2:1 randomization ratio to venetoclax plus LDAC, and placebo plus LDAC arm

With the above assumptions, a total of 133 death events will provide 90% power to detect statistically significant different between treatment arms at alpha level of 0.05. A total of approximately 210 subjects (140 in venetoclax plus LDAC arm and 70 in placebo plus LDAC arm) will be randomized into the study to obtain the 133 death events.

Randomisation: 2:1, 142:68 (actual number), stratified by AML status (secondary, de novo), age (18 – < 75, ≥ 75) and region (US, EU, China, Japan, Rest of world).

Blinding: double blind

Statistical methods

The full analysis set consisting of all randomized subjects will be used for efficacy analyses.

The primary efficacy endpoint is overall survival (OS). Overall survival will be defined as the number of days from the date of randomization to the date of death. Subjects that have not died will be censored at the last known date to be alive. The distribution of overall survival will be estimated for each treatment arm using Kaplan-Meier methodology and compared between treatment arms using the log-rank test stratified by AML status (secondary, de novo) and age (18 - < 75, ≥ 75).

Fixed sequence testing procedure will be used for analyses of the secondary efficacy endpoints. If statistical test is not significant for the primary efficacy endpoint of OS, then statistical significance will not be declared for any of the secondary efficacy endpoints.

Secondary endpoints that are rates will be compared between treatment arms using CMH test stratified by AML status (secondary, de novo) and age (18 - < 75, ≥ 75). In addition, 95% confidence interval will be constructed for CR + CRh. A linear mixed effects regression model with a variable covariance structure will be fitted to the longitudinal data to test for differences between treatment arms.

An interim analysis will be performed at the time of the 100th death event. The Lan-DeMets alpha spending function with O'Brien-Fleming boundary will be used to ensure that the one-sided false positive rate will be 0.025 or less for overall survival. The planned efficacy stopping boundary were p<0.01 (1-sided). Final analysis will be performed at the time of the 133rd death event.

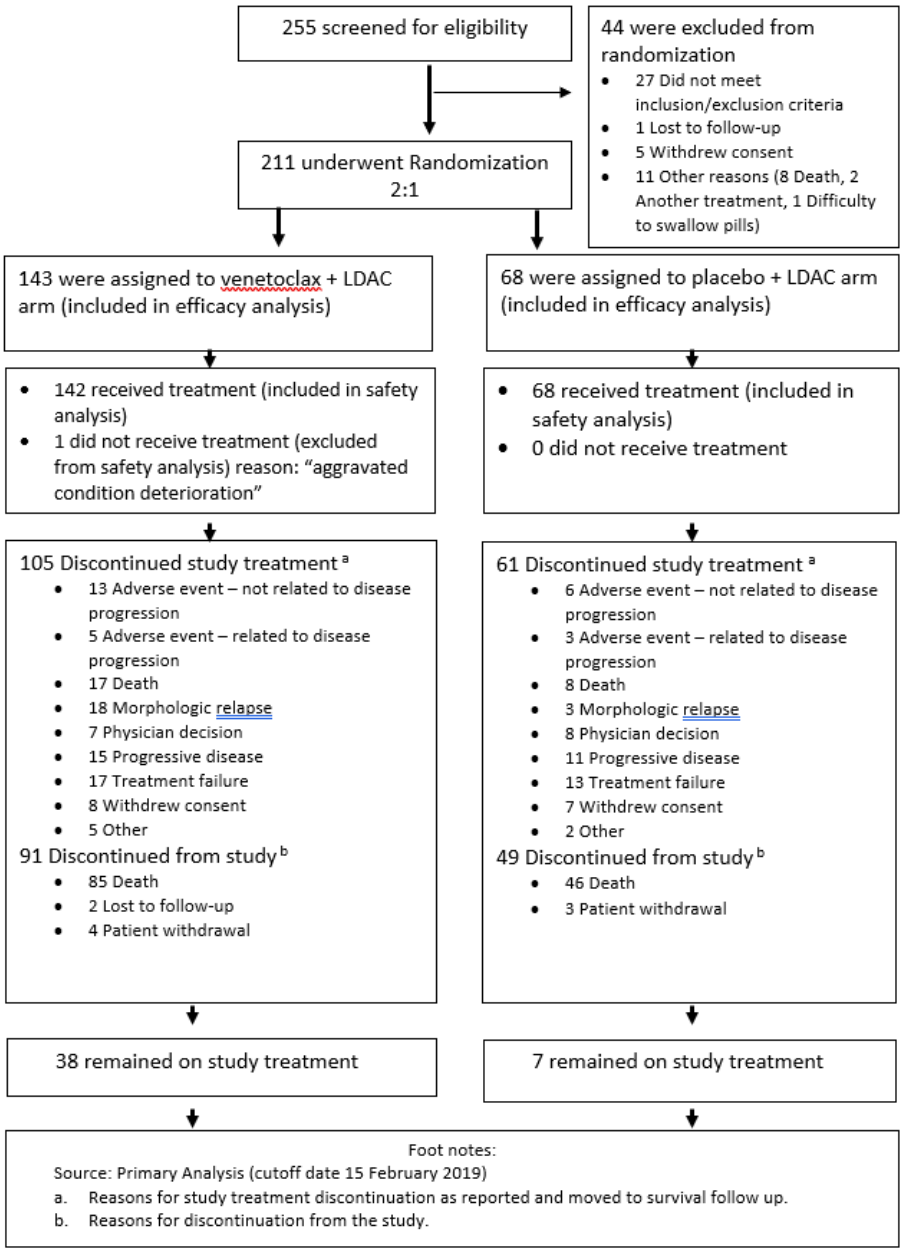
In addition to the final SAP, the following statistical analyses were performed (a selection).

- Cox proportional hazard regression models with stepwise variable selection were performed on OS in the whole population and in the Japan region, respectively, as sensitivity analyses to identify relevant prognostic factors for OS and to better understand the treatment effect on OS when adjusting for these factors.
- Overall survival was summarized for subjects who achieved CR, CR + CRi, or CR + CRh and for subjects who did not achieve CR + CRi or CR + CRh per investigator assessment to characterize the association between achieving a response and survival benefit.
- An additional threshold of less than 10^{-4} was applied in the analyses of MRD responses to evaluate the sensitivity of the threshold on MRD response and the relationship between MRD response and OS.
- In the analyses of EFS, treatment failure was defined as failure to achieve CR, CRi, PR, or MLFS collected on the study drug completion eCRF as assessed by the investigator instead of failure to achieve CR, CRi, or MLFS, after at least 6 cycles of study treatment. This change was made to be consistent with the definition of treatment failure in the study protocol.
- An unplanned 6-month follow-up analysis was performed on all efficacy and safety endpoints.

Results

Participant flow

Primary analysis



As of the data cut-off date for the 6-month follow-up (August 2019), 211 subjects had been randomized: 143 in the VEN + LDAC arm (venetoclax 600 mg + LDAC) and 68 in the PBO + LDAC arm (placebo + LDAC); 103 and 56 patients, respectively, had completed the study.

A total of 180 (85.3%) patients overall discontinued treatment; 117 patients (81.8%) in the VEN + LDAC arm and 63 (92.6%) in the PBO + LDAC arm. Primary reasons for venetoclax discontinuation for ≥ 10% of subjects (VEN + LDAC arm) included morphologic relapse (16.1%), treatment failure and death (12.6% each), progressive disease (11.9%), and AE not related to disease progression (10.5%). The primary reasons for placebo discontinuation for ≥ 10% of subjects (PBO arm) included treatment failure (19.1%), progressive disease (17.6%), physician decision, death, and withdrew decision (11.8%, each).

Primary reasons for LDAC discontinuation for ≥ 10% of subjects overall included treatment failure (14.7%), progressive disease (13.7%), death (12.3%), morphologic relapse (12.3%), and AE not related to disease progression (10%).

Median time on study was 17.5months for the VEN + LDAC arm and 17.7months for the PBO + LDAC arm. Overall, 159 subjects (75.4%) discontinued the study: 103 (72.0%) in the VEN + LDAC arm and 56 (82.4%) in the PBO + LDAC arm. Primary reasons for study discontinuation from the VEN + LDAC arm included death (67.8%), withdrawn consent (2.8%), and lost to follow up; for the comparator, death (77.9%), and withdrawn consent (4.4%).

Conduct of the study

Amendments to protocol

- Amendment 1 (February 2017, 117 subjects): AML subjects ≥ 18 years of age.
- Amendment 2 (October 2017, 59 subjects): to clarify that patients previously treated with venetoclax or other concurrent investigational agents could not be enrolled.
- Amendment 3 (June 2018, 21 subjects): to add evaluation of CR + CRh as a secondary endpoint and of transfusion independence during any consecutive 56 days during the study treatment period as an exploratory endpoint.
- Amendment 4 (November 2018, 0 subjects): 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.
- Amendment 5 (May 2019, 0 subjects): to allow the sponsor to unblind subject treatment assignments following the final analysis results and provide the investigators with this information if requested by them or by the subjects, so that a decision could be made in regard to the subjects' treatment continuation.

Amendments to SAP

In addition to the final SAP, a number of unplanned analyses were performed to further explore the results, see Statistical methods.

Protocol deviations did not impact study results.

Baseline data

At the 6- month follow-up, subjects were predominantly male, 117 subjects (55.5%) and white, 149 subjects (70.6%). Median age was 76 years (range: 36-93). he VEN + LDAC arm had a higher proportion of subjects ≥ 65 compared to the PBO + LDAC arm (92.3% vs 86.8%, respectively). This however is not indicative of an imbalance between arms.

Table 4. Summary of Baseline Disease Characteristics (Full Analysis Set – 6-Month Follow-Up)

Variable	Placebo + LDAC (N = 68) n (%)	Venetoclax 600 mg QD + LDAC (N = 143) n (%)	Total (N = 211) n (%)
ECOG performance status			
0	11 (16.2)	22 (15.4)	33 (15.6)
1	23 (33.8)	52 (36.4)	75 (35.5)
2	25 (36.8)	63 (44.1)	88 (41.7)
3	9 (13.2)	6 (4.2)	15 (7.1)
AML status (reported from EDC)			
De novo AML	45 (66.2)	85 (59.4)	130 (61.6)
Secondary AML	23 (33.8)	58 (40.6)	81 (38.4)
AML status (reported from IVRS/IWRS)			
De novo AML	46 (67.6)	92 (64.3)	138 (65.4)
Secondary AML	22 (32.4)	51 (35.7)	73 (34.6)
Type of secondary AML (reported from EDC)			
Therapy related AML	4	6	10
Post MDS/CMML	19	52	71
Other	0	0	0
AML-MRC			
Yes	27 (39.7)	57 (39.9)	84 (39.8)
No	41 (60.3)	86 (60.1)	127 (60.2)
Cytogenetic risk			
Favorable	3 (4.5)	1 (0.7)	4 (2.0)
Intermediate	43 (65.2)	90 (65.2)	133 (65.2)
Poor	20 (30.3)	47 (34.1)	67 (32.8)
Missing	2	5	7
Bone marrow blast count			
< 30%	18 (26.5)	42 (29.4)	60 (28.4)
≥ 30% - < 50%	22 (32.4)	36 (25.2)	58 (27.5)
≥ 50%	28 (41.2)	65 (45.5)	93 (44.1)
Bone marrow blast count (%)			
n	68	143	211
mean (SD)	47.2 (22.22)	48.4 (24.64)	48.0 (23.84)
median	40.7	44.0	42.8
min, max	4.8, 96.0	5.0, 99.4	4.8, 99.4
CTC grade of neutropenia			
0	15 (22.1)	26 (18.3)	41 (19.5)
1	2 (2.9)	4 (2.8)	6 (2.9)
2	6 (8.8)	8 (5.6)	14 (6.7)
3	15 (22.1)	26 (18.3)	41 (19.5)
4	30 (44.1)	78 (54.9)	108 (51.4)
Missing	0	1	1
Neutrophils value ($\times 10^9$/L)			
n	68	142	210
mean (SD)	1.8 (3.79)	1.1 (1.67)	1.3 (2.57)
median	0.5	0.4	0.5
min, max	0.0, 20.4	0.0, 8.8	0.0, 20.4
CTC grade of anemia			
0	2 (2.9)	0	2 (0.9)
1	6 (8.8)	19 (13.3)	25 (11.8)
2	38 (55.9)	86 (60.1)	124 (58.8)
3	22 (32.4)	38 (26.6)	60 (28.4)
4	0	0	0
Hemoglobin value (g/L)			
n	68	143	211
mean (SD)	94.8 (72.17)	103.3 (118.23)	100.6 (105.50)
median	86.1	86.0	86.0
min, max	58.0, 670.0	56.0, 960.0	56.0, 960.0

Bone marrow blast count (%)			
n	68	143	211
mean (SD)	47.2 (22.22)	48.4 (24.64)	48.0 (23.84)
median	40.7	44.0	42.8
min, max	4.8, 96.0	5.0, 99.4	4.8, 99.4
CTC grade of neutropenia			
0	15 (22.1)	26 (18.3)	41 (19.5)
1	2 (2.9)	4 (2.8)	6 (2.9)
2	6 (8.8)	8 (5.6)	14 (6.7)
3	15 (22.1)	26 (18.3)	41 (19.5)
4	30 (44.1)	78 (54.9)	108 (51.4)
Missing	0	1	1
Neutrophils value ($\times 10^9$/L)			
n	68	142	210
mean (SD)	1.8 (3.79)	1.1 (1.67)	1.3 (2.57)
median	0.5	0.4	0.5
min, max	0.0, 20.4	0.0, 8.8	0.0, 20.4
CTC grade of anemia			
0	2 (2.9)	0	2 (0.9)
1	6 (8.8)	19 (13.3)	25 (11.8)
2	38 (55.9)	86 (60.1)	124 (58.8)
3	22 (32.4)	38 (26.6)	60 (28.4)
4	0	0	0
Hemoglobin value (g/L)			
n	68	143	211
mean (SD)	94.8 (72.17)	103.3 (118.23)	100.6 (105.50)
median	86.1	86.0	86.0
min, max	58.0, 670.0	56.0, 960.0	56.0, 960.0
Prior HMA used			
Yes	14 (20.6)	28 (19.6)	42 (19.9)
No	54 (79.4)	115 (80.4)	169 (80.1)
Antecedent hematologic history of MDS			
Yes	17 (25.0)	47 (32.9)	64 (30.3)
No	51 (75.0)	96 (67.1)	147 (69.7)
RBC or platelet transfusion within 8 weeks prior to the first dose of study drug			
Yes	56 (82.4)	111 (77.6)	167 (79.1)
No	12 (17.6)	32 (22.4)	44 (20.9)
RBC transfusion within 8 weeks prior to the first dose of study drug			
Yes	54 (79.4)	104 (72.7)	158 (74.9)
No	14 (20.6)	39 (27.3)	53 (25.1)
Platelet transfusion within 8 weeks prior to the first dose of study drug			
Yes	24 (35.3)	52 (36.4)	76 (36.0)
No	44 (64.7)	91 (63.6)	135 (64.0)
FLT3 mutation from central lab			
ITD	6 (11.5)	10 (8.9)	16 (9.8)
TKD	1 (1.9)	6 (5.4)	7 (4.3)
ITD and TKD	0	0	0
ITD and other	0	1 (0.9)	1 (0.6)
TKD and other	0	1 (0.9)	1 (0.6)
Other	2 (3.8)	2 (1.8)	4 (2.4)
Subtotal FLT3	9 (17.3)	20 (17.9)	29 (17.7)
Not detected	43 (82.7)	92 (82.1)	135 (82.3)
Missing	16	31	47

IDH1 or IDH2 mutation from central lab			
IDH1 R132X	5 (9.6)	11 (9.8)	16 (9.8)
IDH2 R140X	8 (15.4)	9 (8.0)	17 (10.4)
IDH2 R172X	0	3 (2.7)	3 (1.8)
Subtotal (IDH1 or IDH2)	12 (23.1)	21 (18.8)	33 (20.1)
Not detected	40 (76.9)	91 (81.3)	131 (79.9)
Missing	16	31	47
TP53 mutation from central lab			
Detected	9 (17.3)	22 (19.6)	31 (18.9)
Not detected	43 (82.7)	90 (80.4)	133 (81.1)
Missing	16	31	47
NPM1 mutation from central lab			
Detected	7 (13.5)	19 (17.0)	26 (15.9)
Not detected	45 (86.5)	93 (83.0)	138 (84.1)
Missing	16	31	47
Baseline hepatic impairment			
Yes	21 (30.9)	37 (25.9)	58 (27.5)
No	47 (69.1)	106 (74.1)	153 (72.5)
Baseline renal impairment			
Yes	52 (76.5)	112 (78.3)	164 (77.7)
No	16 (23.5)	31 (21.7)	47 (22.3)

Extent of exposure

At the time of the time of the 6-month follow-up (15 August 2019), the median duration of venetoclax exposure was 4.1 months (range: 0-23.5). Median duration of placebo exposure was 1.7 months (range: 0.1-20.2). There were 29 patients (20.4%) with 1 venetoclax dose reduction. A total of 46 patients (32.4%) had 1 venetoclax dose interruption due to any reason, of which 23 (16.2%) due to count recovery. Overall, the median duration of LDAC exposure was 2.2 months (range: 0-23.4); 3.5 months in the VEN + LDAC arm and 1.3 months in the comparator arm.

Outcomes and estimation

Primary endpoint: OS

Primary analysis of OS (Feb. 2019)

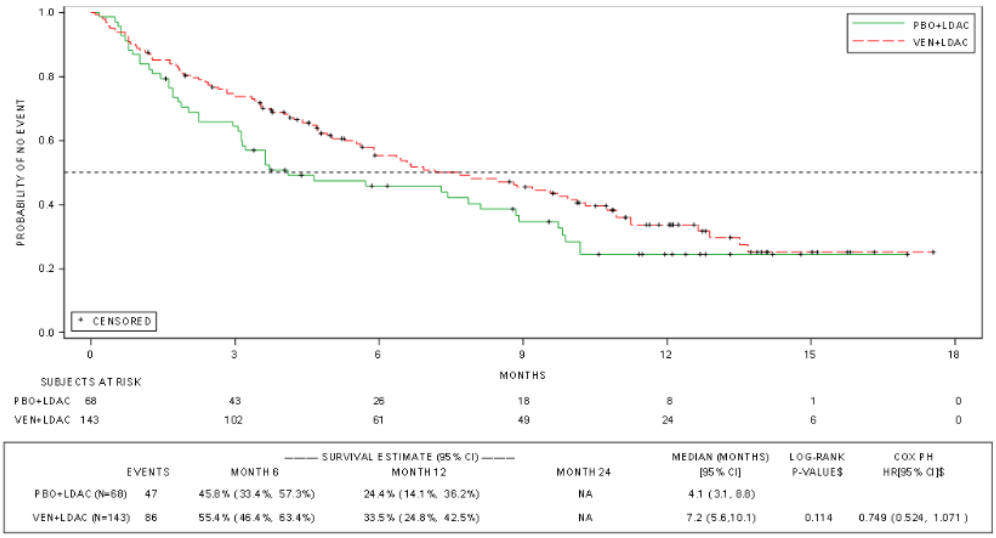
Table 5. Analysis of Overall Survival (Full Analysis Set)

	Placebo + LDAC (N = 68)	**Venetoclax 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, -)	- (11.2, -)
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:		**VEN + LDAC vs. PBO + LDAC**
Stratified[a]		*p-value*[a]
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 subjects; NA = not available; PBO = placebo; QD = once daily; VEN = venetoclax

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

Analysis of Overall Survival (Full 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+LDAC (N=68)	47	45.8% (33.4%, 57.3%)	24.4% (14.1%, 36.2%)	NA	4.1 (3.1, 6.8)		
VEN+LDAC (N=143)	86	55.4% (46.4%, 63.4%)	33.5% (24.8%, 42.5%)	NA	7.2 (5.6,10.1)	0.114	0.749 (0.524, 1.071)

Sensitivity analysis for OS

Table 6. 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 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)

Post-hoc analysis OS at 6 months follow up

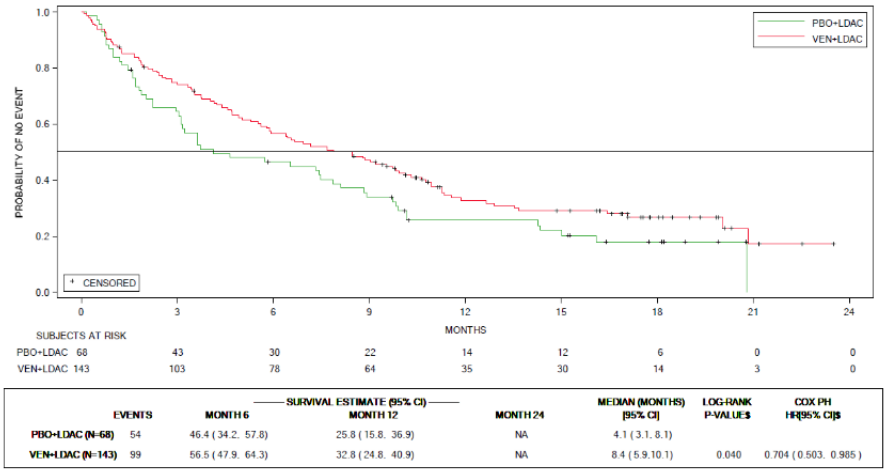
Table 15. Analysis of Overall Survival (Full Analysis Set – 6-Month Follow-Up)

	Placebo + LDAC (N = 68)	Venetoclax 600 mg QD + LDAC (N = 143)
Events (deaths) - n (%)	54 (79.4%)	99 (69.2%)
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, 8.1)	8.4 (5.9, 10.1)
75th (95% CI)	14.3 (8.8, 20.8)	20.1 (11.9, -)
6-month survival estimate (95% CI)	46.4% (34.2%, 57.8%)	56.5% (47.9%, 64.3%)
12-month survival estimate (95% CI)	25.8% (15.8%, 36.9%)	32.8% (24.8%, 40.9%)
24-month survival estimate (95% CI)	NA	NA
Treatment comparison:		**VEN + LDAC vs. PBO + LDAC**
Stratified[a]		*p-value*[a]
p-value from log-rank test		0.040
Cox proportional hazard model		
Hazard ratio (95% CI)		0.704 (0.503, 0.985)
p-value		0.041

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 subjects; NA = not available; PBO = placebo; QD = once daily; VEN = venetoclax

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

Figure 4. Analysis of Overall Survival (Full Analysis Set – 6-Month Follow-Up)



AML = acute myeloid leukemia; CI = confidence interval; HR = hazard ratio; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LDAC = low dose cytarabine; N = sample size; NA = not available; PBO = placebo; PH = proportional hazard; VEN = venetoclax

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

Post-hoc analysis OS at 12 months follow up

Table 17. Overall Survival at the Primary Analysis and with Additional Follow-up of 6 Months and 12 Months.

	Primary Analysis		Additional 6 Months		Additional 12 Months	
	PBO+ LDAC N=68	VEN+ LDAC N= 143	PBO+ LDAC N=68	VEN+ LDAC N= 143	PBO+ LDAC N=68	VEN+ LDAC N= 143
Median (95% CI) [a]	4.1 (3.1, 8.8)	7.2 (5.6, 10.1)	4.1 (3.1, 8.1)	8.4 (5.9, 10.1)	4.1 (3.1, 8.1)	8.4 (5.9, 10.3)
HR (95% CI) [b]	0.749 (0.524, 1.071)		0.704 (0.503, 0.985)		0.709 (0.511, 0.983)	
P-value [c]	0.114		0.040 [c]		0.038 [c]	

Data cut-off dates: 15 February 2019 for Primary Analysis, 15 August 2019 for +6-month analysis and 15 February 2020 for +12-month analysis.

CI = confidence interval; LDAC = low-dose cytarabine; PBO = placebo; VEN = venetoclax

Median is from Kaplan-Meier estimate.

Stratified Cox proportional hazards model.

P-values are from stratified log-rank test and are nominal for the additional 6- and 12-month analyses.

Sources: Table Q2A__1.2, Table Q2A__2.2

Table 16. Multivariate Analysis of Overall Survival Including Identified Baseline Demographics and Disease Characteristics as Covariates (Full Analysis Set – 6-Month Follow-Up)

Cox Regression Analysis Using Stepwise Selection			
Covariate	**Adjusted HR**	**95% CI**	**p-value**
Arm (VEN + LDAC vs LDAC)	0.647	[0.461, 0.909]	(0.012)
Age group (< 75 vs ≥ 75 years)	0.586	[0.400, 0.858]	(0.006)
AML status (de novo vs secondary)	0.613	[0.438, 0.858]	(0.004)
Baseline ECOG (< 2 vs ≥ 2)	0.497	[0.345, 0.717]	(< 0.001)
Cytogenetics risk (intermediate vs poor)	0.578	[0.409, 0.817]	(0.002)

AML = acute myeloid leukemia; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; HR = hazard ratio; LDAC = low-dose cytarabine; 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.

Secondary endpoints (primary analysis, Feb. 2019)

CR+CRi

Table 7. Analysis of Best Response of CR + CRi and Best IWG Response Based on Investigators' Assessment (Full Analysis Set)

	Placebo + LDAC (N = 68)	Venetoclax 600 mg QD + LDAC (N = 143)	p-value[a]	p-value[b]
CR + CRi rate (as best response) - n (%) [95% CI][c]				
CR	5 (7.4) [2.4, 16.3]	39 (27.3) [20.2, 35.3]	< 0.001***	< 0.001***
CRi	4 (5.9) [1.6, 14.4]	29 (20.3) [14.0, 27.8]		
CR + CRi	9 (13.2) [6.2, 23.6]	68 (47.6) [39.1, 56.1]	< 0.001***	< 0.001***
Subjects with best response of CR + CRi – mean (SD) median [range]				
Time to first response (months)				
CR + CRi	3.3 (2.16) 3.7 [0.9 - 6.5]	1.6 (1.06) 1.1 [0.8 - 4.7]		
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]		
CRi	4.0 (2.00) 3.8 [1.7 - 6.5]	1.8 (1.08) 1.2 [0.8 - 4.3]		
CR + CRi	3.8 (2.69) 3.7 [0.9 - 9.2]	2.1 (1.46) 1.2 [0.8 - 5.9]		
Best IWG response - n (%)				
CR	5 (7.4)	39 (27.3)		
CRi	4 (5.9)	29 (20.3)		
Partial remission (PR)	0	3 (2.1)		
Morphologically leukemia free state (MLFS)	1 (1.5)	7 (4.9)		
Resistant disease (RD)	37 (54.4)	41 (28.7)		
Confirmed morphologic relapse (MR)	0	0		
Disease progression (PD)	4 (5.9)	4 (2.8)		
Discontinued with no response data (DS)	16 (23.5)	17 (11.9)		
Non-response, but still active (NR)	1 (1.5)	3 (2.1)		
CR + CRi rate (as best response) by initiation of Cycle 2 - n (%) [95% CI][c]				
CR	2 (2.9) [0.4, 10.2]	23 (16.1) [10.5, 23.1]		
CRi	0	26 (18.2) [12.2, 25.5]		
CR + CRi	2 (2.9) [0.4, 10.2]	49 (34.3) [26.5, 42.7]	< 0.001***	< 0.001***

AML = acute myeloid leukemia; CI = confidence interval; CR = complete remission; CR + CRi = composite complete remission rate; CRi = complete remission with incomplete blood count recovery; IVRS = Interactive Voice Response System; IWG = International Working Group; IWRS = Interactive Web Response System; LDAC = low dose cytarabine; N = sample size; n = number of subjects; QD = once daily; SD = standard deviation

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. p-value is from Fisher's exact test.

c. 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.

CR+CRh

Table 8. Analysis of Best Response of CR + CRh (Full Analysis Set)

	Placebo + LDAC (N = 68)	Venetoclax 600 mg QD + LDAC (N = 143)	p-value[a]	p-value[b]
CR + CRh rate (as best response) - n (%) [95% CI][c]				
CR	5 (7.4) [2.4, 16.3]	39 (27.3) [20.2, 35.3]	< 0.001***	< 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***	< 0.001***
Subjects 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]		
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][c]				
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***	< 0.001***

CR: 27.3% (95% CI; 20.2, 35.3) vs 7.4% (95% CI; 2.4, 16.3)

Transfusion independence:

Table 9. Summary of Post-Baseline Transfusion Independence (Full Analysis Set)

	Placebo + LDAC (N = 68)	Venetoclax 600 mg QD + LDAC (N = 143)	p-value[a]	p-value[b]
Post-baseline transfusion independence rate - n (%) [95% CI][c]				
RBC and platelet	11 (16.2%) [8.4%, 27.1%]	53 (37.1%) [29.1%, 45.5%]	0.002**	0.002**
Treatment difference (VEN-PBO) 95% CI[c]		20.9% [9.1%, 32.7%]		
RBC	12 (17.6%) [9.5%, 28.8%]	58 (40.6%) [32.4%, 49.1%]	0.001**	< 0.001***
Treatment difference (VEN-PBO) 95% CI[c]		22.9% [10.8%, 35.0%]		
Platelet	22 (32.4%) [21.5%, 44.8%]	68 (47.6%) [39.1%, 56.1%]	0.040*	0.039*
Treatment difference (VEN-PBO) 95% CI[c]		15.2% [1.4%, 29.0%]		
Duration of post-baseline transfusion independence (days)				
RBC and platelet				
N	11	53		
mean (SD)	158.2 (87.54)	176.1 (113.31)		
median	182.0	132.0		
min, max	56, 312	56, 435		
RBC				
N	12	58		
mean (SD)	156.3 (90.94)	169.9 (111.81)		
median	146.0	118.5		
min, max	56, 312	62, 435		
Platelet				
N	22	68		
mean (SD)	157.5 (94.18)	194.6 (121.59)		
median	112.0	163.5		
min, max	56, 343	56, 511		

Fatigue: no difference between arms

EFS

Table 12. Summary of Event-Free Survival Based on Investigators' Assessment (Full Analysis Set)

	Placebo + LDAC (N = 68)	Venetoclax 600 mg QD + LDAC (N = 143)
Number of subjects with events – n (%)	54 (79.4%)	100 (69.9%)
Confirmed morphologic relapse/disease progression – n	18	42
Treatment failure – n	13	16
Death – n	23	42
Number of subjects without an event – n (%)	14 (20.6%)	43 (30.1%)
Duration of event-free survival (months)		
25th (95% CI)	1.0 (0.8, 1.3)	1.9 (1.3, 2.7)
median (95% CI)	2.0 (1.6, 3.1)	4.7 (3.7, 6.4)
75th (95% CI)	6.7 (3.7, 9.9)	11.2 (8.9, -)
No event rate at Month 6 (95% CI)	26.2% (16.0%, 37.6%)	41.9% (33.3%, 50.3%)
No event rate at Month 12 (95% CI)	12.6% (5.1%, 23.5%)	22.5% (15.1%, 30.8%)
No event rate at Month 18 (95% CI)	NA	NA
Treatment comparison:		**VEN + LDAC vs. PBO + LDAC**
Stratified[a]		*p-value*[a]
p-value from log-rank test		0.002**
Cox proportional hazard model		
Hazard ratio (95% CI)		0.583 (0.416, 0.817)
p-value		0.002**

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 subjects; NA = not available; PBO = placebo; QD = once daily; VEN = venetoclax

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

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.

MRD

Table 13. Summary of MRD Value (Full Analysis Set)

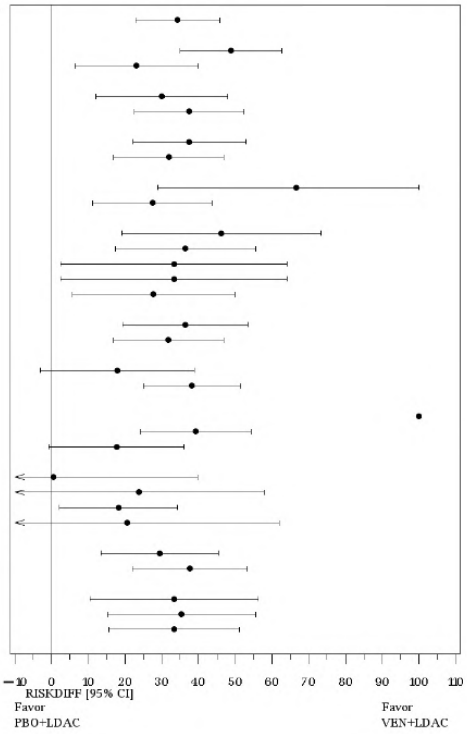
	Placebo + LDAC (N = 68)	Venetoclax 600 mg QD + LDAC (N = 143)	p-value[a]	p-value[b]
Best MRD value (%)				
N	44	113		
mean (SD)	16.74 (21.798)	6.61 (14.316)		
Quartiles				
25%	1.20	0.19		
median	7.45	0.42		
75%	22.41	3.83		
min, max	0.049, 90.940	0.000, 81.164		
Best MRD value - n (%)				
$< 10^{-3}$	2 (2.9)	11 (7.7)		
$\geq 10^{-3}$	42 (61.8)	102 (71.3)		
$< 10^{-4}$	0	9 (6.3)		
$\geq 10^{-4}$	44 (64.7)	104 (72.7)		
Missing	24 (35.3)	30 (21.0)		
MRD ($< 10^{-3}$) and CR + CRi response - n (%) [95% CI][c]	1 (1.5) [0.0, 7.9]	8 (5.6) [2.4, 10.7]	0.162	0.277
MRD ($< 10^{-3}$) and CR + CRh response - n (%) [95% CI][c]	1 (1.5) [0.0, 7.9]	8 (5.6) [2.4, 10.7]	0.162	0.277
MRD ($< 10^{-4}$) and CR + CRi response - n (%) [95% CI][c]	0	6 (4.2) [1.6, 8.9]	0.088	0.180
MRD ($< 10^{-4}$) and CR + CRh response - n (%) [95% CI][c]	0	6 (4.2) [1.6, 8.9]	0.088	0.180
MRD value at the end of Cycle 4 (%)				
N	16	64		
mean (SD)	12.25 (18.393)	5.31 (14.042)		
Quartiles				
25%	1.13	0.23		
median	5.87	0.49		
75%	14.74	2.05		
min, max	0.153, 66.050	0.000, 71.601		
MRD value at the end of Cycle 4 - n (%)				
$< 10^{-3}$	0	4 (2.8)		
$\geq 10^{-3}$	16 (23.5)	60 (42.0)		
$< 10^{-4}$	0	3 (2.1)		
$\geq 10^{-4}$	16 (23.5)	61 (42.7)		
Missing	52 (76.5)	79 (55.2)		
MRD ($< 10^{-3}$) at the end of Cycle 4 and CR + CRi response - n (%) [95% CI][c]	0	4 (2.8) [0.8, 7.0]	0.173	0.308
MRD ($< 10^{-3}$) at the end of Cycle 4 and CR + CRh response - n (%) [95% CI][c]	0	4 (2.8) [0.8, 7.0]	0.173	0.308
MRD ($< 10^{-4}$) at the end of Cycle 4 and CR + CRi response - n (%) [95% CI][c]	0	3 (2.1) [0.4, 6.0]	0.218	0.553
MRD ($< 10^{-4}$) at the end of Cycle 4 and CR + CRh response - n (%) [95% CI][c]	0	3 (2.1) [0.4, 6.0]	0.218	0.553

Ancillary analyses

Secondary endpoints by key baseline groups, primary analysis (Feb. 2019)

CR + CRi RATE BASED ON INVESTIGATORS' ASSESSMENT BY SUBGROUP
(FULL ANALYSIS SET)

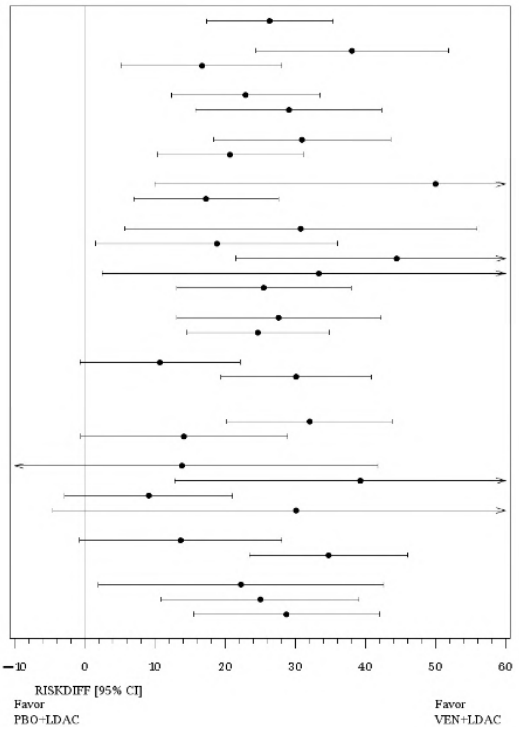
	PBO + LDAC n/N (%)	VEN + LDAC n/N (%)	RISKDIFF [95% CI] VEN + LDAC vs.PBO + LDAC
ALL SUBJECTS	9/ 68 (13.2)	68/143 (47.6)	34.32 [22.8 ,45.8]
GENDER			
FEMALE	1/ 29 (3.4)	34/ 65 (52.3)	48.86 [35.0 ,62.7]
MALE	8/ 39 (20.5)	34/ 78 (43.6)	23.08 [6.3 ,39.9]
AGE (YEARS)			
18 - < 75	4/ 28 (14.3)	27/ 61 (44.3)	29.98 [12.0 ,48.0]
>= 75	5/ 40 (12.5)	41/ 82 (50.0)	37.50 [22.6 ,52.4]
AML STATUS			
DE NOVO	8/ 45 (17.8)	47/ 85 (55.3)	37.52 [22.1 ,52.9]
SECONDARY	1/ 23 (4.3)	21/ 58 (36.2)	31.86 [16.9 ,46.8]
TYPE OF SECONDARY AML			
THERAPY RELATED TO AML	0/ 4	4/ 6 (66.7)	66.67 [28.9 ,100.0]
POST MDS/CMML	1/ 19 (5.3)	17/ 52 (32.7)	27.43 [11.2 ,43.7]
REGION			
US	0/ 6	6/ 13 (46.2)	46.15 [19.1 ,73.3]
EU	4/ 26 (15.4)	29/ 56 (51.8)	36.40 [17.3 ,55.5]
JAPAN	1/ 9 (11.1)	8/ 18 (44.4)	33.33 [2.5 ,64.1]
CHINA	0/ 6	3/ 9 (33.3)	33.33 [2.5 ,64.1]
REST OF WORLD	4/ 21 (19.0)	22/ 47 (46.8)	27.76 [5.7 ,49.8]
BASELINE ECOG			
GRADE < 2	6/ 34 (17.6)	40/ 74 (54.1)	36.41 [19.3 ,53.5]
GRADE >= 2	3/ 34 (8.8)	28/ 69 (40.6)	31.76 [16.8 ,46.8]
SUBJECTS WHO RECEIVED PRIOR HMA FOR MDS			
YES	1/ 14 (7.1)	7/ 28 (25.0)	17.86 [-3.1 ,38.8]
NO	8/ 54 (14.8)	61/115 (53.0)	38.23 [25.1 ,51.4]
CYTOGENETIC RISK CATEGORIZATION			
FAVORABLE	0/ 3	1/ 1 (100)	100.00 [100.0 ,100.0]
INTERMEDIATE	7/ 43 (16.3)	50/ 90 (55.6)	39.28 [24.2 ,54.3]
POOR	2/ 20 (10.0)	13/ 47 (27.7)	17.66 [-0.7 ,36.0]
MOLECULAR MARKER			
FLT3	4/ 9 (44.4)	9/ 20 (45.0)	0.56 [-38.6 ,39.7]
IDH1/2	4/ 12 (33.3)	12/ 21 (57.1)	23.81 [-10.2 ,57.9]
TP53	0/ 9	4/ 22 (18.2)	18.18 [2.1 ,34.3]
NPM1	4/ 7 (57.1)	14/ 18 (77.8)	20.63 [-20.8 ,62.0]
AML WITH MYELODYSPLASIA RELATED CHANGES (AML-MRC)			
YES	2/ 27 (7.4)	21/ 57 (36.8)	29.43 [13.5 ,45.4]
NO	7/ 41 (17.1)	47/ 86 (54.7)	37.58 [22.0 ,53.2]
BONE MARROW BLAST COUNT			
<30%	3/ 18 (16.7)	21/ 42 (50.0)	33.33 [10.4 ,56.2]
30-<50%	2/ 22 (9.1)	16/ 36 (44.4)	35.35 [15.2 ,55.5]
>=50%	4/ 28 (14.3)	31/ 65 (47.7)	33.41 [15.6 ,51.2]



LDAC = LOW DOSE CYTARABINE, PBO = PLACEBO, VEN = VENETOCLAX, RISKDIFF = RISK 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 18FEB2019.

ANALYSIS OF CR + CRh BY THE INITIATION OF CYCLE 2 BY SUBGROUP
(FULL ANALYSIS SET)

	PBO + LDAC n/N (%)	VEN + LDAC n/N (%)	RISKDIFF [95% CI] VEN + LDAC vs.PBO + LDAC
ALL SUBJECTS	3/ 68 (4.4)	44/143 (30.8)	26.36 [17.4 ,35.4]
GENDER			
FEMALE	1/ 29 (3.4)	27/ 65 (41.5)	38.09 [24.4 ,51.8]
MALE	2/ 39 (5.1)	17/ 78 (21.8)	16.67 [5.2 ,28.1]
AGE (YEARS)			
18 - < 75	0/ 28	14/ 61 (23.0)	22.95 [12.4 ,33.5]
>= 75	3/ 40 (7.5)	30/ 82 (36.6)	29.09 [15.8 ,42.3]
AML STATUS			
DE NOVO	3/ 45 (6.7)	32/ 85 (37.6)	30.98 [18.4 ,43.6]
SECONDARY	0/ 23	12/ 58 (20.7)	20.69 [10.3 ,31.1]
TYPE OF SECONDARY AML			
THERAPY RELATED TO AML	0/ 4	3/ 6 (50.0)	50.00 [10.0 ,90.0]
POST MDS/CMML	0/ 19	9/ 52 (17.3)	17.31 [7.0 ,27.6]
REGION			
US	0/ 6	4/ 13 (30.8)	30.77 [5.7 ,55.9]
EU	3/ 26 (11.5)	17/ 56 (30.4)	18.82 [1.6 ,36.0]
JAPAN	0/ 9	8/ 18 (44.4)	44.44 [21.5 ,67.4]
CHINA	0/ 6	3/ 9 (33.3)	33.33 [2.5 ,64.1]
REST OF WORLD	0/ 21	12/ 47 (25.5)	25.53 [13.1 ,38.0]
BASELINE ECOG			
GRADE < 2	3/ 34 (8.8)	27/ 74 (36.5)	27.66 [13.1 ,42.2]
GRADE >= 2	0/ 34	17/ 69 (24.6)	24.64 [14.5 ,34.8]
SUBJECTS WHO RECEIVED PRIOR HMA FOR MDS			
YES	0/ 14	3/ 28 (10.7)	10.71 [-0.7 ,22.2]
NO	3/ 54 (5.6)	41/115 (35.7)	30.10 [19.4 ,40.8]
CYTOGENETIC RISK CATEGORIZATION			
FAVORABLE	0/ 3	0/ 1	- [-]
INTERMEDIATE	2/ 43 (4.7)	33/ 90 (36.7)	32.02 [20.2 ,43.8]
POOR	1/ 20 (5.0)	9/ 47 (19.1)	14.15 [-0.6 ,28.9]
MOLECULAR MARKER			
FLT3	1/ 9 (11.1)	5/ 20 (25.0)	13.89 [-14.1 ,41.8]
IDH1/2	1/ 12 (8.3)	10/ 21 (47.6)	39.29 [12.8 ,65.8]
TP53	0/ 9	2/ 22 (9.1)	9.09 [-2.9 ,21.1]
NPM1	1/ 7 (14.3)	8/ 18 (44.4)	30.16 [-4.5 ,64.8]
AML WITH MYELODYSPLASIA RELATED CHANGES (AML-MRC)			
YES	2/ 27 (7.4)	12/ 57 (21.1)	13.65 [-0.8 ,28.1]
NO	1/ 41 (2.4)	32/ 86 (37.2)	34.77 [23.5 ,46.0]
BONE MARROW BLAST COUNT			
<30%	2/ 18 (11.1)	14/ 42 (33.3)	22.22 [1.9 ,42.6]
30-<50%	0/ 22	9/ 36 (25.0)	25.00 [10.9 ,39.1]
>=50%	1/ 28 (3.6)	21/ 65 (32.3)	28.74 [15.5 ,42.0]



Study M14-387

Phase 1/2 Study of venetoclax in combination with low-dose cytarabine in treatment-naïve subjects with acute myelogenous leukemia who are ≥ 60 years of age and who are not eligible for standard anthracycline-based induction therapy.

First Subject First Visit: 31 December 2014

Last Subject Last Visit: has not yet occurred;

Data cutoff for interim CSR: 19 July 2019

Methods

The study consisted of 3 portions. The first was a Phase 1 (dose-escalation portion), that evaluated the safety and PK profile of venetoclax administered with LDAC with the objectives of defining the MTD and generating data to support a RPTD. A subsequent initial Phase 2 portion evaluated whether the RPTD had sufficient efficacy and acceptable toxicity to warrant further development of the combination therapy. Subsequently, a Phase 2, Cohort C was enrolled to evaluate the ORR for subjects who were allowed additional supportive medications (e.g., strong CYP3A inhibitors), if medically indicated.

Study participants

Main inclusion criteria: ≥ 60 years of age; AML ineligible for standard induction; no prior treatment for AML with the exception of hydroxyurea, allowed through the first cycle of study treatment, and treatment for prior MDS; ECOG: 0-2 for patients ≥ 75 years of age and 0-3 ≥ 60 to 74 years.

Treatments

In portion 1, 18 patients received daily po doses of venetoclax ranging from 200 to 2000 mg, in combination with cytarabine 20 mg/m^2 d1-10 for 2 cycles (a cycle has 28 days). In portion 2, 53 patients received venetoclax at the suggested target dose of 600 mg. In portion 3, 21 patients received the same treatment, with additional supportive medication as needed.

Outcomes/endpoints

Primary: ORR (CR+CRi+PR)

Secondary: leukemia response (rates of complete remission [CR], complete remission with incomplete blood count recovery [CRi], partial remission [PR], and morphologically leukemia-free status [MLFS]), duration of response (DOR), and overall survival (OS)

Outcomes and estimation

In subjects treated with venetoclax (600 mg) in combination with LDAC (n=82), the median duration of survival follow-up was 41.7 months and ORR was 54.9% (45/82). The CR+CRi rate was 53.7% with a CR rate of 25.6% and a CRi rate of 28%.

The median duration of CR + CRi was 9.8 months, DoCR 14.8 months, and DoCRi 4.7 months.

The CR+CRh rate was 46.3% with a mDoR of 11 months; the CRh was 20.7%, with a median duration of 6.6 months. The median OS was 9.7 months, in comparison to LDAC monotherapy, with a mOS of 5 to 6 months. Among patients who achieved CR+CRh, the mOS was 19.8 months; for those who did not, the mOS was 3.7 months. In CR+CRi patients the mOS was 18.4 months

60/82 subjects (73.2%) were dependent on RBC or platelet transfusion at baseline and 27/60 previously dependent subjects (45%) became transfusion independent while receiving study drugs. Of the 22 subjects who were independent of both RBC and platelet transfusion at baseline, 10/22 subjects (45.5%) achieved a 56-day or greater RBC and platelet transfusion-free period while actively receiving study drugs.

Results in subpopulations with poor prognosis

- Cytogenetic risk group: CR+ CRh rate of 57.1%, CR + CRi rate of 63.3%, and a CR rate of 34.7% were observed in the intermediate risk group (n=49) and a CR + CRh rate of 34.6%, CR + CRi rate of 42.3%, and a CR rate of 15.4% in the poor risk group (n=26), with a mDOR of CR + CRh of 11.9 months and 5.6 months, respectively, and 10.8 months and 4.7 months for CR+CRi. mOS: 14.2 months and 4.8 months, respectively. Patients achieved transfusion independence regardless of cytogenetic risk group.

- Age: for AML ≥ 75 years old (n= 40) the results were: CR + CRh rate of 55%, CR + CRi rate of 60% and a CR rate of 27.5% compared to 42 patients <75 years old (n = 42, who had a CR + CRh rate of 38.1%, a CR+ CRi rate of 47.6%, and a CR rate of 23.8%, the mDOR of CR + CRh was 15 months, of CR+ CRi was 14.8 months, and of CR was 25.9 months for subjects ≥ 75 years old, compared to 10 months, 6.1 months, and 11.6 months, respectively, for subjects < 75 years old. The mOS for ≥ 75 was 14.9 months compared 6.5 months in patients < 75 years old. Among the 40 subjects ≥ 75 years of age, 24/40 subjects (60%) achieved RBC transfusion independence and 25/40 subjects (62.5%) achieved platelet transfusion independence compared to 35.7% and 54.8%, respectively, for subjects < 75 years of age.

- Primary/secondary AML: Secondary AML, AML arising from an antecedent hematologic disorder, or AML after exposure to chemotherapy or radiation is a well-recognized poor prognostic feature for patients with newly diagnosed AML. Among the 40 patients who received venetoclax (600 mg) in combination with LDAC with secondary AML, 32.5% achieved a CR + CRh and 35.0% achieved a CR + CRi (CR rate: 5%); a CR + CRh rate of 59.5% and a CR+ CRi rate of 71.4% (CR rate: 45.2%) were achieved in subjects who had primary AML (n=42). The mDoR of CR + CRh was 8.3 months, of CR+ CRi 8.1 months, and of CR was 9.6 months, compared to 31.2, 10.8, and 25.9 months, respectively, for subjects who had primary AML. The mOS was 4 months vs 15.7 months, respectively. In secondary AML, 15/40 patients (37.5%) achieved RBC transfusion independence and 20/40subjects (50%) achieved platelet transfusion independence compared to 57.1% and 66.7%, respectively, for subjects who had primary AML.

- Prior HMA treatment for antecedent hematological disorders (poor prognosis; these patients are excluded from most treatment-naïve AML studies of low intensity therapy), n=24: 33.3% achieved a CR + CRh and a CR + CRi each (CR rate: 4.2%) while a CR + CRh rate of 51.7% and a CR + CRi rate of 62.1% (CR rate: 34.5%) were observed in subjects not previously treated with an HMA (n = 58). The mDOR of CR + CRh was 5.5 months,of CR+ CRi 5.3months, and of CR 7.2 months, 16.9, 11.6, and 25.9 months, respectively, for subjects who did not receive a prior HMA for antecedent hematological disorders. The mOS was 4.1 months vs 11.7 months. Among the 24 subjects who received a prior HMA for antecedent hematological disorders treated with venetoclax 600mg in combination with LDAC, 9/24 subjects (37.5%) achieved RBC transfusion independence and 12/24 subjects (50.0%) achieved platelet transfusion independence compared to 51.7% and 62.1%, respectively, for subjects not treated with a prior HMA.

- AML with MDS-related change, n=40: 47.5% achieved a CR + CRh and 52.5% achieved a CR + CRi (CR rate: 20%); a CR + CRh rate of 45.2% and a CR+ CRi rate of 54.8% (CR rate: 31%) were achieved in subjects who had AML with no MDS-related changes (n=42). The mDOR of CR + CRh was 10 months, CR+ CRi 9.8 months, and of CR 12.1 months for subjects who had AML with MDS-related changes, compared to 15, 10.8, and 25.9 months, respectively, for subjects who had AML with no MDS-related changes. The mOS was 10.1months vs 9.0 months in AML with no MDS-related changes. 18/40 subjects (45%) achieved RBC transfusion independence and 62.5% platelet transfusion independence compared to 50% and 54.8%, respectively, for subjects who had AML with no-MDS-related changes.

- Biomarkers: Response rates (CR/CRh/CRi) and mOS for subjects with IDH 1/2 or NPM1 mutations were greater than response rates and longer than the median OS for the overall population (subjects treated with venetoclax [600 mg] in combination with LDAC) which is consistent with the better prognosis for subjects with these mutations compared to subjects without IDH 1/2 or

NPM1 mutations. The patients with FLT-3 and TP53 mutations had lower response rates and shorter median OS compared to overall population; however, the response rates are clinically meaningful for this difficult-to-treat subject population who typically have poor prognosis compared to subjects without FLT-3 or TP53 mutations. IDH 1/2 (n = 18): 12 subjects (66.7%) achieved CR + CRh and 13 subjects (72.2%) achieved CR+ CRi with a CR rate of 38.9%, the mOS was 15.9 months. FLT-3 (n=15): 5 patients (33.3%) achieved CR + CRh and 6 (40%) CR + CRi with a CR rate of 20%, with a mOS of 6.5 months. TP53 (n = 10): 2 patients achieved CR + CRh and 3 achieved CR + CRi with a CR rate of 0; mOS was 3.7 months. NPM1 (n = 9): 8 patients (88.9%) achieved CR + CRh and 8 subjects (88.9%) achieved CR + CRi with a CR rate of 77.8%; the mOS was not reached [95% CI: 0.5, -]; the 12-month survival rate was 88.9%.

- MRD: among the 38 patients treated with venetoclax (600 mg) in combination with LDAC who achieved a CR + CRh, 34.2% a best MRD value of< 0.1% with a median OS of 29.6 months (survival rate at 12 months: 92.3%) and 25 subjects had a best MRD value of ≥ 0.1% with a median OS of 18.4 months (survival rate at 12 months: 75.1%). CRh is a clinically meaningful response as demonstrated by DOR, OS, transfusion independence rates, duration of transfusion independence, effect on AML-related comorbidities such as rates of infections, and time to hospitalization as compared to non-responders.

- For subjects who experienced an AE that resulted in a dose reduction or dose interruption, the CR, CR + CRh, and CR + CRi rates remained similar to or greater than the rates of subjects that had no dose reduction or interruption. A CR rate of 31.3%, a CR + CRh rate of 58.3%, and a CR + CRi rate of 68.8% were achieved in the dose-interrupted/-reduced subject population (n=48); whereas, a CR rate of 17.6%, a CR + CRh rate of 29.4%, and a CR + CRi rate of 32.4% were achieved in the subject population with no dose interruption or reduction(n=34). The mDORs were greater than or similar for subjects who had a dose interruption or reduction compared to subjects with no dose interruption or reduction. For subjects who had a dose interruption or reduction, the median duration of CR was 30.9 months, of CR + CRh 14.3months, and of CR + CRi was 9.8 months, compared to 11.8, 10.2, and 10.2 months, respectively, for subjects who did not have a dose interruption or reduction.

Summary of main studies

Summary of Efficacy for Study M15-656

Title: a randomized, double-blind, placebo-controlled phase 3 study of venetoclax in combination with azacitidine versus azacitidine in treatment naïve subjects with acute myeloid leukemia who are ineligible for standard induction therapy			
Study identifier	EudraCT 2016-001466-28		
Design	Randomized, double-blind, placebo-controlled Phase 3 study		
	Duration of Main phase:		First Subject First Visit: 02 Feb 2017 Last Subject Last Visit: Ongoing Data cut-off: 04 Jan 2020
	Duration of Run-in phase:		3-day ramp up beginning with venetoclax 100 mg dose on day 1 to reach the final dose of 400 mg on day 3 of cycle 1.
Hypothesis	Superiority		
Treatments groups	Ven+ azacitidine		Venetoclax 400 mg orally QD on Dd1–28 plus azacitidine 75 mg/m^2 sc or iv (per local label) QD for 7 days, N = 286
	placebo+Aza		Placebo orally QD on d1–28 plus azacitidine 75 mg/m2 SC or IV (per local label) QD for 7 days, N = 145
Endpoints and definitions	CR rate	Complete remission rate	The proportion of subjects who achieve CR at any time point during the study. CR is defined as absolute neutrophil count > 10^3/μL, platelets > 10^5/μL, red cell transfusion (RBC) independence, and bone marrow with < 5% blasts, and absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
	CRi rate	Complete remission with incomplete blood count recovery rate	The proportion of subjects who achieve CRi at any time point during the study. CRi is defined by all criteria as for CR except for residual neutropenia ≤ 10^3/μL or thrombocytopenia ≤ 10^5/μL. RBC transfusion dependence is also defined as CRi.
	CRh rate	Complete remission with partial hematologic recovery rate	The proportion of subjects who achieve CRh at any time point during the study. CRh is defined as 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.
	CR + CRi rate		
	CR + CRh rate		
	OS	Overall survival	The number of days from the date of randomization to the date of death.

	--	Postbaseline transfusion independence rate	The proportion of subjects known to achieve postbaseline transfusion independence. Postbaseline transfusion independence is defined as a period of at least 56 days with no RBC or platelet transfusion between the first dose of study drug and the last dose of study drug + 30 days , or disease progression, or confirmed morphological relapse, or post-treatment therapy, or death, or data cutoff date, whichever occurred earlier.
	MRD response rate	Minimal/Measurable residual disease response rate	The proportion of subjects who achieve either CR, CRi, or CRh and a best MRD value $< 10^{-3}$ of residual blasts per leukocytes as measured centrally in bone marrow.
	EFS	Event-free survival	The number of days from randomization to the date of progressive disease, relapse from CR or CRi, treatment failure defined as failure to achieve CR, CRi or MLFS after at least 6 cycles of study treatment, or death from any cause.

Database lock	18 Mar 2020		
Results and Analysis			
Analysis description	**Primary and Secondary Analyses**		
Analysis population and time point description	For all endpoints except the dual primary endpoint of CR + CRi: Full (Efficacy) Analysis Set: All subjects randomized under protocol amendment 1 and later versions; excludes 2 subjects randomized under the original protocol. Data cut-off: 04 Jan 2020 For CR + CRi: Efficacy Analysis Set, Group 2 - Including the First 226 Subjects for CR + CRi IA1. Data cut-off: 01 October 2018		
Descriptive statistics and estimate variability	Treatment Group	Ven + Aza N = 286	Pbo + Aza N = 145
	Primary Endpoints		
	CR + CRi, n (%) (for the First 226 pat, IA1)	96/147(65.3)	20/79 (25.3)
	95% CI	57.0, 73.0	16.2, 36.4
	OS, median (months)	14.7	9.6
	95% CI	11.9, 18.7	7.4, 12.7
	HR	0.662 (0.518, 0.845)	
	Secondary Efficacy Endpoints		
	CR + CRi, n (%) (Full Analysis Set, Group 2)	190 (66.4)	41 (28.3)
	95% CI	60.6, 71.9	21.1, 36.3
	CR + CRh, n (%)	185 (64.7)	33 (22.8)
	95% CI	58.8, 70.2	16.2, 30.5
	Postbaseline transfusion independence		
	RBC and platelets, n (%)	166 (58.0)	49 (33.8)
	95% CI	52.1, 63.8	26.2, 42.1
	RBC, n (%)	171 (59.8)	51 (35.2)

	95% CI	53.9, 65.5	27.4, 43.5
	Platelets, n (%)	196 (68.5)	72 (49.7)
	95% CI	62.8, 73.9	41.3, 58.1
	EFS, median (months)	9.8	7.0
	95% CI	8.4, 11.8	5.6, 9.5
	MRD, n (with an assessment by the cutoff date)	216	104
	MRD < 10^{-3} and CR + CRi response, n (%)	67 (23.4)	11 (7.6)
	95% CI	18.6, 28.8	3.8, 13.2
	MRD < 10^{-3} and CR + CRh response, n (%)	64 (22.4)	9 (6.2)
	95% CI	17.7, 27.7	2.9, 11.5
Notes	[a] Cochran-Mantel-Haenszel test stratified by age (18 – < 75, ≥ 75 years) and cytogenetics (intermediate risk, poor risk) from IVRS/IWRS. [b] Log-rank test stratified by age (18 – < 75, ≥ 75 years) and cytogenetics (intermediate risk, poor risk) from IVRS/IWRS. [c] Cox Proportional Hazard Model stratified by age (18 – < 75, ≥ 75 years) and cytogenetics (intermediate risk, poor risk) from IVRS/IWRS. [d] A linear mixed-effects regression model that includes the following factors: baseline score, stratification factors (age and cytogenetics) treatment arm, visit, and treatment arm by visit interaction. Only subjects with both baseline and post-baseline data are included.		

Summary of Efficacy for Study M14-358

Title: a phase 1b study of abt-199 (gdc-0199) in combination with azacitidine or decitabine in treatment-naïve subjects with acute myelogenous leukemia who are ≥ 60 years of age and who are not eligible for standard induction therapy		
Study identifier	EudraCT 2014-000687-18	
Design	Phase 1b open-label, non-randomized, multicenter study in 2 stages: a dose escalation stage and a dose expansion stage with 2 expansion arms, in addition to drug-drug interaction (DDI) sub-study	
	Duration of Main phase:	First subject, first dose of venetoclax:19 Nov 2014 Last subject, last visit: ongoing Data cutoff: 19 Jul 2019
	Duration of Run-in phase:	Cohorts 1 – 3: venetoclax ramp up Days 2-6 to target dose of 400 mg (Cohort 1) or 800 mg (Cohort 2); ramp up Days 2-5 to 800 mg (Cohort 3). Cohort 4: venetoclax ramp up Days 2-6 to target dose of 1200 mg Dose expansion stage: venetoclax ramp up Days 1-3 to target dose of 400 mg or ramp up Days 1-4 to target dose of 800 mg DDI substudy: venetoclax ramp up Days 2-6 to target dose of 400 mg
Hypothesis	Not applicable	
Treatment groups	Dose Escalation Stage	

	Arm A	venetoclax 400 mg + decitabine 4 cycles of 28 days each, N = 23 (4 cohorts, up to 6 subjects each) Cohorts 1 – 3, venetoclax Cycle 1:oral QD ramp up d2-6 to target dose of 400 mg (cohort 1) or 800 mg (cohort 2); ramp up d2-5 to 800 mg (Cchort 3). Cycle 2 and beyond:oral, QD, Days 1-28 Cohort 4, venetoclax Cycle 1:ora QD d2-21, ramp up d 2-6 to target dose of 1200 mg Cycle 2 and beyond: oral, QD, d1-21 All cohorts, decitabine Cycles 1-4:iv infusion, 20 mg/m^2 over 1 hour, d1-5
	Arm B	venetoclax 400 mg + azacitidine 4 cycles of 28 days each, N = 22 (4 cohorts, up to 6 subjects each) Cohorts 1-3, venetoclax Cycle 1: oral QD, ramp up d2-6 to target dose of 400 mg (cohort 1) or 800 mg (cohort 2); ramp up d 2-5 to 800 mg (cohort 3) Cycle 2 and beyond: oral, QD, d1-28 Cohort 4, venetoclax Cycle 1:oral, QD, d 2-21, ramp up d2-6 to target dose of 1200 mg Cycle 2 and beyond: oral, QD, d1-21 All cohorts, azacitidine Cycles 1-4: 75 mg/m^2 iv or sc, d1-7
	Dose Expansion Stage: Expansion 1	
	Arm D1	venetoclax 400 mg (with ramp up d1-4 in cycle1) 4 cycles of 28 days each, N = 25 decitabine Cycles 1-4:20 mg/m^2 iv d1-5
	Arm D2	venetoclax 800 mg 4 cycles of 28 days, N = 25 (with ramp up d1-4 in cycle 1) decitabine Cycles 1-4: 20 mg/m^2 iv, d1-5
	Arm E1	venetoclax 400 mg (with ramp up d1-3 in cycle 1) 4 cycles of 28 days, N = 25 azacitidine Cycles 1-4: 75 mg/m^2 iv or sc d1-7
	Arm E2	venetoclax 800 mg (with ramp up d1-4 in cycle1) 4 cycles of 28 days, N = 25 azacitidine Cycles 1-4:75 mg/m^2 iv or sc, d1-7
	Dose Expansion Stage: Expansion 2	
	Arm G	venetoclax 400 mg (with ramp up d1-3 cycle1) 4 cycles of 28 days, N = 55 azacitidine Cycles 1-75 mg/m^2 iv or sc d1-7

Endpoints and definitions	CR rate	Complete remission rate	The proportion of subjects who achieve CR at any time point during the study. Per protocol: CR is defined as absolute neutrophil count ≥ 10^3/µL, platelets ≥ 10^5/µL, red blood cell (RBC) transfusion independence, and bone marrow with < 5% blasts. Modified: CR is defined as ANC > 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. CR responses not meeting modified criteria were downgraded to CRi or CRh. Differences between values defined by per protocol criteria and values defined by modified criteria were in CR rate and CR duration only.		
	CRi rate	Complete remission with incomplete blood count recovery rate	The proportion of subjects who achieve CRi at any time point during the study. CRi is defined as bone marrow with < 5% blasts, absolute neutrophils < 10^3/µL or platelets < 10^5/µL (thrombocytopenia).		
	CRh rate	Complete remission with partial hematologic recovery rate	The proportion of subjects who achieve CRh at any time point during the study. CRh is defined as bone marrow with < 5% blasts, absolute neutrophil count (ANC) > 0.5 × 10^3/µL (1 week [≥ 7 days] platelet transfusion-free period prior to the hematology laboratory sample collection) without recovery of platelets > 0.5 × 10^5/µL and ANC > 10^3/µL, which would define CR.		
	CR + CRi rate				
	CR + CRh rate				
	--	Duration of response	The number of months from the date of first response to relapse or death due to disease progression.		
	OS	Overall survival	The number of days from the date of first dose to the date of death.		
	--	Postbaseline transfusion independence rate	The number of subjects known to achieve postbaseline transfusion independence. Postbaseline transfusion independence is defined as a period of at least 56 days with no RBC or platelet transfusion between the first dose of study drug and the last dose of study drug + 30 days, disease progression (including clinical progression), or death, or data versioning date, whichever occurs earlier.		
Database lock	30 Aug 2019				
Results and Analysis					
Analysis description					
Analysis population and time point description	Full Analysis Set:All subjects who received at least 1 dose of venetoclax. All 212 subjects enrolled in the study were included in the Full Analysis Set. Data cut-off:19 Jul 2019				
Descriptive statistics and estimate variability	Treatment group	All Doses[a] Venetoclax + Azacitidine	400 mg Venetoclax + Azacitidine	All Doses[a] Venetoclax + Decitabine	**400 mg Venetoclax + Decitabine**
	Number of subjects	127	84	73	**31**
	Best Response				

	CR + CRi, n (%)	84 (66.1)	60 (71.4)	53 (72.6)	23 (74.2)
	95% CI[c]	57.2, 74.3	60.5, 80.8	60.9, 82.4	55.4, 88.1
	CR + CRh, n (%)	77 (60.6)	54 (64.3)	50 (68.5)	22 (71.0)
	95% CI[c]	51.6, 69.2	53.1, 74.4	56.6, 78.9	52.0, 85.8
	CR, n (%)	53 (41.7)	37 (44.0)	37 (50.7)	17 (54.8)
	95% CI[c]	33.0, 50.8	33.2, 55.3	38.7, 62.6	36.0, 72.7
	DoR				
	CR + CRi, median (months)	17.9	21.9	13.6	15.0
	95% CI[d]	13.4, 26.5	15.1, 30.2	7.2, 30.0	7.2, 30.0
	CR+CRh, median (months)	18.1	21.7	12.2	15.3
	95% CI[d]	13.3, 26.5	14.6, 30.3	7.5, 30.2	7.2, 30.2
	CR, median (months)	21.2	23.5	30.0	21.3
	95% CI[d]	15.1, 30.2	15.1, 30.2	7.5, --	6.9, --
	Overall Survival				
	median, months	14.9	16.4	16.6	16.2
	95% CI[d]	11.3, 20.5	11.3, 24.5	12.4, 26.8	9.1, 27.8
	Postbaseline transfusion independence				
	RBC, n (%)	80 (63.0)	54 (64.3)	47 (64.4)	19 (61.3)
	95% CI[c]	54.0, 71.4	53.1, 74.4	52.3, 75.3	42.2, 78.2
	Platelets, n (%)	91 (71.7)	59 (70.2)	58 (79.5)	27 (87.1)
	95% CI[c]	63.0, 79.3	59.3, 79.7	68.4, 88.0	70.2, 96.4

Notes

[a] Includes subjects who received 400 mg, 800 mg, or 1200 mg of venetoclax.

[b] Subjects received 400 mg venetoclax + IV decitabine 20 mg/m^2 + oral posaconazole 300 mg.

[c] 95% confidence interval is from the exact binomial distribution.

[d] Kaplan-Meier estimate.

Summary of Efficacy for Study M16-043

Title: 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 ineligible for intensive chemotherapy		
Study identifier	EudraCT 2016-003900-30	
Design	Phase 3, randomized, double-blind, placebo-controlled, multicenter study, 2 treatment arms	
	Duration of main phase:	First Subject First Visit: 24 May 2017 Last Subject Last Visit: Ongoing Data cut-off: 15 February 2019 for primary analysis; 15 August 2019 for 6-month follow-up analysis
	Duration of Run-in phase:	4-day ramp up starting at 100 mg dose on d1, 200 mg dose on d2, 400 mg dose on d3, and 600 mg dose on d4 of cycle 1
Hypothesis	Superiority	

Treatments groups	Venetoclax + LDAC		Venetoclax 600 mg orally QD on d1-28 plus LDAC 20 mg/m^2 sc QD on d1-10. 28-day cycles will continue until DP or unacceptable toxicity or intolerance. N = 143
	Placebo + LDAC		Placebo plus LDAC 20 mg/m^2 scin the same fashion as above. N = 68
Endpoints and definitions	OS	Overall survival	Number of days from the date of randomization to the date of death.
	CR rate	Complete remission rate	The proportion of subjects who achieve CR at any time point during the study. CR is defined as no morphologic evidence of AML and absolute neutrophil count > 10^3/µL, platelets > 10^5/µL, red blood cell (RBC) transfusion independence, and bone marrow with < 5% blasts, absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
	CRi rate	Complete remission with incomplete blood count recovery rate	The proportion of subjects who achieve CRi at any time point during the study. CRi is defined as all criteria as CR except for residual neutropenia ≤ 10^3/µL or thrombocytopenia ≤ 10^5/µL. If all criteria for CR are met except RBC transfusion independence, this also fulfills CRi criteria.
	CRh rate	Complete remission with partial hematologic recovery rate	The proportion of subjects who achieve CRh at any time point during the study. CRh is defined as 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.
	CR + CRi rate		
	CR + CRh rate		
	--	Postbaseline transfusion independence rate	The proportion of subjects who achieve a period of at least 56 days with no red blood cell (RBC) or platelet transfusion between the first dose of study drug and the last dose of study drug + 30 days.
	MRD response rate	Minimal/Measurable residual disease response rate	The number of subjects who achieve either CR, CRi, or CRh and a best MRD response < 10^{-3} of residual blasts per leukocytes as measured centrally in bone marrow.
	EFS	Event-free survival	The number of days from randomization to the date of progressive disease, relapse from CR or CRi, treatment failure defined as failure to achieve CR, CRi or MLFS, or death from any cause.
Database lock	Primary analysis: 02 Apr 2019 Post-hoc 6-month follow-up analysis: 18 Oct 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set: All randomized subjects. Data cut-off: 15 February 2019 for primary analysis		
Descriptive statistics and estimate variability	**Primary Efficacy Endpoint**		
	Treatment group	Ven + LDAC N = 143	Placebo + LDAC N = 68

	OS, median duration (months)	7.2	4.1
	95% CI	5.6, 10.1	3.1, 8.8
	Secondary Efficacy Endpoints		
	CR + CRi, n (%)	68 (47.6)	9 (13.2)
	95% CI	39.1, 56.1	6.2, 23.6
	CR + CRi, n (%) by initiation of Cycle 2	49 (34.3)	2 (2.9)
	95% CI	26.5, 42.7	0.4, 10.2
	CR + CRh, n (%)	67 (46.9)	10 (14.7)
	95% CI	38.5, 55.4	7.3, 25.4
	CR + CRh, n (%) by initiation of Cycle 2	44 (30.8)	3 (4.4)
	95% CI	23.3, 39.0	0.9, 12.4
	Postbaseline Transfusion Independence		
	RBC, n (%)	58 (40.6)	12 (17.6)
	95% CI	32.4, 49.1	9.5, 28.8
	Platelets, n (%)	68 (47.6)	22 (32.4)
	95% CI	39.1, 56.1	21.5, 44.8
	MRD < 10^{-3} and CR + CRi response, n (%)	8 (5.6)	1 (1.5)
	95% CI	2.4, 10.7	0.0, 7.9
	MRD < 10^{-3} and CR + CRh response, n (%)	8 (5.6)	1 (1.5)
	95% CI	2.4, 10.7	0.0, 7.9
Effect estimate per comparison	Primary Endpoint	Comparison groups	Venetoclax + LDAC vs Placebo + LDAC
	OS	*p-value*[a] Hazard ratio[c] (95% CI)	0.114 0.749 (0.524, 1.071)
	Secondary Endpoints		
	EFS	*P-value*[a,b] Hazard ratio[c] (95% CI)	0.002 0.583 (0.416, 0.817)
Analysis description	**6-Month Follow-up Analysis (post-hoc)**		
Analysis population and time point description	Full Analysis Set: All randomized subjects. Data cut-off: 15 August 2019		
Descriptive statistics and estimate variability	Primary Efficacy Endpoint		
	Treatment group	Ven + LDAC N = 143	Placebo + LDAC N = 68
	OS, median duration (months)	8.4	4.1
	95% CI	5.9, 10.1	3.1, 8.8
	Secondary Efficacy Endpoints		
	CR + CRi, n (%)	69 (48.3)	9 (13.2)

	95% CI	39.8, 56.8	6.2, 23.6
	CR + CRi, n (%) by initiation of Cycle 2	49 (34.3)	2 (2.9)
	95% CI	26.5, 42.7	0.4, 10.2
	CR + CRh, n (%)	69 (48.3)	10 (14.7)
	95% CI	39.8, 56.8	7.3, 25.4
	CR + CRh, n (%) by initiation of Cycle 2	44 (30.8)	3 (4.4)
	95% CI	23.3, 39.0	0.9, 12.4
	EFS, median duration (months)	4.9	2.1
	95% CI	3.7, 6.4	1.5, 3.2
	MRD		
	$< 10^{-3}$ and CR + CRi response, n (%)	9 (6.3)	1 (1.5)
	95% CI	2.9, 11.6	0.0, 7.9
	$< 10^{-3}$ and CR + CRh response, n (%)	9 (6.3)	1 (1.5)
	95% CI	2.9, 11.6	0.0, 7.9
Effect estimate per comparison	Primary Endpoint	Comparison groups	Venetoclax + LDAC vs Placebo + LDAC
	OS	*P-value*[a,b] Hazard ratio[c] (95% CI)	0.040 0.704 (0.503, 0.985)
	Secondary Endpoints		
	EFS	*P-value*[a,b] Hazard ratio[c] (95% CI)	0.002 0.610 (0.442, 0.841)
Notes	LS = least squares; SE = standard error [a] Log-rank test stratified by age (18 - < 75, ≥ 75) and AML status (de novo, secondary) (18 to < 75, ≥ 75) from interactive voice response system (IVRS)/interactive web response system (IWRS). [b] Nominal *P-values*. [c] Cox proportional hazard model stratified by age (18 - < 75, ≥ 75) and AML status (de novo, secondary) (18 to < 75, ≥ 75) [d] Cochran-Mantel-Haenszel test stratified by age (18 - < 75, ≥ 75) and AML status (de novo, secondary) (18 to < 75, ≥ 75) [e] A linear mixed-effects regression model that includes the following factors: baseline score, stratification factors (age and cytogenetics), treatment arm, visit and treatment arm by visit interaction. Only subjects with both baseline and post-baseline data are included.		

Summary of Efficacy for Study M14-387

Title: A Phase 1/2 Study of Venetoclax in Combination with Low-Dose Cytarabine in Treatment-Naïve Subjects with Acute Myelogenous Leukemia Who Are ≥ 60 Years of Age and Who Are Not Eligible for Standard Anthracycline-Based Induction Therapy	
Study identifier	EudraCT 2014-002610-23

Design	Phase 1/2, nonrandomized, multicenter study consisting of 3 distinct portions: a Phase 1 dose-escalation portion to define the maximum tolerated dose (MTD) and generate data to support a recommended Phase 2 dose (RP2D); an initial Phase 2 portion to evaluate whether the RP2D had sufficient efficacy and acceptable toxicity to warrant further development of the combination therapy; and a Phase 2, Cohort C portion to evaluate the overall response rate (ORR) for subjects allowed additional supportive medications (strong cytochrome P450 [CYP]3A inhibitors) if medically indicated		
	Duration of Main phase:		First subject, first visit: 31 Dec 2014 Last subject, last visit: ongoing Efficacy data cut-off: 19 Jul 2019
	Duration of Run-in phase:		3-day ramp up for all dose groups except 1200 mg, 1600 mg, and 2000 mg groups which had a 5-day ramp up
	Duration of Extension phase:		Not applicable
Hypothesis	Not applicable		
Treatment groups	Phase 1: 2 cycles of 28 days each; N = 18, doses of 200, 400, 600, 800, 1200, 1600 and 2000 mg of venetoclax plus cytarabine 20 mg/m^2 sc d1-10		
	Initial Phase 2, 2 Cycles of 28 days each, N = 53		
	venetoclax + LDAC		Same schedule as Dose Level 1 600 mg
	Phase 2 Cohort C, 2 Cycles of 28 days each, N = 23 (21 received drug)		
	venetoclax + LDAC		venetoclax 600 mg (oral QD) Cycle 1: ramp up starting at 100 mg on d1, 200 mg on d2, 400 mg on d3 to 600 mg on d4-28. Cycle 2: 600 mg, d1-28 cytarabine 20 mg/m^2 sc all cycles d1-10
Endpoints and definitions	Primary Endpoint		
	ORR	Objective response rate	CR + CRi + PR
	Secondary Endpoints		
	CR rate	Complete remission rate	The proportion of subjects who achieve CR at any time point during the study. CR is defined as absolute neutrophil count (ANC) ≥ 10^3/µL, platelets ≥ 10^5/µL, red blood cell (RBC) transfusion independence, and bone marrow with < 5% blasts
	CRi rate	Complete remission with incomplete blood count recovery rate	The proportion of subjects who achieve CRi at any time point during the study. CRi is defined as lack of morphologic evidence of leukemia (blasts < 5%), and platelet counts < 10^5/µL or ANC < 10^3/µL

	CRh rate	Complete remission with partial hematologic recovery rate	The proportion of subjects who achieve CRh at any time point during the study. CRh is defined as bone marrow with < 5% blasts, ANC > 0.5 × 10^3/μL, and platelet counts > 0.5 × 10^5/μL (1-week [≥ 7 days] platelet transfusion-free period prior to the hematology laboratory sample collection) without recovery of platelets ≥ 10^5/μL and ANC ≥ 10^3/μL, which would define CR.
	CR + CRi rate	--	The proportion of subjects who achieve CR or CRi (each defined above) at any time point during the study.
	CR + CRh rate	--	The proportion of subjects who achieve CR or CRh each defined above) at any time point during the study.
	PR	Partial response rate	The proportion of subjects who achieve PR at any time point during the study. PR is defined as all hematologic values for CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.
	--	Duration of response	The number of days from date that subject achieved the endpoint (CR, CR+CRi, CR+CRh, CRi, CRh) to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest.
	OS	Overall survival	The number of days from the date of first dose to the date of death.
	--	Postbaseline transfusion independence rate	The number of subjects known to achieve postbaseline transfusion independence. Postbaseline transfusion independence is defined as a period of at least 56 days (≥ 56 days) with no RBC or platelet transfusion from first dose of study drug to the last dose of study drug + 30 days, disease progression (including clinical progression), or death, whichever is earlier.

Database lock	15 Oct 2019			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set: All subjects who received at least 1 dose of venetoclax. Data cut-off: 19 Jul 2019			
Descriptive statistics and estimate variability	Treatment group	Venetoclax 600 mg QD or 800 mg QD + LDAC	**Venetoclax 600 mg QD + LDAC**	**Venetoclax 600 mg QD + LDAC (Without Prior MPN[a])**
	N	92	82	78
	ORR, n (%)	49 (53.3)	45 (54.9)	45 (57.7)
	95% CI[b]	42.6, 63.7	43.5, 65.9	46.0, 68.8
Analysis Description	**Secondary Analyses**			
	Best Response			
	CR + CRi, n (%)	48 (52.2)	44 (53.7)	44 (56.4)

	CR + CRh, n (%)	42 (45.7)	38 (46.3)	38 (48.7)
	CR, n (%)	22 (23.9)	21 (25.6)	21 (26.9)
	CRi, n (%)	26 (28.3)	23 (28.0)	23 (29.5)
	CRh, n (%)	20 (21.7)	17 (20.7)	17 (21.8)
	PR, n (%)	1 (1.1)	1 (1.2)	1 (1.3)
	Duration of Response			
	CR + CRi, median (months)	9.8	9.8	9.8
	CR + CRh, median (months)	11.9	11.0	11.0
	CR, median (months)	14.8	14.8	14.8
	CRi, median (months)	3.5	4.7	4.7
	CRh, median (months)	5.6	6.6	6.6
	OS, median (months)	9.0	9.7	10.1
	95% CI[c]	5.6, 13.3	5.7, 14.0	6.1, 14.2
	Postbaseline transfusion independence rate			
	RBC, n (%)	41 (44.6)	39 (47.6)	38 (48.7)
	Platelets, n (%)	53 (57.6)	48 (58.5)	47 (60.3)
Notes	a. MPN = myeloproliferative neoplasm. b. 95% confidence interval is from the exact binomial distribution. c. Kaplan-Meier estimate.			

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The current extension of indication application includes two randomized, double-blind phase 3 studies for newly-diagnosed AML patients ineligible for intensive chemotherapy, supported by two phase 1 trials, all ongoing:

- Study M15-656 is a randomized, double-blind, placebo-controlled phase 3 study of venetoclax in combination with azacitidine versus placebo in combination with azacitidine. Study M14-358 is a non-randomized Phase 1b study of venetoclax in combination with azacitidine or decitabine.
- Study M16-043 is a randomized, double-blind, placebo-controlled phase 3 study of venetoclax in combination with low-dose cyatarabine (LDAC) versus placebo in combination with LDAC. Study M14-387 is a non-randomized phase 1/2 study of venetoclax in combination with LDAC

Study M15-656 – venetoclax + AZA vs placebo + AZA

This phase 3, multicenter, randomized, double-blind, placebo-controlled trial was conducted as confirmatory for phase 1b study M14-358. The clinical data cut-off date was January 2020. The study enrolled patients from February 2017 to May 2019.

Eligible patients were ≥18 years with a confirmed diagnosis of previously untreated AML and ineligible for standard induction therapy if: ≥75 years of age or had at least one of the following coexisting conditions precluding intensive chemotherapy: a history of congestive heart failure for which treatment was warranted or an ejection fraction ≤50% or chronic stable angina, a diffusing capacity of the lung for carbon monoxide of ≤65%, and an ECOG of 2 or 3. Patients with previous HMA therapy or chemotherapy for MDS were excluded, as well as those with favourable cytogenetic risk.

The primary endpoints were OS and composite complete remission rate (CR+CRi). Note that for the US, the primary endpoint was OS. The secondary endpoints were rate of CR, rate of CR and CRh, proportion of patients achieving composite complete remission (CR or CRi) by initiation of cycle 2, DOR, transfusion independence rate, MRD response rate, fatigue improvement and PRO assessments and EFS.

The study was randomized 2:1 (287:146). The stratification factors were age, region and cytogenetics. The primary analysis for CR + CRi was to occur 6 months after the first 225 subjects were randomized. Region will not be included in the stratified efficacy analysis since it is not considered as a prognostic factor. A significance level of 0.01 out of 0.05 (two-sided) was to be allocated for this analysis (the rest, a 0.04 significance level was allocated to the OS analysis). The intention-to-treat population included all 431 patients who underwent randomization.

Venetoclax was administered orally, once daily. For mitigation of the tumor lysis syndrome during cycle 1, the dose of venetoclax was 100 mg on day 1 and 200 mg on day 2; on day 3, the target dose of 400 mg was reached and continued until day 28. In all subsequent 28-day cycles, the dose of venetoclax was initiated at 400 mg daily. Azacitidine at a dose of 75 mg/m^2 sc or iv was administered in both arms on days 1-7 of every 28-day cycle.

Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a complete remission or a complete remission with incomplete hematologic recovery. Patients continued to receive treatment until disease progression or unacceptable toxic effects, until they withdrew consent, or until they met any protocol-defined criteria.

Except for patients who withdrew consent, all patients who discontinued a trial regimen were followed for survival.

Study M16-043 – venetoclax + LDAC vs placebo + LDAC

This randomized double-blind placebo-controlled phase 3 study enrolled patients between May 2017 and November 2018 across 76 sites. The data cut-off for the primary analysis was February 2019. An additional post-hoc follow-up analysis was performed 6 months later (August 2019).

Patients age ≥18 years with previously untreated AML ineligible for intensive chemotherapy were enrolled. Patients were considered ineligible for intensive induction chemotherapy if they were age ≥75 years or age 18-74 years and fulfilled at least 1 criterion associated with lack of fitness for intensive induction chemotherapy, including: ECOG 2 to 3, cardiac history of congestive heart failure requiring treatment or ejection fraction ≤50% or chronic stable angina, diffusion capacity of the lung for carbon monoxide ≤65%, creatinine clearance 30-45 mL/min, moderate hepatic impairment with total bilirubin 1.5 to 3 x ULN. Patients with secondary AML with or without prior treatment with HMAs for MDS were included; those with secondary AML from underlying myeloproliferative neoplasms were not. Exclusion criteria included prior therapy for AML (except hydroxyurea before or during the first cycle of study treatment) and any previous exposure to cytarabine for any indication.

The primary objective was OS, while secondary objectives were complete remission (CR); CR+CR with partial hematologic recovery (CRh); CR plus CR with incomplete hematologic recovery (CRi); proportion of patients with CR/CRi and CR/CRh by initiation of therapy cycle 2; rate of transfusion independence; event-free survival (EFS); minimal residual disease (MRD); response rates and OS in the subsets of patients with mutations in NPM1, IDH1/2, FLT3, or TP53; and PROs.

The planned sample size was 210 patients randomized 2:1(143:68); 133 events were required to be observed at the time of the primary analysis. The study was designed to detect a 45.5% reduction in mortality with 90% power and a significance level with 2-sided a of 0.05. An interim analysis was planned when 75% of death events occurred. The O'Brien-Fleming boundary was used to control the type 1 error rate at 0.05 (2 sided). Randomization was stratified by AML status (secondary vs de novo), age (18 to75 vs ≥75), and region. A number of unplanned analyses were performed to further explore the inconclusive OS results from the primary analysis and a post-hoc interim analysis with an additional 6 months of patient follow-up was added. The pre-planned procedure to control the type 1-error at 2-sided 5%-level will not hold. Accordingly, these post-hoc analyses to explore the OS outcome increase the risk of a false positive conclusion.

Venetoclax administration began at 100 mg on day 1 and increased stepwise over 4 days to reach the target dose of 600 mg (100, 200, 400, and 600 mg); dosing was continued at 600 mg per day from day 4 through day 28 and for all subsequent cycles. LDAC 20 mg/m2 sc daily was administered in both arms on days 1 to 10 for all cycles. Patients could continue receiving treatment until progression or until study treatment discontinuation criteria were met. Patients remained on study for OS assessment and follow-up, even if they initiated additional lines of treatment.

Response assessments were performed after cycle 1 (patients with resistant disease after cycle 1 had repeat assessments after cycle 2 or 3 to observe the initial CR/CRi response) and every 3 cycles thereafter (starting at the end of cycle 4 and continuing until PD) until 2 consecutive samples confirmed CR or CRi. Assessments were also performed if there was suspected relapse and/or at the final study visit.

Efficacy data

Study M15-656 – venetoclax + AZA vs placebo + AZA

In both groups, the median age was 76 years, and 60% of the patients were male; 61% of patients were ≥75 yo. Secondary AML was reported in 25.2% of the patients in the experimental arm and in 24.1% of

the patients in the control group, and poor cytogenetic risk was reported in 36.4% and 38.6%, respectively. In all, 141/286 patients in the experimental arm and 65/145 in the control arm had at least two reasons for ineligibility for intensive therapies.

The median duration of exposure in the experimental arm was 7.6 months (range: 0.1-30.7) and in the control arm 4.3 months (range: 0.1-24). Patients received venetoclax for a median of 7 cycles (range: 1-30) versus 4.5 cycles (range: 1-26) in the comparator arm.

The most common reason for trial discontinuation during the follow-up for survival was death: 161 patients (56%) in the venetoclax + azacitidine arm and 109 patients (75%) in the control group. The reasons for deaths, especially as DP, should be tabulated and presented, as the participant flow does not clarify this issue.

Regarding the primary endpoint (OS), the median duration of follow-up was 20.5 months (range, <0.1 to 30.7). At the time of the analysis, 73 of the patients in the experimental arm and 16 of the patients in the control group remained on study treatment. The median overall survival was 14.7 months (95% CI 11.9-18.7) in the venetoclax + azacitidine arm and 9.6 months (95% CI 7.4-12.7) in the control group (HR 0.66; 95% CI, 0.52-0.85).

Composite complete remission (CR+CRi) was achieved in 66.4% of the patients in the venetoclax + azacitidine arm and 28.3% of the patients in the control group; CR+CRi before the initiation of cycle 2 was achieved in 43.4% vs 7.6% of patients, respectively.

The median time to first response (either CR or CRi) was 1.3 months (range 0.6 to 9.9) and 2.8 months (range, 0.8 to 13.2), respectively. The median duration of CR+CRi was 17.5 months (95% CI 13.6-NR) in the venetoclax + azacitidine arm and 13.4 months (95% CI 5.8-15.5) in the control group.

CR was achieved in 36.7% and 17.9% of the patients, respectively, and the duration of CR was 17.5 months vs 13.3 months. Similarly, CR+CRh was achieved in 64.7% of the patients in the venetoclax + azacitidine arm and in 22.8% of those in the control group; this endpoint was reached before the beginning of cycle 2 in 39.9% vs 5.5% of patients, respectively.

The median time to first response was 1 month (range, 0.6-14.3) and 2.6 months (range, 0.8-13.2), and the duration of response was 17.8 months (95% CI 15.3-NR) and 13.9 months (95% CI 10.4-15.7), respectively.

The incidence of post-baseline transfusion independence was higher among patients in the venetoclax + azacitidine arm than the control group. Red-cell transfusion independence occurred in 59.8% vs 35.2%, while platelet transfusion independence occurred in 68.5% vs 49.7%, respectively.

In the analysis of the molecular subgroups, the combination of azacitidine plus venetoclax was associated with a higher rate of CR+CRi than with aza alone. In patients with IDH1 or IDH2 mutations, the CR+CRi rate was 75.4% in the venetoclax + azacitidine arm and 10.7% in the control group; in those with FLT3 mutations, the CR+CRi rate was 72.4% vs 36.4%, respectively; in those with NPM1, 66.7% vs 23.5%, respectively; and in those with TP53, 55.3% and 0%, respectively.

In patients who achieved CR+CRi, MRD negativity was observed in 23.4% of the patients who received venetoclax + azacitidine and in 7.6% of those in the control group.

The median overall survival among patients with de novo AML (i.e., in those with no history of MDS, myeloproliferative disorder, or exposure to potentially leukemogenic agents) was 14.1 months in the venetoclax + azacitidine arm and 9.6 months in the control group (HR 0.67; 95% CI 0.51-0.90). The mOS among patients with secondary AML was 16.4 months and 10.6 months, respectively (HR 0.56; 95% CI 0.35-0.91). Among patients with an intermediate cytogenetic risk, the median overall survival was 20.8 months in the venetoclax + azacitidine arm and 12.4 months in the control group (HR, 0.57;

95% CI 0.41-0.79), whereas in those with a poor cytogenetic risk, the mOS was 7.6 months and 6 months, respectively (HR 0.78; 95% CI 0.54-1.1).

The median event-free survival was 9.8 months (95% CI 8.4-11.8) in the venetoclax + azacitidine arm and 7 months (95% CI 5.6-9.5) in the control group (HR 0.63; 95% CI 0.50-0.80). In CR+CRi with MRD <10-3, OS at 24 months was 73.6% in the experimental arm and 63.6% in the control group.

In patients with IDH1 or IDH2 mutations at baseline, overall survival at 12 months was 66.8% among those in the venetoclax+azacitidine arm, as compared with 35.7% among those in the control group (HR 0.35; 95% CI 0.20-0.60).

Supporting phase 1b study M14-358

Only 31 patients received venetoclax + decitabine in this early phase, non-randomized study, to support this particular combination in the application dossier, since study M15-656 did not include patients treated with venetoclax and decitabine.

In patients who received venetoclax at the proposed dose of 400 mg in combination with decitabine, the CR + CRi rate was 74.2%, with a CR rate of 54.8% and a CRi rate of 19.4%. The median duration of CR + CRi was 15 months (95% CI: 7.2, 30 months). In subjects treated with 400 mg venetoclax in combination with decitabine, mOS was 16.2 months (95% CI: 9.1, 27.8 months) with a minimum duration of study follow up of 40 months. The rate of transfusion independence for RBC was 61.3% and for platelets 87.1%, with a duration of transfusion independence of 110 days for both RBC and platelets.

The extrapolation of effect between the two HMAs, decitabine and azacitidine, when adding venetoclax,is supported by their similar mechanism of action.

Study M16-043 – venetoclax + LDAC vs placebo + LDAC

For the primary analysis, the median treatment duration was 3.9 months with a median of 4 cycles delivered in the experimental arm, vs. 1.7 months and 2 cycles, respectively. The median follow-up time was 12 months for both arms. Post-study therapy was received by 33 (23%) of 143 patients in the venetoclax + LDAC arm and 30 (44%) of 68 in the placebo arm. No patients went on to stem cell transplantation after study treatment.

The primary reasons for discontinuation of study drug (venetoclax plus LDAC, n=105/143, vs placebo plus LDAC, n=61/68) were: treatment failure (12% vs 19%), PD (11% vs 16%), death (12% for both), withdrawal of consent (6% vs 10%), AEs not related to disease progression (9% for both), AEs related to disease progression (4% for both), physician decision (5% vs 12%), morphologic relapse (13% vs 4%), and other (4% vs 3%). The reasons for deaths, especially as PD, should be tabulated and presented, as the participant flow does not clarify this issue.

As for demographics and clinical characteristics of patients enrolled in the study, the median age was 76 years, 32.8% had poor cytogenetic risk, 38.4% had secondary AML, 19.9% had prior HMA exposure, and baseline mutations in TP53, FLT3, IDH1/2, or NPM1 were detected in 18.9%, 17.7%, 20.1%, and 15.9% of patients (in whom data were available), respectively. Baseline characteristics had similar frequencies between arms, except for the rates of secondary AML from EDC (40.6% vs 33.8%), which were more frequent in the venetoclax arm.

At the time of the primary analysis, 38/143 and 7/68 patients were alive in the experimental and control arm, respectively. The mOS was 7.2 months (95% CI 5.6-10.1) vs 4.1 months (95% CI 3.1-8.8), with a HR of 0.749 (95% CI 0.52-1.07). The primary endpoint OS was not met at the time of pre-planned analysis. Imbalances in baseline characteristics (secondary AML, prior hematologic disorder–related secondary AML, and poor cytogenetic risk) between the randomized arms, as well as increased

administrative censoring in the venetoclax arm before the median OS time, may have affected the analyses, according to the MAH.

A post-hoc analysis with an additional 6 months of patient follow-up, now with a majority of patients censored in both arms beyond the median OS time, showed an increase in the mOS in the venetoclax arm (8.4 months vs the same 4.1 months for control), with an HR of 0.70 (95% CI 0.50-0.99); however type 1-error control was lost. Furthermore, it is notable that the driver of making this analysis apparently "positive", is a drift in the HR estimate rather than increased power due to 20 more events.

At the time of the primary analysis, CR/CRi was achieved in 47.6% of patients in the venetoclax arm, compared with 13.2% in the placebo arm, with CR achieved in 27.3% and 7.4% of patients, respectively. The median DoR of CR was 11 months. Responses were also achieved more rapidly with addition of venetoclax, with CR/CRi before initiation of cycle 2 observed in 34.3% vs 2.9%.

The median EFS was of 4.7 months (95% CI 3.7-6.4) vs 2 months (95% CI 1.6-3.1), HR 0.58.

As for transfusion independence, the RBC rates were 40.6% vs 17.6% in favour of the experimental arm, and 47.6 vs 32.4%, for platelets. Upon confirmation of morphologic CR or CRi, only 6% (8 of 143) of those in the venetoclax arm and 1% (1 of 68) of those in the placebo arm had a flow cytometric MRD level of <0.1%.

Response rates and OS times were also determined for subsets of patients with baseline intermediate or poor cytogenetic risk, somatic mutations in TP53, IDH1/2, FLT3, or NPM1, and key baseline prognostic factors. A longer OS for the experimental arm was observed in these (small) subgroups, with the exception of mutant FLT3, which were detected in 29 patients: 9 in the control arm and 20 in the experimental arm. Among the FLT3 mutation–positive patients in the placebo arm, 3 had coexisting NPM1 mutations, and all 3 (100%) such patients achieved CR/CRi; among the 20 FLT3 positive patients in the venetoclax arm, 6 had coexisting NPM1 mutations and the 5 patients treated achieved CR/CRi; in contrast, only 4 of the remaining 14 (29%) FLT3 patients without NPM1 mutations achieved CR/CRi, with a median OS of 2.2 months. Similarly, mOS for patients with coexisting FLT3 and NPM1 mutations was 10.2 months in the placebo arm and not yet reached in the venetoclax arm.

No PRO improvements were observed in the experimental arm.

Supporting phase 1/2 study M14-387. Venetoclax+LDAC

This was a study venetoclax in combination with low-dose cytarabine in treatment-naïve subjects with acute myelogenous leukemia who are ≥ 60 years of age and who are not eligible for standard anthracycline-based induction therapy. In subjects treated with venetoclax (600 mg target dose) in combination with LDAC (n=82), ORR was 54.9% (45/82). The CR+CRi rate was 53.7% with a CR rate of 25.6%. The median duration of CR was 15 months.

The efficacy of venetoclax as an add-on to azacitidine was demonstrated in the M15-656, and the magnitude of add-on efficacy was clinically relevant. Furthermore, due to the similarity of the pharmacology of azacytidine and decitabine, corroborated by a single arm study in the latter combination, the positive B/R shown in M15-656, is extended to the combination with decitabine.

The efficacy in combination with LDAC is more complicated. The M16-043 study was not positive on its primary endpoint, OS. An updated analysis with 153 rather than 133 events, shows a drift in the HR from 0.75 to 0.70, and a p-value of 0.04. In response to the list of questions, the Applicant provided a second updated OS analysis with 12 months additional follow up data. At this second updated analysis, the HR was similar to the first updated analysis at 6 months follow up: HR 0.709, with a p-value of 0.038. Both updated analyses are however not alpha-protected and cannot be understood simply as a more powered analysis, since the reason for its "positivity" is not the accrual of events but a swaying HR in a small sample; however, a detrimental effect may be excluded.

The M16-043 study showed an increment of CR from 7% to 27% when adding venetoclax to LDAC, with a median DoR of 11 months. This is not alpha protected but demonstrates the significant contribution of venetoclax to sum regimen activity. The CR rate is a replication of what was found in the phase 1 M14-387 study where the CR rate was 25% and a median DoR of 15 months.

Additional experts consultation

The CHMP consulted the Scientifc Advisory group Oncology (SAG) on the following question:

In study M16-043 (Viale-C), the clinical benefit of adding venetoclax to LDAC could not be established on overall survival (the primary endpoint), by the commonly accepted statistical standard of evidence. Do you, notwithstanding this, consider that the clinical benefit of this combination has been established in the target population (first line AML patients not eligible for intensive chemotherapy)? If so, what is the basis of your inference?

The SAG noted the primary efficacy analysis of study M16-043 (VIALE-C) of venetoclax in combination with low dose cytarabine (LDAC) for the treatment of acute myeloid leukaemia (AML) in patients not eligible for intensive chemotherapy. The trial included 19.9% of patients with prior hypomethylating agents exposure.

The primary analysis did not allow rejecting the null hypothesis of no difference in overall survival (OS), with a logrank p-value of 0.114, and a HR of 0.749 (95% CI 0.52-1.07).

The reported p-value of .04 for a more mature subsequent secondary analysis has to be interpreted in the light of lack of multiplicity adjustment and does not allow to conclude formally that there is a statistically significant difference between treatment groups.

Therefore, the SAG concurred that the study failed to show a statistically significant difference in OS for venetoclax+LDAC v. placebo+LDAC, and that the stated primary objective of the trial was not met.

The assessment benefited of a well-conducted randomized clinical trial for which effort the sponsor has to be recognised.

The SAG discussed the possible reasons for this outcome, including true lack of effect v. an over-ambitious expected treatment effect on OS (HR=.55) resulting in relatively few events for the primary analysis (N=133). However, such reasons would only be hypothesis-generating and cannot make up for the lack of demonstrated effect.

Notwithstanding the lack of a demonstrated effect on OS based on the primary efficacy analysis, the SAG considered secondary analyses of OS and secondary endpoints like complete response rate of 27.3% v. 7.4% and transfusion-independence of 37.1 v. 16.2, for venetoclax + LDAC versus placebo + LDAC, respectively. Thus, the available information also clearly showed that venetoclax was associated with anti-tumour activity when used in combination with LDAC but the SAG concluded that there was considerable uncertainty about the overall significance of the activity in terms of patient benefit.

A number of efficacy subgroup analyses were submitted and these may potentially be helpful in exploring homogeneity of effect, identifying subgroups with clearly higher activity (or lack thereof, fully acknowledging the lack of power to detect small effects due to the small sample size of the trial, N= 143 v 68 for venetoclax+LDAC and placebo+LDAC, respectively).

These analyses failed to identify any subgroups with clearly outstanding effect. Conversely, they failed to show any detectable effect in terms of OS in certain subgroups like patients with prior treatment with hypomethylating agents (HR=.81), FLT3 mutation (HR=1.11), patients with poor cytogenetic risk (HR=1.04), or good (ECOG <2) performance status (HR=.95). Thus, subgroup analyses presented did not allow to suggest a clinically relevant effect even in a subgroup of patients.

The SAG also noted that it is difficult to draw supporting evidence from other trials with venetoclax due to the different settings and populations, especially since the trials were run in parallel with likely selection bias.

In conclusion, the SAG agreed that the nature and magnitude of anti-tumour activity observed on the basis of complete response and associated transfusion independence was of doubtful clinical significance and the subgroup analyses presented failed to identify any patients with a clear effect. Overall, no clinically relevant benefit has been established in the target population or any of the subgroups considered, based on primary and secondary analyses of efficacy and anti-tumour activity.

While agreeing on the overall conclusions, a few SAG members expressed that given the favourable and consistent signs of activity observed, venetoclax + LDAC might be a useful treatment option for some patients in whom hypomethylating agents cannot be used, although they agreed that it was difficult to identify, based on evidence, what characteristics would define such patients, and that statistically rigorous evidence of efficacy to justify the addition of venetoclax to standard LDAC is lacking.

2.4.4. Conclusions on the clinical efficacy

A clinically relevant benefit of venetoclax in terms of OS gain has been established in combination with azacitidine, and by extrapolation with decitabine in patients who are ineligible for intensive chemotherapy.

With regards to the combination with LDAC, efficacy has not been established based on the primary endpoint, OS. A SAG on the 30th March did not support the notion that clinical benefit has been established based on a secondary endpoint such as CR.

2.5. Clinical safety

Introduction

The clinical safety evaluation of venetoclax for this type II variation includes all subjects who received at least 1 dose of venetoclax for the treatment of AML. All subjects in the safety population had AML. This safety population includes

- 283 subjects treated with 400 mg venetoclax in combination with AZA and 144 subjects treated with placebo in combination with AZA in Study M15-656;
- 212 subjects treated with venetoclax at varying doses in combination with the HMAs, AZA or DEC in Study M14-358;
- 142 subjects treated with 600 mg venetoclax in combination with LDAC and 68 subjects treated with placebo in combination with LDAC in Study M16-043;
- 92 subjects treated with venetoclax at varying doses in combination with LDAC in Study M14-387, and 32 subjects treated with venetoclax monotherapy in Study M14-212.

All subjects have at least 6 months of follow-up.

Patient exposure

Patients exposure consist of a total of 622 AML subjects who received venetoclax and 212 subjects who received placebo in combination with AZA or LDAC in completed and ongoing studies.

Numbers of subjects exposed to venetoclax are summarized in Table 11 for all subjects receiving the proposed doses of venetoclax in combination with AZA, DEC, or LDAC and included in the safety evaluation.

Table 18. Number of Subjects Exposed to Venetoclax by Target Dose

Study	Received Venetoclax Dose, mg QDa	
Category	400	600
M15-656		
Combination with AZA	283	-
M14-358		
Combination with AZA	84	-
Combination with DEC	31	-
M16-043		
Combination with LDAC	-	142
M14-387		
Combination with LDAC	-	82

LDAC = low dose cytarabine; QD = once daily
[a] Subjects are categorized by their cohort target dose assigned at study entry, unless otherwise noted.
Cross reference: Study M15-656 Interim CSR Table 14.1__1.1.1.1, Table 14.1__1.1.1.2; Study M14-358 Interim CSR Table 14.1__7.1.1, Table 14.1__7.1.2; Study M16-043 Interim CSR Table 14.1__1.1.1A; Study M14-387 Interim CSR Table 14.1__7.1

Duration of exposure is summarised in table 10.

Table 10. Duration of Exposure to Venetoclax or Placebo in AML Subjects Receiving Target Doses

	Placebo or Venetoclax + HMA				Placebo or Venetoclax + LDAC		
Duration[a]	M15-656 Placebo + AZA N = 144	M15-656 Venetoclax (400 mg) + AZA N = 283	M14-358 Venetoclax (400 mg) + AZA N = 84	M14-358 Venetoclax (400 mg) + DEC N = 31	M16-043 Placebo + LDAC N = 68	M16-043 Venetoclax (600 mg) + LDAC N = 142	M14-387 Venetoclax (600 mg) + LDAC N = 82
	n (%)				n (%)		
0 to 4 weeks	31 (21.5)	45 (15.9)	8 (9.5)	3 (9.7)	23 (33.8)	29 (20.4)	12 (14.6)
> 4 to 8 weeks	18 (12.5)	22 (7.8)	5 (6.0)	1 (3.2)	13 (19.1)	16 (11.3)	11 (13.4)
> 8 to 12 weeks	18 (12.5)	29 (10.2)	9 (10.7)	2 (6.5)	10 (14.7)	14 (9.9)	7 (8.5)
> 12 to 16 weeks			7 (8.3)	6 (19.4)	2 (2.9)	6 (4.2)	7 (8.5)
> 16 to 20 weeks	23 (16.0)	20 (7.1)	4 (4.8)	2 (6.5)	3 (4.4)	11 (7.7)	6 (7.3)
> 20 to 24 weeks			7 (8.3)	0	1 (1.5)	4 (2.8)	3 (3.7)
> 24 to 28 weeks	5 (3.5)	27 (9.5)	4 (4.8)	2 (6.5)	2 (2.9)	8 (5.6)	3 (3.7)
> 28 to 32 weeks			5 (6.0)	0	4 (5.9)	4 (2.8)	2 (2.4)
> 32 to 36 weeks	11 (7.6)[b]	24 (8.5)[b]	5 (6.0)	0	1 (1.5)	9 (6.3)	2 (2.4)
> 36 to 52 weeks	8 (5.6)[c]	10 (3.5)[c]	4 (4.8)	5 (16.1)	4 (5.9)	17 (12.0)	8 (9.8)
> 52 weeks	30 (20.8)	106 (37.5)	26 (31.0)	10 (32.3)	5 (7.4)	24 (16.9)	21 (26.9)
Summary Statistics, Months							
Mean (SD)	6.7 (6.55)	9.9 (8.25)	10.4 (10.19)	12.6 (13.28)	3.7 (4.69)	6.3 (6.04)	8.2 (9.22)
Median	4.3	7.6	6.4	5.7	1.7	4.1	4.2
Min - Max	0.1 – 24.0	0.0 – 30.7	0.1 – 38.1	0.5 – 41.8	0.1 – 20.2	0.0 – 23.5	0.2 – 41.8
Number of Cycles							
Mean (SD)	6.9 (6.53)	8.8 (7.32)	9.6 (9.51)	10.9 (11.09)	4.1 (4.99)	6.1 (5.47)	8.0 (8.70)
Median	4.5	7.0	6.0	6.0	2.0	4.0	5.0
Min – Max	1.0 – 26.0	1.0 – 30.0	1.0 – 37.0	1.0 – 38.0	1.0 – 21.0	1.0 – 22.0	1.0 – 43.0
Cycles, n (%)							
1	33 (22.9)	45 (15.9)	9 (10.7)	3 (9.7)	26 (38.2)	32 (22.5)	12 (14.6)
2	16 (11.1)	32 (11.3)	10 (11.9)	2 (6.5)	14 (20.6)	21 (14.8)	16 (19.5)
3	12 (8.3)	16 (5.7)	12 (14.3)	6 (19.4)	8 (11.8)	10 (7.0)	7 (8.5)
4	11 (7.6)	15 (5.3)	4 (4.8)	3 (9.7)	3 (4.4)	13 (9.2)	3 (3.7)
5	11 (7.6)	13 (4.6)	4 (4.8)	1 (3.2)	1 (1.5)	7 (4.9)	7 (8.5)

AZA = azacytidine; DEC = decitabine; LDAC = low-dose cytarabine; SD = standard deviation
[a] Duration measured as months rather than weeks in Study M15-656.
[b] Duration is > 8 months to 10 months in Study M15-656.
[c] Duration is > 10 months to 12 months in Study M15-656.
Cross reference: Study M15-656 Interim CSR Table 14.1__5.1.1; Study M14-358 Interim CSR Table 14.1__7.1.1, Table 14.1__7.1.2; Study M16-043 Interim CSR Table 14.1__2.1A; Study M14-387 Interim CSR Table 14.1__7.1

Among subjects in **Study M15-656** treated with placebo in combination with AZA, median duration of placebo was 4.3 months (range, 0.1 to 24.0 months). Subjects receiving placebo in combination with AZA also received a median of 3.8 months of AZA (range, 0.1–23.4 months). Among subjects in this study treated with venetoclax 400 mg in combination with AZA, median duration of venetoclax was 7.6 months (range, 0.0 to 30.7 months). Subjects receiving venetoclax in combination with AZA also received a median of 7.0 months of AZA (range, 0.0–30.5 months).

In **Study M14-358**, 84 subjects received venetoclax 400 mg in combination with AZA and 31 subjects received venetoclax 400 mg in combination with DEC. The median duration of venetoclax among subjects receiving the 400 mg dose was 6.4 months (range, 0.1–38.1 months) in combination with AZA and 5.7 months (range, 0.5–41.8 months) in combination with DEC.

When exposure is considered in number of cycles, median duration of venetoclax (400 mg) in combination with AZA was 6 cycles (range, 1 to 37 cycles). These subjects received a median of 4.0 cycles of AZA (range, 1–29 cycles). Among 31 subjects treated with venetoclax (400 mg) in combination with DEC, median duration of venetoclax was 6 cycles (range, 1–38 cycles).

Among subjects in **Study M16-043** treated with placebo in combination with LDAC, as of the data cut-off date, median duration of placebo was 1.7 months (range, 0.1 to 20.2 months); median number of cycles was 2.0 (range, 1.0 to 21.0 cycles). Subjects receiving placebo in combination with LDAC also received a median of 1.3 months of LDAC (range, 0.0–19.9 months). Among subjects in this study treated with venetoclax 600 mg in combination with LDAC, median duration of venetoclax was 4.1 months (range, 0.0 to 23.5 months); median number of cycles was 4.0 (range 1 to 22). Subjects receiving venetoclax in combination with LDAC also received a median of 3.5 months of LDAC (range, 0.0–23.4 months).

In Study **M14-387**, 82 subjects received venetoclax 600 mg in combination with LDAC. Median duration of venetoclax among subjects receiving the 600 mg dose was 4.2 months (range, 0.2–41.8 months) in combination with LDAC. When evaluated based on number of treatment cycles, the subjects who received venetoclax (600 mg) with LDAC had a median duration of 5 cycles of venetoclax (range, 1–43 cycles). These subjects received a median of 3 cycles of LDAC (range, 1 – 36 cycles).

Table 13. Summary of Demographic Characteristics: Placebo or Venetoclax in Combination with HMAs or LDAC

Characteristic, n (%)	**M15-656 Placebo + Azacitidine (N = 146)**	**M15-656 Venetoclax (400 mg) + Azacitidine (N = 287)**	**M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)**	**M14-358 Venetoclax (400 mg) + Decitabine (N = 31)**	**M16-043 Placebo + LDAC (N = 68)**	**M16-043 Venetoclax (600 mg) + LDAC (N = 143)**	**M14-387 Venetoclax (600 mg) + LDAC (N = 82)**
Sex/Gender							
Male	87 (59.6)	173 (60.3)	51 (60.7)	15 (48.4)	39 (57.4)	78 (54.5)	53 (64.6)
Female	59 (40.4)	114 (39.7)	33 (39.3)	16 (51.6)	29 (42.6)	65 (45.5)	29 (35.4)
Race							
White	109 (74.7)	218 (76.0)	71 (91.0)	27 (87.1)	47 (69.1)	102 (71.3)	75 (94.9)
Asian	33 (22.6)	66 (23.0)	1 (1.3)	0	20 (29.4)	39 (27.3)	2 (2.5)
Black/African American	3 (2.1)	3 (1.0)	4 (5.1)	1 (3.2)	1 (1.5)	2 (1.4)	2 (2.5)
Native Hawaiian/Pacific Islander	0	0	1 (1.3)	2 (6.5)	0	0	0
American Indian/Alaska Native	1 (0.7)	0	0	1 (3.2)	0	0	0
Mixed	0	0	1 (1.3)	0	0	0	0
Missing[a]	0	0	6	0	0	0	3
Age[b]							
Mean (SD)	75.0 (5.80)	75.5 (6.11)	75.0 (6.17)	72.8 (4.96)	74.3 (8.63)	75.1 (8.09)	74.9 (5.67)
Median	76.0	76.0	74.5	72.0	76.0	76.0	74.0
Min, Max	60.0, 90.0	49.0, 91.0	61.0, 90.0	65.0, 86.0	41.0, 88.0	36.0, 93.0	63.0, 90.0
Age group[c]							
< 75 years	65 (44.5)	122 (42.5)	42 (50.0)	23 (74.2)	29 (41.2)	65 (45.5)	42 (51.2)
≥ 75 years	81 (55.5)	165 (57.5)	42 (50.0)	8 (25.8)	39 (57.4)	78 (54.5)	40 (48.8)
Region							
US	25 (17.1)	51 (17.8)	70 (83.3)	29 (93.5)	6 (8.8)	13 (9.1)	51 (62.2)
Non-US	-	-	14 (16.7)	2 (6.5)	-	-	31 (37.8)

Characteristic, n (%)	M15-656 Placebo + Azacitidine (N = 146)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 287)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 143)	M14-387 Venetoclax (600 mg) + LDAC (N = 82)
EU	59 (40.4)	116 (40.4)	-	-	26 (38.2)	56 (39.2)	-
China	13 (8.9)	24 (8.4)	-	-	6 (8.8)	9 (6.3)	-
Japan	13 (8.9)	24 (8.4)	-	-	9 (13.2)	18 (12.6)	-
Rest of world	36 (24.7)	72 (25.1)	-	-	21 (30.9)	47 (32.9)	-

HMA = hypomethylating agent; IVRS/IWRS = Interactive Voice Response System/Interactive Web Response System; LDAC = low dose cytarabine; SD = standard deviation; US = United States

a. Percentages are calculated in non-missing and non-unknown values.

b. For Study M16-043, as reported from IVRS/IWRS.

c. For Study M15-656 and M16-043, as reported from IVRS/IWRS.

Cross reference: Study M15-656 Interim CSR Table 14.1__3.1.2.2; Study M14-358 Interim CSR Table 14.1__3.1, Table 14.1__3.2; Study M16-043 Interim CSR Table 14.1__1.5.1A; Study M14-387 Interim CSR Table 14.1__3

Table 14. Summary of Baseline Disease Characteristics: Placebo or Venetoclax in Combination with HMAs or LDAC

Characteristic, n (%)	M15-656 Placebo + Azacitidine (N = 146)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 287)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 143)	M14-387 Venetoclax (600 mg) + LDAC (N = 82)
Cytogenetic risk[a]							
Favorable	0	0	0	0	3 (4.5)	1 (0.7)	0
Intermediate	89 (61.0)	183 (63.8)	50 (59.5)	16 (51.6)	43 (65.2)	90 (65.2)	49 (59.8)
Poor	57 (39.0)	104 (36.2)	33 (39.3)	15 (48.4)	20 (30.3)	47 (34.1)	26 (31.7)
No mitoses	0	0	1 (1.2)	0	0	0	7 (8.5)
Missing	0	0	0	0	2	5	0
AML disease type[b]							
Primary/de novo	110 (75.3)	215 (74.9)	63 (75.0)	22 (71.0)	45 (66.2)	85 (59.4)	42 (51.2)
Secondary (prior MDS and therapy-related AML)	36 (24.7)	72 (25.1)	21 (25.0)	9 (29.0)	23 (33.8)	58 (40.6)	40 (48.8)
ECOG performance status							
0	23 (15.8)	37 (12.9)	14 (16.7)	7 (22.6)	11 (16.2)	22 (15.4)	12 (14.6)
1	58 (39.7)	120 (41.8)	44 (52.4)	20 (64.5)	23 (33.8)	52 (36.4)	46 (56.1)
2	60 (41.1)	113 (39.4)	24 (28.6)	4 (12.9)	25 (36.8)	63 (44.1)	23 (28.0)
3	5 (3.4)	17 (5.9)	2 (2.4)	0	9 (13.2)	6 (4.2)	1 (1.2)
Bone marrow blast							
< 30%	41 (28.1)	85 (29.6)	24 (28.6)	7 (22.6)	18 (26.5)	42 (29.4)	27 (33.3)
≥ 30% - < 50%	33 (22.6)	61 (21.3)	29 (34.5)	14 (45.2)	22 (32.4)	36 (25.2)	18 (22.2)
≥ 50%	72 (49.3)	141 (49.1)	31 (36.9)	10 (32.3)	28 (41.2)	65 (45.5)	36 (44.4)
Missing[c]	0	0	0	0	0	0	1[d]
CTC grade: neutropenia							
0	29 (20.0)	53 (18.5)	11 (13.1)	6 (19.4)	15 (22.1)	26 (18.3)	14 (17.1)
1	11 (7.6)	7 (2.4)	11 (13.1)	2 (6.5)	2 (2.9)	4 (2.8)	3 (3.7)
2	14 (9.7)	20 (7.0)	6 (7.1)	0	6 (8.8)	8 (5.6)	6 (7.3)
3	31 (21.4)	48 (16.7)	17 (20.2)	4 (12.9)	15 (22.1)	26 (18.3)	14 (17.1)
4	60 (41.4)	159 (55.4)	39 (46.4)	19 (61.3)	30 (44.1)	78 (54.9)	45 (54.9)
Missing[c]	1	0	0	0	0	1	0
CTC grade: anemia							
0	2 (1.4)	2 (0.7)	1 (1.2)	0	2 (2.9)	0	-
1	18 (12.3)	39 (13.6)	7 (8.3)	9 (29.0)	6 (8.8)	19 (13.3)	3 (3.7)
2	74 (50.7)	158 (55.1)	50 (59.5)	15 (48.4)	38 (55.9)	86 (60.1)	47 (57.3)
3	52 (35.6)	88 (30.7)	26 (31.0)	7 (22.6)	22 (32.4)	38 (26.6)	32 (39.0)
CTC grade: thrombocytopenia							
0	19 (13.0)	36 (12.5)	6 (7.1)	3 (9.7)	9 (13.2)	10 (7.0)	6 (7.3)
1	28 (19.2)	61 (21.3)	18 (21.4)	8 (25.8)	12 (17.6)	22 (15.4)	14 (17.1)
2	25 (17.1)	44 (15.3)	8 (9.5)	6 (19.4)	9 (13.2)	22 (15.4)	16 (19.5)
3	42 (28.8)	78 (27.2)	25 (29.8)	12 (38.7)	19 (27.9)	41 (28.7)	20 (24.4)
4	32 (21.9)	68 (23.7)	27 (32.1)	2 (6.5)	19 (27.9)	48 (33.6)	26 (31.7)
Any transfusion within 8 weeks[e]							
Yes	82 (56.2)	156 (54.4)	55 (65.5)	23 (74.2)	56 (82.4)	111 (77.6)	60 (73.2)
No	64 (43.8)	131 (45.6)	29 (34.5)	8 (25.8)	12 (17.6)	32 (22.4)	22 (26.8)

AML = acute myeloid leukemia; CTC = circulating tumor cells; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; HMA = hypomethylating agent; LDAC = low dose cytarabine; SD = standard deviation; US = United States

a. For one subject in Study M14-358, favorable risk was excluded by fluorescence in situ hybridization (FISH); insufficient mitosis.
b. For Study M16-043, AML status as reported from EDC.
c. For missing values, percentages are calculated on non-missing and non-unknown values.
d. In Study M14-387, Subject 31211 had baseline sample inadequate for blast analysis; bone marrow sample prior to screening had confirmed AML diagnosis and subject was without intervening therapy.
e. Within 8 weeks prior to first dose of venetoclax or placebo; includes red blood cell and platelet transfusion.

Note: Data cutoff dates were as follows: 04 Jan 2020 (Study M15-656); 19 Jul 2019 (Study M14-358); 15 Aug 2019 (Study M16-043); and 19 Jul 2019 (Study M14-387).

Cross reference: Study M15-656 Interim CSR Table 14.1__3.1.2.2; Study M14-358 Interim CSR Table 14.1__4.1.1, Table 14.1__4.1.2; Study M16-043 Interim CSR Table 14.1__1.5.1A; Study M14-387 Interim CSR Table 14.1__4.1

Disposition for subjects assigned to receive venetoclax at the proposed doses in combination with HMAs or LDAC is summarized in Table 12.

Table 19. Subject Disposition: AML Subjects Randomized to Receive Placebo or Venetoclax at the Proposed Doses in Combination with HMAs or LDAC

	Placebo or Venetoclax + HMA				**Placebo or Venetoclax + LDAC**		
Disposition, n	**M15-656 Placebo + AZA[a] N = 146**	**M15-656 Venetoclax (400 mg) + AZA[a] N = 287**	**M14-358 Venetoclax (400 mg) + AZA N = 84**	**M14-358 Venetoclax (400 mg) + DEC N = 31**	**M16-043 Placebo + LDAC N = 68**	**M16-043 Venetoclax (600 mg) + LDAC N = 143**	**M14-387 Venetoclax (600 mg) + LDAC N = 82**
Enrolled and treated with study drug	144	283	84	31	68	142	82
Ongoing in study and receiving venetoclax or placebo as of data version date[b]	16	73	9	3	5	25	4
Discontinued venetoclax/placebo	128	210	75	28	63	117	78
Primary reason for venetoclax/placebo discontinuation, n (%)							
AE: Not progression	13 (8.9)	44 (15.3)	17 (20.2)	3 (9.7)	6 (8.8)	15 (10.5)	14 (17.1)
AE: Progression	5 (3.4)	5 (1.7)	3 (3.6)	1 (3.2)	3 (4.4)	5 (3.5)	8 (9.8)
Investigator request/ physician decision	9 (6.2)	17 (5.9)	2 (2.4)	1 (3.2)	8 (11.8)	8 (5.6)	9 (11.0)
Progressive disease per protocol	21 (14.4)	9 (3.1)	27 (32.1)	12 (38.7)	**12 (17.6)**	**17 (11.9)**	32 (39.0)
Toxicity	-	-	1 (1.2)	0	-	-	0
Withdrew consent	22 (15.2)	26 (9.1)	2 (2.4)	1 (3.2)	8 (11.8)	8 (5.6)	7 (8.5)
Morphologic relapse	15 (10.3)	64 (22.3)	0	0	3 (4.4)	23 (16.1)	0
Treatment failure	13 (8.9)	4 (1.4)	0	0	**13 (19.1)**	**18 (12.6)**	0
Death	24 (16.4)	39 (13.6)	0	0	8 (11.8)	18 (12.6)	0
Other[c]	6 (4.1)	2 (0.7)	23 (27.4)	10 (32.3)	2 (2.9)	5 (3.5)	8 (9.8)
Primary reason for study discontinuation, n (%)							
AE: Not progression	-	-	14 (16.7)	2 (6.5)	-	-	11 (13.4)
AE: Progression	-	-	0	0	-	-	8 (9.8)
Investigator request	-	-	5 (6.0)	0	-	-	4 (4.9)
Progressive disease per protocol with death	-	-	3 (3.6)	4 (12.9)	-	-	10 (12.2)
Progressive disease per protocol without death	-	-	32 (38.1)	11 (35.5)	-	-	22 (26.8)
Death	110 (75.3)	162 (56.4)	0	0	53 (77.8)	97 (67.8)	0
Lost to follow-up	2 (1.4)	5 (1.7)	0	0	0	2 (1.4)	0
Withdrew consent	1 (0.7)	7 (2.4)	4 (4.8)	2 (6.5)	3 (4.4)	4 (2.8)	7 (8.5)
Other	0	0	16 (19.0)	8 (25.8)	0	0	16 (19.5)

AE = adverse event; LDAC = low dose cytarabine; N/A = not applicable; NR = not reported; – denotes reason not provided
[a] For Study M15-656, data for subjects from Group 1 (n = 1 placebo + AZA, n = 1 venetoclax + AZA) were added to subjects from Group 2 where appropriate, and for those calculations, n = 1 was also added to the total numbers of subjects.
[b] Data version dates: Study M15-656, 04 January 2020; Study M14-358, 19 July 2019; Study M16-043, 15 August 2019; Study M14-387 Interim CSR, 19 July 2019.
[c] In Study M15-656, the terms "Lost to follow up" and "Non-compliance with study drug" (1 event each group) were added to the category of "Other"; these terms are not used in the other studies.

Cross reference: Study M15-656 Interim CSR Table 14.1__1.1.2.1, Table 14.1__1.1.2.2, Table 14.1__2.1.1, Table 14.1__2.1.2, Table 14.1__2.3.1, Table 14.1__2.3.2; Study M14-358 Interim CSR Table 14.1__1.1.1, Table 14.1__1.1.2, Table 14.1__2.1.1, Table 14.1__2.1.2, Table 14.1__2.4.1, Table 14.1__2.4.2; Study M16-043 Interim CSR Table 14.1__1.1.1A, Table 14.1__1.4.1A, Table 14.1__1.4.3A; Study M14-387 Interim CSR Table 14.1__1.1, Table 14.1__2.1, Table 14.1__2.3

The majority of subjects in the ongoing studies had discontinued venetoclax as of the database version dates for those individual studies. The common primary reasons for venetoclax discontinuation (reported for > 10% of subjects in any venetoclax treatment group) were AE not related to progression, investigator request, progressive disease, morphologic relapse, treatment failure, death, and other reasons (hematopoietic stem cell transplant, logistical reasons). Among subjects who received placebo, the common reasons for placebo discontinuation were investigator request, progressive disease, withdrew consent, treatment failure, and death.

The common primary reasons for study discontinuation (reported for > 10% of subjects in any venetoclax treatment group) were death, AE not related to progression, progressive disease with or without death, and other reasons. Among subjects who received placebo, the most common reason for study discontinuation was death.

As of the respective study cutoff dates, 118 subjects treated with venetoclax in combination with AZA (Study M15-656, n = 109; Study M14-358, n = 9), 3 subjects treated in combination with DEC (Study M14-358, n = 3), and 43 subjects treated in combination with LDAC (Study M16-043, n = 39; Study M14-387, n = 4), remained ongoing for continuation of treatment, disease progression and/or survival follow-up. Also ongoing for disease assessment and/or survival follow-up were 31 subjects treated with placebo in combination with AZA (Study M15-656) and 12 subjects treated with placebo in combination with LDAC (Study M16-043).

Adverse events

Study M15-656

Table 20

Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events (Safety Analysis Set Group 1 and Group 2)

	Placebo + Azacitidine (N=144) n (%)	Venetoclax 400 mg QD + Azacitidine (N=283) n (%)	Total (N=427) n (%)
Subjects with:			
Any adverse event (AE)	144 (100)	283 (100)	427 (100)
Any AE with NCI-CTCAE toxicity grade >=3	139 (96.5)	279 (98.6)	418 (97.9)
Any AE with NCI-CTCAE toxicity grade 3 or 4	136 (94.4)	276 (97.5)	412 (96.5)
Any AE with NCI-CTCAE toxicity grade 3	120 (83.3)	264 (93.3)	384 (89.9)
Any AE with NCI-CTCAE toxicity grade 4	98 (68.1)	223 (78.8)	321 (75.2)
Any reasonable possibility Venetoclax/Placebo-related AE$	**96 (66.7)**	**241 (85.2)**	**337 (78.9)**
Any reasonable possibility Azacitidine-related AE$	108 (75.0)	246 (86.9)	354 (82.9)
Any AE leading to Venetoclax/Placebo discontinuation	29 (20.1)	69 (24.4)	98 (23.0)
Any AE leading to Azacitidine discontinuation	29 (20.1)	68 (24.0)	97 (22.7)
Any AE leading to Venetoclax/Placebo interruption	82 (56.9)	204 (72.1)	286 (67.0)
Any AE leading to Azacitidine interruption	67 (46.5)	188 (66.4)	255 (59.7)
Any AE leading to Venetoclax/Placebo reduction	6 (4.2)	7 (2.5)	13 (3.0)
Any AE leading to Azacitidine reduction	2 (1.4)	34 (12.0)	36 (8.4)
Any AE leading to Venetoclax/Placebo interruption/reduction	84 (58.3)	204 (72.1)	288 (67.4)
Any AE leading to Azacitidine interruption/reduction	67 (46.5)	190 (67.1)	257 (60.2)
Fatal AE (AE leading to death)	29 (20.1)	64 (22.6)	93 (21.8)
All death#	109 (75.7)	159 (56.2)	268 (62.8)

Data included are subject to a cutoff date of 04JAN2020.
Group 1: Enrolled under original protocol.
Group 2: Enrolled not under original protocol.
$ As assessed by investigator.
# Includes non treatment emergent deaths.

Study M14-358

Table 14.3__1.1.1.1 Overview of number and percentage of subjects with treatment-emergent adverse events - part I (safety analysis set)

	Venetoclax 400 mg + AZA (N=84) n (%)		Venetoclax 800 mg + AZA (N=37) n (%)		Venetoclax 1200 mg + AZA (N=6) n (%)	
Subjects with:						
Any adverse event (AE)	84	(100)	37	(100)	6	(100)
Any Ae with NCI-CTCAE grade 3 or 4	82	(97.6)	36	(97.3)	6	(100)
Any Ae with NCI-CTCAE grade 3 or above	82	(97.6)	36	(97.3)	6	(100)
Any AE reasonable possibility venetoclax	76	(90.5)	34	(91.9)	6	(100)
Any AE reasonable possibility AZA	77	(91.7)	36	(97.3)	6	(100)
Any AE leading to hospitalization	64	(76.2)	28	(75.7)	3	(50.0)
Any AE leading to venetoclax discontinuation	21	(25.0)	10	(27.0)	1	(16.7)
Any AE leading to AZA discontinuation	18	(21.4)	9	(24.3)	1	(16.7)
Any AE leading to venetoclax interruption	57	(67.9)	22	(59.5)	3	(50.0)
Any AE leading to AZA interruption	47	(56.0)	20	(54.1)	3	(50.0)
Any AE leading to venetoclax reduction	1	(1.2)	0		2	(33.3)
Any AE leading to AZA reduction	4	(4.8)	0		0	
Fatal AE (AE leading to death)	13	(15.5)	6	(16.2)	1	(16.7)
All death #	56	(66.7)	28	(75.7)	6	(100)

AZA = azacitidine.
Note: MedDra version is 21.0.
Note: subjects are counted once in each entry, regardless of the number of events they may have had.
Includes non treatment emergent deaths.

Table 14.3__1.1.1.2 Overview of number and percentage of subjects with treatment-emergent adverse events - part ii (safety analysis set)

	Venetoclax 400 mg + DEC (N=31) n (%)		Venetoclax 800 mg + DEC (N=37) n (%)		Venetoclax 1200 mg + DEC (N=5) n (%)	
Subjects with:						
Any adverse event (ae)	31	(100)	37	(100)	5	(100)
Any Ae With nci-ctcae grade 3 or 4	31	(100)	37	(100)	4	(80.0)
Any Ae With nci-ctcae grade 3 or above	31	(100)	37	(100)	4	(80.0)
Any Ae Reasonable possibility venetoclax	25	(80.6)	35	(94.6)	4	(80.0)
Any Ae Reasonable possibility dec	28	(90.3)	31	(83.8)	4	(80.0)
Any Ae Leading to hospitalization	24	(77.4)	24	(64.9)	4	(80.0)
Any Ae Leading to venetoclax discontinuation	8	(25.8)	5	(13.5)	2	(40.0)
Any Ae Leading to dec discontinuation	4	(12.9)	4	(10.8)	2	(40.0)
Any Ae Leading to venetoclax interruption	20	(64.5)	25	(67.6)	4	(80.0)
Any Ae Leading to dec interruption	18	(58.1)	22	(59.5)	3	(60.0)
Any Ae leading to venetoclax reduction	2	(6.5)	3	(8.1)	2	(40)
Any Ae leading to DEC reduction	6	(19.4)	0		0	
Fatal ae (ae leading to death)	6	(19.4)	3	(8.1)	0	
All Deaths#	25	(80.6)	24	(64.9)	1	(20.0)

Dec = decitabine.
Note: meddra version is 21.0.
Note: subjects are counted once in each entry, regardless of the number of events they may have had.
includes non treatment emergent deaths.

M16-043

Table 14.3__1.1.1 Overview of number and percentage of subjects with treatment-emergent adverse events (safety analysis set)

	Placebo + LDAC (N=68) n (%)	Venetoclax 600 mg QD + LDAC (N=142) n (%)
Subjects with:		
Any adverse event (AE)	67 (98.5)	141 (99.3)
Any AE with NCI-CTCAE toxicity grade >= 3	65 (95.6)	138 (97.2)
Any AE with NCI-CTCAE toxicity grade 3 or 4	63 (92.6)	135 (95.1)

Any AE with NCI-CTCAE toxicity grade 3	60 (88.2)	121 (85.2)
Any AE with NCI-CTCAE toxicity grade 4	38 (55.9)	101 (71.1)
Any reasonable possibility venetoclax/placebo-related AE$	**46 (67.6)**	**103 (72.5)**
Any reasonable possibility LDAC -related AE$	49 (72.1)	105 (73.9)
Any AE leading to venetoclax/placebo discontinuation	16 (23.5)	36 (25.4)
Any AE leading to LDAC discontinuation	16 (23.5)	36 (25.4)
Any AE leading to venetoclax/placebo interruption	36 (52.9)	89 (62.7)
Any AE leading to LDAC interruption	32 (47.1)	81 (57.0)
Any AE leading to venetoclax/placebo reduction	4 (5.9)	13 (9.2)
Any AE leading to LDAC reduction	0	4 (2.8)
Any AE leading to venetoclax/placebo interruption/reduction	36 (52.9)	92 (64.8)
Any AE leading to LDAC interruption/reduction	32 (47.1)	82 (57.7)
Fatal AE (AE leading to death)	14 (20.6)	33 (23.2)
All death	47 (69.1)	86 (60.6)

LDAC = low dose cytarabine.
Note: data included are subject to a cut-off date of 15feb2019; $ as assessed by investigator.

Table 14.3__1.1.1 overview of number and percentage of subjects with treatment-emergent adverse events (safety analysis set)

	Venetoclax (600 mg QD OR 800 mg QD) + LDAC (N=92) n (%)	Venetoclax 600 mg QD + LDAC (N=82) n (%)	Venetoclax 600 mg QD + LDAC (without prior MPN) (N=78) n (%)
Subjects with:			
Any adverse event (ae)	92 (100)	82 (100)	78 (100)
Any AE with NCI-CTCAE grade 3 or 4	90 (97.8)	80 (97.6)	76 (97.4)
Any AE with NCI-CTCAE grade 3 or above	90 (97.8)	80 (97.6)	76 (97.4)
Any AE reasonable possibility venetoclax	82 (89.1)	73 (89.0)	69 (88.5)
Any AE reasonable possibility LDAC	88 (95.7)	79 (96.3)	75 (96.2)
Any AE leading to hospitalization	79 (85.9)	71 (86.6)	67 (85.9)
Any AE leading to venetoclax discontinuation	32 (34.8)	27 (32.9)	25 (32.1)
Any AE leading to LDAC discontinuation	34 (37.0)	29 (35.4)	27 (34.6)
Any AE leading to venetoclax interruption	52 (56.5)	48 (58.5)	47 (60.3)
Any AE leading to LDAC interruption	44 (47.8)	41 (50.0)	40 (51.3)
Any AE leading to venetoclax reduction	7 (7.6)	6 (7.3)	6 (7.7)
Any AE leading to LDAC reduction	1 (1.1)	1 (1.2)	1 (1.3)
Fatal AE (AE leading to death)	20 (21.7)	16 (19.5)	15 (19.2)
All Deaths#	77 (83.7)	67 (81.7)	63 (80.8)

LDAC = low dose cytarabine. MPN = myeloproliferative neoplasm.
Note: MedDra version is 21.0.
Note: subjects are counted once in each entry, regardless of the number of events they may have had.
Includes non treatment emergent deaths.

Table 15. Treatment-Emergent Adverse Events Reported in ≥ 20% of AML Subjects Receiving Placebo or Venetoclax in Combination with HMAs or LDAC

SOC and PT, n (%)a	M15-656 Placebo + Azacitidine (N = 144)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 283)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 142)	M14-387 Venetoclax (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)
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)

SOC and PT, n (%)a	M15-656 Placebo + Azacitidine (N = 144)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 283)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 142)	M14-387 Venetoclax (600 mg) + LDAC (N = 82)
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)
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; HMA = hypomethylating agent; LDAC = low dose cytarabine; PT = preferred term; SOC = system organ class

a. MedDRA version 21.0 for all studies.

Cross reference: Study M15-656 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; Study M16-043 Interim CSR Table 14.3__1.1.2A; Study M14-387 Interim CSR Table 14.3__1.2.1

Table 17. Treatment-Emergent Adverse Events with a Reasonable Possibility of Being Related to Venetoclax or Placebo Reported in ≥ 10% of AML Subjects Receiving Placebo or Venetoclax in Combination with HMAs or LDAC

SOC and PT, n (%)[a]	M15-656 Placebo + Azacitidine (N = 144)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 283)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 142)	M14-387 Venetoclax (600 mg) + LDAC (N = 82)
Any AE	96 (66.7)	241 (85.2)	76 (90.5)	25 (80.6)	47 (69.1)	106 (74.6)	73 (89.0)
Blood and lymphatic system disorders	57 (39.6)	191 (67.5)	34 (40.5)	12 (38.7)	30 (44.1)	77 (54.2)	46 (56.1)
Anaemia	20 (13.9)	56 (19.8)	18 (21.4)	3 (9.7)	9 (13.2)	28 (19.7)	20 (24.4)
Febrile neutropenia	**11 (7.6)**	**79 (27.9)**	11 (13.1)	10 (32.3)	**6 (8.8)**	**24 (16.9)**	14 (17.1)
Leukopenia	16 (11.1)	51 (18.0)	1 (1.2)	0	2 (2.9)	11 (7.7)	2 (2.4)
Neutropenia	31 (21.5)	101 (35.7)	11 (13.1)	2 (6.5)	**7 (10.3)**	**49 (34.5)**	19 (23.2)
Thrombocytopenia	32 (22.2)	96 (33.9)	15 (17.9)	3 (9.7)	16 (23.5)	45 (31.7)	22 (26.8)
Gastrointestinal disorders	62 (43.1)	140 (49.5)	52 (61.9)	20 (64.5)	20 (29.4)	66 (46.5)	55 (67.1)
Constipation	18 (12.5)	32 (11.3)	12 (14.3)	4 (12.9)	5 (7.4)	6 (4.2)	4 (4.9)
Diarrhoea	16 (11.1)	68 (24.0)	20 (23.8)	6 (19.4)	5 (7.4)	19 (13.4)	24 (29.3)
Nausea	29 (20.1)	78 (27.6)	37 (44.0)	15 (48.4)	15 (22.1)	39 (27.5)	45 (54.9)
Vomiting	18 (12.5)	45 (15.9)	19 (22.6)	5 (16.1)	6 (8.8)	19 (13.4)	19 (23.2)
General disorders and administration site conditions	17 (11.8)	71 (25.1)	26 (31.0)	10 (32.3)	10 (14.7)	29 (20.4)	32 (39.0)
Fatigue	6 (4.2)	28 (9.9)	18 (21.4)	7 (22.6)	4 (5.9)	12 (8.5)	22 (26.8)
Infections and infestations	**26 (18.1)**	**104 (36.7)**	18 (21.4)	5 (16.1)	**11 (16.2)**	**33 (23.2)**	18 (22.0)
Investigations	25 (17.4)	57 (20.1)	50 (59.5)	13 (41.9)	10 (14.7)	31 (21.8)	31 (37.8)
Blood bilirubin increased	2 (1.4)	10 (3.5)	2 (2.4)	1 (3.2)	1 (1.5)	5 (3.5)	13 (15.9)
Lymphocyte count decreased	2 (1.4)	2 (0.7)	0	2 (6.5)	1 (1.5)	1 (0.7)	15 (18.3)
Neutrophil count decreased	0	8 (2.8)	23 (27.4)	7 (22.6)	3 (4.4)	8 (5.6)	11 (13.4)
Platelet count decreased	1 (0.7)	11 (3.9)	23 (27.4)	11 (35.5)	4 (5.9)	7 (4.9)	17 (20.7)
White blood cell count decreased	1 (0.7)	9 (3.2)	26 (31.0)	12 (38.7)	3 (4.4)	8 (5.6)	22 (26.8)
Metabolism and nutrition disorders	21 (14.6)	78 (27.6)	18 (21.4)	7 (22.6)	13 (19.1)	39 (27.5)	40 (48.8)
Decreased appetite	12 (8.3)	42 (14.8)	10 (11.9)	4 (12.9)	6 (8.8)	15 (10.6)	17 (20.7)
Hypocalcaemia	1 (0.7)	6 (2.1)	2 (2.4)	0	2 (2.9)	3 (2.1)	10 (12.2)
Hypokalaemia	5 (3.5)	21 (7.4)	0	1 (3.2)	3 (4.4)	5 (3.5)	9 (11.0)
Hyponatraemia	2 (1.4)	2 (0.7)	0	0	1 (1.5)	3 (2.1)	9 (11.0)
Musculoskeletal and connective tissue disorders	3 (2.1)	8 (2.8)	3 (3.6)	4 (12.9)	3 (4.4)	2 (1.4)	10 (12.2)
Nervous system disorders	9 (6.3)	29 (10.2)	15 (17.9)	3 (9.7)	3 (4.4)	11 (7.7)	10 (12.2)
Dysgeusia	1 (0.7)	8 (2.8)	9 (10.7)	1 (3.2)	1 (1.5)	3 (2.1)	1 (1.2)
Psychiatric disorders	3 (2.1)	9 (3.2)	1 (1.2)	1 (3.2)	0	3 (2.1)	11 (13.4)
Respiratory, thoracic and mediastinal disorders	10 (6.9)	29 (10.2)	7 (8.3)	1 (3.2)	6 (8.8)	10 (7.0)	11 (13.4)
Skin and subcutaneous tissue disorders	7 (4.9)	38 (13.4)	9 (10.7)	4 (12.9)	5 (7.4)	9 (6.3)	10 (12.2)

AML = acute myeloid leukemia; HMA = hypomethylating agent; LDAC = low dose cytarabine; PT = preferred term; SOC = system orga n class.

a. MedDRA version 21.0 for all studies.

Cross reference: Study M15-656 Interim CSR Table 14.3__1.3.1; Study M14-358 Interim CSR Table 14.3__1.3.1.1.1, Table 14.3__1.3.1.1.2; Study M16-043 Interim CSR Table 14.3__1.3.1A; Study M14-387 Interim CSR Table 14.3__1.3.1.1

Grade ≥ 3 Adverse Events

Table 21. Treatment-Emergent Adverse Events with NCI CTCAE ≥ Grade 3 Reported in ≥ 10% of Subjects Receiving Proposed Doses of Venetoclax in Combination with HMAs or LDAC

SOC and PT, n (%)[a]	M15-656 Placebo + Azacitidine (N = 144)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 283)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 142)	M14-387 Venetoclax (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)

SOC and PT, n (%)[a]	M15-656 Placebo + Azacitidine (N = 144)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 283)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 142)	M14-387 Venetoclax (600 mg) + LDAC (N = 82)
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)

HMA = hypomethylating agent; LDAC = low-dose cytarabine; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

a. MedDRA version 21.0 for all studies.

Treatment-emergent Adverse Events of Clinical Interest

- **Hematologic adverse events**

Hematologic adverse events including severe neutropenia, anemia, and thrombocytopenia are expected features of the AML disease process and are common AEs reported in AML patients receiving HMA or LDAC as monotherapy or in combination with venetoclax. At baseline across all studies, approximately 50% of the subjects had ≥ Grade 3 neutropenia, 40% had ≥ Grade 3 thrombocytopenia, and 30% had Grade 3 anemia. Grade ≥ 3 AEs with preferred terms in the Blood and Lymphatic System Disorders SOC were reported for ≥ 70% of subjects treated with venetoclax at the target doses in combination with AZA, DEC, and LDAC in each of the Phase 3 and Phase 1 studies. Similarly, ≥ 68% of subjects who received placebo in combination with HMAs or LDAC in the Phase 3 studies also had Grade ≥ 3 AEs in this SOC.

Neutropenia

In Study M15-656, a higher percentage of subjects receiving venetoclax in combination with AZA reported AEs in the neutropenia search compared to subjects receiving placebo with AZA (71.0% and 44.4%, respectively). A greater percentage of subjects in the venetoclax plus AZA treatment arm reported febrile neutropenia (41.7% and 18.8%, respectively) compared to the placebo with AZA treatment arm. AEs ≥ Grade 3 within the neutropenia search (subset for selected adverse events) were reported in a higher percentage of subjects in the venetoclax plus AZA treatment arm compared to the placebo plus AZA treatment arm (70.7% versus 43.1%, respectively). Incidence of serious AEs within the neutropenia search (subset for selected adverse events) was higher among subjects in the venetoclax with AZA treatment arm compared to those in the placebo with AZA treatment arm (33.6% and 11.8%, respectively).

In Study M16-043, a higher percentage of subjects receiving venetoclax in combination with LDAC reported AEs in the neutropenia search (subset for selected AEs) compared to subjects receiving placebo with LDAC (68.3% and 45.6%, respectively). A generally similar percentage of subjects in the venetoclax and placebo treatment arms reported febrile neutropenia (32.4% and 29.4%, respectively) and neutrophil count decreased (7.0% and 4.4%, respectively).

- **Serious infections**

Serious events within the SOC of Infections and Infestations were reported for 57.2% of subjects receiving venetoclax with AZA in Study M15-656, compared with 43.8% of subjects receiving placebo with AZA. In Study M16-043, serious infections were reported for 37.3% of subjects treated with venetoclax in combination with LDAC and for a similar percentage of subjects treated with placebo and LDAC (36.8%). Pneumonia was the most common individual SAE of infection in both treatment arms.

Infections led to venetoclax discontinuation in approximately 7% to 12% of subjects treated with venetoclax combination with HMAs or LDAC and in approximately 7% to 9% of subjects treated with placebo in combination with AZA or LDAC. Approximately 6% to 15% of subjects treated with venetoclax combination with HMAs or LDAC had infections that led to death; infections leading to death were similar among subjects who received placebo with AZA (7.6%) or LDAC (10.3%).

In Study M15-656, SAEs within the SOC of Infections and Infestations were reported in 63 subjects (43.8%) treated with placebo in combination with AZA; the most common SAEs (affecting ≥ 5% of subjects) in this treatment arm included PTs of pneumonia (22.2%) and sepsis (8.3%). SAEs within the SOC of Infections and Infestations were reported in 162 subjects (57.2%) treated with venetoclax in combination with AZA; the most common SAEs in this treatment arm included PTs of pneumonia (16.6%) and sepsis (5.7%).

In Study M16-043, SAEs within the SOC of Infections and Infestations were reported in 25/68 subjects (36.8%) treated with placebo in combination with LDAC; SAEs affecting ≥ 5% of subjects in this treatment arm included pneumonia (10.3%), sepsis (5.9%), and septic shock (5.9%). SAEs of Infections and Infestations were reported in 53/142 subjects (37.3%) treated with venetoclax in combination with LDAC; the most common SAEs in this treatment arm included the PTs of pneumonia (14.1%) and sepsis (5.6%).

- **Tumour Lysis Syndrome:**

In Study M15-656, among subjects who received placebo or venetoclax 400 mg in combination with AZA, 0 and 3 (1.1%) subjects respectively reported events of TLS, all of which occurred during ramp up and within the 7 days of study drug administration in Cycle 1.

In Study M16-043, no events of TLS were reported among subjects who received placebo in combination with LDAC; 8 AEs of TLS (5.6%) were reported among subjects treated with venetoclax 600 mg in combination with 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 were associated with death in 2/8 subjects. Both of these subjects were considered of high risk: one subject had been hospitalized at the time of initiation of therapy and had pulmonary alveolar haemorrhage and pneumonia as additional causes of death, and the other subject had renal insufficiency.

- **Haemorrhage**

The risk of bleeding events (the most frequent of which was epistaxis) appeared to be somewhat increased among subjects who received venetoclax in combination with AZA, DEC, or LDAC compared to subjects who received placebo in combination with AZA or LDAC. AEs of any grade defined by a Haemorrhages SMQ were reported for 37% to 62% of subjects. However, Grade ≥ 3 bleeding events were reported for only 10.2% and 11.3% of subjects treated at the proposed venetoclax doses in combination with AZA or LDAC, and serious events of haemorrhage were reported for < 10% of subjects in Studies M15-656 and M16-043 (higher in Study M14-387).

Serious adverse event/deaths/other significant events

In all studies, SAEs were reported in a majority of subjects treated with venetoclax in combination with AZA, DEC, or LDAC at the proposed doses and were not increased compared to subjects treated with placebo in combination with AZA or LDAC. Among subjects who received placebo or venetoclax in combination with AZA, SAEs were experienced by 72.9% of subjects who received placebo and by 83.0% of subjects who received venetoclax 400 mg in Study M15-656 and by 77.4% of subjects who received venetoclax 400 mg with AZA in Study M14-358. Also in Study M14-358, 80.6% of subjects who received venetoclax in combination with DEC experienced SAEs. Among subjects who received placebo or venetoclax in combination with LDAC, SAEs were experienced by 61.8% of subjects who received placebo and 66.9% of subjects who received venetoclax 600 mg in Study M16-043, and by 91.5% of subjects who received venetoclax 600 mg with LDAC in Study M14-387.

Table 16. Serious Adverse Events Reported for SOCs and PTs with ≥ 5% of AML Subjects Receiving Proposed Doses of Venetoclax in Combination with HMAs or LDAC

SOC and PT, n (%)[a]	M15-656 Placebo + Azacitidine (N = 144)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 283)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 142)	M14-387 Venetoclax (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)

AML = acute myeloid leukemia; LDAC = low dose cytarabine; PT = preferred term; SOC = system organ class

a. MedDRA version 21.0.

Death

Table 19. Summary of Deaths Among AML Subjects Receiving Proposed Doses of Venetoclax or Placebo in Combination with HMAs or LDAC

	M15-656 Placebo + Azacitidine (N = 144)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 283)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 142)	M14-387 Venetoclax (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

Cross reference: Study M15-656 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; Study M16-043 Interim CSR Table 14.3__2.6.1A; Study M14-387 Interim CSR Table 14.3__2.3.2

Table 20. Treatment-Emergent Adverse Events Leading to Death, by SOC and PT, Among AML Subjects Receiving Proposed Doses of Venetoclax or Placebo in Combination with HMAs or LDAC

SOC and PT, n (%)a	M15-656 Placebo + Azacitidine (N = 144)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 283)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 142)	M14-387 Venetoclax (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
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

SOC and PT, n (%)a	M15-656 Placebo + Azacitidine (N = 144)	M15-656 Venetoclax (400 mg) + Azacitidine (N = 283)	M14-358 Venetoclax (400 mg) + Azacitidine (N = 84)	M14-358 Venetoclax (400 mg) + Decitabine (N = 31)	M16-043 Placebo + LDAC (N = 68)	M16-043 Venetoclax (600 mg) + LDAC (N = 142)	M14-387 Venetoclax (600 mg) + LDAC (N = 82)
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
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

AML = acute myeloid leukemia; HMA = hypomethylating agent; LDAC = low dose cytarabine; PT = preferred term; SOC = system orga n class.

a. MedDRA version 21.0 for all studies.

Cross reference: Study M15-656 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; Study M16-043 Interim CSR Table 14.3__2.5.2A; Study M14-387 Interim CSR Table 14.3__2.3.1

Laboratory findings

Changes from baseline in haematology and clinical chemistry laboratory values were analyzed over the length of the studies. The data were reviewed, and laboratory changes were assessed for any clinically meaningful trends. Because the studies are ongoing and some subjects remain in follow up, final laboratory values will be addressed in the final CSRs after the studies are completed. No clinically

meaningful trends have been observed for clinical chemistry or hematology variables as of the data cutoff dates for these studies. In both Studies M15-656 and M16-043, a greater proportion of subjects in the venetoclax treatment arms had Grade ≥ 3 hemoglobin, low neutrophils, and low platelets compared to the placebo treatment arms, in combination with either AZA or LDAC.

Among subjects treated with venetoclax or placebo in combination with AZA in Study M15-656, 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 subjects in each arm for low hemoglobin, low platelets, low leukocytes, and low neutrophils, and at least 40% of subjects in each arm for low lymphocytes (venetoclax with AZA, 70.0%; placebo with AZA, approximately 40%). In Study M15-656, more subjects who received venetoclax versus placebo, 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 subjects receiving venetoclax with AZA compared to placebo with AZA experienced increased bilirubin both overall (53.2% vs 39.6%) and Grade 3 or 4 (7.4% vs 4.2%).

Among subjects treated with either venetoclax or placebo in combination with LDAC in Study M16-043, 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%, venetoclax with LDAC; 17.6% placebo with LDAC) high glucose (13.4%, venetoclax with LDAC; 10.2% placebo with LDAC), and low phosphate (11.9%, venetoclax with LDAC; 19.1% placebo with LDAC) (Study M16 043 Interim CSR Table 14.3__4.2.4A). There were no clinically important trends for any of these parameters.

In Study M16-043, shifts in hematology values were observed in ≥ 50% of subjects in each arm for low hemoglobin, low platelets, and low leukocytes, and in ≥ 40% of subjects in each arm for low neutrophils; shifts were also observed for low lymphocytes (≥ 40% of subjects receiving venetoclax with LDAC, ≥ 25% for subjects receiving placebo with LDAC) (Study M16-043 Interim CSR Table 14.3__4.1.4A). More subjects who received venetoclax versus placebo, 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%) (Study M16 043 Interim CSR Table 14.3__4.1.3A). Of note, leukocyte count may include circulating leukemia blast cells whereas neutrophil count does not include circulating blast cells and is a more specific assessment of neutrophil counts. Accordingly, reductions in leukocytes from baseline may include both subjects who have reduced their normal leukocytes as well as subjects who have reduced their leukemic blast cells.

Laboratory findings in subjects treated with venetoclax in combination with LDAC in Study M14-387 were consistent with those in Study M16-043.

In most subjects, treatment-emergent myelosuppression was adequately managed with dose interruption or reduction. Grade 3 – 4 decreases in hemoglobin, platelet count, white blood cell count, neutrophils, and lymphocytes were common at baseline among subjects treated with venetoclax or placebo in combination with AZA or LDAC.

Subjects with liver enzyme values meeting criteria for potential drug-induced liver injury are discussed. It must be noted that many subjects had elevations in bilirubin, likely due to haemolysis as a result of repeated red cell transfusions in an AML setting.

Interpretations of worsening from baseline to the final value are pending since subjects remain in follow up on these studies. These data will be presented in the final CSRs.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Across the studies, there were no clinically meaningful trends or differences between treatment arms in subject weight, blood pressure (including diastolic and systolic values), heart rate, or body temperature; however, there was a higher incidence of AEs of hypotension in the venetoclax arms of Studies M16-043 and M15-656 compared with the placebo arms of those studies. No clinically significant issues were noted in other physical findings or observations related to safety.

No clinically significant ECGs were reported among subjects treated with placebo or venetoclax in combination with AZA in Study M15-656; in Study M14 358, 3 subjects who received venetoclax in combination with AZA (n = 2) or DEC (n = 1) had clinically significant ECG abnormalities post-baseline, none of which were assessed by the investigator as related to venetoclax or any other study drug. There were no reports of ECG abnormalities among subjects who received venetoclax in combination with LDAC in Study M6-043; however, 1 subject in this study who received placebo with LDAC had an AE of ECG abnormality that was assessed as not related to study drug. One subject who received venetoclax with LDAC in Study M14-387 had a clinically significant ECG abnormality, also assessed as not related to study drug.

Safety in special populations

Sex

Some numerical differences were noted in the overall incidence of AEs, Grade ≥ 3 AEs, and SAEs between male and female subjects, however there were no differences in the overall safety profile.

Age

Of the 283 patients with newly diagnosed AML treated in the VIALE-A (venetoclax + azacitidine arm) clinical trial, 96% were ≥65 years of age and 60% were ≥75 years of age. Of the 31 patients treated with venetoclax in combination with decitabine in the M14-358 clinical trial, 100% were ≥65 years of age and 26% were ≥75 years of age.

The overall incidence of AEs, Grade ≥ 3 AEs, and SAEs was similar between subjects with age < 75 years and age ≥75 years treated with venetoclax in combination with AZA in Studies M15-656 and M14-358, or with venetoclax in combination with DEC in Study M14-358. Likewise, overall incidence of AEs, Grade ≥ 3 AEs, and SAEs was similar between subjects with age < 75 years and age ≥ 75 years treated with venetoclax in combination with LDAC in Studies M16-043 and M14-387.**Race**

The majority of subjects in Studies M14-358 and M14-387 were white, it is difficult to compare safety data on the basis of race.

Renal function

Among subjects treated with venetoclax in combination with HMAs, mild to moderate renal impairment did not appear to affect the safety profile.

Among subjects treated with venetoclax in combination with LDAC, no clinically significant differences in AE rates were observed among the renal impairment subgroups.

Hepatic function

There were no notable differences in safety profile based on hepatic function at baseline.

Safety related to drug-drug interactions and other interactions

To evaluate the impact of co-administration with a strong CYP3A inhibitor, posaconazole was administered in combination with venetoclax 400 mg and DEC in a DDI sub-study (N = 12) as part of

Study M14-358. In this substudy, on Cycle 1 Days 21 to 28, a reduced daily dose of venetoclax of 100 mg or 50 mg was co-administered with posaconazole. Results from the DDI substudy showed that, with venetoclax dose adjustment, the use of posaconazole in patients receiving venetoclax in combination with DEC did not negatively affect the safety profile of venetoclax, suggesting that CYP3A inhibitors may provide an acceptable risk-benefit profile for subjects who have a medical need for these medications while receiving venetoclax as treatment for AML (M14-358 Interim CSR and Summary of Clinical Pharmacology Studies [Module 2, Section 2.7.2]).

The effects of co-administration of CYP3A inhibitors on venetoclax apparent clearance (CL/F) were also evaluated in the population pharmacokinetic analysis. The final model indicated that administration of strong CYP3A inhibitors resulted in an approximately 82% decrease in apparent clearance of venetoclax, and generally comparable effects of posaconazole versus other strong CYP3A inhibitors.

Discontinuation due to adverse events

None subject in the pivotal studies have discontinued study due to AEs. Treatment with venetoclax was discontinued due to AEs by 15.3% and 10.5% of subjects in studies M15-656 and M-16-043 respectively. Placebo was discontinued due to Es by 8.9% and 8.8%, respectively.

Post marketing experience

Based on post-marketing data to date, the safety profile demonstrated in the clinical trial setting is consistent with what has been observed through real-world use. The most recent Periodic Safety Update Report (PSUR), dated 07 February 2020, summarizes interval and cumulative benefit-risk information regarding venetoclax for the reporting interval of 05 June 2019 through 04 December 2019. As of the date of the PSUR, the estimated cumulative subject exposure from company-sponsored interventional clinical trials for venetoclax was 4,243 patients. The worldwide post-marketing patient exposure to venetoclax was estimated to be 5,964 patient treatment years (PTY) for all approved indications (CLL and AML) during the reporting interval. The estimated cumulative post-marketing patient exposure since first approval is 16,784 PTY.

2.5.1. Discussion on clinical safety

The safety data from two pivotal studies (M15-656 and M15-043) and two supportive studies (M14-358 and M14-387) are submitted within this type II variation. This safety data was not presented in the context of or compared to the aggregate safety data for venetoclax. The applicant has taken conservative approach and presented safety data in section 4.8 of the SmPC showing the highest frequency of ADRs seen in either CLL or AML studies. However, this approach cannot be supported since some ADRs have been reported only in patients with CLL or AML. It is recommended to present ADRs in patients with CLL and AML in separate tables or in separate columns of the sane table.

The safety data for patients with AML are derived from 622 and 212 subjects who received venetoclax or placebo, respectively, in combination with AZA, DEC or LDAC. Of these 622 subjects, 398 received 400 mg of venetoclax and 224 received 600 mg of venetoclax.

More than half of the patients in pivotal studies were male and older than 75 years and had primary AML. Around 40% of patients at baseline had ECOG performance status of 2, and around half of the patients in either study or control groups had grade 4 neutropenia, grade 2 anaemia and grade 3 or 4 thrombocytopenia. The baseline condition should be taken into account assessing safety of venetoclax.

The median duration of exposure to venetoclax was longer than to placebo in pivotal studies: 7.0 (0.0-30.7) and 4.3 (0.1-24.0) months, respectively, in study M15-656, and 4.1 (0.0-23.5) and 1.7 (0.1-20.2) months, respectively, in study M16-043. More patients in venetoclax group than in placebo group had duration of exposure longer than one year (52 weeks) in both pivotal studies: 37.5% and 20.8% in study M15-656, and 16.9% and 7.4%, respectively in study M16-043.

All or almost all patients in the studies have experienced any AEs, and around 95% of patients have had Grade 3 or 4 AEs. Rates and types of adverse events (AEs), Grade 3/4 AEs, and serious adverse events (SAEs) reported among subjects with AML who received venetoclax in combination with either HMAs or LDAC were generally similar to those reported for subjects who received placebo in combination with AZA or LDAC, with a few exceptions. The most common AEs experienced by subjects treated with venetoclax at the proposed doses in combination with either HMA or LDAC included gastrointestinal events, febrile neutropenia, cytopenias, fatigue, and pneumonia.

Late onset (> 90 days) AEs of at least grade 3 were hepato-biliary disorders, injury/poisoning/procedural complications, and nervous system disorders. The applicant is requested to compare the incidence and type of late onset AEs in the CLL studies with the AML studies and discuss whether an SmPC comment is deemed necessary.

Rate of discontinuation, interruption or reduction of venetoclax/placebo due to AEs was similar in the pivotal studies. 20.1% and 23.5% discontinued placebo, and 24.4% and 25.4% discontinued venetoclax in studies M15-656 and M15-043, respectively. More than half of patients have interrupted venetoclax or placebo. Interruption of venetoclax was slightly higher that interruption of placebo. Reduction rate of venetoclax or placebo was low and similar between groups.

SAEs reported in these studies are consistent with what would be expected in an AML population. Incidence of SAEs was 5% to 10% higher among subjects who received venetoclax in combination with AZA or LDAC compared to subjects who received placebo with AZA or LDAC. The most common SAEs across all treatment groups were febrile neutropenia, pneumonia, and sepsis.

Hematologic adverse events including anemia, neutropenia, febrile neutropenia, and thrombocytopenia were higher in subjects who received venetoclax in combination with AZA or LDAC, compared to those who received placebo in combination with AZA or LDAC. Grade ≥ 3 AEs in the Blood and Lymphatic System Disorders SOC were reported for ≥ 70% of subjects treated with venetoclax at the target doses and ≥68% of subjects with placebo in combination with AZA, DEC, and LDAC. The assessment of hematologic events as risks attributable to venetoclax is complex due to concomitant use of HMA or LDAC as well as the disease process of AML.

Grade ≥ 3 febrile neutropenia was more common in subjects treated with venetoclax in combination with AZA, DEC or LDAC than in subjects receiving placebo with AZA or LDAC. Across all venetoclax combinations, febrile neutropenia was the primary AE leading to dose interruptions and/or reductions.

In the phase 3 studies Infection events were reported for 84.5% and 64.8% of subjects treated with venetoclax in combination with AZA or LDAC, respectively, compared to subjects treated with placebo in combination with AZA (67.4%) or in combination with LDAC (60.3%). Grade ≥ 3 events of infection were reported in 63.6% and 43.0% of subjects who received venetoclax in combination with AZA or LDAC, respectively, and were consistent with subjects who received placebo with these agents (51.4% and 50.0%). Pneumonia was the most common Grade ≥ 3 infection and serious infection for all treatment groups. Serious events of infection were reported for 57.2% of subjects receiving venetoclax with AZA in study M15-656, compared with 43.8% of subjects receiving placebo with AZA; in study M16-043, serious infections were reported for 37.3% of subjects treated with venetoclax in combination with LDAC and for a similar percentage of subjects treated with placebo and LDAC (36.8%). Infections led to venetoclax

discontinuation in approximately 7% to 12% of subjects treated with venetoclax in combination with HMAs or LDAC and in approximately 7% to 9% of subjects treated with placebo in combination with AZA or LDAC. Approximately 9% to 15% of subjects treated with venetoclax in combination with AZA or LDAC had infections that led to death; in the placebo controlled studies, infections leading to death were numerically increased in the venetoclax arm compared with the placebo arm both among subjects who received venetoclax or placebo with AZA (9.2% [venetoclax plus AZA] vs 7.6% [placebo plus AZA]) and among subjects who received venetoclax or placebo with LDAC (14.8% [venetoclax plus LDAC] vs 10.3% [placebo plus LDAC]).

TLS has not been identified as an important risk in AML subjects treated with venetoclax at the target dose in combination with HMAs, (3 events in Study M15-656; 0 events in study M14-358) or LDAC (8 events in study M16-043; 2 events in study M14-387); 2 fatal events of TLS were reported in subjects treated with venetoclax 600 mg in combination with LDAC in Study M16-043. No events of TLS were reported during treatment ramp up in subjects treated with placebo in combination with either AZA or LDAC.

Most Venetoclax treated subjects experienced a TLS event at day 1 or 2 of the dose ramp up and thus at a low dose of venetoclax of 20-200 mg. The dose ramp-up for patients with AML differs from that with CLL, as dose increase in CLL patients gradually increases per week and for AML in 3/4 days the maximum dosage is achieved. The higher than expected incidence of TLS for the combination of venetoclax in AML is not caused by the higher final dosage per se, but presumably by the start dose and/or speed of the ramp up schedule. The applicant is requested whether data is available, or PK modelling could be used to propose a lower starting dose and/or slower ramp up schedule.

30-day and 60-day mortality rates were similar in venetoclax and placebo groups. The main cause of death was disease progression in all patient groups but one – in subjects receiving venetoclax in combination with AZA in study M15-656 both disease progression and non-disease progression were main causes of death.

The percentage of subjects with AEs leading to death was similar with the addition of venetoclax to HMA or LDAC to the reference therapies, reported for 15.5% to 23.2% of subjects across all studies in subjects who were treated with venetoclax at proposed doses in combination with AZA, DEC, or LDAC and for 20.1% to 20.6% of subjects treated with placebo in combination with AZA or LDAC. Infections were the most common AEs leading to death.

A part of patients from the study M14-358 receiving venetoclax with DEC participated in DDI study with posaconazole. The combination with posaconazole did not negatively affect the safety profile of venetoclax.

2.5.2. Conclusions on clinical safety

The safety profile of venetoclax in patients with AML is overall consistent with what is already known in venetoclax treated patients with CLL, however the frequency of some common AEs, neutropenia, febrile neutropenia, infections, is higher in AML population. No new safety signal has been identified.

The section 4.8 of the SmPC has been updated accordingly.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6.2 with the following content:

Safety concerns

Table: Summary of Safety Concerns

Important identified risks	• Tumor lysis syndrome • Neutropenia • Serious infection
Important potential risks	• Embryofetal toxicity • Medication error • Richter's transformation (for CLL only) • Second primary malignancy • Toxicity in patients with severe hepatic impairment
Missing information	• Safety in severe renal impairment • Safety in long-term exposure (> 12 months) (for CLL only)

Pharmacovigilance plan

Table : On-going and Planned Additional Pharmacovigilance Activities

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
CLL				
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Study M14-032 A Phase 2 Open-label Study of the Efficacy and Safety of ABT-199 (GDC-0199) in Chronic Lymphocytic Leukaemia Subjects with Relapse or Refractory to B-cell Receptor Signaling Pathway Inhibitor Therapy Ongoing	Assess the efficacy and safety of venetoclax monotherapy in subjects with CLL relapsed after or refractory to treatment with ibrutinib or idelalisib	Safety in long-term exposure (> 12 months) of venetoclax Second primary malignancy and Richter's transformation	Interim CSR Final CSR	Report submitted March 2018 December 2022

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study GO28667 (MURANO) Multicenter, Phase III, Open-Label, Randomised Study in Relapsed/ Refractory Patients with Chronic Lymphocytic Leukaemia to Evaluate the Benefit of venetoclax (GDC-0199/ABT-199) Plus Rituximab Compared with Bendamustine Plus Rituximab Ongoing	Evaluate the safety and efficacy of venetoclax and rituximab compared with BR in subjects with R/R CLL	Overall safety profile (provide comparator data) Richter's transformation and secondary primary malignancy	Primary analysis and interim CSR completed Final report	December 2017 December 2022
Study M13-982 A Phase 2 Open-Label Study of the Efficacy of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukaemia Harboring the 17p Deletion Ongoing	Evaluate the safety and efficacy of venetoclax monotherapy in subjects with R/R CLL in the presence of 17p del or *TP53* mutations	Safety in long-term exposure (> 12 months) of venetoclax Second primary malignancy and Richter's transformation	Interim CSR Final CSR	Report submitted June 2018 May 2021
Study M12-175 A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukaemia and Non-Hodgkin Lymphoma Ongoing	Assess the safety profile; characterize PK; determine MTD, RPTD, and lead-in period regimen of venetoclax monotherapy in subjects with R/R CLL (Arm A) or NHL (Arm B)	Safety in long-term exposure (> 12 months) of venetoclax Second primary malignancy and Richter's transformation	Interim CSR Final CSR	September 2019 May 2021
Study P16-562 Prospective Observational Cohort Study to Assess the Long Term Safety of Venetoclax in the Swedish Cohort of Chronic Lymphocytic Leukaemia Patients	To characterize long term safety of venetoclax including determining the incidence of select adverse events in CLL patients exposed to venetoclax.	Safety in long-term exposure (> 12 months) of venetoclax • Select list of adverse events: • Second primary malignancies	Interim CSR Final report	Every second year over a study period of 8 years Planned December 2025

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates

Ongoing		• Richter's transformation (DLBCL, HL)
		• Opportunistic serious infections
		• Autoimmune hematological event
		  ○ Other autoimmune hemolytic anemia
		  ○ Idiopathic thrombocytopenic purpura
		• Tumor Lysis syndrome
		• Hematologic adverse event
		  ○ Anemia
		  ○ Thrombocytopenia
		  ○ Neutropenia
		• Pneumonia
		• Febrile Neutropenia
		• Diarrhea
		• Nausea/Vomit
		• Upper respiratory tract infection
		• Fatigue
		• Hyperphosphatemia
		• Constipation		

Study M16-185 A Study to Assess the Effect of Venetoclax on the Pharmacokinetics of Ethinyl estradiol/Levonorgestrel in Female Patients with Hematologic Malignancies Planned	Open-label study to assess the effect of venetoclax on the pharmacokinetics of oral contraceptives in hematologic malignancy patients	Use in patients who require oral contraceptives	Study planned	Date for submission cannot be specified since the Agency agreed to conduction of this study when the indication is potentially widened to a younger population

Risk minimisation measures

Table : Summary Table of Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures
Tumor lysis syndrome (TLS)	Routine risk minimization measures:

Safety Concern	Risk Minimization Measures
	Posology and method of administration, including prophylactic measures for TLS, are described in section 4.2 of the SmPC (CLL and AML). Warnings and precautions for TLS are listed in section 4.4 of the SmPC (CLL and AML). Interaction with other medicinal products is described in section 4.5 of the SmPC (CLL and AML). TLS is described in section 4.8 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Packaging design and language to facilitate adherence to the dose-titration schedule • Pack size and package leaflet Additional risk minimization measures: None
Neutropenia	Routine risk minimization measures: Posology and method of administration are described in section 4.2 of the SmPC (CLL and AML). Warnings and precautions for neutropenia are listed in section 4.4 of the SmPC (CLL and AML). Neutropenia is listed as a very common adverse reaction in section 4.8 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine. • Use of treatment should be initiated and supervised by specialist • Package leaflet Additional risk minimization measures: None
Serious infection	Routine risk minimization measures: Posology and method of administration are described in Section 4.2 of the SmPC (CLL and AML). Supportive measures for infections associated with neutropenia are described in section 4.4 of the SmPC (CLL and AML). Observed infections and infestations are tabulated in section 4.8 (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist • Package leaflet Additional risk minimization measures: None
Embryofetal toxicity	Routine risk minimization measures:

Safety Concern	Risk Minimization Measures
	Language concerning embryofetal toxicity is included in section 4.6 and section 5.3 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet Additional risk minimization measures: None
Medication error	Routine risk minimization measures: Posology and method of administration are described in section 4.2 of the SmPC (CLL and AML). Description of contents of venetoclax container, including dose strength, shape and color of tablets, in section 3 and section 6.5 of SmPC (CLL). Language concerning overdose is included in section 4.9 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • In CLL, each carton will be dispensed weekly to the patient during the first 4 weeks of the dose titration • In AML, only 100 mg tablets will be dispensed to minimize medication errors • Labeling and packaging layout (immediate and outer packaging) has been designed to minimize medication errors • Pack size and package leaflet Additional risk minimization measures: None
Richter's transformation (for CLL only)	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist Additional risk minimization measures: None
Second primary malignancy	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist Additional risk minimization measures: None

Safety Concern	Risk Minimization Measures
Toxicity in Patients with severe hepatic impairment	Routine risk minimization measures: Posology and method of administration of dose adjustments in patients with severe hepatic impairment are described in section 4.2 of the SmPC (CLL and AML). PK study results pertaining to hepatic impairment are described in section 5.2 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medication • Use of treatment should be initiated and supervised by specialist • Package leaflet Additional risk minimization measures: None
Safety in severe renal impairment	Routine risk minimization measures: Section 4.2 of the SmPC advises that safety and efficacy have not yet been established in certain populations (CLL and AML). Section 5.2 of the SmPC presents PK study results pertaining to renal impairment (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet Additional risk minimization measures: None
Safety in long-term exposure (> 12 months) (for CLL only)	Routine risk minimization measures: Median duration of treatment is included in section 5.1 of the SmPC (CLL) Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists Additional risk minimization measures: None

2.7. Update to the Product Information

As a consequence of this variation, sections 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor corrections in the SmPC.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet

has been submitted by the MAH and has been found acceptable for the following reasons: The overall changes to the layout are small. The indications have been separated with new sub-headings. The different dosing schemes have been highlighted with sub-headings and different colours for each indication in order to ensure correct dosage.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This discussion refers to the combination of venetoclax with a hypomethylating agent (azacitidine or decitabine), for the treatment of adult patients with newly-diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

3.1.2. Available therapies and unmet medical need

In the 1970s, the '7+3' regimen (7 days of cytarabine and 3 days of anthracycline) became available and remains the mainstay of curative-intent standard of care for NDAML. In the last twenty years, new drugs such as hypomethylating agents (azacitidine, decitabine) have been introduced in the therapeutic arsenal for patients considered unfit for standard chemotherapy.

After a stagnation of decades in the treatment of AML, the recent years witnessed a wave of approvals and applications in the US and EU, mostly addressing specific mutations (e.g FLT3 with midostaurin, quizartinib, crenolanib, gilteritinib; IDH1 and IDH2 inhibitors ivosidenib and enasidenib), improved formulations of 'old' drugs (Vyxeos, liposomal cytarabine and daunorubicine at a 5:1 molar ratio), products targeting tumoral antigens (anti-CD33 gemtuzumab ozogamicin) or specific pathways (HH/GLI inhibitor glasdegib).

3.1.3. Main clinical studies

The current extension of indication application includes two randomized, double-blind phase 3 studies for newly-diagnosed AML patients ineligible for intensive chemotherapy, supported by two phase 1 trials, all ongoing:

- Study M15-656 is a randomized, double-blind, placebo-controlled phase 3 study of venetoclax in combination with azacitidine versus placebo in combination with azacitidine. Study M14-358 is a non-randomized Phase 1b study of venetoclax in combination with azacitidine or decitabine.
- Study M16-043 is a randomized, double-blind, placebo-controlled phase 3 study of venetoclax in combination with low-dose cyatarabine (LDAC) versus placebo in combination with LDAC. Study M14-387 is a non-randomized phase 1/2 study of venetoclax in combination with LDAC.

3.2. Favourable effects

Study M15-656 – venetoclax + azacitidine vs placebo + azacitidine

- The mOS for patients receiving venetoclax + azacitidine was 14.7 months (95% CI 11.9-18.7), in comparison with 9.6 months (95% CI 7.4-12.7) in the control group, with a HR of 0.66 (95% CI, 0.52-0.85).
- The CR+CRi rate was 66.4% (95% CI 60.6-71.9) in the experimental arm vs 28.3% (95% CI 21.1-36.3) in the control arm.
- 43% of the patients who received venetoclax + azacitidine had a first response (either CR or CRi) before the initiation of cycle 2 (vs 7.6% in the control arm), with a median time to first response of 1.3 months for CR (range 0.6 to 9.9) and 2.8 months for CRi (range, 0.8 to 13.2), respectively. The median duration of CR+CRi was 17.5 months (95% CI 13.6-NR) in the venetoclax + azacitidine arm and 13.4 months (95% CI 5.8-15.5) in the control group.
- The higher remission rates resulted in increases in the incidence of transfusion independence: RBC 59.8% in the venetoclax + azacitidine arm compared to 35.2% in the control group; platelets: 68.5% and 49.7%, respectively.
- In CR+CRi patients, MRD negativity at 10-3 level was observed in 23.4% (95% CI 18.6-28.8) of the patients who received azacitidine plus venetoclax and in 7.6% (95% CI 3.8-13.2) of those in the control group.
- The mEFS was 9.8 months (95% CI 8.4-11.8) in the experimental arm and 7 months (95% CI 5.6-9.5) in the control group (HR 0.63; 95% CI 0.50-0.80).

Study M14-358 – venetoclax in combination with decitabine

- In patients who received venetoclax at the proposed dose of 400 mg in combination with decitabine, the CR + CRi rate was 74.2%, with a CR rate of 54.8% and a CRi rate of 19.4%. The median duration of CR + CRi was 15 months (95% CI: 7.2, 30 months).
- In subjects treated with 400 mg venetoclax in combination with decitabine, mOS was 16.2 months (95% CI: 9.1, 27.8 months) with a minimum duration of study follow up of 40 months.
- The rate of transfusion independence for RBC was 61.3% and for platelets 87.1%, with a duration of transfusion independence of 110 days for both RBC and platelets.

3.3. Uncertainties and limitations about favourable effects

In Study M15-656 – venetoclax + azacitidine , even if the rate of CR+CRi was improved across AML genomic risk groups and these improvements in responses were translated into an increased overall survival in some of the evaluated subgroups, most notably among patients with either de novo or secondary AML, intermediate cytogenetic risk, and IDH1 or IDH2 mutations, these findings should be interpreted with caution due the small number of patients in each of these subgroups. It should be noted that patients with core-binding factor AML and those who had previously received HMAs were excluded from the study.

3.4. Unfavourable effects

Overall, the risks associated with the combination of venetoclax with an HMA or LDAC are consistent with the established safety profiles of the agents and natural history of AML.

Venetoclax + azacitidine

All subjects in venetoclax 400 mg + AZA and in placebo + AZA groups experiences AEs. The most common AEs experienced in ≥ 20% of AML Subjects receiving venetoclax or placebo were thrombocytopenia (45.9% and 40.3% respectively), neutropenia (42.0% and 29.2%, respectively), febrile neutropenia (41.7% and 18.8%, respectively), pneumonia (23.0% and 27.1%, respectively). TEAEs possibly related to venetoclax or placebo reported in ≥10% of subjects were neutropenia (35.7% and 21.5% respectively), thrombocytopenia (33.9% and 22.2% respectively), febrile neutropenia (27.9% and 7.6 respectively), and infections (36.7% and 18.1% respectively); ≥Grade 3 AEs reported in ≥10% of subjects receiving venetoclax or placebo were thrombocytopenia (44.5% and 38.2% respectively), neutropenia (42.0% and 28.5%, respectively), febrile neutropenia (41.7% and 18.8%, respectively), pneumonia (19.8% and 25%, respectively). Most important serious AEs reported more often reported in venetoclax group were febrile neutropenia, bacteraemia, septic shock, and those reported more often in placebo group were pneumonia, sepsis, malignant neoplasm progression.

Venetoclax + decitabine

Any AE has been experienced by 90.5% of subjects receiving Venetoclax 400 mg with AZA and by 80.6% of subjects receiving venetoclax 400 mg with DEC. TEAEs possibly related to study drug reported more often in DEC group were febrile neutropenia (32.3% vs 13.1%), in AZA group were anaemia (21.4% vs 9.7%), neutropenia (13.1% vs 6.5%), thrombocytopenia (17.9% vs 9.7%). Serious AES reported more often in DEC group were febrile neutropenia (41.9% vs 31.0%), bacteraemia (16.1% vs 3.6%), pneumonia (29.0% vs 26.2%), sepsis (6.5% vs 3.6%).

3.5. Uncertainties and limitations about unfavourable effects

Overall the known safety profile was confirmed, and there is one minor uncertainty remaining.

The majority of subjects experienced a TLS at a low dose of venetoclax of 20-200 mg in the beginning of the dose-ramp up. A lower starting dose than 100 mg could be explored, as the CLL starting dose is 20 mg.

3.6. Effects Table

Table 1. Effects Table for Venclyxto in combination with HMAs or LDAC for the treatment of newly-diagnosed AML in patients ineligible for standard therapy

Effect	Treatment	Control
Favourable Effects		
Study M15-656	**Ven + Aza N = 286**	**Pbo + Aza N = 145**
Primary Endpoints		
CR + CRi, n (%) (for the First 226 pat, IA1) Data cutoff: Oct. 2018	96/147(65.3)	20/79 (25.3)
95% CI	57.0, 73.0	16.2, 36.4
OS, median (months) Data cutoff : Jan 2020	14.7	9.6
95% CI	11.9, 18.7	7.4, 12.7
HR	0.662 (0.518, 0.845)	
Secondary Efficacy Endpoints		
CR + CRi, n (%) (Full Analysis Set, Group 2)	190 (66.4)	41 (28.3)
95% CI	60.6, 71.9	21.1, 36.3
CR + CRh, n (%)	185 (64.7)	33 (22.8)
95% CI	58.8, 70.2	16.2, 30.5
Postbaseline transfusion independence		
RBC, n (%)	171 (59.8)	51 (35.2)
95% CI	53.9, 65.5	27.4, 43.5
Platelets, n (%)	196 (68.5)	72 (49.7)
95% CI	62.8, 73.9	41.3, 58.1
EFS, median (months)	9.8	7.0
95% CI	8.4, 11.8	5.6, 9.5
MRD, n (with an assessment by the cutoff date)	216	104
MRD < 10^{-3} and CR + CRi response, n (%)	67 (23.4)	11 (7.6)
95% CI	18.6, 28.8	3.8, 13.2
Study M16-043	**Ven + LDAC N = 143**	**Placebo + LDAC N = 68**
Primary Efficacy Endpoint		
Full Analysis Set: All randomized subjects. Data cut-off: 15 February 2019 for **primary analysis**		
Treatment group	Ven + LDAC N = 143	Placebo + LDAC N = 68

Effect	Treatment	Control
OS, median duration (months)	7.2	4.1
95% CI	5.6, 10.1	3.1, 8.8
HR	0.749 (0.524, 1.071)	
Secondary Efficacy Endpoints		
CR + CRi, n (%)	68 (47.6)	9 (13.2)
95% CI	39.1, 56.1	6.2, 23.6
CR + CRi, n (%) by initiation of Cycle 2	49 (34.3)	2 (2.9)
95% CI	26.5, 42.7	0.4, 10.2
CR + CRh, n (%)	67 (46.9)	10 (14.7)
95% CI	38.5, 55.4	7.3, 25.4
CR + CRh, n (%) by initiation of Cycle 2	44 (30.8)	3 (4.4)
95% CI	23.3, 39.0	0.9, 12.4
Postbaseline Transfusion Independence		
RBC, n (%)	58 (40.6)	12 (17.6)
95% CI	32.4, 49.1	9.5, 28.8
Platelets, n (%)	68 (47.6)	22 (32.4)
95% CI	39.1, 56.1	21.5, 44.8
MRD < 10^{-3} and CR + CRi response, n (%)	8 (5.6)	1 (1.5)
95% CI	2.4, 10.7	0.0, 7.9
EFS	HR 0.583 (0.416, 0.817)	
6-Month Follow-up Analysis (post-hoc)		
Full Analysis Set: All randomized subjects. Data cut-off: 15 August 2019		
Primary Efficacy Endpoint		
Treatment group	Ven + LDAC N = 143	Placebo + LDAC N = 68
OS, median duration (months)	8.4	4.1
95% CI	5.9, 10.1	3.1, 8.8
HR	0.704 (0.503, 0.985)	
Secondary Efficacy Endpoints		
CR + CRi, n (%)	69 (48.3)	9 (13.2)
95% CI	39.8, 56.8	6.2, 23.6
CR + CRi, n (%) by initiation of Cycle 2	49 (34.3)	2 (2.9)
95% CI	26.5, 42.7	0.4, 10.2
CR + CRh, n (%)	69 (48.3)	10 (14.7)
95% CI	39.8, 56.8	7.3, 25.4

Effect	Treatment	Control
CR + CRh, n (%) by initiation of Cycle 2	44 (30.8)	3 (4.4)
95% CI	23.3, 39.0	0.9, 12.4
EFS, median duration (months)	4.9	2.1
95% CI	3.7, 6.4	1.5, 3.2
HR	0.610 (0.442, 0.841)	
MRD		
$< 10^{-3}$ and CR + CRi response, n (%)	9 (6.3)	1 (1.5)
95% CI	2.9, 11.6	0.0, 7.9

Study M14-358

Data cutoff:	July 2019	**Venetoclax 400 mg + Decitabine (n=31)**
CR + CRi, n (%)		23 (74.2)
95% CI[c]		55.4, 88.1
CR + CRh, n (%)		22 (71.0)
95% CI[c]		52.0, 85.8
CR, n (%)		17 (54.8)
95% CI[c]		36.0, 72.7
DoR		
CR + CRi, median (months)		15.0
95% CI[d]		7.2, 30.0
CR+CRh, median (months)		15.3
95% CI[d]		7.2, 30.2
CR, median (months)		21.3
95% CI[d]		6.9, --
Overall Survival		
median, months		16.2
95% CI[d]		9.1, 27.8
Postbaseline transfusion independence		
RBC, n (%)		19 (61.3)
95% CI[c]		42.2, 78.2
Platelets, n (%)		27 (87.1)
95% CI[c]		70.2, 96.4

Unfavourable Effects

M15-656			**Venclyxto 400 mg + AZA N=283**	**Placebo + AZA N=144**
Any AE		%	100	100
≥grade 3		%	96.5	98.6

Effect		Treatment	Control
TEAE related ≥10%	%	66.7	85.2
SAE ≥5%	%	72.9	83.0
Febrile neutropenia	%	29.7	10.4
Pneumonia	%	16.6	22.2
Sepsis	%	5.7	8.3
Septic shock	%	2.5	0.7
Death	%		
≤30 days after 1st dose	%	7.4	6.3
≤60 days after 1st dose	%	15.2	16.7
AE leading to discontinuation	%	24.4	20.1
AE leading to interruption	%	72.1	56.9
AE leading to reduction	%	2.5	4.2
M16-043		**Venclyxto 600 mg + LDAC N=142**	**Placebo + LDAC N=68**
Any AE	%	99.3	98.5
≥grade 3	%	97.2	95.6
TEAE related ≥10%	%	76.4	69.1
SAE ≥5%	%	66.9	61.8
Febrile neutropenia	%	16.9	17.6
Pneumonia	%	14.1	10.3
Sepsis	%	5.6	5.9
Septic shock	%	3.5	5.9
Death	%		
≤30 days after 1st dose	%	12.7	16.2
≤60 days after 1st dose	%	20.4	30.9
AE leading to discontinuation	%	25.4	23.5
AE leading to interruption	%	62.7	52.9
AE leading to reduction	%	9.2	5.9
M14-358		**Venclyxto 400 mg + AZA N=84**	**Venclyxto 400 mg + DEC N=31**
Any AE	%	100	100
≥grade 3	%	97.6	100
TEAE related ≥10%	%	90.5	80.6
SAE ≥5%	%	77.4	80.6
Febrile neutropenia	%	31.0	41.9
Pneumonia	%	26.2	29
Sepsis	%	3.6	6.5
Septic shock	%	1.3	3.2
Death	%		
≤30 days after 1st dose	%	2.4	6.5
≤60 days after 1st dose	%	8.3	9.7
AE leading to discontinuation	%	25.0	27.0
AE leading to interruption	%	67.9	59.5
AE leading to reduction	%	1.2	0

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Prolongation of OS has been shown when venetoclax is administered with azacitidine, and, by extrapolation, with decitabine.

No new safety signals were observed; the majority of the TEAE rates are essentially consistent with the established safety profiles of the agents and natural history of AML. The risks known to be associated with

the use of Venclyxto (e.g. neutropenia, febrile neutropenia, serious infections) are manageable through medical management with routine clinical assessment.

In conclusion, the OS benefit shown when venetoclax is added to azacytidine or decitabine, outweighs the additional toxicity.

3.7.2. Additional considerations on the benefit-risk balance

As regards venetoclax added to LDAC, no OS gain was demonstrated by established standard. A SAG was consulted and asked to consider whether clinical benefit could still be considered to have been shown. Informed by the SAG consultation, it is not considered that benefits have been established to outweigh the additional toxicity. Subsequently, the venetoclax and LDAC combination indication was withdrawn from this application.

3.8. Conclusions

The B/R of venclyxto for use in combination with azacitidine or decitabine, for the treatment of adult patients with newly-diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy, is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication for Venclyxto (venetoclax) in combination with Hypomethylating Agents (HMAs) for the treatment of adult patients with newly-diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. As a consequence, Sections 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor corrections in the SmPC.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Venclyxto is not similar to Dacogen, Rydapt, Mylotarg, Vyxeos liposomal, Xospata and Daurismo within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Venclyxto-H-C-Product Number-II-Var.No'

Attachments

1. SmPC, Package Leaflet (changes highlighted), as a relevant example with changes highlighted as adopted by the CHMP on 22 April 2021

Appendices

1. CHMP AR on similarity dated 22 April 2021
2. CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies dated 22 April 2021

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.