EUnetHTA Joint Action 3 WP4

Relative effectiveness assessment of pharmaceutical technologies

VENETOCLAX WITH A HYPOMETHYLATING AGENT FOR THE TREATMENT OF ADULT PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKAEMIA (AML) WHO ARE INELIGIBLE FOR INTENSIVE CHEMOTHERAPY

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Assessment Report

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Disclaimer

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Conflict of interest

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse event
AHD	Antecedent haematologic disorder
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical (classification system)
AUC	Area under the curve
AZA	Azacitidine
BM	Bone marrow
BSC	Best supportive care
CCR	Conventional care regimen
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK	Creatine kinase
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum concentration
CML	Chronic myeloid leukaemia
CMML	Chronic myelomonocytic leukaemia
CNS	Central nervous system
CR	Complete remission
CRh	Complete remission with partial haematologic recovery
CRi	Complete remission with incomplete haematologic recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DEC	Decitabine
DLCO	Diffusing capacity of the lungs for carbon monoxide
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EDC	Electronic data capture
EFS	Event-free survival
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU-CTR	EU Clinical Trials Register
EudraCT	EU Drug Regulating Authorities Clinical Trials Database
EUnetHTA	European Network for Health Technology Assessment
FAB	French-American-British system
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
G-CSF	Granulocyte colony-stimulating factor

GHS/QoL	Global Health Status/Quality of Life
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCT	Haematopoetic cell transplantation
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hh	Hedgehog
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IC	Intensive chemotherapy
ICD-10	International Classification of Diseases Version 10
ICTRP	International Clinical Trials Registry Platform
IPSS	International Prognostic Scoring System
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITD	Internal tandem duplication
IV	Intravenous
IWG	International Working Group
LDAC	Low-dose cytarabine
MAH	Marketing authorisation holder
MCT	Meaningful change threshold
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory activities
MeSH	Medical Subject Headings
MLFS	Morphologic leukaemia-free state
MPN	Myeloproliferative neoplasm
MR	Morphologic relapse
MRC	Myelodysplasia-related changes
MRD	Minimal/measurable residual disease
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMA	Network meta-analysis
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PBO	Placebo
PD	Progressive disease
PICO	Population, Intervention, Comparator, Outcome
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PSW	Propensity score weighting
QD	Once a day
RAEB-t	Refractory anaemia with excess blasts in transformation
REA	Relative Effectiveness Assessment
RBC	Red blood cell
RCT	Randomised controlled trial

RD	Resistant disease
RR	Risk ratio
SAE	Serious adverse event
SC	Subcutaneous
SD	Stable disease
SEER	Surveillance, Epidemiology and End Results
SLR	Systematic literature review
SPC	Summary of product characteristics
SOC	System organ class
SWOG	Southwestern Oncology Group
TC	Treatment choice
TEAE	Treatment-emergent adverse event
TLS	Tumour lysis syndrome
T_{max}	Time to reach the maximum concentration
TTD	Time to deterioration
ULN	Upper limit of normal
VAS	Visual Analogue Scale
VEN	Venetoclax
WBC	White blood cell
WHO	World Health Organization

EXECUTIVE SUMMARY OF THE ASSESSMENT OF VENETOCLAX

Introduction

Acute myeloid leukaemia (AML) is a malignant disease of the bone marrow (BM). It is characterised by clonal expansion of immature blast cells in peripheral blood and BM, resulting in ineffective erythropoiesis and BM failure (1, 2). Clinical manifestations of AML reflect the accumulation of poorly differentiated myeloid cells in BM, peripheral blood and other organs, with leukocytosis and the occurrence of anaemia and thrombocytopenia (3). Symptoms of AML include loss of appetite and weight, fatigue, fever, night sweats, weakness, headaches, shortness of breath, frequent infections, bruising and bleeding and, in rare cases, leukostasis (4). The initial assessment of patients with newly diagnosed AML focuses on patient fitness for standard induction and consolidation chemotherapy, which consists of the "7 + 3" regimen (7 days of continuous cytarabine infusion with 3 days of an anthracycline such as daunorubicin or idarubicin) and is generally offered to eligible patients as first-line therapy. Treatment options for patients ineligible for standard chemotherapy are limited (3). Decitabine or azacitidine is currently the first choice for patients with newly diagnosed ALM who are unfit for standard induction and consolidation therapy. Other treatment options are low-dose cytarabine (LDAC) or best supportive care (BSC). Glasdegib in combination with LDAC is also approved in the EU for treatment of adult patients with newly diagnosed AML who are not eligible for standard intensive chemotherapy, but is currently not recommended in the European Society for Medical Oncology (ESMO) guidelines (5).

There is no commonly accepted definition of ineligibility for intensive induction therapy and the clinical decision is based on individual assessment.

Objective and scope

The objective of this assessment was to assess venetoclax in combination with a hypomethylating agent (HMA; azacitidine or decitabine) for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

Scope of the assessment

Description	Assessment scope
	PICO 1
Population	Adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy.[1] [2] International Classification of Diseases Version 10: code C92.0
Intervention	**Venetoclax** (400 mg orally once a day) in combination with a hypomethylating agent (azacitidine or decitabine)[3] Synonyms for venetoclax: Venclexta, Venclyxto, GDC-0199, ABT-199, RG-7601
Comparison	• Azacitidine • Decitabine • Low-dose cytarabine (LDAC) • Glasdegib in combination with LDAC • Best supportive care (national differences exist; may include hydroxyurea, 6-mercaptopurine, 6-thyoguanine, low-dose melphalan, transfusion support, anti-infective therapies, among others)[4] •
Outcomes	Effectiveness: • Overall survival • Health-related quality of life

[1] The relevant population will be in accordance with the final marketing authorisation for the product and the indication may be adjusted during the European Medicines Agency (EMA) approval process.

[2] Several subgroup analyses may be considered (de novo and secondary AML including myelodysplastic syndrome [MDS], mutational status and cytogentic risk, among others).

[3] Venetoclax will be assessed in accordance with its final marketing authorisation using the dosing and combination defined in the summary of product characteristics (SmPC).

[4] Heuser M, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Ann Oncol. 2020;31(6):697–712. Döhner H, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424–47.

	• Complete remission (CR) • Composite CR: CR plus CR with incomplete haematologic recovery (CR + CRi) • Event-free survival • Transfusion independence Safety: • Serious adverse events (AEs) • Grade ≥3 AEs, including treatment-related AEs • Fatal AEs, including treatment-related fatal AEs • Overall AEs • Treatment discontinuations and dose reductions due to AEs
Study type	Effectiveness: Randomised controlled trials Safety: If suitable evidence syntheses (systematic reviews [SRs]/health technology assessment [HTA] reports) are available: • Evidence syntheses (SRs/HTA reports) • Primary studies (as described for the next point) published after the last search date for the latest SR/HTA document If suitable evidence syntheses (SRs/HTA reports) are NOT available: • Randomised controlled trials • Nonrandomised controlled trials • Observational studies

Methods

The PTJA16 assessment was based on the data and analyses included in the submission dossier prepared by the Marketing Authorisation Holder (MAH). The Authoring Team verified the completeness of the data and analyses as a part of the assessment process. In addition, the methods for data analyses and synthesis applied by the MAH (AbbVie) were checked for compliance with the European Network for Health Technology Assessment (EUnetHTA) requirements for the submission dossier and applicable EUnetHTA guidelines (https://www.eunethta.eu/methodology-guidelines/) and assessed with regard to scientific validity.

Literature search and assessment approach

The systematic literature search was performed in October 2020. The MAH searched in all three mandatory bibliographic databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, the Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE) were searched. The searches in bibliographic databases were complemented by searches in ClinicalTrials.gov. Furthermore, a number of conference proceedings were searched via Ovid for abstracts published since 2017.

The inclusion and exclusion criteria of the studies identified were specified according to the global Population, Intervention, Comparator, Outcome (PICO) used by the MAH, which encompasses the final EUnetHTA PICO. The EUnetHTA project plan specified inclusion of nonrandomised and observational studies on safety in addition to randomised controlled trials (RCTs). The MAH search strategies were restricted to randomised and nonrandomised trials. The MAH selection criteria for the EUnetHTA-specific PICO were limited to RCTs for both efficacy and safety data. Nonrandomised trials were excluded. The MAH submission file is thus only partly compliant with the requirements in the project plan. An Information Specialist critically assessed the MAH-reported information retrieval process and verified the completeness of the evidence base by using supplementary searches in the International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register (EU-CTR).

In general, the literature searches in the submission dossier were well documented, and the numbers of studies associated with information retrieval are consistent between the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, reporting of searches and the lists of studies included and excluded. The study pool is complete regarding journal articles in English on RCTs. Observational studies were listed separately as being excluded. In total, six unique RCTs met the

eligibility criteria for the assessment. Information used for assessment of the clinical effectiveness and safety was extracted from the submission dossier and verified against the clinical study reports (CSRs) or other original documentation provided in the submission dossier. Submitted CSRs were used to complete missing data for efficacy and safety in the core submission dossier.

VIALE-A was the only RCT with a direct comparison of efficacy and safety for venetoclax in combination with a HMA versus a relevant comparator (azacitidine) and is considered the primary source of evidence for the assessment. The remaining five studies were selected by the MAH as data sources for potential indirect comparisons of venetoclax in combination with HMA versus LDAC, glasdegib in combination with LDAC, and BSC.

The revised Cochrane risk-of-bias tool for randomised trials (RoB2) was used to assess the risk of bias for each outcome in VIALE-A. The results of the risk-of-bias assessments were used in Grading of Recommendations, Assessment, Development and Evaluation (GRADE) to rate the certainty of evidence at the outcome level.

The Authoring Team considered the phase 1b study M14-358 and the phase 3 study VIALE-C as evidence to support VIALE-A. as they provide additional evidence on the efficacy and/or safety of venetoclax in the relevant patient population. Results from the LDAC arm in the VIALE-C study were used in a submitted indirect treatment comparison (ITC) versus the venetoclax + azacitidine arm of VIALE-A.

On 22nd April 2021 the Committee for medicinal Products for Human Use (CHMP) adopted a positive opinion recommending venetoclax in combination with a HMA. While VIALE-A was the primary study for venetoclax in combination with azacitidine, the combination of venetoclax with decitabine was approved based on similar mechanism of action and results from the M14-358 study reporting similar efficacy and safety as venetoclax in combination with azacitidine (VIALE-A).

Eight patient organisations provided inputs in response to the open call for patient input: the Association of Cancer Patients in Finland (Finland); MOHA (Hungary); Blodkreftforeningen (Norway); Hrvatska Udruga Leukemija i Limfomi (Croatia); Patientforeningen for Lymfekræft og Leukæmi (Denmark); Diagnoza Leukemie, z.s. (Czech Republic); Leukaemia Care (United Kingdom); and Deutsche Leukämie- & Lymphom-Hilfe (Germany). They provided their perspectives on the impact of AML, patient-relevant outcomes and current therapy options.

Results

Overall the MAH has submitted comprehensive evidence that includes complete CSRs from VIALE-A and the supportive study M14-358, a report on the systematic literature search, and protocols and reports on the feasibility assessments for ITCs and the ITC performed versus LDAC.

VIALE-A study

VIALE-A was a phase 3, randomised, double-blind, placebo-controlled, multicentre study evaluating the efficacy and safety of venetoclax in combination with azacitidine versus placebo in combination with azacitidine in treatment-naïve subjects with AML aged ≥18 years who were considered as not eligible for standard induction therapy. The study included patients with de novo AML, AML evolving from myelodysplastic syndrome (MDS) and other antecedent haematologic disorders (AHDs) and AML after previous cytotoxic therapy or radiation (secondary AML). Patients with previous HMA therapy, venetoclax and/or chemotherapy for MDS were excluded. The patients included were aged ≥75 years or had comorbidities that precluded the use of intensive induction chemotherapy, according to at least one of the following criteria: baseline Eastern Cooperative Oncology Group performance status (ECOG PS) score of 2–3; severe cardiac or pulmonary comorbidity; moderate hepatic impairment; creatinine clearance (CLcr) ≥30 to 45 ml/min; or other comorbidity that the physician judges to be incompatible with chemotherapy (modified Ferrara criteria). All eligible patients were randomised at a ratio of 2:1. In the venetoclax + azacitidine arm, subjects were treated with venetoclax orally once a day (QD) plus azacitidine QD subcutaneously (SC) or intravenously (IV). In the placebo + azacitidine arm, subjects were treated with placebo orally QD plus azacitidine QD SC or IV. Patients continued to receive treatment cycles (28 days in length) until disease progression or unacceptable toxicity, withdrawal of consent, or other protocol criteria for discontinuation were met.

The main results from the direct evidence (VIALE-A) are as follows.

- **Overall survival:** The median overall survival (OS) was 14.7 months with venetoclax + azacitidine and 9.6 months in the placebo + azacitidine arm. The combination of venetoclax and azacitidine was superior to azacitidine alone, with an improvement in OS of 5.1 months reported (hazard ratio [HR] 0.662, 95% confidence interval [CI] 0.518, 0.845; p<0.001). The median follow-up duration was 20.5 months (range <0.1 to 30.7). The study is still ongoing and the final OS analyses will be performed when 360 events have been reported.

  Only two patients in the intervention arm and one patient in the control arm proceeded to transplant, and thus the OS data reported are considered to be unaffected by subsequent stem cell transplants.

- **Remission:** The rates of investigator-assessed complete remission (CR) and CR with incomplete haematologic recovery (CRi) for two different data cutoff points in VIALE-A were consistent over time. The composite complete remission rate (CR + CRi) was significantly higher for subjects in the venetoclax + azacitidine arm (66.4%) than for subjects in the placebo + azacitidine arm (28.3%). The number of patients with no available response data because of study discontinuation was 30/286 (10.5%) in the venetoclax + azacitidine arm and 20/145 (13.8%) in the comparator arm.

- **Subgroup analyses:** The prespecified subgroups included sex, age group, region, baseline ECOG PS, type of AML, cytogenetic risk, molecular markers and AML with myelodysplasia-related changes (AML-MRC). The subgroup analyses showed a consistent survival benefit for subjects in the venetoclax + azacitidine arm in most of the subgroups analysed. For patients with mutations in the *IDH1* or *IDH2* genes, a lower HR than for the overall population was observed, with an OS rate at 12 months of 66.8% for the venetoclax + azacitidine arm and 35.7% for the control arm (HR 0.345, 95% CI 0.20, 0.60; p<0.001). This finding is consistent with the higher composite complete remission (CR + CRi) incidence in this subgroup (75.4% in the venetoclax + azacitidine arm vs. 10.7% in the control arm; p<0.001).

- **Transfusion independence:** Venetoclax + azacitidine statistically significantly improved the percentage of subjects who achieved postbaseline transfusion independence for both red blood cells (RBCs) and platelets (58.0%) in comparison to azacitidine alone (33.8%).

- **Event-free survival:** Venetoclax + azacitidine significantly improved event-free survival (EFS), compared to placebo + azacitidine. The median EFS duration according to investigator assessment was 9.8 months (95% CI 8.4,11.8) for the venetoclax + azacitidine arm and 7.0 months (95% CI 5.6, 9.5) for the control arm.

- **Patient-reported outcomes:** The change from baseline in the Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue score was compared between the two treatment arms at each postbaseline visit. No clinically meaningful differences in mean change from baseline between the venetoclax + azacitidine and placebo + azacitidine arms were reported. In both treatment arms patients experienced an initial reduction in fatigue, and the combination treatment with venetoclax and azacitidine was not associated with any increase in fatigue.

  Subjects in both treatment arms experienced improvement in quality of life. A numerically greater change from baseline in European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) scores was observed in the venetoclax + azacitidine arm compared to the placebo + azacitidine arm on Day 1 of all cycles, except for Cycle 19, but there were no clinically meaningful differences in mean change from baseline between the treatment arms.

  Time to deterioration (TTD) of quality of life as measured using the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) Visual Analogue Scale (VAS) was assessed based on a deterioration of at least the meaningful change threshold (MCT) of 7 points. For the whole population, subjects in the venetoclax + azacitidine arm experienced significantly longer median TTD (10.7 months) in comparison to those in the placebo + azacitidine arm (3.9 months; p ≤ 0.05).

- **Safety:** All patients in VIALE-A experienced adverse events (AEs), with comparable rates between the treatment arms for grade ≥3 AEs, deaths due to AEs and treatment discontinuations. Haematologic AEs (overall and grade ≥3) as well as infections and infestations were more

frequent in the venetoclax + azacitidine arm than in the placebo + azacitidine arm. The incidence of SAE was approximately 10% higher in venetoclax + azacitidine than in placebo + azacitidine. The most common SAEs across both treatment arms were febrile neutropenia (29.7% vs. 10.4%), pneumonia (16.6% vs. 22.2%) and sepsis (5.7% vs. 8.3%) in the venetoclax + azacitidine arm and placebo + azacitidine arm respectively. Although the incidence of deaths due to AEs was similar in the two arms, the frequency of venetoclax-related AE was slightly higher than the frequency of placebo-related AEs. The 30-day mortality rate was similar in both treatment arms.

M14-358 study

The supportive M14-358 study was a phase 1b, open-label, nonrandomised, dose-finding study that evaluated the safety of venetoclax combined with decitabine or azacitidine and the preliminary efficacy of these combinations in treatment naïve-patients with AML aged ≥60 years who are not eligible for standard induction therapy because of comorbidity or other factors. This was a nonrandomised study and only descriptive statistics were used. In this assessment, results are only included for subgroups treated with the approved dose of 400 mg of venetoclax (venetoclax 400 mg + azacitidine, n=84; venetoclax + decitabine, n=31).

The main results from study M14-358 are as follows.

- **Remission**: The composite complete remission rate (CR + CRi) was 74.2% in the venetoclax + decitabine group and 71.4% in the venetoclax + azacitidine group, which is in line with the rate achieved with venetoclax + azacitidine in VIALE-A.

- **Transfusion independence:** For the venetoclax + azacitidine group , 61.9% of patients achieved postbaseline transfusion independence for both RBCs and platelets, compared to 61.3% of patients in the venetoclax + decitabine group..

Indirect comparisons

The MAH performed a propensity score weighting (PSW) analysis for indirect comparison of venetoclax + azacitidine versus LDAC that was based on individual patient data from the venetoclax + azacitidine arm in VIALE-A and the LDAC arm in VIALE-C. The results indicate that venetoclax + azacitidine is associated with responses and time-to event outcomes that are generally well above those reported for LDAC. Potential differences in the safety profiles for comparison of these regimens were not analysed and inferences on the comparability of safety cannot be drawn.

The feasibility assessment of possible network meta-analysis (NMA) by the MAH concluded that a NMA which included the comparators specified in the PICO was not feasible.

Discussion

Direct evidence was only identified for venetoclax + azacitidine versus azacitidine alone (VIALE-A). Patient and disease characteristics, including the stratification factors, were in general well balanced between the treatment arms. The study was double-blinded and the intention-to-treat population included all 431 patients who underwent randomisation. The proportions of patients who discontinued the study because of withdrawal of consent or who were lost to follow-up were low in both treatment arms (<3%). The risk of bias is considered low for the primary endpoint of OS and the rate of composite complete remission (CR + CRi) and the secondary outcome of transfusion independence; the certainty of this evidence according to GRADE is considered moderate.

Relative efficacy of venetoclax vs. LDAC was assessed on the basis of an ITC. The relative efficacy of venetoclax versus identified comparators such as BSC, decitabine and glasdegib in combination with LDAC was not assessed. The potential study network depended on the azacitidine–LDAC link and the azacitidine–BSC link on the basis of the azacitidine studies AZA-AML-001 and AZA-001. Glasdegib + LDAC was connected via the LDAC arm in the BRIGHT-AML study. However, the NMA feasibility assessment conducted by the MAH concluded that NMA were not feasible for reasons related to differences in both study design and the characteristics of the patient populations included. It is the opinion of the Authoring Team that it would be of added value to actually perform the NMA despite the limitations and possible lack of robustness of the outcomes to provide an opportunity to explore in more

detail the uncertainty of the existing evidence (i.e., bias and direction of bias) and to highlight evidence gaps.

For the comparison with glasdegib + LDAC (BRIGHT-AML study population), population-adjusted methods could be applied in which differences in patient populations are adjusted for to a certain degree.

Conclusion

The combination of venetoclax and azacitidine was superior to azacitidine alone, with an improvement of 5.1 months in OS observed (HR 0.662, 95% CI 0.518, 0.845; p<0.001).

The safety profile of azacitidine + venetoclax is consistent with the known profiles of both agents and with expectations for an older AML population. Haematologic AEs (overall and grade ≥3) as well as infections and infestations were more frequent in the venetoclax + azacitidine arm than in the control arm. The incidence of SAEs was approximately 10% higher in the venetoclax + azacitidine arm than in the control arm; febrile neutropenia, pneumonia and sepsis were the most common SAEs in the treatment groups.

The certainty of the evidence reported for OS and safety according to GRADE is considered moderate.

Patient-reported outcome (PRO) data from different health-related quality of life (HRQoL) instruments were collected. Overall, no additional deterioration in HRQoL was observed when adding venetoclax to azacitidine. The certainty of the PRO data according to GRADE is considered low owing to the small number of patients still reporting beyond early treatment cycles and possible attrition bias.

The only indirect comparisons submitted by the MAH included a comparison versus LDAC which indicated that venetoclax + azacitidine was associated with responses and time-to-event outcomes that are generally well above those reported on LDAC. No firm conclusion on the comparative effectiveness or safety versus LDAC can be drawn. No conclusion can be drawn on the comparative effectiveness of venetoclax + azacitidine versus glasdegib + LDAC or BSC.

Since other relevant comparisons (direct or indirect) were not submitted for venetoclax + azacitidine versus comparators of interest (e.g., BSC and glasdegib in combination with LDAC), this is considered an evidence gap.

1 BACKGROUND

1.1 Overview of the disease or health condition

1.1.1 Disease description

Acute myeloid leukaemia (AML; International Classification of Diseases Version 10: code C92.0) is a group of heterogeneous haematologic malignancies characterised by clonal expansion and accumulation of myeloid blasts in peripheral blood, BM and/or other tissues, coupled with abnormal or poor differentiation of haematopoetic cells (1, 2). Clinical manifestations of AML are a reflection of the accumulation of poorly differentiated myeloid cells in BM, peripheral blood and other organs, with leukocytosis and the occurrence of anaemia and thrombocytopenia (3). Symptoms of AML include loss of appetite and weight, fatigue, fever, night sweats, weakness, headaches, shortness of breath, frequent infections, bruising and bleeding, and, in rare cases, leukostasis (4). Although children can be affected, AML is primarily a disease of older adults (6).

The exact cause of AML is unknown, but several environmental factors have been identified, including exposure to certain chemicals, cytotoxic chemotherapy, radiation and retroviruses. In some cases, AML presents as an evolution of a previous blood disorder with clonal haematopoiesis (such as MDS, chronic myeloproliferative neoplasms or paroxysmal nocturnal haemoglobinuria), which is known as secondary AML (7, 8). In rare cases, AML is associated with certain genetic disorders and familial disorders. Most cases of AML are de novo malignancies. The frequency of secondary AML has been reported as 19.8% and 36.4% in two different studies and this form was associated with a low likelihood of receiving intensive treatment, lower complete remission rates and inferior survival (9, 10). MDS is a group of haematological disorders with a risk of progression to AML. Despite overlapping clinical phenotypes, differences in genetic mutation profiles allow distinction of MDS or MDS-derived AML from de novo AML (8).

As AML symptoms are nonspecific, a disorder is often discovered following routine blood tests. The diagnosis of AML is confirmed by morphologic results revealing a myeloid blast count of ≥20% of nucleated cells in a BM or peripheral blood specimen, supported by immunophenotyping, and cytogenetic and molecular genetic testing [6]. Regardless of blast percentage, the diagnosis of AML is also confirmed by the presence of cytogenetic abnormalities t(15;17) (q32;p13.2), t(8;21) (q22;q22.1), inv(16) (p13.1q22) or t(16;16)(p13.1;q22) (5). According to European LeukemiaNet (ELN) guidelines, targeted molecular genetic testing should include mutations in *NPM1*, *CEBPA* and *RUNX1* genes for definition of disease categories; *FLT3* for its prognostic value and potential targeted treatment; and *TP53* and *ASXL1* for their association with poor prognosis (8). *FLT3* internal tandem duplication (ITD) mutations are found in approximately 25% of newly diagnosed AML cases and have poor prognosis in cases of high allelic ratio (≥0.5) (8, 11).

Patient-associated prognostic factors (e.g., age, comorbidities, poor performance status) predict treatment-related early death and guide AML therapy, whereas disease-related prognostic factors (e.g., white cell count, prior MDS or cytotoxic therapy, genetic changes in leukaemia cells) predict resistance to current standard therapy (1). However, genetic abnormalities are powerful prognostic factors and cytogenetic changes are considered the single strongest prognostic factor for CR and OS (3, 8).

1.1.2 Disease classification and risk stratification

In 2016, a revised version of World Health Organization (WHO) classification defined six major disease entities: AML with recurrent genetic abnormalities; AML with myelodysplasia-related features; therapy-related AML; AML not otherwise specified; myeloid sarcoma; and myeloid proliferation related to Down syndrome (12).

Genetic mapping for AML patients led to the identification of numerous mutated genes. The association of these genetic abnormalities with clinical presentation, therapeutic response, relapse rates and OS facilitated the development of molecular classification and risk stratification schemas by WHO and ELN (13).

Using cytogenetic and molecular genetic profiling, AML patients can be stratified into three risk categories (favourable, intermediate and adverse/poor/unfavourable) according to guidelines from the ELN, National Comprehensive Cancer Network (NCCN) and Southwestern Oncology Group (2, 8, 14).

in Appendix 1**: Guidelines for diagnosis and management** provides more details.

Advances in the treatment of AML have led to significant improvements in outcomes for younger patients. However, the prognosis for elderly patients, who account for the majority of new cases, remains poor (3). Despite cytogenetic markers and disease classification and risk stratification schemes, stratification and treatment decisions are still challenging for AML patients aged >60 years. Age represents one of the most adverse prognostic indicators for response to treatment and OS. The incidence of AML increases with age, which may be partly explained by aggregation of adverse cytogenetic changes and gene mutations over time. Patients aged >60 years without adverse genetic factors could benefit from better treatment options (13).

1.1.3 Epidemiology: incidence, prevalence and survival

AML, the most common type of acute leukaemia among adults, accounts for approximately 80% of cases (3). The annual incidence of AML among European adults is 3.7 cases per 100,000 individuals, ranging from 3.0 in the Netherlands, France (males only) and Germany to 5.4 in Denmark (15, 16) . In the USA, a study using data from the Surveillance, Epidemiology and End Results (SEER) programme reported an age-adjusted annual AML incidence of 4.3 per 100,000 individuals (6). The annual age-adjusted incidence rates per 100,000 individuals appear to be higher for men than for women, particularly after the age of 50 years (6, 16, 17).

The median age at diagnosis is approximately 70 years (17, 18). The incidence of AML is age-dependent and increases from 1.3 cases per 100,000 individuals in the population aged <65 years to 12.2 in the group aged >65 years (3). Overall, AML accounts for 62% of leukaemia deaths and the estimated median OS for AML is 8.5 months (6) . Advances in AML treatment have led to significant improvements in long-term outcomes for younger patients. However, advancing age is still associated with poorer prognosis, with 70%–80% of patients aged ≥65 years dying of AML within 1 year after diagnosis (6, 19, 20). The 5-year relative survival rate for children and adolescents (aged 0–19 years) is 62.8%, but this declines to 48.8%, 28.0% and 5.4% for patients aged 20–49 years, 50–64 years and ≥65 years, respectively (18). Survival is particularly poor among patients ineligible for intensive chemotherapy, with a 1-year survival rate of 15%–20% and a 5-year survival rate of just 5% in this group (18, 21) .

For 2019, the prevalence of AML was estimated to be 13 per 100,000 individuals in the EU, which is equivalent to a total of approximately 69,000 patients (15). As approximately 30%–50% of AML patients are ineligible for intensive chemotherapy, the target population in the EU is estimated to be between 20,700 and 34,500 people in total (22). For the USA, the SEER-estimated prevalence of AML is 19 per 100,000 population (6).

1.1.4 Clinical outcomes

OS, event-free survival (EFS), and CR are commonly evaluated as primary endpoints in late-phase AML clinical trials, whereas disease-free survival and relapse-free survival are less frequently used (23).

OS is the gold standard of clinical trials and is considered the most clinically relevant endpoint. It is an unambiguous and unbiased endpoint but requires lengthy trials. EFS, an early indicator of treatment benefit, is not highly correlated with OS (23) . CR is defined as a BM blast count of <5% with the absence of circulating blasts and blasts with Auer rods, the absence of extramedullary disease, an absolute neutrophil count of ≥1.0 × 10^9 /l and a platelet count of ≥100 × 10^9 /l (8). CR is the first goal of AML induction chemotherapy and is associated with longer survival (23). CR with incomplete hematologic recovery (CRi; all the CR criteria except for residual neutropenia [<1.0 × 10^9 /l] or thrombocytopenia [<100 × 10^9 /l]) represents a less complete yet clinically meaningful response (6, 23) . Although treatment may extend OS for AML patients, it may also cause significant toxicity and impairment of HRQoL (24). HRQoL is an important factor in clinical decision-making, and it was shown that elderly AML patients value quality above length of life. Poor HRQoL at AML diagnosis has been associated with shorter OS (25). A patient's transfusional dependence markedly contributes to poor HRQoL due to hospitalisation, transfusion procedures and associated AEs (26). Other outcomes of interest include safety outcomes that may also be associated with HRQoL during treatment.

1.2 Current clinical practice

The mainstay of standard intensive induction therapy consists of the "7 + 3" regimen, which combines 7 days of continuous-infusion cytarabine with 3 days of an anthracycline (daunorubicin or idarubicin), and is generally offered to patients as first-line therapy. The regimen is usually appropriate for patients with intermediate to favourable prognosis and a low risk of treatment-related mortality, for example, younger patients with good performance status and normal kidney function, albumin level and platelet count (3). CR is achieved in 60%–80% of younger adults and 40%–60% of adults aged ≥60 years (8). For eligible patients, postremission strategies comprise intensive chemotherapy and/or autologous or allogeneic haematopoetic cell transplantation (HCT) and depend on genetic risk stratification (8).

Elderly patients are more likely to have an adverse cytogenetic risk profile, poor performance status and significant comorbidities, are less likely to respond to chemotherapy and are often more susceptible to treatment-related toxicities (3). The majority of elderly patients are not able to tolerate standard intensive chemotherapy and allogeneic HCT and have poor prognosis and survival (8). However, any decision on a treatment strategy should be based on an evaluation of the fitness of an elderly patient and not on numerical age itself (27).

1.2.1 European clinical practice guidelines

An overview of treatment guidelines that currently apply for elderly patients with de novo or secondary AML who are ineligible for intensive chemotherapy are presented in Appendix 1: Guidelines for diagnosis and management.

ESMO clinical practice guidelines for diagnosis, treatment and follow-up

The initial assessment of patients with newly diagnosed AML focuses on a patient's fitness for standard induction and consolidation chemotherapy. Patients with underlying heart, kidney, lung or liver disease, mental illness, an ECOG PS score ≥3 and age ≥75 years are considered ineligible for intensive chemotherapy. These pre-existing factors are the strongest predictors of poor outcome (i.e., nonrelapse induction-related mortality) (5).

Karyotype and mutational analysis is essential to guide clinical decisions and treatment and to predict prognosis. According to the 2017 ELN recommendations, three risk groups have been identified: favourable, intermediate and adverse. Patients for whom a low risk of relapse is predicted if they are treated with induction and consolidation chemotherapy are considered as the favourable-risk AML group. The adverse-risk AML group consist of patients with complex cytogenetic and poor-risk genetic aberrations, as well as patients who failed to achieve CR after two induction cycles, regardless of their cytogenetic/genetic status. The intermediate-risk AML group includes patients with genetic and cytogenetic abnormalities not classified as favourable or adverse (5, 8).

All AML cases should be assigned to either standard induction and consolidation chemotherapy or nonintensive chemotherapy. As a first-line treatment for patients ineligible for standard intensive therapy, participation in a clinical trial is strongly encouraged. If there is no trial available, treatment with a HMA (azacitidine or decitabine) is the the first choice. Given the moderate effects of HMAs, LDAC remains an alternative to HMAs in the first-line treatment of AML patients who are ineligible for standard induction and consolidation chemotherapy, except in patients with adverse-risk cytogenetics for which LDAC has very poor activity (28).BSC with, for example hydroxycarbamide or low-dose melphalan is also mentioned as an option, especially for patients with MDS progressing to AML during treatment with HMA. (5). After four cycles of induction therapy, patients who experience a clinical benefit should continue treatment until progression or intolerance. Another option for patients responding to initial treatment is to undergo allogeneic HCT using reduced-intensity conditioning, which may cure a proportion of these patients (5).

On the basis of preliminary data, the ESMO guidelines consider venetoclax in combination with a HMA or LDAC to be superior for AML patients ineligible for standard intensive chemotherapy, but also note that randomised trials are still ongoing and are needed to recommend the use of venetoclax with confidence (5).

However, on the basis of results from the VIALE-C phase 3 trial, the recent Committee for medicinal Products for Human Use (CHMP) assessment concluded that a convincing OS benefit had not been

established for venetoclax in combination with LDAC and the application for regulatory approval of this combination was withdrawn by the MAH during the regulatory assessment (29).

Glasdegib is a potent inhibitor of the hedgehog (Hh) pathway and exerts its action by binding to and blocking Smoothened, a transmembrane protein involved in Hh signal transduction. Aberrant Hh signalling has been identified in many solid tumour types and in haematological malignancies . Glasdegib in combination with LDAC is approved in the USA and was also recently approved in the EU for treatment of adult patients newly diagnosed with AML who are not eligible for standard intensive chemotherapy. It is currently not recommended in the ESMO guidelines (5).

Comparison of 5-day and 10-day decitabine treatments in patients with newly diagnosed AML showed almost identical response rates and OS between the two arms. Therefore, a 5-day schedule is recommended if decitabine is chosen , which is in line with its approved dosing schedule (30, 31).

There are no known predictive markers for recommending one HMA over the other. HMA treatment is usually continued until disease progression or intolerance, but may be terminated after at least four consecutive cycles if the patient has not responded or derived a clinical benefit.

Patients with MDS progressing to AML during treatment with azacitidine present a significant therapeutic challenge. Current evidence shows that 21%–43% of patients with AML pretreated with HMAs and who received HMA and venetoclax achieved a response (5).

Value frameworks are under development that aims to establish “Clinical Benefit Scales” also for haematological malignancies with a potential for valuable complementary information to the ESMO clinical practice guidelines on the efficacay and safety of new treatments (32).

2017 ELN recommendations from an international expert panel

In 2017, the ELN published recommendations on the diagnosis and management of adult patients with AML. The document is not a clinical practice guideline, but an expert consensus statement (8).

For older patients who are not candidates for intensive chemotherapy, the strongly recommended treatment option is enrolment in a clinical trial. Other treatment options include low-intensity therapy (HMAs or LDAC) and BSC. LDAC is generally well tolerated and has CR rates ranging from 15% to 25% (28). Regarding HMAs, an increase in median OS with decitabine versus mostly LDAC (7.7 vs. 5.0 months) was observed, whereas azacitidine increased the median survival (10.4 vs. 6.5 months) compared to conventional care regimens (standard induction chemotherapy, LDAC or supportive care only) (33, 34). Azacitidine may be particularly advantageous in AML with adverse cytogenetic features. Superiority of azacitidine over conventional care regimens was previously shown in AML with 20%–30% blasts. To observe a maximal response with azacitidine or decitabine, up to six courses may be needed. However, if patients show no response after three courses, they are unlikely to respond with further therapy. Treatment of unfit and most older patients with AML is currently unsatisfactory (8).

BSC is an option for patients who cannot tolerate any antileukaemia therapy or do not wish to receive any therapy. BSC consists of anti-infective and antifungal therapy, transfusion support of blood and blood products and hydroxyurea (8).

Treatment pathway for venetoclax

In the 2021 NCCN guidelines, venetoclax in combination with HMA or LDAC is recommended for treatment of patients aged ≥60 years who are not candidates for intensive chemotherapy or decline it and without actionable mutations. Venetoclax with HMA or LDAC is also recommended for patients withwith *IDH1*, *IDH2* or *FLT3* mutations (2).

According to the 2020 ESMO guideline, venetoclax in combination with HMAs or LDAC is considered to be superior for AML patients ineligible for standard intensive chemotherapy. However, the recommendations were based on preliminary data, and the guideline notes that randomised trials are ongoing and are needed to recommend venetoclax use with confidence (5). The final approved indication for venetoclax in the EU includes only the combination of venetoclax and a HMA (29).

Glasdegib has only been approved recently in the EU and is so far not included in the ESMO guidelines or ELN recommendations. However, in the 2021 NCCN guidelines, glasdegib in combination with LDAC is recommended for treatment of patients aged ≥60 years who are not candidates for intensive chemotherapy or decline it and have no actionable mutations (2).

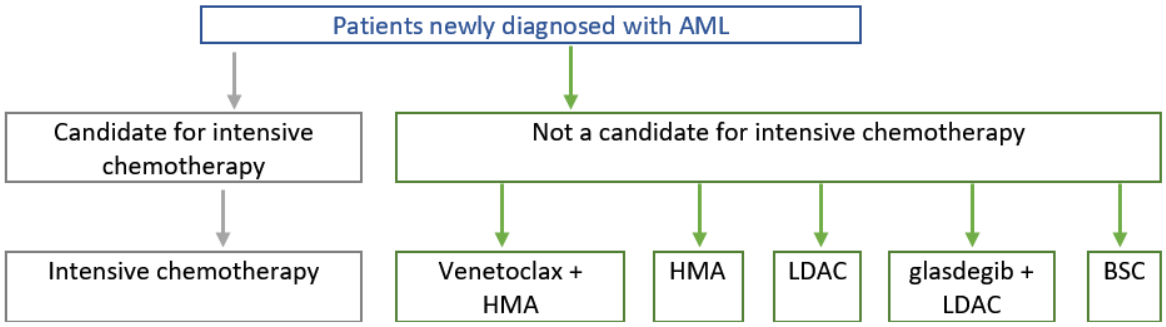


Figure 1.1 Positioning of venetoclax in the treatment pathway for patients with AML
Source: Adapted from the submission dossier (5, 8, 35).
Abbreviations: AML=acute myeloid leukaemia; HMA=hypomethylating agent; LDAC=low-dose cytarabine; BSC=best supportive care.

1.3 Features of the intervention

Venetoclax is a first-in-class, highly selective, potent, oral BCL2 inhibitor that restores programmed cell death (apoptosis) in cancer cells (36-40). Overexpression of BCL2 has been demonstrated in AML cells, where it mediates tumour cell survival and is associated with resistance to chemotherapeutics. Venetoclax helps to restore apoptosis by binding directly to BCL2 protein. This mechanism of action – targeting BCL2 protein – is innovative and completely distinct in the treatment of AML. HMAs indirectly increase sensitivity to BCL2 inhibition in AML cells by modifying the relative levels of BCL2 family members (22).

Features of the available interventions are presented in Table 1.1. Administration and dosing details for venetoclax are summarised in Table 1.2.

Table 1.1. Features of the interventions available

Nonproprietary name	Venetoclax	Azacitidine	Decitabine	Cytarabine [a]	Glasdegib
Proprietary name	Venclyxto	Vidaza	Dacogen	Cytarabine	Daurismo
Registered EMA indication	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. Venclyxto in combination with a HMA is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.	Vidaza is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with: • Intermediate- and high-risk MDS according to the IPSS • Chronic myelomonocytic leukaemia with 10%–29% marrow blasts without myeloproliferative disorder • AML with 20%–30% blasts and multilineage dysplasia according to the WHO classification • AML with >30% marrow blasts according to the WHO classification.	Dacogen is indicated for the treatment of adult patients with newly diagnosed de novo or secondary AML according to the WHO classification who are not candidates for standard induction chemotherapy.	Cytarabine is indicated for induction of remission in AML in adults and children and for other acute leukaemias in adults and children.	Daurismo is indicated, in combination with LDAC for the treatment of newly diagnosed de novo or secondary AML in adult patients who are not candidates for standard induction chemotherapy.
Prospective marketing authorisation holder	AbbVie Deutschland GmbH & Co. KG	Celgene Europe B.V.	Janssen-Cilag International NV	Pfizer	Pfizer Europe MA EEIG

Contraindications	Hypersensitivity to the active substance or to any of the excipients. In patients with CLL, concomitant use of strong CYP3A inhibitors at initiation and during the dose-titration phase. In all patients, concomitant use of preparations containing St. John's wort.	Hypersensitivity to the active substance or to any of the excipients. Advanced malignant hepatic tumours. Breast-feeding.	Hypersensitivity to decitabine or to any of the excipients. Breast-feeding.	Therapy with cytarabine should not be considered in patients with pre-existing drug-induced bone marrow suppression, unless the clinician feels that such management offers the most hopeful alternative for the patient. Cytarabine should not be used in the management of nonmalignant disease, except for immunosuppression. Hypersensitivity to the active substance or to any of the excipients.	Hypersensitivity to the active substance or to any of the excipients.
Drug class	Antineoplastic agents, other antineoplastic agents	Antineoplastic agents, pyrimidine analogues	Antineoplastic agents, antimetabolites, pyrimidine analogues	Antineoplastic agents, pyrimidine analogues	Antineoplastic agents, other antineoplastic agents
Active substance(s)	Venetoclax	Azacitidine	Decitabine	Cytarabine	Glasdegib
Pharmaceutical formulation(s)	Film-coated tablets (10, 50 and 100 mg)	Powder for suspension for injection (25 mg/ml)	Powder for concentrate for solution for infusion (50 mg)	Solution for injection or infusion (20 mg/ml)	Film-coated tablet (25 and 100 mg)
ATC code	L01XX52	L01BC07	L01BC08	L01BC01	L01XJ03
In vitro diagnostics required	—	—	—	—	—
Monitoring required	Complete blood counts should be monitored throughout the treatment period. Monitoring of any signs and symptoms of infection is required. Pre-dose: To prevent TLS, assessment of blood chemistry (potassium, uric acid, phosphorus, calcium and creatinine) and correction of pre-existing abnormalities before	Liver function tests, serum creatinine and serum bicarbonate should be determined before initiation of therapy and each treatment cycle. Complete blood counts should be performed before initiation of therapy and as needed to monitor response and toxicity, but at a minimum, before each treatment cycle. Cardiopulmonary	Patients should be monitored for signs and symptoms of infection. Complete blood and platelet counts should be performed regularly, as clinically indicated and before each treatment cycle. Liver and renal function tests should be performed before initiation of therapy and each treatment cycle, and as clinically indicated.	Frequent platelet and leukocyte counts are mandatory. Periodic checks of bone marrow and liver and kidney functions should be performed. Cardiopulmonary assessment before and during the treatment should be considered. Monitoring for neurological adverse reactions, TLS	Complete blood counts, electrolytes and renal and hepatic functions should be assessed before initiation and at least once weekly for the first month. Electrolytes and renal function should be monitored once monthly for the duration of therapy. Serum CK levels should be obtained before initiation and as indicated clinically thereafter (e.g., if

	initiation of treatment with venetoclax is necessary. At initiation and dose titration, intensive monitoring to reduce the risk of TLS should be performed for patients with renal impairment. Post-dose: For patients at risk of TLS, blood chemistries should be monitored at 6–8 h after each new dose during titration and at 24 h after reaching the final dose. For patients with risk factors for TLS, additional measures should be considered, including increased laboratory monitoring.	assessment before and during the treatment should be considered. Patients should be monitored closely for TLS and necrotising fasciitis.	Patients, especially those with a history of cardiac disease, should be monitored for signs and symptoms of heart failure.	and pancreatitis is also advised.	muscle signs and symptoms are reported). ECG should be monitored before and approximately 1 week after initiation, and then once monthly for the next 2 months to assess for QT corrected for heart rate (QTc) prolongation. ECG should be repeated if abnormal. Patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities or those who are taking medicinal products with known QT-prolonging effects may require more frequent and ongoing ECG monitoring. Abnormalities should be managed promptly.
Orphan designation	No	No	Yes	No	Yes
Advanced therapy medicinal product	No	No	No	No	No

Source: (29, 30, 41, 42).

[a] There is variation in indications, contraindications and proposed monitoring, as well as marketing authorisation holders.

Abbreviations: AML=acute myeloid leukaemia; ATC=Anatomical Therapeutic Chemical; CK=creatine kinase; CLL=chronic lymphocytic leukaemia; ECG=electrocardiogram; EMA=European Medicines Agency; HMA=hypomethylating agent; IPSS=International Prognostic Scoring System; LDAC=low-dose cytarabine; MDS=myelodysplastic syndrome; TLS=tumour lysis syndrome; WHO=World Health Organization.

Table 1.2. Administration and dosing of the technology

<table>
<tr><th></th><th>Venetoclax</th></tr>
<tr><td>Method of administration</td><td>Tablets to be taken orally</td></tr>
<tr><td>Doses</td><td>10 mg, 50 mg and 100 mg tablets</td></tr>
<tr><td>Dosing frequency</td><td>Recommended dose is once daily</td></tr>
<tr><td>Standard length of a course of treatment</td><td>100 mg on Day 1, 200 mg on Day 2 and 400 mg on Day 3 and beyond</td></tr>
<tr><td>Standard interval between courses of treatment</td><td>Continuously until disease progression or unacceptable toxicity</td></tr>
<tr><td>Standard number of repeat courses of treatment</td><td>Continuously until disease progression or unacceptable toxicity</td></tr>
<tr><td>Dose adjustments</td><td>Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk of TLS at initiation and during the dose titration phase and the risk of other toxicities.
If a CYP3A inhibitor must be used, patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used before initiating the CYP3A inhibitor should be resumed 2–3 days after discontinuation of the inhibitor. The recommendations for managing drug–drug interactions if a CYP3A inhibitor must be used are summarised below.

<table>
<tr><th>Inhibitor</th><th>Initiation and dose titration phase</th><th>Steady daily dose (after dose titration phase)</th></tr>
<tr><td>Strong CYP3A inhibitor</td><td>Day 1: 10 mg
Day 2: 20 mg
Day 3: 50 mg
Day 4: 100 mg or less</td><td>Reduce venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons)</td></tr>
<tr><td>Moderate CYP3A inhibitor</td><td colspan="2">Reduce venetoclax dose by at least 50%</td></tr>
</table>

Venetoclax dosing may be interrupted as needed for management of haematologic toxicities and blood count recovery according to the table below.

<table>
<tr><th>Adverse reaction</th><th>Occurrence</th><th>Dosage modification</th></tr>
<tr><td colspan="3">Haematologic adverse reactions</td></tr>
<tr><td rowspan="3">Grade 4 neutropenia (ANC <500 /µl) with or without fever or infection; or grade 4 thrombocytopenia (platelet count <25 × 10^3 /µl)</td><td>Occurrence before achieving remission [a]</td><td>In most instances, do not interrupt venetoclax in combination with azacitidine or decitabine because of cytopenias before achieving remission.</td></tr>
<tr><td>First occurrence after achieving remission and lasting at least 7 days</td><td>Delay the subsequent cycle of venetoclax in combination with azacitidine or decitabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia.
On resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine or decitabine.</td></tr>
<tr><td>Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer</td><td>Delay the subsequent cycle of venetoclax in combination with azacitidine or decitabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia.
On resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine or decitabine, and reduce venetoclax duration by 7 days during each subsequent</td></tr>
</table>
</td></tr>
</table>

			cycle, such as 21 days instead of 28 days.
	Nonhaematologic adverse reactions		
	Grade 3 or 4 nonhaematologic toxicities	Any occurrence	Interrupt venetoclax if not resolved with supportive care. On resolution to grade 1 or baseline level, resume venetoclax at the same dose.

Source:(43).
[a] Consider bone marrow evaluation.
Abbreviations: ANC=absolute neutrophil count; G-CSF=granulocyte colony-stimulating factor; HMA=hypomethylating agent; LDAC=low-dose cytarabine; TLS=tumour lysis syndrome.

2 OBJECTIVE AND SCOPE

The aim of this EUnetHTA Joint Relative Effectiveness Assessment is to compare the clinical effectiveness and safety of venetoclax in the target patient populations with relevant comparators. The target patient populations and relevant comparators (according to the requirements of the EUnetHTA partners) are defined in the project scope in Table 2.1.

Table 2.1. Scope of the assessment

Description	Assessment scope
Population	Adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy.[5] [6] International Classification of Diseases Version 10: code C92.0 Medical Subject Headings (MeSH) terms: Leukemia, Myeloid, Acute Tree number(s): C04.557.337.539.275 MeSH unique ID: D015470
Intervention	Venetoclax (400 mg orally once a day) in combination with a hypomethylating agent (azacitidine or decitabine) [7] Synonyms for venetoclax: Venclexta, Venclyxto, GDC-0199, ABT-199, RG-7601
Comparison	• Azacitidine • Decitabine • Low-dose cytarabine (LDAC) • Glasdegib in combination with LDAC • Best supportive care (national differences exist; may include: hydroxyurea, 6-mercaptopurine, 6-thyoguanine, low-dose melphalan, transfusion support and anti-infective therapies, among others)[8] Available MeSH data for comparators: <u>Azacitidine</u> Unique ID: D001374 Tree numbers: D02.145.150 D03.383.742.680.245.217 D13.570.685.245.217 D13.570.800.286.300 <u>Decitabine</u> Unique ID: D000077209 Tree numbers: D02.145.150.500 D03.383.742.680.245.217.500 D13.570.685.245.217.500 D13.570.800.286.300.500 <u>LDAC</u> Unique ID: D003561 Tree numbers: D03.383.742.680.245.453 D13.570.065.300 D13.570.685.245.453 Synonym for glasdegib: PF-04449913
Outcomes	<u>Effectiveness:</u> • Overall survival

[5] The relevant population will be in accordance with the final marketing authorisation for the product and the indication may be adjusted during the EMA procedure. The CHMP gave a positive opinion for the treatment of this population on 22nd April 2021.

[6] Several subgroup analyses may be considered (de novo and secondary AML including MDS, mutational status and cytogentic risk, among others).

[7] Venetoclax will be assessed in accordance with its final marketing authorisation using the dosing and combination defined in the SPC. The CHMP gave a positive opinion on this combination and dose on 22nd April 2021.

[8] Heuser M, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Ann Oncol. 2020;31(6):697–712. Döhner H, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424–47.

	• Health-related quality of life • Complete remission (CR) • Composite CR: CR + CR with incomplete haematologic recovery (CR + CRi) • Event-free survival • Transfusion independence Safety: • Serious adverse events (AEs) • Grade ≥3 AEs, including treatment-related AEs • Fatal AEs, including treatment-related fatal AEs • Overall AEs • Treatment discontinuations and dose reductions due to AEs
Study type	Effectiveness • Randomised controlled trials Safety: If suitable evidence syntheses (systematic reviews [SRs]/health technology assessment [HTA] reports) are available: • Evidence syntheses (SRs/HTA reports); and • Primary studies (as described for the next point) published after the last search date for the latest SR/HTA document. If suitable evidence syntheses (SRs/HTA reports) are NOT available: • Randomised controlled trials • Nonrandomised controlled trials • Observational studies

The present assessment was based on the data and analysis included in the submission dossier prepared by the MAH (AbbVie).

The scope of the assessment deviates from the scope described in the project plan as follows.

- **Intervention**: The original scope included two different interventions, venetoclax (400 mg orally QD) in combination with a HMA (azacitidine or decitabine) and venetoclax (600 mg orally QD) in combination with LDAC. The second intervention is now not relevant for the final scope as the CHMP positive opinion is limited to venetoclax (400 mg orally QD) in combination with a HMA (azacitidine or decitabine). The final scope for the assessment has been adapted accordingly.
- **Literature search**: While the EUnetHTA PICO focused on the final indication, the MAH applied a broader (global) PICO for their systematic literature review (SLR). Some of the search terms and combinations of terms used were less relevant as the approved indication is more limited. Overall, the deviation for the literature search had no practical consequences for identification of relevant studies since the EUnetHTA PICO was incorporated in the global search by the MAH.
- **Information retrieval**: The inclusion criteria considering study design used by the MAH for information retrieval differed from the criteria specified by the EUnetHTA Authoring Team in the PICO. The MAH restricted inclusion to RCTs only.
- **Selection of studies identified**: The EUnetHTA project plan limited efficacy data to results based on RCT studies. For safety data the inclusion criteria were expanded to include nonrandomised and observational studies in addition to randomised trials. This difference in requirements considering study design was not followed by the MAH. In the submission dossier, all the studies that were included were restricted to RCTs for all outcomes in the EUnetHTA PICO. This restriction excluded potential safety information for individual treatments based on results from nonrandomised clinical trials or observational trials and was not aligned with the EUnetHTA PICO.
- Only RCTs were included in the PICO for efficacy outcomes. However, the phase 1b M14-358 study is included as supportive evidence for efficacy and safety outcomes in this assessment of the intervention (venetoclax + a HMA). This study was considered as supportive to the pivotal VIALE-A study in the regulatory process and final approval of venetoclax + a HMA.

3 METHODS

This assessment is based on the data and analyses included in the submission dossier prepared by the MAH. During the assessment, the completeness of the data and analyses in the submission dossier was verified. Furthermore, the methods for data analysis and synthesis applied by the MAH were checked against the EUnetHTA submission dossier requirements and applicable EUnetHTA Guidelines and assessed with regard to scientific validity.

3.1 Information retrieval

The evidence base for the drug combination under assessment as provided by the MAH was reviewed by the Authoring Team. Search strategies were checked for appropriateness and the results of the information retrieval included in the submission dossier from the MAH were checked for completeness against a search in study registries and against the studies included in the regulatory assessment report. The Information Specialist conducted supplementary searches in the ICTRP and EU-CTR to check for possible incompleteness of the study pool.

The SLR performed by the MAH aimed to identify efficacy and safety studies of all relevant treatment alternatives including treatments still in the pipeline for AML in newly diagnosed or treatment-naïve patients who are ineligible for intensive chemotherapy. Inclusion and exclusion criteria were specified according to the global PICO used by the MAH and are listed in Table 3.1. All of the relevant details are included in Tables 7.1 and 7.2 in the core submission file (22). The original search strategies from October 2020 were wider but are still valid after the recent CHMP approval of the final wording for the relevant indication in April 2021. The original criteria used for the MAH searches encompass the final EUnetHTA PICO as stated in the project plan for PTJA16 (Venetoclax in combination with either azacitidine or decitabine in treatment of AML in treatment-naïve patients who are ineligible for intensive chemotherapy).

The MAH searched in all three mandatory bibliographic databases (MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials) in addition to CDSR and DARE. The searches in bibliographic databases were complemented by searches in a clinical trial registry (ClinicalTrials.gov). Furthermore, a number of conference proceedings were searched via Ovid for abstracts published since 2017. More details are included in Section 7.3.1 of the core submission file (22).

The MAH search consisted of terms related to the population (AML) combined with terms for interventions and comparators and was limited by a filter for study design (RCTs and non-RCTs only). The MAH did not use any restrictions related to publication date, but the bibliographic database search was limited to publications in English. As required by EUnetHTA standards, the searches were conducted within 3 months of first submission to EUnetHTA in December 2020 (Table 3.1).

In total 18 publications corresponding to six unique RCTs met the eligibility criteria for the assessment. Only one study directly comparing the efficacy and safety of venetoclax in combination with a HMA versus a relevant comparator (azacitidine) was identified (VIALE-A). The other five studies were selected by the MAH as data sources for indirect comparisons of venetoclax in combination with a HMA versus other relevant comparators (LDAC, glasdegib + LDAC and BSC). A PRISMA flow chart is included in Figure 7.1 in the core submission dossier (22).

A summary of the publications included and excluded in the SLR by the MAH is available in Appendix Sections 8.1.4 and 8.1.5 in the core submission dossier (22).

Table 3.1 includes a summary of the information retrieval process and the results for study selection.

Table 3.1. Summary of the information retrieval and study selection process used by the MAH

Element	Details
List of studies submitted by the MAH	For a list of studies included by the MAH, see Table 4.1 and Table 4.2
Databases and trial registries searched	• MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions • EMBASE • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) • Ovid Northern Light Life Sciences Conference Abstracts • Conference websites of the European Hematology Association; American Society of Clinical Oncology; British Society for Haematology; European Society for Medical Oncology; American Society of Hematology • ClincalTrials.gov • National Institute of Health and Care Excellence (NICE) • Scottish Medicines Consortium
Search date	13th October 2020
Keywords	acute myeloid leukemia; venetoclax; azacitidine; decitabine (+ a number of other drugs for treating AML not relevant to the EUnetHTA PTJA16 assessment); randomized controlled trials; non-randomized controlled trials
Inclusion criteria	This summary table refers to the EUnetHTA-specific PICO P: Treatment-naive adult patients (age ≥18 years) with AML who are ineligible for intensive chemotherapy I/C: Studies with at least one of the following regimens: venetoclax + azacitidine, venetoclax + decitabine, venetoclax + LDAC, azacitidine, LDAC, decitabine, glasdegib + LDAC, best supportive care (varies by country, may include hydroxyurea, 6-mercaptopurine, 6-thyoguanine, low-dose melphalan, transfusion support, anti-infective therapies, among others) O: Studies reporting at least one of the following outcomes: overall survival, complete remission, complete remission with incomplete blood count recovery, composite complete remission, complete remission with partial haematologic recovery, duration of remission, event-free survival, minimal/measurable residual disease, grade 3 or 4 adverse events, discontinuation due to adverse events S: Randomised controlled trials
Exclusion criteria	P: Not adult, not human, not treatment-naive AML, patients with HIV, HBV, or HCV infection, acute promyelocytic leukaemia I/C: Studies without any of the regimens listed in the inclusion criteria O: Studies not reporting any of the outcomes listed in the inclusion criteria S: Editorials, letters, comments, case reports of individual patients, errata and notes, observational studies, SLRs and meta-analyses or review articles
Date restrictions	No date restrictions in the mandatory databases
Other search limits or restrictions	Bibliographic databases: English language ClinicalTrials.gov: Intervention studies; with results

Source: Tables 7.1 and 7.2 in the submission dossier (22).
Abbreviations: AML=acute myeloid leukaemia; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; LDAC=low-dose cytarabine; MAH=marketing authorisation holder; PICO=Population, Intervention, Comparator, Outcome; RCT=randomised controlled trial; SLR=systematic literature review.

3.1.1 Literature search and selection of studies: critical assessment of the method

The evidence base provided by MAH with regard to the drug under assessment was reviewed by the Authoring Team. The Information Specialist critically assessed the method used for information retrieval by the MAH. In general, the literature searches in the submission dossier were well documented, and the numbers of studies identified via information retrieval are consistent between the PRISMA diagram, reporting of the searches and the lists of studies included and excluded studies. (Appendix 8.1 in the core submission dossier).

The essential elements of the PICO are well reflected by the search strategy. The search terms were deemed as relevant, although some of the terms used reflect a broader indication than the indication approved by CHMP. This includes use of combinations of text words with Medical Subject Headings (MeSH) terms or Emtree terms whenever applicable and application of Boolean operators. The MAH used filters for study design to identify both RCT studies and non-RCT studies across different search platforms. The Authoring Team performed a simple validation of the MEDLINE search strategy and the results confirmed that the strategy retrieved the journal articles included in the submission dossier (Appendix 6: Information retrieval).

The overall assessment indicates only minor flaws in the search (Appendix 6: Information retrieval). The most important issue not conforming to the EUnetHTA standard was that the MAH only searched one clinical trial registry (ClinicaTrials.gov) out of the three clinical trials registries that are recommended as standard; the EU-CTR and ICTRP registries were not searched. The Information Specialist conducted supplementary searches in the ICTRP and EU-CTR to check for possible incompleteness of the study pool. While the MAH only searched for trials of interventions with results for the condition AML, the EUnetHTA Authoring Team searched for trials of venetoclax in combination with either azacitidine or decitabine with or without results, and without any limitation regarding intervention.

To address this, the Authoring Team checked the tables for excluded studies in the core submission dossier (Table 8.2 Full-text articles excluded [N=142] and Table 8.3 Additional full-text articles excluded based on additional criteria for EUnetHTA [N=64]). Neither the supplementary and updated searches of study registers nor the review of studies excluded by the MAH identified any relevant new studies.

3.2 Data extraction

Information used for assessment of clinical effectiveness and safety was extracted from the submission dossier and verified against the CSR or other original documentation provided in the submission dossier. During the assessment phase, the Authoring Team discovered some issues with incomplete data in the core submission dossier, so for the required completeness of the efficacy and safety data the submitted CSRs were used as the primary source.

3.3 Risk-of-bias assessment

The RoB2 quality rating tool developed by the Cochrane Collaboration (version 5.1.0; March 2011) was used to assess the risk of bias in randomised trials (44). Risk of bias at the study level was assessed for six different domains:

- Method used to generate the sequence of randomisation (random sequence generation);
- Method used to mask the sequence of allocation to treatment (allocation concealment);
- Measures used to ensure the blindness of the study with respect to treatment assignment (blinding of participants, medical personnel and outcome assessors);
- Completeness of the data for each outcome considered (incomplete outcome data);
- Selective description of the results (selective outcome reporting); and
- Other sources of bias (e.g., bias due to early interruption of the study because of the benefits without an appropriate stopping rule, use of a nonvalidated measurement instrument, incorrect statistical analysis).

For each domain, two independent assessors judged the risk of bias (low risk, high risk or unclear) on the basis of the information retrieved from the full-text publications, the protocols and the submission dossier. The results for the risk-of-bias assessment are presented at both the study level and the outcome level. Only the main study (VIALE-A) was assessed for risk of bias.

3.4 Results and analyses for the studies included

The information in the submission dossier on the study design, study methods, populations, endpoints (patient relevance, validity and operationalisation) and study results was evaluated. The results from this evaluation are presented and were used for identification of relevant analyses and considered for the conclusions of the assessment report.

3.4.1 Sensitivity analysis

To evaluate the robustness of results, sensitivity analyses with regard to methodological factors presented in the submission dossier and the corresponding methods applied were evaluated. These methodological factors arise from decisions made within the framework of the process for retrieval and assessment of information, for example, the specification of cutoffs for the time points for data collection or the choice of effect measures.

3.4.2 Subgroup analysis and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the submission dossier and the corresponding methods applied were evaluated. The evaluation also includes the justification for the choice of cutoffs if quantitative characteristics were categorised.

3.4.3 Indirect comparisons

The methods applied for indirect comparisons and, if applicable, the justification in the event of deviations from the required approaches were evaluated (45).

3.4.4 Certainty of the evidence

To rate the quality of the evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)-method was applied (46).

The quality of the evidence for each outcome (the body of evidence for each outcome) was rated according to factors outlined in the GRADE approach. The following factors may impact the decision to downgrade the quality of evidence in an RCT: study limitations (risk of bias); inconsistencies in the results; indirectness of evidence; imprecision; and publication bias. The RoB2 results were used for this rating, which was performed independently by at least two assessors. Any disagreement was resolved via discussion and involvement of a third assessor.

3.5 Patient involvement

An open call for patient input was published on the EUnetHTA website on 21st September 2020. The questions were based on the HTA international questionnaire template that was adapted for this project and covered the following topics:

- The impact of AML on patient quality of life;
- Impact of AML on carers and unpaid care-givers;
- Experiences with currently available treatment options; and
- Expectations and requirements for a new medicine for AML.

All responses received by EUnetHTA from patient organisations are summarised in Section 5: Patient involvement of this report.

4 RESULTS

4.1 Information retrieval

The MAH searched in all three mandatory bibliographic databases (MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) in addition to CDSR and DARE. The searches in bibliographic databases were complemented by searches in a clinical trial registry (ClinicalTrials.gov). Furthermore, a number of conference proceedings were searched via Ovid for abstracts published since 2017. For more details see Section 7.3.1 in the core submission dossier (22).

The Information Specialist conducted supplementary searches in ICTRP and EU-CTR to check for possible incompleteness of the study pool. The searches in these registries identified 116 records (Appendix 6: Information retrieval). The majority of studies identified investigates venetoclax used in combination with other substances than HMAs and none of the studies identified had published any results. Therefore, no new studies could be included in the study pool despite the updated and expanded search. The check for completeness of the study pool submitted by the MAH proved that the pool was complete.

Information retrieval by the MAH was carried out according to the PICO requirements with the exception of restricted study design. In the submission dossier, all the studies included were restricted to RCTs for the whole EUnetHTA PICO, even though nonrandomised controlled studies and observational studies were considered as eligible designs, if relevant, according to the EUnetHTA PICO for safety data. For additional details and a PRISMA flow chart, see Section 7.3 in the submission dossier (22).

A total of six studies were considered relevant by the MAH for this assessment. In addition, two studies were considered as supportive for efficacy and/or safety for the combination of venetoclax and a HMA. For details, see Table 7.3 in the core submission dossier. One of those studies was not considered relevant by the Authoring Team (31) (Table 4.1).

4.2 Studies included in the assessment

The studies listed in Table 4.1 were included in the assessment.

Table 4.1. Study pool: list of relevant studies used for the assessment

Study reference/ID	Study category		
	Study for marketing authorisation of the technology under assessment [a]	Sponsored or third-party study [b]	Documentation available [c]
VIALE-A (NCT02993523)	Yes	Sponsored	Core submission dossier (22) CSR and protocol (47) Full-text publication (48) EPAR (29)
AZA-AML-001 [d] (NCT01074047, 2009-012346-23)	Yes	Sponsored	Full-text publication (33) EPAR (41)
AZA-001 [d] (NCT00071799)	Yes	Sponsored	Full-text publication (49) EPAR (50)
DACO-016 [d] (NCT00260832, 2005-004503-11)	Yes	Sponsored	Full-text publication (34) EPAR (30)
BRIGHT-AML 1003 [d] (NCT01546038; EudraCT: 2012-000684-24) Only the AML subgroup	Yes	Sponsored	Full-text publication (51) EPAR (42)
Supportive studies			
M14-358	Yes	Sponsored	Full-text publication (52)

(NCT02203773) Supportive for VIALE-A on efficacy and safety			CSR report (53) EPAR (29) Core submission dossier (22)
VIALE-C (NCT03069352) Supportive for VIALE-A on safety	No	Sponsored	Full-text publication (54) CSR (55) EPAR (29) Core submission dossier (22)

Abbreviations: AML=acute myeloid leukaemia; CSR=clinical study report; EPAR=European Public Assessment Report; EudraCT=EU Drug Regulating Authorities Clinical Trials Database.
[a] If "yes", also indicate the reference(s) for the data.
[b] Study sponsored by the marketing authorisation holder or in w hich the marketing authorisation holder participated financially in some other w ay.
[c] Include references for the study registry entries and, if available, the reports on study design and/or results listed in the study registries.
[d] Studies considered for potential indirect treatment comparisons.

4.3 Studies excluded

Table 4.2 lists the studies that were included in the submission dossier provided by the MAH but were excluded for further consideration in this assessment.

Table 4.2. Studies excluded

Study reference/ID	Reason for non-consideration of the study
Short et al., 2019	This was a phase 2, randomised, open-label, single-centre trial to assess the efficacy of decitabine given in either 5-day or 10-day schedules. The trial only compared the approved 5-day schedule of decitabine versus the "off-label" 10-day schedule of decitabine and therefore is not considered to add relevant evidence to this assessment.

Source: (31).

4.4 Characteristics of studies of venetoclax in combination with a HMA

4.4.1 VIALE-A

A detailed description of the characteristics of the VIALE-A study can be found in Table 4.3 and Table 4.4.

VIALE-A is a phase 3, randomised, double-blind, placebo-controlled, multicentre study evaluating the efficacy and safety of venetoclax in combination with azacitidine versus placebo in combination with azacitidine in treatment-naïve subjects with AML aged ≥18 years who are not eligible for standard induction therapy because of age or comorbidities. The venetoclax combination was studied in adult patients aged ≥75 years or who had comorbidities that precluded the use of intensive induction chemotherapy according to at least one of the following criteria: baseline ECOG PS score of 2–3; severe cardiac or pulmonary comorbidity; moderate hepatic impairment; creatinine clearance ≥30 to <45 ml/min; or other comorbidity the physician judges to be incompatible with chemotherapy (Ferrara criteria (56) with modifications; Table 4.3).

AML patients eligible for VIALE-A included de novo AML; AML evolving from MDS and other AHDs; and AML after previous cytotoxic therapy or radiation (secondary AML). Subjects must have received no prior treatment for AML, with the exception of hydroxyurea. Patients with previous HMA therapy, venetoclax and/or chemotherapy such as LDAC for MDS were excluded, as well as those with favourable cytogenetic risk. Subjects were required to have ECOG PS score of 0–2 if aged ≥75 years or 0–3 if aged 18–74 years, adequate renal function, and adequate liver function.

Eligible patients were randomised in a 2:1 ratio to receive either venetoclax plus azacitidine or placebo plus azacitidine. In the venetoclax + azacitidine arm, subjects were treated with venetoclax orally QD plus azacitidine QD SC or IV; in the placebo + azacitidine arm, subjects were treated with placebo orally QD plus azacitidine QD SC or IV. All subjects started study drugs (investigational product and reference therapy) on Cycle 1, Day 1. Venetoclax or placebo was administered with a 3-day ramp up beginning

with the 100-mg dose of venetoclax on Day 1 to reach the final dose of 400 mg of venetoclax on Day 3 of Cycle 1. During titration (Cycle 1), patients received prophylaxis for tumour lysis syndrome and were hospitalised for monitoring. Dosing was continued at 400 mg until Day 28, and then in all subsequent 28-day cycles. Subjects were to receive azacitidine 75 mg/m^2 for 7 days of each cycle, beginning on Day 1.

Patients continued to receive treatment cycles (28 days in length) until disease progression or unacceptable toxicity, withdrawal of consent or other protocol criteria for discontinuation were met (48). Except for patients who withdrew consent, all patients who discontinued a trial regimen were followed for survival.

For the randomisation process, patients were stratified by age (18 to <75 years vs. ≥75 years), cytogenetic risk (intermediate risk vs. poor risk) and region (USA, Europe, China, Japan, rest of the world). The study design is illustrated in Figure 4.1.

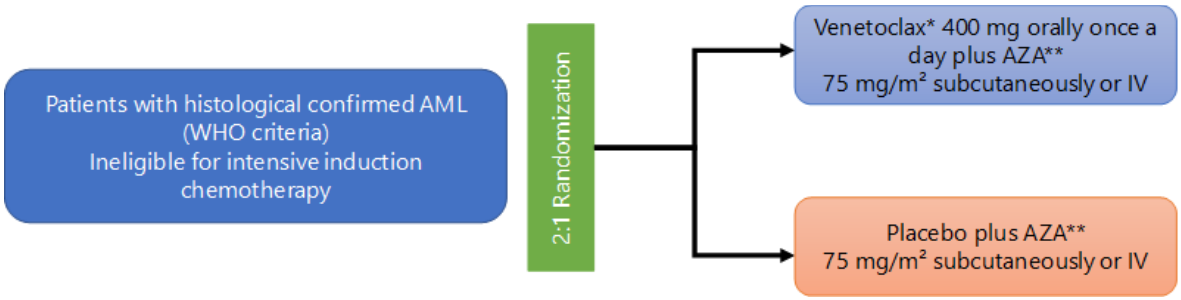


Figure 4.1. VIALE-A study design

Source: (22, 48).
* Venetoclax (oral) daily ramp-up in Cycle 1: 100 mg on Day 1, 200 mg on Day 2, 400 mg on Day 3 until Day 28; subsequent 28-day cycles at 400 mg.
** Azacitidine; 75 mg/m^2 IV or subcutaneously on Days 1–7 for each 28-day cycle.
Abbreviations: AML=acute myeloid leukaemia; AZA=azacitidine; IV=intravenous; WHO=World Health Organization.

The study started to include patients in February 2017, with recruitment completed in May 2019. The study is still ongoing. A total of 431 patients were randomised: 286 to the venetoclax + azacitidine arm and 145 to the placebo + azacitidine arm.

4.4.2 M14-358 (supportive study, including combination with the HMAs decitabine and azacitidine)

Venetoclax was approved by the EMA in combination with HMAs. The pivotal study (VIALE-A) provided results only for venetoclax in combination with azacitidine and did not include patients treated with venetoclax and decitabine. Azacitidine was chosen as the only combination therapy with venetoclax in VIALE-A since the dose-finding study M14-358 proved similar efficacy and safety for the two combinations with venetoclax. Similar efficacy and safety profiles of these substances were also expected because of their similar mechanisms of action and support from the literature (57). The EMA approved the combination of venetoclax with decitabine on the basis of previous results showing similar efficacy and safety to the combination with azacitidine and considered the M14-358 study as a relevant supportive study (29).

M14-358 was a phase 1b, open-label, nonrandomised, multicentre study evaluating the safety of orally administered venetoclax combined with decitabine or azacitidine and the preliminary efficacy of these combinations in treatment-naïve patients with AML aged ≥60 years who are not eligible for standard induction therapy because of comorbidity or other factors.

The study consisted of two phases: a dose escalation phase to define the recommended dose of venetoclax combined with a HMA and a dose expansion phase. During dose escalation, oral venetoclax was administered at 400, 800 or 1200 mg daily in combination with either decitabine (20 mg/m^2, Days 1–5, IV) or azacitidine (75 mg/m^2, Days 1–7, IV or SC). The number of patients required for the dose-escalation phase depended on the toxicities observed as the trial progressed, and 45 patients were

enrolled. On the basis of the preliminary safety and efficacy data, two venetoclax dosing schedules (400 mg and 800 mg) were evaluated separately in the expansion stage, in combination with either decitabine or azacitidine. According to efficacy, safety and exposure/response data, the venetoclax dose of 400 mg was identified as the target dose in combination with azacitidine and decitabine.

Expansion 1 (n=100) enrolled subjects aged ≥65 years, with 50 subjects each treated with venetoclax (400 or 800 mg; 25 subjects each) in combination with azacitidine or decitabine. Expansion 2 (n=55) enrolled subjects aged ≥60 years treated with venetoclax (400 mg) in combination with azacitidine. Subjects enrolled in Expansion 2 had to fulfil modified Ferrara criteria for ineligibility for intensive chemotherapy.

The study started to include patients in: November 2014. The data cutoff for the reported interim analyses (3rd) was 19th July 2019 and the study is still ongoing.

In this assessment, results are only included for subgroups treated with the approved 400-mg dose of venetoclax (venetoclax 400 mg + azacitidine [n=84] and venetoclax + decitabine [n=31]).

4.4.3 VIALE-C (supportive for safety)

VIALE-C was a randomised (2:1), double-blind, placebo-controlled ,multicentre phase 3 study evaluating the efficacy and safety of venetoclax in combination with LDAC in patients with newly diagnosed AML who were ineligible for intensive chemotherapy. Patients in VIALE-C completed a 4-day titration schedule to a final dose of 600 mg once daily dose during the first cycle of treatment and received venetoclax 600 mg daily on Days 1- 28 plus LDAC (cytarabine 20 mg/m^2 SC) once daily on Days 1-10. Placebo orally once daily was administered on Days 1–28 plus LDAC SC s.c once daily on Days 1–10.

A total of 211 patients were randomised, 143 to the venetoclax + LDAC arm and 68 to the placebo + LDAC arm. At the time of the primary analysis for OS, patients had median follow-up of 12 months. The median OS was 7.2 months (95% CI 5.6–10.1) in the venetoclax + LDAC arm compared to 4.1 months (95% CI 3.1–8.8) in the placebo + LDAC arm. The HR for OS was 0.75 (95% CI 0.52–1.07; p=0.114) and the study failed to establish a statistically significant OS benefit with venetoclax + LDAC compared to LDAC alone. For information on the study design, patient characteristics and key efficacy results, see Appendix 4: Comparator and supportive studies.

Table 4.3. Characteristics of the studies on venetoclax in combination with azacitidine

Study reference/ID	Study design	Patient population	Intervention (number of randomised patients)	Comparator(s) (number of randomised patients)	Study duration and data cut off(s)	Primary outcome; patient-relevant secondary outcomes
Direct comparison: VEN + AZA vs. AZA						
VIALE-A	Phase 3, randomised, double-blind, placebo-controlled, multicentre study Study sites: Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Norway, Poland, Portugal, Russia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey and USA	Patients aged ≥18 years with previously untreated AML according to the WHO criteria. Ineligible for treatment with a standard cytarabine and anthracycline induction regimen because of age or comorbidities, defined as: • Age ≥75 years; **or** • Age ≥18–74 years with at least one of the following comorbidities: – ECOG PS 2 or 3 – History of CHF requiring treatment or ejection fraction ≤50% or chronic stable angina – DLCO ≤65% or FEV1 ≤65% – Creatinine clearance ≥30 to <45 ml/min – Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 × ULN – Any other comorbidity incompatible with intensive chemotherapy. Patients must have a projected life expectancy of at least 12 weeks. Patients must have ECOG PS: • 0–2 for patients aged ≥75 years	VEN + AZA (N=286)	Placebo + AZA (N=145)	First patient in: 02 February 2017 Enrolment completed (433 patients) 31 May 2019? 1st interim analyses: data cutoff 1st October 2018 2nd interim analyses: data cutoff 4th January 2020 Median follow-up for OS was 20.5 months (range <0.1–30.7). The study is still ongoing. Planned final analysis will be performed when 360 events have been reported. The estimated completion date is 23rd May 2021.	Dual primary endpoint: OS (intention to treat) and Composite CR rate (CR + CRi) Secondary: • CR rate • Rates of RBC and platelet transfusion independence • CR rates and OS in molecular and cytogenetic subgroups • EFS • HRQoL • Safety

Study reference/ID	Study design	Patient population	Intervention (number of randomised patients)	Comparator(s) (number of randomised patients)	Study duration and data cut off(s)	Primary outcome; patient-relevant secondary outcomes
		• 0–3 for patients aged 18–74 years Patients must have adequate renal and liver functions.				
Supportive study on VEN + AZA or VEN + decitabine						
M14-358	Phase 1b, open-label, nonrandomised, multicentre study	Key inclusion criteria: • Confirmed AML according to the WHO criteria • Ineligible for treatment with a standard cytarabine and anthracycline induction regimen because of comorbidity or other factors • No prior treatment for AML with the exception of hydroxyurea • ECOG PS of 2 for subjects aged ≥75 years or 0–3 for subjects aged 60–74 years • Adequate kidney and liver functions as described in the protocol	All treated patients (N=200) • VEN 400 mg (N=115; 84 AZA, 31 DEC) • VEN 800 mg (N=74; 37 each AZA and DEC) • VEN 1200 mg (N=11; 6 AZA, 5 DEC)	NA	First patient on 19th November 2014 Enrolment completed Interim analyses (3rd) from data cutoff on 19th July 2019 Median study duration: VEN 400 mg + AZA, 28.1 months (range 24.9–55.4) VEN 400 mg + DEC, 39.5 months (range 37.2 –56.1) Study is still ongoing	Pharmacokinetics: (C_{max}, T_{max}, AUC) Safety Efficacy: • CR • CRi • ORR (CR + CRi + PR) • OS

Source: (22, 47, 48, 52, 53).
Abbreviations: AML=acute myeloid leukaemia; AUC=area under the curve; AZA=azacitidine; CHF=congestive heart failure; C_{max}=maximum concentration observed; CR=complete remission; CRi=complete remission with incomplete haematologic recovery; DEC=decitabine; DLCO=diffusing capacity of the lungs for carbon monoxide; ECOG PS=Eastern Cooperative Oncology Group performance status; EFS=event-free survival; FEV1=forced expiratory volume in 1 second; HRQoL=health-related quality of life; ORR=overall response rate; OS=overall survival; PR=partial response; RBC=red blood cell; T_{max}=time to reach C_{max}; ULN=upper limit of normal; VEN=venetoclax; WHO=World Health Organization.

Table 4.4. Characterisation of the interventions and comparators

Study reference / ID	Venetoclax + AZA	AZA	Pretreatment, concomitant/prohibited medications
VIALE-A M15-656	Venetoclax orally QD, ramp up in Cycle 1: 100 mg Day 1, 200 mg Day 2, 400 mg Days 3–28; subsequent 28-day cycles at 400 mg plus AZA 75 mg/m^2, SC or IV, on Days 1–7 every 28-day cycle Treatment duration: patients continued to receive treatment cycles (28 days in length) until disease progression or unacceptable toxicity, withdrawal of consent or other protocol criteria for discontinuation were met. Venetoclax dosing may be interrupted as needed for management of haematologic toxicities and blood count recovery.	Placebo orally QD plus AZA 75 mg/m^2, SC or IV on Days 1–7 every 28-day cycle Treatment duration: patients continued to receive treatment cycles (Day 1–7 every 28-day cycle) until disease progression or unacceptable toxicity, withdrawal of consent, or other protocol criteria for discontinuation were met.	- Antihyperuricaemia agents and IV hydration were administered 2–3 days before starting treatment with venetoclax in patients with high uric acid levels or at risk of TLS and could be continued through the titration phase. - Strong CYP3A inducers were not allowed during ramp up and throughout the study? (dose modification of venetoclax is recommended for use with CYP3A inhibitors; concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk of TLS and other toxicities).
	Venetoclax + AZA or decitabine		
M14-358	Dose escalation: (n=45) Venetoclax QD, ramp up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3 until maximum dose is reached (400, 800 or 1200 mg); max dose until Day 28; subsequent 28-day cycles at 400, 800 or 1200 mg plus AZA (75 mg/m^2, days 1–7, IV or SC) or DEC (20 mg/m^2, days 1–5, IV) Expansion: (n=155) Venetoclax QD, ramp up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, (600 mg Day 4, 800 mg Day 5) until Day 28; subsequent 28-day cycles at 400 or 800 mg plus AZA 75 mg/m^2 SC or IV on Days 1–7 every 28-day cycle or DEC (20 mg/m^2, Days 1–5, IV) Treatment duration: Treatment could continue as long as the subject showed a response, continued to benefit or exhibited a haematological response (i.e., in the absence of relapse or resistant disease).		

Source: (22, 43, 47, 53).
Abbreviations: AZA=azacitidine; DEC=decitabine; IV=intravenous; QD=once a day; SC=subcutaneous; TLS=tumour lysis syndrome.

Table 4.5 shows the mean and median treatment duration and the planned follow-up duration and observation period for some of the individual outcomes in VIALE-A and M14-358.

In VIALE-A the median exposure duration was 7.6 months (range 0.1–30.7) in the venetoclax + azacitidine arm and 4.3 months (range 0.1–24) in the placebo + azacitidine arm. Subjects received treatment for a median of seven cycles (range 1–30) in the venetoclax arm versus 4.5 cycles (range 1–26) in the comparator arm.

The study duration in VIALE-A is event-driven, with the first OS analyses performed at 270 events (second interim analyses) and the final OS analyses planned when a total of 360 events are reported.

Table 4.5. Information on the course of the VIALE-A and M14-358 studies (including planned follow-up duration)

Outcome category	Planned follow-up	Intervention	Comparator
VIALE-A		**Venetoclax 400 mg+ azacitidine N=286**	**Placebo + azacitidine N=145**
Treatment duration (months)			
Median (range) Mean (standard deviation)	—	7.6 (0.1–30.7) 9.9 (8.25)	4.3 (0.1–24.0) 6.7 (6.55)
Observation period (months)			
Overall survival (data cutoff 4th January 2020) Median (95% CI) [a] Mean (standard deviation)	Until date of death from any cause. Study is event-driven, with the final overall survival analyses planned at 360 deaths.	 20.7 (20.1–22) NR	 20.2 (19.6–22.4) NR
Health-related quality of life	PRO data were collected on or within 3 days before Cycle 1 Day 1 and then every other cycle throughout the study, including the final visit.	NR	NR
Transfusion independence	Transfusion dependence on RBCs and platelets was one of the measures recorded for disease response. No details on follow-up reported.	NR	NR
Composite complete remission (CR + CRi) [b]	Minimum 6-month follow-up since randomisation.	NR	NR
Adverse events and serious adverse events	From the start of study drug and continuously until 30 days following discontinuation of study drug.	NR	NR
M14-358		**Venetoclax 400 + azacitidine N=84**	**Venetoclax 400 + decitabine N=31**
Treatment duration [months]			
Median (range) Mean (standard deviation)	—	6.4 (0.1–38.1) 10.4 (10.19)	5.7 (0.5–41.8) 12.6 (13.28)
Observation period [months]			
Overall survival (months) (data cutoff 19th July 2019) Median (95% CI) [c] Mean (standard deviation)	Until date of death from any cause.	 28.9 (0.4–42.0) NR	 40.4 (0.7–42.7) NR

Source: (22, 29, 47, 53)
[a] Median follow-up for overall survival reported at the second interim analysis, corresponding to 270 events.
[b] First interim primary analysis of composite complete remission, including the first 226 patients. Data cutoff 1st October 2018.
[c] Median follow-up for survival (defined as duration from first dose of study drug to the last known date alive or study cutoff date, whichever is earlier).
Abbreviations: CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete haematologic recovery; NR=not reported.

Table 4.6 shows the characteristics of the patients in the studies included (VIALE-A and M14-358).

In VIALE-A the median age for the total population was 76 years (range 49–91), 76% of the patients were white, 60% were male, and ECOG PS at baseline was 0 or 1 for 55% of patients, 2 for 40% of patients and 3 for 5% of patients; 75% had de novo AML and 25% had secondary AML. In terms of cytogenetic risk, 63% had intermediate and 37% had poor risk, with efficacy not investigated for patients with good risk. Cytogenetic risk status was based on the NCCN guidelines for AML (58).

Patients were ineligible for intensive chemotherapy; other than age, the main reason for ineligibility was ECOG PS of 2 or 3. Other reasons included cardiac, pulmonary, hepatic and renal comorbidities (Table 4.3).

Baseline disease characteristics in VIALE-A were generally well balanced between the treatment arms (Table 4.6). More patients had mild or moderate hepatic impairment in the placebo + azacitidine arm (28.0%) than in the venetoclax + azacitidine arm (21.0%). More patients had mild or moderate renal impairment in the venetoclax + azacitidine arm (78.7%) than in the comparator arm (71.7%). A higher proportion of patients had neutropenia in the venetoclax + azacitidine arm (72%) than in the azacitidine arm (62%). The BM blast count was <30% for 29% of patients, 30%–<50% for 22% of patients, and ≥50% for 49% of patients. The distribution of the predefined blast count categories was balanced across the treatment arms at study baseline.

For patients in the venetoclax (400 mg) + azacitidine arm in M14-358 (n=84), the median age was 74.5 years. Patients had intermediate (59.5%) or poor (39.3%) cytogenetic risk, and 25% had secondary AML. In total, 31% had ECOG PS of ≥2 and 36.9% had a BM blast count of ≥50% at baseline. The majority of subjects (79.8%) fulfilled the objective criteria used to define ineligibility for intensive therapy (modified Ferrara criteria).

In the venetoclax (400 mg) + decitabine arm in M14-358 (n=31), the median age was 72.0 years. Patients had intermediate (51.6%) or poor (48.4%) cytogenetic risk, and 29% had secondary AML. In total, 12.9% of patients had ECOG PS ≥2 and 32.3% had a BM blast count of ≥50% at baseline. Objective criteria used to define ineligibility for intensive therapy were fulfilled by 41.9% of the patients. A lower percentage of patients in both dose arms had ECOG PS ≥2 compared to the venetoclax + azacitidine arm in VIALE-A.

Table 4.6. Baseline characteristics of the VIALE-A and M14-358 study populations

	VIALE-A		**M14-358 (supportive study)**	
	Venetoclax + azacitidine N=286	**Azacitidine N=145**	**Venetoclax 400 mg + azacitidine N=84**	**Venetoclax 400 mg + decitabine N=31**
Demographics				
Sex, n (%)				
Female Male	114 (39.9) 172 (60.1)	58 (40.0) 87 (60.0)	51 (60.7)	15 (48.4)
Age category, n (%)				
18 to <75 years ≥75 years	121(42.3) 165 (57.7)	64 (44.1) 81 (55.9)	NR	NR
Age (years)				
Mean (standard deviation) Median (range)	75.6 (6.08) 76.0 (49.0–91.0)	75.1 (5.70) 76.0 (60.0–90.0)	NR 74.5 (61–90)	NR 72 (65–85)
Disease characteristics				
Type of AML, n (%)				
De novo AML Secondary AML	214 (74.8) 72 (25.2)	110 (75.9) 35 (24.1)	NR 21 (35)	NR 9 (29)
Type of secondary AML, n (%)				
Therapy-related Post MDS/CMML	26 (36.1) 46 (63.9)	9 (25.7) 26 (74.3)	NR	NR
AML with MRC, n (%)	92 (32)	49 (34)	NR	NR

ECOG PS, n (%)				
0 1 2 3	37 (12.9) 120 (42.0) 113 (39.5) 16 (5.6)	23 (15.9) 58 (40.0) 59 (40.7) 5 (3.4)	14 (16.7) 44 (52.4) 24 (28.6) 2 (2.4)	7 (22.6) 20 (64.5) 4 (12.9) 0
Cytogenetic risk (from EDC), n (%)				
Intermediate Poor	182 (63.6) 104 (36.4)	89 (61.4) 56 (38.6)	50 (59.5) 33 (39.3)	16 (51.0) 15 (48.4)
Somatic mutations, n/N [a] (%)				
IDH1 or *IDH2* *FLT3* ITD or TKD *NPM1* *TP53*	61/245 (25) 29/206 (14) 27/163 (17) 38/163 (23)	28/127 (22) 22/108 (20) 17/86 (20) 14/86 (16)	NR	NR
Bone marrow blast count, n (%)				
<30% ≥30 to <50% ≥50%	85 (30) 61 (21) 140 (49)	41 (28) 33 (23) 71 (49)	24 (28.6) 29 (34.5) 31 (36.9)	7 (22.6) 14 (45.2) 10 (32.3)
Baseline transfusion dependence, n (%) [b]				
Red cells Platelets	144 (50) 68 (24)	76 (52) 32 (22)	51 (60.7) 27 (32.1)	23 (74.2) 5 (16.1)
Baseline cytopenia grade ≥3 [c]				
Anaemia, n (%) Neutropenia, n/N (%) Thrombocytopenia, n (%)	88 (31) 206/286 (72) 145 (51)	52 (36) 90/144 (62) 73 (50)	NR	NR
Number of reasons for ineligibility for standard induction therapy, n (%)				
1 2 3 ≥4	145 (50.7) 99 (34.6) 32 (11.2) 10 (3.5)	80 (55.2) 47 (32.4) 16 (11.0) 2 (1.4)	NR	NR
Met modified Ferrari criteria, n (%)	—	—	67 (79.8)	13 (41.9)
Baseline hepatic impairment, n (%) [d]	60 (21.0)	40 (28.0)	NR	NR
Baseline renal impairment, n (%) [e]	225 (78.7)	104 (71.7)	NR	NR

Source: (22, 29, 47, 48, 53).
[a] 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.
[b] Within 8 weeks before the first dose of study drug or randomisation for nontreatment.
[c] Cytopenia was graded according to the Common Terminology Criteria for Adverse Events.
[d] Bilirubin ≤1 mg/dl and AST >40 U/l or bilirubin >1 mg/dl.
[e] Creatinine clearance of ≥30 to <90 ml/min.
Abbreviations: AML=acute myeloid leukaemia; ANC=absolute neutrophil count; AST=aspartate transaminase; CMML=chronic myelomonocytic leukaemia; ECOG PS=Eastern Cooperative Oncology Group performance status; EDC=electronic data capture; ITD=internal tandem duplication; MDS=myelodysplastic syndrome; MRC=myelodysplasia-related changes; NR=not reported; TKD=tyrosine kinase domain.

4.5 Statistics

4.5.1 VIALE-A

The primary outcome/endpoint in VIALE-A was OS and the composite complete remission rate (CR + CRi). The secondary outcomes/endpoints were the rate of CR, rate of CR and complete response with partial haematologic recovery (CRh), proportion of patients achieving composite complete remission (CR + CRi) by initiation of Cycle 2, duration of response, transfusion independence rate, minimal/measurable residual disease (MRD), fatigue improvement, PRO assessments and EFS. Analyses of the efficacy endpoints were performed on the full analysis set, defined as all randomised patients.

The sample size calculation in the study was based on the following assumptions:

- The significance level of 0.05 (two-sided) was split to assign 0.01 significance level to the CR + CRi rate analysis and a 0.04 significance level to the OS analysis;
- A CR + CRi rate of 28% for the placebo arm and 55% for the venetoclax arm;
- Median OS of 10.4 months for the placebo arm and 14.9 months for the venetoclax arm;
- Interim analysis of OS at 75% of death events with the O'Brien–Fleming boundary, setting the cutoff date for this analysis when the 270th subject death was observed; and
- A 2:1 randomisation ratio to the venetoclax and placebo arms.

A total of 225 patients would give 88% power to detect statistically significant differences in the CR + CRi rate between the treatment arms at a two-sided alpha level of 0.01. A total of 360 death events would provide 86.7% power to detect a statistically significant difference in OS between the treatment arms at a two-sided alpha level of 0.04.

The primary endpoints were analysed according to the following:

- CR + CRi: 6 months after the first 225 patients were randomised.
- OS:
    - Interim analysis 1: at the same time as the primary analysis of CR + CRi;
    - Interim analysis 2: at the time of 270 OS events; and
    - Final analysis: at the time of 360 OS events.

Analyses of the efficacy endpoints were performed by treatment arm and strata assigned at the time of randomisation, namely age (18 to <75 years, ≥75 risk) , cytogenetic risk (intermediate risk, poor risk) and region

The time-to-event endpoints OS and EFS were compared between the arms using the log-rank test and the distribution was estimated for each treatment arm using the Kaplan–Meier method. Median OS and EFS with corresponding 95% CIs were calculated by treatment arm. The stratified HR with 95% CI was estimated from a stratified Cox proportional-hazards model.

If a patient had survived, the data were censored at the date on which the patient was last known to be alive on or before the data cutoff date, selecting the last available date for the study procedure for an individual patient (AE start date, BM 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 ECOG PS).

The CR + CRi rate and the secondary endpoints (other than EFS) were compared using the stratified Cochran–Mantel–Haenszel test, with 95% CIs estimated by treatment arm using the Clopper–Pearson exact method.

The changes in HRQoL from baseline were analysed using linear mixed-effects regression models with covariance structures to test for differences between the treatment arms. Stratification factors and treatment were included as fixed effects, along with time and a treatment × time interaction. The lowest Bayesian information criterion was used to select the correlation structure for the repeated-measures analyses. The correlation structures tested were unstructured with compound symmetry and first-order autoregressive.

Safety endpoints were SAEs, grade ≥3 AEs, fatal AEs and treatment discontinuation. Analyses of safety were performed on the safety analysis set, defined as all subjects who received at least one dose of study drug. The safety endpoints were summarised by the number and percentage of patients experiencing an AE by treatment arm.

To control for the familywise error rate at interim and final analyses, the alpha split, recycling, Lan DeMets alpha spending function and hierarchical testing strategies were applied. The two-sided

significance level was 0.01 for the primary endpoint of CR + CRi and 0.04 for OS. A significance level of 0.05 was set for secondary endpoints in fixed sequence testing. If the statistical test for the primary endpoint of OS was nonsignificant, then significance could not be declared for any of the secondary endpoints.

The following subgroup analyses for the efficacy endpoints CR + CRi rate and OS were defined:

- Sex (male, female);
- Age (18–<65 years, 65–<75 years, ≥75 years);
- Region (US, EU, China, JP, Asian, rest of the world);
- Baseline ECOG PS (<2, ≥2);
- Type of AML (de novo, secondary, therapy-related AML);
- Cytogenetic risk (intermediate, poor);
- Molecular marker measured by central laboratory (*FLT3*, *IDH1*/*IDH2*, *TP53*, *NPM1*);
- Antecedent haematologic history of MDS (yes, no);
- AML with myelodysplasia-related changes (yes, no); and
- Poststudy treatment (yes, no).

Overall, the statistical methodology used is deemed acceptable.

4.5.2 Study M14-358

Study M14-358 was a nonrandomised study and only descriptive statistics were used. No formal comparisons between the different dose cohorts or the different combinations were reported.

4.6 Outcomes included

Table 4.7 shows which of the outcomes to be included in the assessment data were available in the studies included.

Table 4.7. Matrix of outcomes in the included studies on venetoclax combined with a HMA

Study reference/ID	Outcomes								
	Overall survival	Composite complete remission (CR + CRi)	HRQoL	Transfusion independence	Event-free survival	Serious AEs	Grade ≥3 AEs	Fatal AEs	Treatment discontinuations
VIALE-A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Supportive study M14-358	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes

Abbreviations: AE=adverse event; HMA=hypomethylating agent; HRQoL=health-related quality of life; CR=complete remission; CRi=complete remission with incomplete haematologic recovery.

4.6.1 Overall survival

In the EU and EU reference countries, the VIALE-A study has dual primary endpoints of the CR + CRi rate (as assessed by the investigator) and OS. OS was defined as the time from date of randomisation to death from any cause (22). It is acknowledged that OS is the preferred endpoint in newly diagnosed AML, as this is considered the gold standard endpoint in clinical trials by both physicians and health

regulatory agencies (59). Additionally, OS is considered a key benefit based on patient feedback. OS is therefore included in this assessment.

4.6.2 Disease response

All subjects had response assessments according to the revised International Working Group response criteria for AML (60). Subject response was assessed by the investigator according to the most recent physical examination, BM results and recent haematology values.

Table 4.8 lists the response criteria in VIALE-A and M14-358.

Table 4.8. Definition of response criteria in AML

CR	Absolute neutrophil count >10^3 /µl, platelets >10^5 /µl, RBC transfusion independence and BM with <5% blasts; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRi	All the same criteria as for 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 haematologic values for CR but with a decrease of at least 50% in the percentage of blasts to 5%–25% in the BM 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 of treatment, with evidence of persistent leukaemia on blood and/or BM examination.
MR	Reappearance of ≥5% blasts after CR/CRi in peripheral blood or BM or development of extramedullary disease.
PD	50% increase in BM blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline) or persistent BM blast percentage of >70% over at least 3 months without at least a 100% improvement in ANC to an absolute level of >0.5 × 10^9 /l (500 /µl) and/or platelet count to >50 × 10^9/l (50,000 /µl) nontransfused; or 50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9 /l (>25,000 /µl); or New extramedullary disease

Source: Adapted from (47)
Abbreviations: ANC=absolute neutrophil count; BM=bone marrow; CR=complete remission; CRi=complete remission with incomplete haematologic recovery; PR=partial remission; MLFS=morphologic leukaemia-free state; RBC=red blood cell; RD=resistant disease; MR=morphologic relapse; PD=progressive disease; WBC=white blood cell.

In VIALE-A, BM assessments were performed at screening, at the end of Cycle 1 and every three cycles thereafter until two consecutive samples confirmed a CR or CRi. The criteria were slightly modified by evaluating progressive disease (PD) according to the ELN recommendations (8). Each subject was assigned to one or more of the following categories on the basis of the investigator assessment: CR; CRi; PR; morphologic leukaemia-free state; resistant disease; PD; indeterminate (not assessable, insufficient data); or morphologic relapse.

In VIALE-A, the composite CR + CRi endpoint was part of the dual primary endpoint, with other response rates defined as secondary endpoints. Response rates are a measure of the antitumour efficacy of a treatment, but the clinical benefit for patients achieving CR or CRi is more uncertain since response rates may not be strongly correlated to longer survival. However, clinical observations suggest that patients who achieve CR may have improved QoL because of fewer transfusions and spending less time in medical facilities than patients without CR, even if survival is not improved; the same may apply with CRi (61). CR and CR + CRi rates are considered as supportive evidence for data on OS.

4.6.3 Health-related quality of life

In VIALE-A, PRO assessment was a secondary objective involving evaluation of whether venetoclax in combination with azacitidine reduces fatigue and improves GHS/QoL according to the 7-item Cancer Fatigue-Short Form (SF) and the GHS/QoL scale of EORTC QLQ-C30. Additional PRO assessments, included as exploratory endpoints, were the impact of venetoclax on EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) and the remaining subscales/items from the EORTC QLQ-C30 and PROMIS Cancer Fatigue SF 7a. The submitted data for HRQoL included in the MAH submission dossier is rather limited but some additional analyses was included in this assessment on the basis of results reported in the CSR and trial publications.

4.6.4 Transfusion independence

The transfusion independence rate was a secondary endpoint in VIALE-A and defined as an exploratory analysis in M14-3585. The postbaseline transfusion independence was defined as a period of at least 56 days with no RBC or platelet transfusion during the evaluation period. The postbaseline transfusion evaluation period was from the date of first dose of the study drug to the date of last dose of the study drug + 30 days, disease progression, confirmed morphological relapse, post-treatment therapy, death or the data cutoff date, whichever occurred earliest. AML disrupts haematopoiesis, and a lower number of transfusions during treatment may be an indicator of clinical benefit to patients (62).This outcome is considered supportive evidence in the assessment.

4.6.5 Event-free survival

EFS was a secondary endpoint and was defined as the number of days from randomisation to the date of PD, confirmed morphologic relapse from CR or CRi, treatment failure (defined as failure to achieve CR, CRi or a morphologic leukaemia-free state after at least six cycles of study treatment) or death from any cause. It remains debatable whether EFS represents a clinical benefit for patients with untreated AML (63). EFS may be a relevant outcome when simulating the course of AML in health economics models used in cost–utility analyses and is considered supportive evidence in this assessment.

4.6.6 Adverse events

The safety of venetoclax or placebo in combination with azacitidine and venetoclax + decitabine was assessed by evaluating study drug exposure, AEs, SAEs, deaths, and changes in laboratory measurements and vital sign parameters.

Analyses of AEs from VIALE-A and M14-358 included only treatment-emergent AEs (TEAEs), that is, AEs with onset on or after the day of the first dose of study drug. Analyses did not include events with onset greater than 30 days after the last dose of study drug. TEAEs were summarised by preferred term within a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA). The percentage of subjects experiencing an AE at a given toxicity grade (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) in relation to the study drug was provided.

4.7 Participant flow

In VIALE-A, 579 patients were screened for eligibility and 433 were randomised. Reasons for the 146 screening failures were not meeting the inclusion/exclusion criteria (98 patients), withdrawal of consent (21 patients) and other reasons not specified (27 patients) (29).

Of patients assigned to study treatment , more patients discontinued the study because of death in the azacitidine-alone arm (74.7%) than in the venetoclax + azacitidine arm (56%). At the cutoff date, 73 patients (25.4%) receiving venetoclax + azacitidine and 16 patients (11%) receiving azacitidine alone were still on treatment with the study medication. The proportions of patients who discontinued the study because of withdrawal of consent or who were lost to follow-up were <3% in both treatment arms (Table 4.9).

Patients who discontinued the study treatment could receive follow-up systemic therapies. Post-treatment systemic therapies for AML were reported for 45 patients (15.7%) in the venetoclax + azacitidine arm and 36 patients (24.8%) in the azacitidine-alone arm. Only two patients (0.7%) in the venetoclax + azacitidine arm received subsequent allogeneic HCT, versus one (0.7%) in the azacitidine-alone arm (47).

Table 4.9. Patient disposition in VIALE-A

VIALE-A	Venetoclax + azacitidine, N	Azacitidine, N
Assigned to study treatment	287	146
Analysed for efficacy [a]	286 [a]	145 [a]
Received treatment (included in safety analyses) [b]	283	144
Discontinued study treatment [b]	**209**	**127**

Disease progression due to adverse events	5	5
Disease progression not related to adverse events	43	13
Withdrew consent	26	22
Physician decision	17	9
Disease progression	9	21
Morphologic relapse	64	15
Treatment failure	4	13
Noncompliance	0	1
Death	39	23
Other	1	5
Discontinued the study	**173**	**112**
Death	161	109
Lost to follow-up	5	2
Patient withdrawal	7	1
Treatment ongoing at data cutoff date [c]	73	16

Source: Adapted from (22, 29).
[a] Two patients (1 in each arm) were not stratified by cytogenetic risk. They were excluded from the efficacy analysis but were included in the safety analysis.
[b] Six patients who did not receive treatment were excluded from the safety analysis set.
[c] Data cutoff 4th January 2020.

4.8 Risk of bias

Risk of bias was assessed for each outcome using the Cochrane RoB2 tool (44). The risk of bias for VIALE-A for the relevant outcomes is described in Table 4.10. The Authoring Team decided not to assess the risk of bias for the supportive studies and the comparator studies in potential ITCs. The decision was justified by the fact that none of these studies was used to generate new evidence for the relative effect.

In general the risk of bias in VIALE-A was low. For detailed information on assessment of the risk of bias, see Appendix 2: Certainty of evidence.

Table 4.10. Risk of bias in VIALE-A

Study reference/ID	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) [a]	Blinding of outcome assessment (detection bias) [b]	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias	Other potential sources of bias
VIALE-A	Low	Low	Low	Low	Low	Low/High*	Low	Low

Source: (44).
[a] For self-reported outcomes including pain, function and global assessment.
[b] For assessor-reported outcomes.
* High for health-related quality of life.

4.9 External validity

Since patients with previous treatment with HMAs, chemotherapy or venetoclax for myelodysplastic syndrome or patients with favourable cytogenetic risk were not included in the studies, the actual treatment effect of venetoclax in combination with HMAs in these settings cannot be estimated. The criteria used to define ineligibility for intensive chemotherapy in the clinical studies may not be

completely aligned with the selection criteria in clinical practice, which also contributes to uncertainty regarding the generalisability of the study results.

Consistency in the treatment effect on OS and remission rate (CR + CRi) in VIALE-A across different patient characteristics (age, cytogenetic risk, type of AML [de novo/secondary AML] and ECOG PS) of the population included was supported by subgroup analyses.

A direct comparison of venetoclax in combination with HMAs was only performed versus azacitidine, with a lack of robust comparative data versus other relevant treatment regimens such as glasdegib + LDAC, BSC and LDAC.

The approved indication includes combination with decitabine as an alternative to azacitidine. Clinical study data for this combination are based on a limited number of patients in a phase 1b study, leading to a higher level uncertainty for the actual efficacy and safety of this combination in clinical practice.

The approved posology for venetoclax in combination with a HMA states that treatment can be administered continuously until disease progression or unacceptability toxicity. In VIALE-A, the median exposure duration in the venetoclax + azacitidine arm was 7.6 months, but whether this will reflect the actual treatment length in clinical practice is not yet known.

Concerning the data reported for OS, the short follow-up (median of 20.5 months at the latest data cutoff in VIALE-A with 75% of the expected total events reported) lends uncertainty to the long-term OS that will be achieved with venetoclax combined with a HMA in clinical practice.

4.10 Results for the clinical effectiveness and safety of venetoclax + HMAs

4.10.1 OS in VIALE-A

The results reported are based on the OS interim analyses for VIALE-A with 75% of the expected total deaths reported. Except for patients who withdrew consent, all patients who discontinued a trial regimen were followed for survival. The median follow-up for the reported OS was 20.7 months (range < 0.1 to 30.7) in the venetoclax + azacitidine arm and 20.2 months (range 0.2 to 28.8) in the comparator arm. As can be seen in Table 4.11, the median OS was 14.7 with venetoclax + azacitidine and 9.6 months with placebo + azacitidine. The venetoclax + azacitidine combination was superior to azacitidine alone, with an improvement in OS of 5.1 months observed.

Table 4.11. Overall survival results from VIALE-A

Outcome	Venetoclax + azacitidine (N=286)		Azacitidine (N=145)		Venetoclax + azacitidine vs. azacitidine
	Patients with event, n (%)	Median time to event, months [95% CI]	Patients with event, n (%)	Median time to event, months [95% CI]	HR [95%-CI][a] p-value [b]
Overall survival [c]	286 161 (56.3)	14.7 [11.9, 18.7]	145 109 (75.2)	9.6 [7.4, 12.7]	Stratified analyses [d] 0.662 [0.518, 0.845] <0.001 Unstratified analyses 0.641 [0.502, 0.819] <0.001
Censored at the start date for post-study treatment before OS events	286 135 (47.2)	19.8 [12.6, 24.4]	145 80 (55.2)	10.1 [6.8, 13.0]	Stratified analyses 0.703 [0.531, 0.929] 0.013

Source: (22, 47, 48).
[a] Based on a Cox proportional-hazards model for venetoclax + azacitidine versus azacitidine.
[b] Two-sided p-value from log-rank test.
[c] Data cutoff date 4th January 2020.
[d] The reported HR stratified by age (18 to <75 years, ≥75 years) and cytogenetic risk (intermediate, poor risk).
Abbreviations: CI=confidence interval; HR=hazard ratio; OS=overall survival.

The OS rate at 1 year was 55.8% (95% CI 49.7%, 61.5%) for venetoclax + azacitidine compared to 43.8% (95% CI 35.5%, 51.8%) in the azacitidine arm. At 2 years, the corresponding OS rates were 36.5% (95% CI 29.7%, 43.4%) and 18.3% (95% CI 11.1%, 27.0%) (47). At the time of analysis, 73 patients (25.4%) in the venetoclax + azacitidine arm and 16 (11%) in the azacitidine arm remained on treatment (48).

Sensitivity analysis results for OS, including censoring at the start of poststudy treatment prior to OS events, were consistent with the primary analyses. Only two patients in the venetoclax + azacitidine arm and one in the placebo+ azacitidine arm proceeded to transplant; thus, the OS data reported are considered to be unaffected by subsequent stem cell transplants.

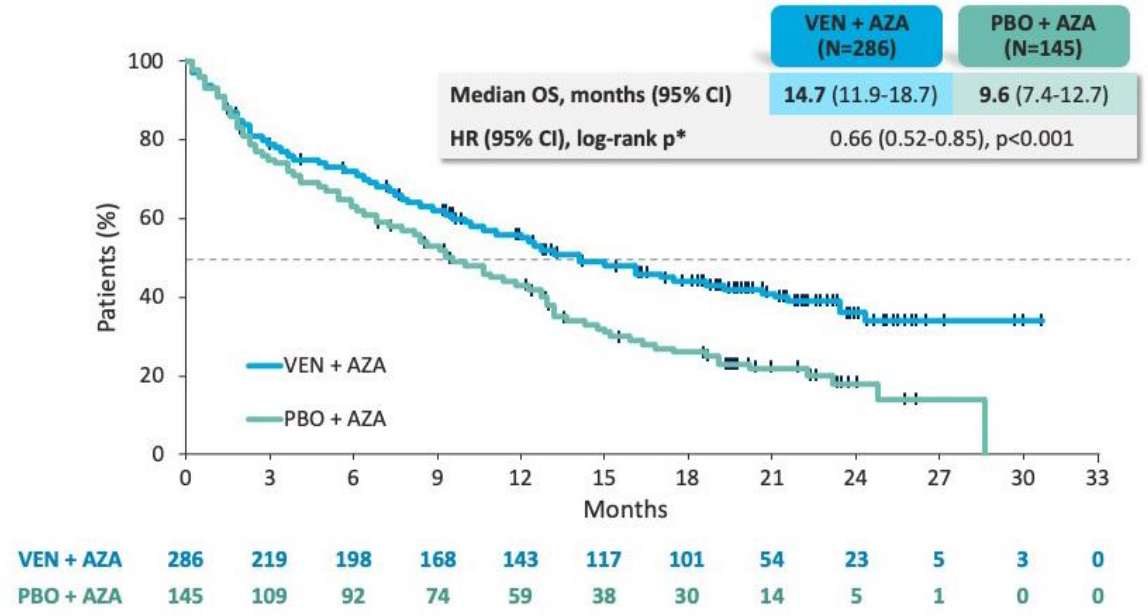


Figure 4.2. Kaplan–Meier estimates of OS with venetoclax + azacitidine versus placebo + azacitidine
Source: (22).
* Log-rank test stratified by age (18–<75 years, ≥75 years) and cytogenetic risk (intermediate risk, poor risk). Tick marks along the curves indicate censored data.
Abbreviations: AZA=azacitidine; CI=confidence interval; HR=hazard ratio; OS=overall survival; PBO=placebo; VEN=venetoclax.

4.10.2 OS in study M14-358

Among subjects treated with 400 mg venetoclax in combination with azacitidine in M14-358 (N=84), the median OS was 16.4 months (95% CI 11.3, 24.5) and the estimated OS rate at 12 months was 56.9% (95% CI 45.6%, 66.7%). Among the 31 subjects treated with 400 mg venetoclax in combination with decitabine, median OS was 16.2 months (95% CI 9.1, 27.8) and the estimated 12-month survival rate was 61.3% (95% CI 42.0%, 75.8%) (53, 64)

4.10.3 Complete remission and composite complete remission

An analysis of investigator-assessed best response of CR + CRi (according to the revised International Working Group response criteria) is presented in Table 4.12 for two different data cuts in VIALE-A. The CR + CRi rate was significantly higher for subjects in the venetoclax + azacitidine arm than for subjects in the placebo + azacitidine arm. The CR + CRi rates from the second interim analyses were similar to those observed at the first analyses including 226 randomised subjects with 6 months of follow-up.

The number of patients with no available response data due to discontinuation from the study was 10.5% (30/286) in the venetoclax + azacitidine arm and 13.8% (20/145) in the comparator arm (47).

Table 4.12. Results for complete remission and composite complete remission in VIALE-A

Outcome	Venetoclax+ azacitidine		Azacitidine		Venetoclax + azacitidine vs. azactidine
	N	Patients with event, n (%) [95% CI] [b]	N	Patients with event, n (%) [95% CI] [b]	p-value [a]
CR + CRi (as best response) c	147	96 (65.3) [57.0–73.0]	79	20 (25.3) [16.2–36.4]	<0.001
CR d	286	105 (36.7) [31.1–42.6]	145	26 (17.9) [12.1–25.2]	<0.001
CRi d	286	85 (29.7) [24.5–35.4]	145	15 (10.3) [5.9–16.5]	
CR + CRi (as best response) d	286	190 (66.4) [60.6, 71.9]	145	41 (28.3) [21.1, 36.3]	<0.001

Source: (29, 47, 48).
[a] The p-value is from a Cochran–Mantel–Haenszel test for venetoclax + azacitidine versus azacitidine, stratified by age (18 to <75 years, ≥75 years) and cytogenetic risk (intermediate risk, poor risk) at the time of randomisation.
[b] The 95% CI is from the exact binomial distribution.
[c] First 226 subjects for CR + CRi interim analysis using data at the cutoff date of 18th October 2018.
[d] Data cutoff date 4th January 2020.
Abbreviations: CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete haematologic recovery.

Response rates including CR + CRi rates were also reported in study M14-358 for the final approved dose of venetoclax in combination with a HMA. This was a nonrandomised phase 1b study and no relative efficacy analyses between treatment arms were planned or reported (Table 4.13).

Table 4.13. Results for the composite complete remission rate in study M14-358

Outcome	Venetoclax 400 mg + azacitidine		Venetoclax 400 mg + decitabine	
	N	Patients with event, n (%) [95% CI] [a]	N	Patients with event, n (%) [95% CI] [a]
CR	84	37 (44.0) [33.2, 55.3]	31	17 (54.8) [36.0, 72.7]
CRi	84	23 (27.4) [18.2, 38.2]	31	6 (19.4) [7.5, 37.5]
CR+CRi (as best response)	84	60 (71.4) [60.5, 80.8]	31	23 (74.2) [55.4, 88.1]

Source: (22, 53).
[a] The 95% CI is from the exact binomial distribution.
Abbreviations: CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete haematologic recovery.

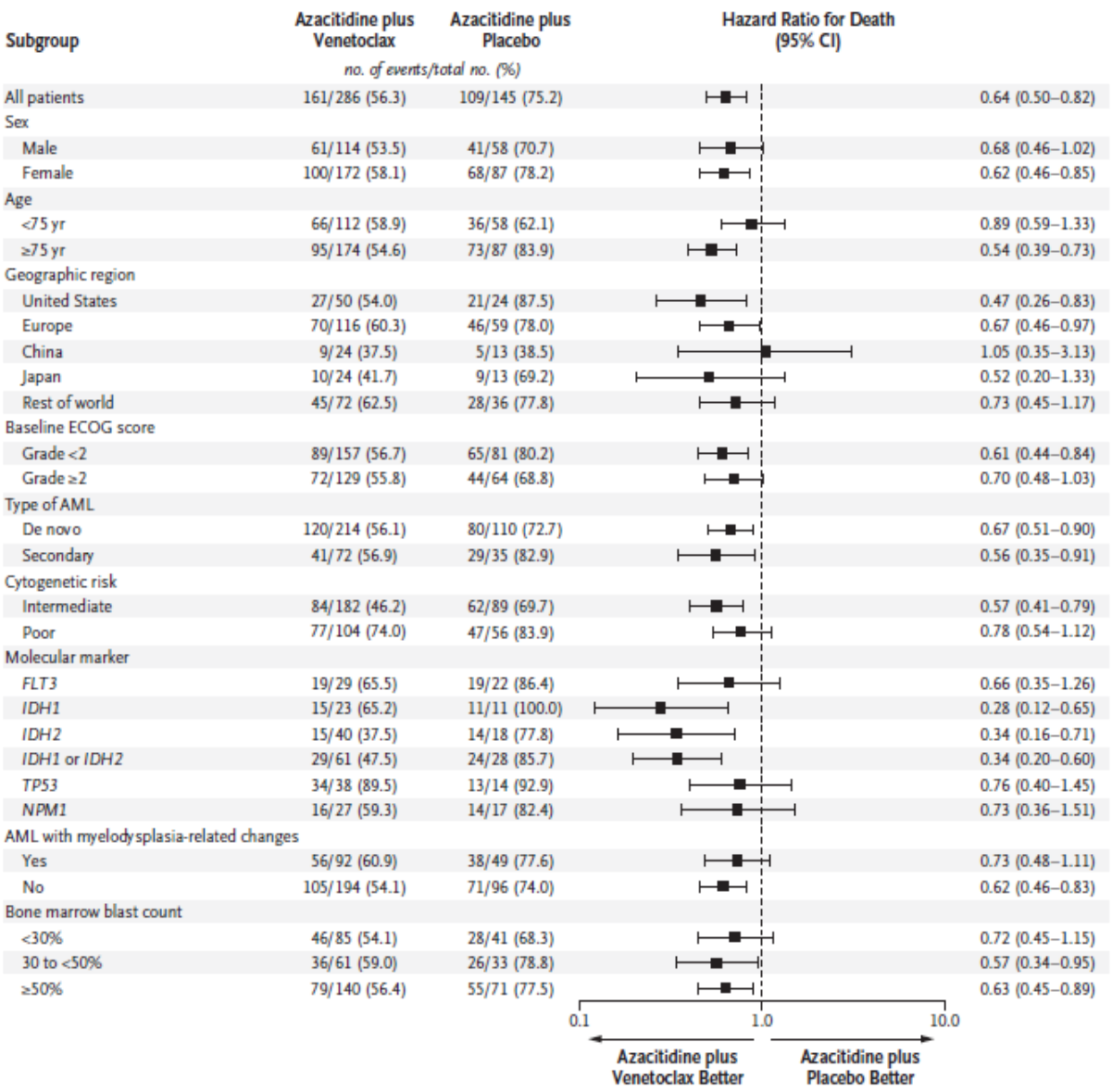
4.10.4 Subgroup analyses in VIALE-A: OS and complete remission rates

The primary analyses for the subgroups were based on investigator assessment. The prespecified subgroups included gender, age group, region, baseline ECOG PS, type of AML, cytogenetic risk, molecular markers and AML-MRC (myelodysplastic related changes). The analyses showed a consistent survival benefit for subjects in the venetoclax + azacitidine arm in most of the subgroups analysed (Figure 4.3).

In patients with *IDH1* or *IDH2* mutations at baseline, an improved hazard ratio compared to the overall population was observed, with OS at 12 months of 66.8% among those in the venetoclax + azacitidine arm, compared to 35.7% among those in the control group (HR 0.345; 95% CI 0.20, 0.60; p<0.001). This finding is consistent with the incidence of composite complete remission (CR + CRi) in this subgroup of 75.4% (95% CI 62.7, 85.5) in the venetoclax + azacitidine group compared to 10.7% (95% CI 2.3, 28.2) in the control group (p<0.001; Figure 4.4).

A potential difference in treatment effect by age on OS and the composite complete remission rate (smaller treatment difference among patients aged <75 years compared to patients ≥ 75 years) was also observed.

A post hoc analysis by BM blast count category (<30%, 30%–<50%, >50%) was also performed.



Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
Male	61/114 (53.5)	41/58 (70.7)	0.68 (0.46–1.02)
Female	100/172 (58.1)	68/87 (78.2)	0.62 (0.46–0.85)
Age			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)

Figure 4.3. Forest plot of overall survival in VIALE-A
Source: (48).
Data cutoff date 4th January 2020.
Abbreviations: AML=acute myeloid leukaemia; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group.

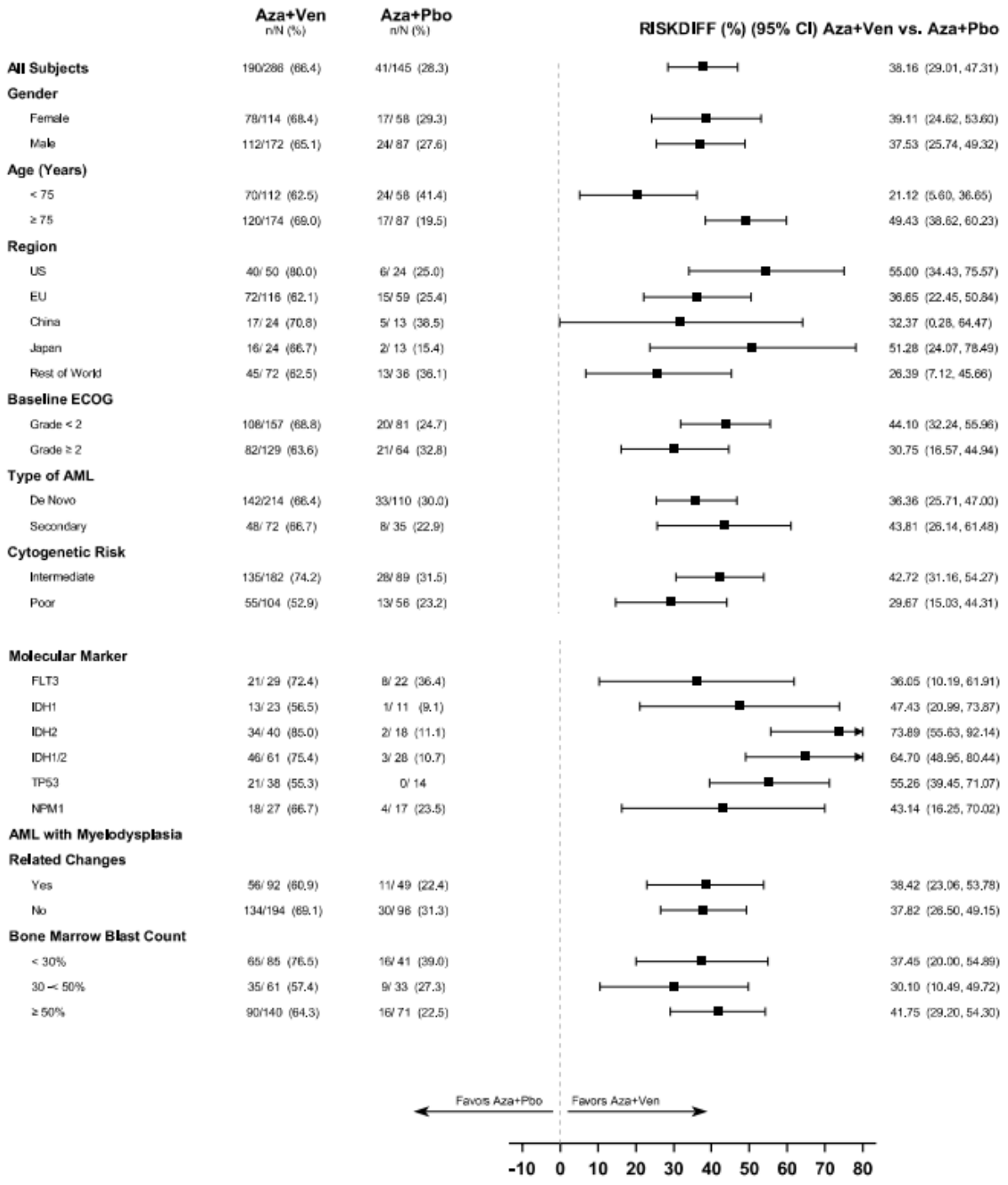


Figure 4.4. Forest plot of the composite complete remission rate in VIALE-A

Source: (48).
Data cutoff date 4th January 2020. The plot shows the percentage risk difference for the composite complete remission rate and 95% CI (exact unconditional method).
Abbreviations: AML=acute myeloid leukaemia; Aza=azacitidine; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; Pbo=placebo; RISKDIFF=risk difference; Ven=venetoclax.

4.10.5 Transfusion independence

In VIALE-A, postbaseline transfusion independence was evaluated both for subjects who were transfusion-dependent before enrolment and for subjects who were transfusion-independent at the time of enrolment. As can be seen in Table 4.14, venetoclax in combination with azacitidine significantly

improved the percentage of subjects who achieved postbaseline transfusion independence for both RBCs and platelets when compared to azacitidine alone.

Table 4.14. Summary of postbaseline transfusion independence in VIALE-A

Transfusion independence [a]	Venetoclax+ azacitidine		Azacitidine		Venetoclax + azacitidine vs. azactidine
	N	Patients with event, n (%) [95% CI]	N	Patients with event, n (%) [95% CI]	Treatment difference [95% CI] p-value [b]
RBC	286	171 (59.8) [53.9, 65.5]	145	51 (35.2) [27.4, 43.5]	24.6% [15.0%, 34.2%] p<0.001
Platelets	286	196 (68.5) [62.8, 73.9]	145	72 (49.7) [41.3, 58.1]	18.9% [9.1%, 28.6%] p<0.001
RBC and platelets	286	166 (58.0) [52.1, 63.8]	145	49 (33.8) [26.2, 42.1]	24.2% [14.7%, 33.8%] p<0.001

Source: (29, 47).
[a] The postbaseline transfusion independence is defined as a period of at least 56 days with no RBC or platelet transfusion during the evaluation period. The duration of postbaseline transfusion independence is defined as the first time period for which a subject receives no RBC/platelet transfusion for at least 56 days during the evaluation period.
Data cutoff date 4th January 2020.
[b] The p-value is from a Cochran–Mantel–Haenszel test for venetoclax + azacitidine versus azacitidine, stratified by age (18 to <75 years, ≥75 years) and cytogenetic risk (intermediate risk, poor risk) at randomisation.
Abbreviations: CI=confidence interval; RBC=red blood cell

Data for transfusion independence were also reported in M14-358 for the approved dose of venetoclax. This was a nonrandomised phase 1 study and no relative efficacy analyses between the treatment arms were planned or reported (Table 4.15).

Table 4.15. Summary of postbaseline transfusion independence in study M14-358

Transfusion independence [a]	Venetoclax 400 mg + azacitidine		Venetoclax 400 mg+ decitabine	
	N	Patients with event, n (%) [95% CI]	N	Patients with event, n (%) [95% CI]
RBC	84	54 (64.3) [53.1, 74.4]	31	19 (61.3) [42.2, 78.2]
Platelets	84	59 (70.2) [59.3, 79.7]	31	27 (87.1) [70.2, 96.4]
RBC and platelets	84	52 (61.9) [50.7, 72.3]	31	19 (61.3) [42.2, 78.2]

Source:(29, 53)
[a] The postbaseline transfusion independence is defined as a period of at least 56 days with no RBC or platelet transfusion during the evaluation period. The duration of postbaseline transfusion independence is defined as the first time period for which a subject receives no RBC/platelet transfusion for at least 56 days during the evaluation period.
Abbreviations: CI=confidence interval; RBC=red blood cell.

4.10.6 EFS in VIALE-A

Venetoclax in combination with azacitidine significantly improved EFS when compared to placebo + azacitidine. The median duration of EFS per investigator assessment was 9.8 months (95% CI 8.4, 11.8) for the venetoclax + azacitidine arm and 7.0 months (95% CI: 5.6, 9.5) for the control arm. Kaplan–Meier curves for EFS are shown in Figure 4.5.

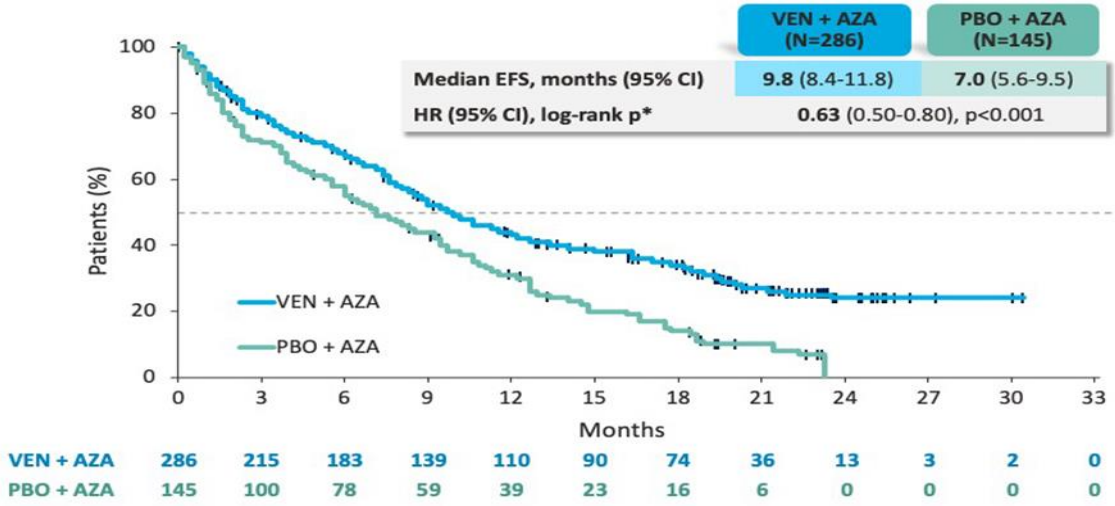


Figure 4.5. Kaplan–Meier curves for event-free survival
Source: (22)].
* Log-rank test stratified by age (18-<75 years, ≥75 years) and cytogenetic risk (intermediate risk, poor risk) at randomisation. Tick marks along the curves indicate censored data. Data included are subject to a cutoff date of 4th January 2020.
Abbreviations: AZA=azacitidine; CI=confidence interval; EFS=event-free survival; HR=hazard ratio; PBO=placebo; VEN=venetoclax.

4.10.7 HRQoL in VIALE-A

The interim analyses of PRO data were based on a cutoff date of 4th January 2020, at which time rather few patients were reporting beyond early treatment cycles.

Fatigue measured with PROMIS Cancer Fatigue-SF
Fatigue was assessed using PROMIS Cancer Fatigue-SF, a 7-item questionnaire assessing the impact and experience of fatigue over the previous 7 days. The mean baseline PROMIS scores were similar in the venetoclax + azacitidine and comparator arms (53.86 and 54.97, respectively). A reduction in fatigue was reported during treatment in both arms (47).

The change in PROMIS fatigue score from baseline was compared between the two treatment arms at each postbaseline visit. A linear mixed-effects regression model with a covariance structure was used and included the following factors: baseline score, stratification factors (age and cytogenetic risk) treatment arm, visit and treatment arm × visit interaction. There were no clinically meaningful differences in mean change from baseline between the venetoclax + azacitidine arm and the placebo + azacitidine arm. In both treatment arms, patients experienced a reduction in fatigue during the earlier treatment cycles, and treatment with venetoclax + azacitidine was not associated with any additional fatigue above that due to azacitidine treatment alone (47).

GHS measured with EORTC QLQ-C30
Changes in EORTC QLQ-C30 GHS were compared between the treatment arms. Baseline scores were similar between the venetoclax + azacitidine arm (52.61) and the placebo + azacitidine arm (55.96). Subjects in both treatment arms experienced improvement in QoL, and a greater change in EORTC QLQ-C30 GHS/QoL scores from baseline was observed in the venetoclax + azacitidine arm than in the placebo + azacitidine arm on Day 1 of all cycles, except Cycle 19, but there were no clinically meaningful differences in mean change from baseline between the treatment arms (47). The median time to deterioration (TTD) for QoL (based on a deterioration of the within-group estimate of at least the meaningful change threshold MCT of 10 points) was numerically longer in the venetoclax + azacitidine arm (16.5 months) than in the control arm (9.3 months), but the difference was not statistically significant (Figure 4.6).

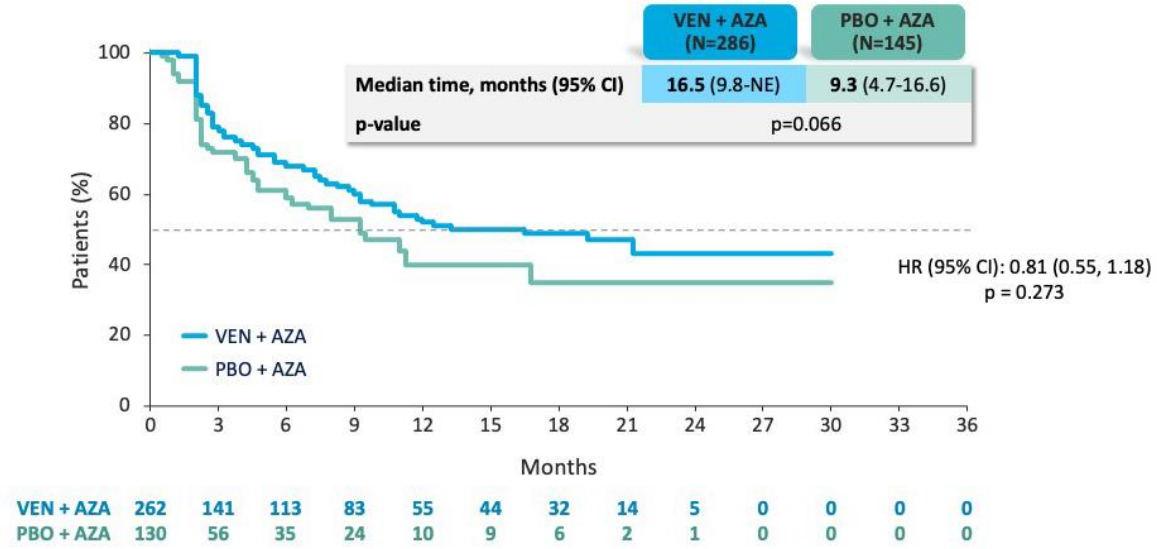


Figure 4.6. Time to deterioration for EORTC-QLQ-C30 Global Health Status
Source: (22, 65)
Time to deterioration of quality of life measured using EORTC QLQ-C30 Global Health Status/Quality of Life was assessed based on a deterioration of the within-group estimate of at least the meaningful change threshold of 10 points. The p-value is for an unadjusted log-rank test.
The adjusted HR of 0.81 (95% CI 0.55–1.18) is based on a Cox proportional-hazards models adjusted for key covariates (age, baseline Eastern Cooperative Oncology Group performance status and patient-reported outcome scores, acute myeloid leukaemia type and cytogenetic risk category).
Abbreviations: AZA=azacitidine; CI=confidence interval; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; HR=hazard ratio; PBO=placebo; VEN=venetoclax.

EQ-5D-5L VAS
A higher VAS score was observed for the venetoclax + azacitidine arm than for the placebo + azacitidine arm at several treatment cycles. TTD for quality of life as measured with EQ-5D-5L VAS was assessed according to a deterioration of at least the MCT of 7 points. For the whole population, patients in the venetoclax + azacitidine arm experienced significantly longer median TTD (10.7 months, 95% CI 7.53, 18.6) than patients in the placebo+ azacitidine arm (3.9 months, 95% CI 2.37, 7.40; p<0.001) (65).

EQ 5D 5L Health Utility Index
A linear mixed-effects regression model with a covariance structure was used to test the change in scores from baseline between the treatment arms. The model includes the following factors: baseline score, stratification factors (age and cytogenetics), treatment arm, visit and treatment arm × visit interaction. There were no significant differences in outcomes between the treatment arms (47).

4.10.8 AEs in VIALE-A and the supportive studies M14-358 and VIALE-C

VIALE-A
A summary of the most common treatment-emerged adverse events (TEAE) of all grades and grade ≥3 TEAEs is presented in Appendix 5: Details of SAFETY.

In VIALE-A, 427 patients were included in the safety analysis, of whom 283 were in the venetoclax + azacitidine arm and 144 were in the placebo + azacitidine arm. The median number of treatment cycles was 7.0 (range 1.0, 30.0) in the venetoclax + azacitidine arm and 4.5 (range 1.0, 26.0) in the placebo + azacitidine arm (22, 47).

During the VIALE-A study period, an AE occurred in every patient in both treatment arms. According to the MedDRA SOC, the highest incidences of AEs of any grade reported for the venetoclax + azacitidine and placebo + azacitidine arms (respectively) were for gastrointestinal disorders (85.2% and 77.8%), infections and infestations (84.5% and 67.4%), and blood and lymphatic system disorders (83.4% and 69.4%), followed by general disorders and administration site conditions (68.9% and 66.0%), metabolism and nutrition disorders (61.8% and 54.9%), and respiratory, thoracic and mediastinal disorders (48.8% and 41.7%) (22, 47).

Common AEs (occurring in ≥15% of subjects), regardless of severity or study drug, reported by a higher percentage of subjects (by ≥5%) in the venetoclax + azacitidine arm versus the placebo + azacitidine arm were thrombocytopenia (45.9% vs. 40.3%), neutropenia (42.0% vs. 29.2%), nausea (43.8% vs. 34.7%), febrile neutropenia (41.7% vs. 18.8%), diarrhoea (41.3% vs. 33.3%), vomiting (29.7% vs. 22.9%), anaemia (27.6% vs. 20.8%), decreased appetite (25.4% vs. 17.4%), peripheral oedema (24.4% vs. 18.1%), leukopenia (20.5% vs. 13.9%) and asthenia (15.5% vs. 8.3%). Common AEs (occurring in ≥15% of subjects) reported by a similar percentage of subjects (<5% difference in incidence) in the venetoclax + azacitidine and placebo + azacitidine arms (respectively) included constipation (42.8% and 38.9%), hypokalaemia (28.6% and 28.5%), pyrexia (23.3% and 22.2%), pneumonia (23.0% and 27.1%) and fatigue (20.8% and 16.7%) (22, 47).

Grade ≥3 AEs

Grade ≥3 AEs (according to the NCI CTCAE) were reported for almost all subjects in the venetoclax + azacitidine (98.6%) and placebo + azacitidine (96.5%) arms. Blood and lymphatic system disorders was the SOC with the highest incidence of grade ≥3 AEs in the venetoclax + azacitidine (82.3%) and placebo + azacitidine (68.1%) arms. There was a higher incidence of grade ≥3 AEs in the venetoclax + azacitidine arm versus the placebo + azacitidine arm for the infections and infestations (63.6% vs. 51.4%), investigations (20.5% vs. 9.0%), respiratory, thoracic and mediastinal disorders (15.5% vs. 10.4%) and gastrointestinal disorders (14.8% vs. 11.8%) SOCs. The most common grade ≥3 AEs (occurring in ≥5% of all subjects) that were reported by a higher percentage of subjects (by ≥2%) in the venetoclax + azacitidine arm versus the placebo + azacitidine arm were thrombocytopenia (45% vs. 38%), neutropenia (42% vs. 29%), febrile neutropenia (42% vs. 19%), anaemia (26% vs. 20%), leukopenia (21% vs. 12%) and atrial fibrillation (6% and 2%). A lower percentage of subjects in the venetoclax + azacitidine arm versus the placebo + azacitidine arm reported grade ≥3 AEs of pneumonia (19.8% vs. 25.0%) and sepsis (6.0% vs. 9.0%) (47).

The incidence of grade ≥3 venetoclax- or placebo-related AEs was higher in the venetoclax + azacitidine arm than in the placebo + azacitidine arm (76.3% vs. 49.3%). The blood and lymphatic system disorders SOC had the highest incidence of grade ≥3 venetoclax- or placebo-related AEs in both the venetoclax + azacitidine (66.4%) and placebo + azacitidine (39.6%) arms. A higher incidence of grade ≥3 venetoclax- or placebo-related AEs in the venetoclax + azacitidine arm versus the placebo + azacitidine arm was also observed in the infections and infestations SOC (29.7% vs. 15.3%). There was generally low incidence of grade ≥3 venetoclax- or placebo-related AEs in the gastrointestinal disorders (3.9% and 6.3%) and cardiac disorders (2.1% and 2.1%) SOCs in both the venetoclax + azacitidine and placebo + azacitidine arms. The most common venetoclax- or placebo-related grade ≥3 AEs (occurring in ≥5% of all subjects) that were reported by a higher percentage of subjects (by ≥2%) in the venetoclax + azacitidine arm versus the placebo + azacitidine arm were neutropenia (35.7% vs. 21.5%), thrombocytopenia (33.6% vs. 20.1%), febrile neutropenia (27.9% vs. 7.6%), anaemia (18.4% vs. 13.9%) and leukopenia (18.0% vs. 9.0%) (47).

Serious AEs

A higher incidence of SAEs was reported in the venetoclax + azacitidine arm (83.0%) than in the placebo + azacitidine arm (72.9%). Infections and infestations was the SOC with the highest incidence of SAEs in both the venetoclax + azacitidine and placebo + azacitidine arms (57.2% and 43.8%, respectively), followed by the blood and lymphatic system disorders SOC (39.9% and 16.7%). The most frequently reported SAEs occurring in ≥2% of patients in the venetoclax + azacitidine arm versus the placebo + azacitidine arm were febrile neutropenia (29.7% vs. 10.4%), anaemia (4.9% vs. 4.2%), neutropenia (4.6% vs. 2.1%), thrombocytopenia (4.2% vs. 1.4%), atrial fibrillation (4.6% vs. 1.4%), cardiac failure (2.1% vs. 2.1%), pyrexia (2.5% vs. 2.1%), pneumonia (16.6% vs. 22.2%), sepsis (5.7% vs. 8.3%), *Escherichia* sepsis (2.8% vs. 1.4%), influenza (2.8% vs. 1.4%), lung infection (2.8% vs. 2.1%), urinary tract infection (2.5% vs. 2.1%) and acute kidney injury (1.8% vs. 3.5%). Serious bleeding events (including epistaxis, haematuria, intracranial haemorrhage, gastrointestinal haemorrhage and melaena) were also more frequently reported in the venetoclax + azacitidine arm (8.8%) than in the placebo + azacitidine arm (5.6%) (47).

AEs leading to death

A similar percentage of subjects in both arms experienced AEs leading to death (64 subjects [22.6%] in venetoclax + azacitidine arm and 29 subjects [20.1%] in the placebo + azacitidine arm). The infections and infestations SOC had the highest incidence of AEs leading to death in both arms and was similar between the venetoclax + azacitidine (9.2%) and placebo + azacitidine (7.6%) arms. Among the subjects

in the venetoclax + azacitidine arm, AEs leading to death that occurred in ≥1% of subjects included pneumonia (11 subjects, 3.9%), sepsis (6 subjects, 2.1%), death not specified (4 subjects, 1.4%), and cardiac arrest, intracranial haemorrhage, respiratory failure and septic shock (3 subjects, 1.1% each). Among the subjects in the placebo + azacitidine arm, AEs leading to death that occurred in ≥1% of subjects included sepsis (5 subjects, 3.5%), pneumonia (3 subjects, 2.1%), and death and cardiac arrest (2 subjects, 1.4% each). The number of patients with a reasonable possibility as assessed by the investigator that venetoclax- or placebo-related AEs led to death was 11 (3.9%) in the venetoclax + azacitidine arm and two (1.4%) in the placebo + azacitidine arm. Azacitidine-related AEs may have led to death in 12 patients (4.2%) in the venetoclax + azacitidine arm and two (1.4%) in the placebo + azacitidine arm (47). The 30-day mortality rate was similar in the venetoclax + azacitidine (7%; n=21) and placebo + azacitidine (6.3%; n=9) arms (22).

Treatment discontinuations and dose reductions due to AEs

Discontinuation of treatment with venetoclax or placebo due to TEAEs were reported for 24.4% of subjects in the venetoclax + azacitidine arm and 20.1% in the placebo + azacitidine arm. The most commonly reported AEs leading to venetoclax or placebo discontinuation in the venetoclax + azacitidine and placebo + azacitidine arm (respectively) were sepsis (1.4% and 3.5%) and pneumonia (1.4% and 2.8%), followed by neutropenia (1.4% and 1.4%), febrile neutropenia (1.4% and 0.7%) and thrombocytopenia (1.1% and 2.1%). For azacitidine, discontinuation of treatment was reported for 24.0% in the venetoclax + azacitidine arm and 20.1% in the placebo + azacitidine arm. The most commonly reported AEs leading to azacitidine discontinuation in the venetoclax + azacitidine arm and placebo + azacitidine arm (respectively) were sepsis (1.4% and 3.5%) and pneumonia (1.4% and 2.8%). AEs that led to discontinuation of azacitidine were generally similar to those reported for venetoclax or placebo (47).

AEs that led to a venetoclax or placebo dose interruption or a dose reduction were reported for 72.1% of subjects in the venetoclax + azacitidine arm and 58.3% in the placebo + azacitidine arm. Febrile neutropenia, neutropenia and pneumonia were the most commonly reported AEs (≥10% of subjects) leading to venetoclax dose interruption or dose reduction, and were reported for 19.8%, 19.4% and 9.5% of subjects, respectively, in the venetoclax + azacitidine arm, and 4.2%, 10.4%, and 13.2% of subjects in the placebo + azacitidine arm. AEs that led to azacitidine dose interruption or dose reduction were also reported for 67.1% subjects in the venetoclax + azacitidine arm and 46.5% in the placebo + azacitidine arm. Neutropenia and febrile neutropenia were the most commonly reported AEs (reported in ≥10% of subjects overall) leading to azacitidine dose interruption or dose reduction (47).

AEs that led to a venetoclax or placebo dose reduction were reported for 2.5% subjects in the venetoclax + azacitidine arm and 4.2% in the placebo + azacitidine arm, whereas azacitidine dose reduction was reported for 12.0% subjects in the venetoclax + azacitidine arm and 1.4% in the placebo + azacitidine arm (47).

M14-358 (supportive study)

A summary of M14-358 safety outcomes is available in Appendix 4: Comparator and supportive studies (Table A11).

For the azacitidine and decitabine group, respectively, the most frequently reported grade ≥3 AEs were haematologic and included febrile neutropenia (39% and 65%), anaemia (30% and 26%), thrombocytopenia (25% and 23%) and neutropenia (20% and 10%). The most common nonhaematologic AEs of any grade (azacitidine group and decitabine group, respectively)were nausea (64% and 65%), diarrhoea (61% and 45%) and constipation (50% and 52%). Serious AEs included febrile neutropenia (31% and 42%), pneumonia (26% and 29%) and sepsis (4% and 7%), as expected in AML patients. The 30-day mortality rates were 2% (n=2) in the azacitidine group and 7% (n=2) in the decitabine group (53).

VIALE-C

In VIALE-C, the most common TEAEs of any grade for venetoclax + LDAC versus placebo + LDAC were thrombocytopenia (46% vs. 40%), neutropenia (49% vs. 18%), nausea (43% vs. 31%), febrile neutropenia (32% vs. 29%) and hypokalaemia (31% vs. 25%). The most frequently reported grade ≥3 AEs, irrespective of cause, were haematologic in nature and included febrile neutropenia (32% vs. 29%), neutropenia (46% vs. 16%), thrombocytopenia (45% vs. 37%) and anaemia (25% vs. 22%). Serious AEs common to patients with AML included febrile neutropenia (16% vs. 18%), pneumonia (13% vs. 10%)

and sepsis (6% in both arms). The 30-day mortality rates were 13% (n=18) in the venetoclax arm and 16% (n=11) in the placebo arm (54).

For further information on efficacy and safety data in comparator studies and the supportive studies, see Appendix 4: Comparator and supportive studies.

4.10.9 Summary of findings for venetoclax + azacitidine versus azacitidine

The quality of the evidence for each outcome in VIALE-A according to factors outlined in the GRADE approach is presented in Table 4.16. For a more detailed description of the GRADE assessment, see Appendix 2: Certainty of evidence.

Table 4.16. Summary of findings for venetoclax + azacitidine versus azacitidine alone in AML according to the GRADE approach

Patient or population: Adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy

Intervention: Venetoclax + azacitidine

Comparison: Azacitidine + placebo

Outcomes	Participants (studies)	Certainty of the evidence (GRADE)	Relative effect [95% CI]	Patients with event, % [95% CI]	
				VEN + AZA	PBO + AZA
Overall survival (median follow-up 20.5 months)	431 (1 RCT)	⊕⊕⊕◯ Moderate [a]	HR 0.66 [0.52–0.85]		
Composite complete remission rate	431 (1 RCT)	⊕⊕⊕◯ Moderate [a]	NR	66.4 [60.6–71.9]	28.3 [21.1–36.39]
Transfusion independence rate [c]	431 (1 RCT)	⊕⊕⊕◯ Moderate [a]	NR	58.0 [52.1–63.8]	33.8 [26.2–42.1]
Health-related quality of life [d]	392 (1 RCT)	⊕⊕◯◯ Low [a,b]	HR 0.81 [0.55–1.188]		
SAEs (mean follow-up 1 month)	427 (1 RCT)	⊕⊕⊕◯ Moderate [a]	RR 1.14 [1.02–1.27]		
Grade >3 AEs (mean follow-up 1 month)	427 (1 RCT)	⊕⊕⊕◯ Moderate [a]	RR 1.02 [0.99–1.06]		
Treatment discontinuations due to AEs (mean follow-up 1 month)	427 (1 RCT)	⊕⊕⊕◯ Moderate [a]	RR 1.21 [0.82–1.78]		

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect .

[a] Only one study and/or wide CI.
[b] Risk of bias due to different attrition rates in the treatment versus the control group.
[c] Tranfusion independence rate for both RBC and platelets
[d] HR for health realted quality of life refers to time to deterioration (TTD) in the EORTC-QLQ-C30/Global Health Status
Abbreviations: AE=adverse event; AML=acute myeloid leukaemia; AZA=azacitidine; CI=confidence interval; GRADE= Grading of Recommendations, Assessment, Development and Evaluation; HR=hazard ratio; NR=not reported; PBO=placebo; RCT=randomised controlled trial; RR=risk ratio; SAE=serious adverse event; VEN=venetoclax.

4.11 Indirect evidence

4.11.1 Indirect treatment comparison: NMA

Direct evidence was only identified for venetoclax in combination with azacitidine versus azacitidine alone (VIALE-A). The appropriateness and feasibility of conducting anchored ITCs of venetoclax combinations versus other relevant comparators such as BSC, decitabine, LDAC and glasdegib in

combination with LDAC was assessed by the MAH. The feasibility of constructing a study network was assessed on the basis of the available linkages (i.e., common trial arms reporting on relevant outcomes). Only RCTs were included, and studies with only one arm of interest were excluded. The rationale given by the MAH for this criterion was to create a complete connected network to enable the ITC with the assumption that a trial that includes one treatment within the PICO and one treatment outside the PICO cannot contribute meaningful information to the network.

The potential network diagram for the OS outcome is illustrated in Figure 4.7.

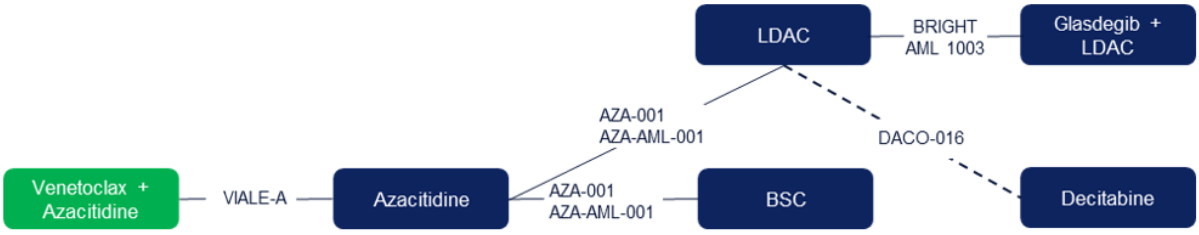


Figure 4.7. Evidence network diagram for overall survival

Source: (66).
The dotted lines for study DACO-016 indicate that the OS hazard ratio was reported for decitabine vs. treatment choice (LDAC or BSC)
Abbreviations: BSC=best supportive care; LDAC=low-dose cytarabine; OS=overall survival.

The MAH performed an NMA feasibility assessment in which study design and patient populations were compared across trials to assess overall comparability, including an appraisal of the risk of bias in relevant trials, a cross-trial heterogeneity assessment and an evaluation of the proportional hazards assumption for OS. According to the MAH, the assessment demonstrated that the systematic differences between the venetoclax pivotal trial (VIALE-A) and the trials providing contrasts to relevant comparators were of a magnitude that would risk producing misleading results, rendering an NMA invalid and noninformative for decision-making.

The MAH performed a propensity score weighting (PSW) analysis for indirect comparison of venetoclax + azacitidine versus LDAC based on individual patient data from the venetoclax + azacitidine arm in VIALE-A and the LDAC arm in VIALE-C (see Section 4.11.3)

A short summary of the relevant comparator studies in the NMA is given below. For further information on the design, baseline characteristics and key efficacy of the comparator studies, see Appendix 4:

BRIGHT-AML 1003 (51, 67)
Glasdegib in combination with LDAC was investigated in a multicentre, randomised, open-label phase 2 study in a total of 132 patients with previously untreated AML or high-risk MDS patients who were not eligible to receive intensive chemotherapy. Ineligibility for intensive chemotherapy involved fulfilling at least one of several criteria, including age ≥75 years, serum creatinine >1.3 mg/dl, severe cardiac disease or ECOG PS of 2. The study included 116 patients with previously untreated de novo or secondary AML. Patients were randomised 2:1 to receive glasdegib (100 mg orally QD) with LDAC (20 mg cytarabine twice daily SC on Days 1–10 of the 28-day cycle; n=78) or LDAC alone (n=38) in 28-day cycles until disease progression or unacceptable toxicity. Patients were stratified at randomisation by prognostic risk factor (good/intermediate or poor) based on cytogenetics.

DACO-016 (34)
Decitabine was studied in an open-label, randomised, multicentre, phase 3 study (DACO-016) in subjects with newly diagnosed de novo or secondary AML, with decitabine (n=242) compared to treatment choice (TC; n=243). TC consisted of the patient's choice with physician's advice of either BSC alone (n=28) or LDAC (20 mg/m^2 cytarabine SC) QD for 10 consecutive days repeated every 4 weeks (n=215). There was no preselection of TC type (LDAC or BSC) before randomisation. Decitabine was administered as a 1-hour intravenous infusion of 20 mg/m^2 QD for 5 consecutive days repeated every

4 weeks. Subjects who were considered candidates for standard induction chemotherapy or patients with favourable cytogenetic risk were not included in the study. Patients had poor or intermediate cytogenetic risk according to the Southwest Oncology Group categorisation (14).

The primary endpoint was OS. For further information. see Appendix 4: Comparator and supportive studies. Patients with MDS (and patients with AML arising from an AHD or MDS) could have had one prior regimen (e.g., azacitidine or decitabine) for the treatment of their prior haematologic disease. The primary endpoint was OS in the glasdegib + LDAC arm in comparison to LDAC alone. For further information, see Appendix 4: Comparator and supportive studies

AZA-001 (49, 50)
Study AZA-001 was an open-label phase 3 trial and included patients with high-risk MDS, modified chronic myelomonocytic leukaemia and AML. Azacitidine + BSC (n=179) was compared to conventional care regimens (CCRs) consisting of BSC alone (n=105), LDAC plus BSC (n=49) or standard intensive chemotherapy plus BSC (n=25). Patients were preselected by their physician to receive one of the three CCR before randomisation and they received the preselected regimen if not randomised to azacitidine. One of the three CCRs (BSC, LDAC or intensive chemotherapy) was selected by investigators on the basis of age, ECOG PS, comorbidities, and institutional, regional or national guidelines. Patients were not considered eligible for haematopoietic stem cell transplantation and had intermediate or poor cytogenetic risk (NCCN 2009 criteria) and ECOG PS ≤2. Patients with secondary MDS were excluded from the study.

Approximately one-third of these patients were classified as having AML under current WHO criteria (20%–30% blasts) and the approved indication based on this study was restricted to AML with 20%–30% blasts and multilineage dysplasia. A preplanned OS analysis compared the effects of azacitidine versus CCR on OS in the AML subgroup (n=113). For further information, see Appendix 4: Comparator and supportive studies.

AZA-AML-001 (33, 41)
The efficacy and safety of azacitidine were studied in an international, multicentre, controlled, open-label, phase 3 study in patients aged ≥65 years with newly diagnosed de novo or secondary AML with >30% BM blasts. Patients were not eligible for haematopoietic stem cell transplantation. Azacitidine (n=241) was compared to CCR (n=247). CCR consisted of BSC alone (n=45), LDAC plus BSC (n=158) or standard intensive chemotherapy with cytarabine and anthracycline plus BSC (n=44). Patients were preselected by their physician to receive one of the three different CCRs before randomisation. Patients received the preselected regimen if not randomised to azacitidine. All study participants could receive BSC, including transient use of hydroxyurea.Patients were required to have ECOG PS of 0–2 and intermediate- or poor-risk cytogenetic abnormalities (NCCN 2009 criteria).

The primary endpoint was OS in the azacitidine arm versus CCR. The study was not powered to demonstrate a statistically significant difference when comparing azacitidine to the preselected CCR treatment subgroups. For further information, see Appendix 4: Comparator and supportive studies.

4.11.2 Critical appraisal of NMA feasibility

In line with the approved indication for venetoclax + HMA (azacitidine or decitabine), the relevant comparators in the EUnetHTA PICO include BSC, azacitidine, decitabine, glasdegib+ LDAC and LDAC alone. Direct evidence was identified for venetoclax in combination with azacitidine versus azacitidine alone in the VIALE-A study. The combination of venetoclax + decitabine was approved in Europe on the basis of data from the supportive study M14-358, the similar mechanism of action of the two HMAs, and published literature supporting similar efficacy and safety profiles of the two HMAs.

Some relevant comparator studies were identified and could be connected in a network. The potential network depended on the azacitidine–LDAC link and the azacitidine–BSC link on the basis of the AZA-AML-001 and AZA-001 azacitidine studies. Glasdegib + LDAC was connected by the LDAC arm in the BRIGHT-AML study. However, the MAH did not perform NMA for reasons related to differences in both study design and the patient populations included.

The risk of bias in the comparator studies was generally rated as high by the MAH because of the open-label design and the lack of complete information in the publications (lack of description of methods for handling missing data and completeness of reporting for all outcomes measured). That MAH also stated

that there are considerable differences between the trials in potentially effect-modifying patient characteristics (e.g., type of AML, ECOG PS, in particular due to different trial-specific inclusion criteria). Hence, the MAH concluded that the central similarity assumption for valid ITCs is ultimately violated (Table 7.6 in the core submission dossier (22)).

The Authoring Team does not support the feasibility assessment process performed by the MAH because the criteria used for inclusion of the studies identified were very strict. Only RCTs with two arms of interest were included in the network, and the value of a more extended network of studies cannot be assessed. The choice of inclusion criteria by the MAH contributed to the conclusion that NMA is not feasible. It is the opinion of the Authoring Team that it would be of value to actually perform the potential comparisons and assess the robustness on the basis of the outputs from the analysis. The results would include and allow an opportunity to explore more tangible outcomes on heterogeneity and inconsistency, providing a more concrete description of uncertainty in the ITCs.

Potential comparison of venetoclax + HMAs versus BSC

Three of the studies identified (AZA-001, AZA-AML-001 and DACO-16) included comparisons of azacitidine or decitabine versus BSC or LDAC. In the decitabine trial, no preselection to BSC before randomisation was performed, and only 28 of the 234 patients in the CCR control arm actually received BSC. Thus, both the study design and the limited number of patients treated with BSC make this trial less feasible for inclusion in an ITC versus BSC.

Comparison of patient characteristics between VIALE-A and the two azacitidine studies reveals that the distribution of cytogenetic risk levels seems to be similar. Since different guidelines are used in the studies to classify cytogenetic risk (NCCN 2009 criteria in the azacitidine trials and updated NCCN 2016 criteria in VIALE-A), significant heterogeneity in mutational/molecular risk factors cannot be excluded. All three studies excluded patients previously treated with HMAs. The AZA-001 study only included patients with low BM blast counts (20%–30%), AZA-AML-001 only included patients with blast counts >30%, while VIALE-A included patients with blast counts across these categories.

The ECOG PS scores for patients were more favourable in the azacitidine studies than in VIALE-A: 22.8 % and 7.3% of patients had ECOG PS 2 in the azacitidine arms in AZA-AML-001 and AZA-001 respectively, compared to 40% in VIALE-A. Furthermore, it is not clear from the inclusion criteria used in the two azacitidine studies whether all patients (in the relevant subgroups) were actually ineligible for intensive chemotherapy.

The azacitidine studies included patients preselected as eligible for BSC before randomisation (63 patients in AZA-001 and 89 in AZA-AML-001). Prespecified exploratory subgroup analyses were performed and some efficacy and safety results for azacitidine versus BSC are available. However, high uncertainty in estimates owing to the small sample size of the BSC subgroup is expected, and the suitability for NMA may be low.

Potential comparison of venetoclax + azacitidineversus glasdegib + LDAC

In the potential network, a comparison of venetoclax + azacitidine versus glasdegib + LDAC depends on the BRIGHT-AML 1003 study in addition to the link to LDAC via the azacitidine studies (AZA-AML-001 and AZA-001).

Comparison of the patient baseline characteristics between VIALE-A and BRIGHT-AML reveals that age, ECOG PS and BM blast count seem to be well aligned across the studies. Similar criteria were used to define eligibility for intensive chemotherapy, but some differences in other prognostic and effect-modifying factors are apparent. The proportion of patients with secondary AML was higher in BRIGHT-AML (>50%) than in VIALE-A (~25%). In BRIGHT-AML, patients with MDS and patients with AML arising from an AHD or MDS could have one prior regimen with a HMA, and 18% of the patients were previously treated with azacitidine or decitabine.

A few patients with good cytogenetic risk status were included in BRIGHT-AML (6.8% of the AML patients) whereas no patients in this category were included in VIALE-A. Overall, the distribution of patients in the intermediate- and high-risk categories seems to be well aligned across the studies. However, since different guidelines were used to classify cytogenetic risk (ELN 2010 in BRIGHT-AML and the NCCN 2016 criteria in VIALE-A), heterogeneity in the distribution of mutational/molecular risk factors across patients in the studies cannot be excluded.

- In conclusion, the Authoring Team did not perform an in-depth appraisal of the feasibility of performing standard NMA using the potential studies. However, an overview revealed several limitations in study design in the azacitidine studies (AZA-AML-001 and AZA-001) and differences in prognostic baseline characteristics between the studies and VIALE-A that might introduce bias in indirect comparisons of venetoclax + azacitidine versus BSC or LDAC.
- Comparison of VIALE-A and BRIGHT-AML revealed that both the design and the similar characteristics of the patient populations could make the studies suitable for an ITC of venetoclax + azacitidine versus glasdegib + LDAC. In the potential network, this comparison also depends on the link to LDAC via the azacitidine studies (AZA-AML-001 and AZA-001), adding further complexity and heterogeneity across the study network. The Authoring Team consider that NMAs could have been performed and the potential bias and direction of bias discussed. For comparison with the BRIGHT-AML population, adjusted methods could be applied in which differences in patient populations are adjusted for to a certain degree. These methods have several limitations, but are applicable once the limitations are assessed and highlighted.
- Since relevant comparisons (direct or indirect) were not submitted for venetoclax in combination with azacitidine versus certain comparators of interest (e.g., BSC and glasdegib in combination with LDAC) this is considered an evidence gap.

4.11.3 ITC based on PSW analysis

Individual patient data from the VIALE-A and VIALE-C trials were used to indirectly compare venetoclax plus azacitidine (VIALE-A) with LDAC alone (VIALE-C) using a PSW technique. A propensity score analysis was deemed appropriate according to the MAH because of the high degree of similarity between the study populations, study designs and baseline characteristics of the VIALE-A and VIALE-C trials (Appendix 4: Comparator and supportive studies).

The baseline covariates were selected on the basis of prior research regarding AML prognostic factors and potential confounders and included age, race, sex, AML status, AML-MRC, history of MDS status, ECOG PS, cytogenetic risk category and BM blasts. For a further a description of the methods and analyses, see the core submission dossier 8.2.2 (22). No safety outcomes were included in the ITC.

Results from ITC of venetoclax + azacitidine versus LDAC

The main propensity score analyses included all patients treated in the venetoclax +azacitidine arm (n=286) in VIALE-A and all patients treated with LDAC in VIALE-C without prior HMA use and without favourable cytogenetic risk (n=50) were included. The results of this analysis showed that venetoclax + azacitidine was associated with significantly prolonged OS and EFS and significantly higher CR + CRi rates in comparison to LDAC. For completeness, the main results are presented below. Owing to high uncertainty for the methods used, the results should be regarded as descriptive only.

Table 4.17. Results for overall survival via propensity score analyses for venetoclax + azacitidine versus LDAC

Treatment	N	Events	Before weighting			After weighting		
			Median OS (95% CI)	HR (95% CI)	p-value	Median OS (95% CI)	HR (95% CI)	p-value
LDAC	50	40	6.13 (2.23, 8.90)			7.43 (3.15, 10.18)		
VEN + AZA	285	190	14.69 (11.53, 18.69)	0.47 (0.33, 0.67)	<0.001*	14.69 (12.12, 19.25)	0.50 (0.35, 0.73)	<0.001*

Source: (66).
* Statistically significant at a level of 0.05.
Abbreviations: AZA=azacitidine; CI= confidence interval; HR=hazard ratio for OS for VEN + AZA versus LDAC; LDAC=low-dose cytarabine; OS=overall survival.

An additional analysis limited to the subgroup of patients with BM blasts >30% was performed that included 206 patients treated with venetoclax + azacitidine in VIALE-A and 50 patients treated with

LDAC in VIALE-C (regardless of whether they had prior HMA use or favourable cytogenetic risk). Similar results were obtained within this subpopulation of patients with >30% BM blasts.

4.11.4 Critical appraisal of ITC based on propensity score

A comparison of venetoclax + azacitidine versus LDAC alone is considered relevant in a limited number of countries where azacitidine is restricted; one actual setting is when azacitidine as monotherapy is not recommended for treating AML in patients with >30% BM blasts who are not eligible for intensive chemotherapy. The comparison versus LDAC may be relevant when LDAC is being considered for use in the most unfit patients, especially from a toxicity point of view. From an efficacy point of view, LDAC monotherapy is considered a suboptimal regimen compared to venetoclax + azacitidine. In the propensity score analyses, only efficacy outcomes were included (OS, EFS and CR + CRi). The potential differences in safety profiles in comparing these to regimens that are considered relevant were not analysed and inferences regarding the comparability of safety cannot be drawn.

Selection of the baseline covariates for PSW was based on prior research regarding AML prognostic factors and potential confounders, which are considered clinically relevant. PSW analyses have limitations, and incorrect specification of a propensity score model or the presence of unmeasured effect modifiers or prognostic variables that are imbalanced can result in a biased estimate.

The main PSW analyses excluded patients with prior HMA use and favourable cytogenetic risk in the LDAC arm of VIALE-C (n=50), since patients with these characteristics were excluded in VIALE-A. When including all patients in the LDAC arm of VIALE-C (n=66) in the analyses, only minor changes in the results were observed.

Overall, and based on both the adjusted efficacy outcomes and unadjusted outcomes in the analyses submitted, the results indicate that venetoclax + azacitidine is associated with responses and time-to event outcomes that are generally well above those reported for LDAC. However, studies with an LDAC arm other than VIALE-C were not included in ITCs with venetoclax + azacitidine, and the size of the relative efficacy estimate between the two interventions might not be generalisable. An NMA including other relevant studies with LDAC informing the contrast between azacitidine and LDAC could be relevant for comparison.

5 PATIENT INVOLVEMENT

Patient organisations stressed that AML is an extremely serious and life-threatening illness with a huge impact on both patients themselves and their families and care-givers. Patients face potentially long-term isolation due to hospitalisation, lost ability to work, lower confidence, loss of control over their own body and life, stigma, social exclusion and social distancing. They experience feelings of anxiety, disbelief, denial, anger, fear, blame, guilt, isolation and depression. Their life is also severely impacted by the side effects of treatments and the disease itself (pain, fatigue, anxiety, feeling weak or breathless, memory loss and loss of concentration). AML affects patients' families and care-givers as well. Low resistance to infections and treatment-related fatigue make patients largely dependent on their care-givers who take responsibility for patient care, treatment schedules, household chores and avoidance of potential infections, which all make a social life very challenging. For many care-givers, daily life involve great mental pressure as well as physical challenges. The patient's inability to work can put greater financial pressure on the care-giver.

For fit and younger patients with AML, standard induction therapy and in certain cases transplantation are the preferred treatment options. Current treatment options for patients not eligible for standard induction therapy are limited to azacitidine, decitabine, LDAC and BSC. Glasdegib + LDAC has recently been approved, but its use is still limited in the EU. These treatment options for patients not eligible for standard induction therapy have limited efficacy, low response rates and high relapse rates. Further treatment options are welcomed to improve survival and allow a choice of treatment. Patients mentioned prolonged survival as a key expected benefit of new therapies. A reduction in side effects was also considered important, as well as limited impact on quality of life, which should ideally be enhanced. Oral administration was seen as an advantage over the intravenous treatments that are currently available.

As mainly older patients and patients with comorbidities tend to be those who cannot tolerate chemotherapy or newer targeted agents, these are also the patients who have the fewest treatment options. As there is a clear unmet need for patients not suitable for intensive chemotherapy regimens, new therapeutic alternatives should be available as soon as possible so that these patients are not left behind.

6 DISCUSSION

6.1 Question and scope

Venetoclax in combination with a HMA is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

For patients with AML who are ineligible for intensive chemotherapy, European guidelines recommend low-intensity treatment options such as a HMA (e.g., azacitidine or decitabine monotherapy) and LDAC monotherapy or BSC. Glasdegib in combination with LDAC is another therapy that has recently received market authorisation for this indication. The patient organisations stated that oral administration of venetoclax is seen as an advantage over the IV treatments that are currently available.

The prognosis for elderly patients (>60 years), who are not able to tolerate intensive chemotherapy and who account for the majority of new AML cases, remains poor (3).

No strict consensus is established for a definition of ineligibility for intensive chemotherapy. The assessment of eligibility for intensive or nonintensive chemotherapy is complex and in clinical practice is based on patient-specific risk–benefit analyses (5). A definition of unfitness for intensive chemotherapy is given in the Ferrara criteria (56) and a modification of these criteria was used in the studies with venetoclax in AML.

6.2 Information retrieval

Information retrieval performed by the MAH was in accordance with EUnetHTA requirements. The studies identified were included in the final study pool according to criteria specified in the EUnetHTA PICO. There were some minor deviations from the PICO. Rather strict criteria were used to identify relevant comparator studies for ITCs; that is, only RCTs were included and studies with only one arm of interest were excluded. The choice of inclusion criteria by the MAH may have contributed to the conclusion that ITCs are not feasible.

This assessment is mainly based on the evidence from the phase 3 study investigating venetoclax + azacitidine versus azacitidine alone, with some support from the phase 1b dose-finding M14-358 study. This study also investigated the efficacy and safety of venetoclax among relevant subgroups that included venetoclax at the approved dose in combination with azacitidine or decitabine.

6.3 Design and conduct of clinical studies: efficacy and safety data

6.3.1 Results from direct evidence: VIALE-A study

The combination of venetoclax and azacitidine was superior to azacitidine alone, with an improvement in OS of 5.1 months observed (HR 0.662, 95% CI 0.518–0.845; p<0.001). Results from different sensitivity analyses for OS, including censoring OS at the start of poststudy treatment before OS events, were consistent with the primary analyses.

The study is still ongoing and the results from the final OS analyses are not yet reported. The median duration of follow-up was 20.5 months and the analyses based on the data cutoff of 4th January 2020 are still considered immature lending uncertainty to the long-term OS that will be achieved with venetoclax combined with a HMA in clinical practice.

A composite complete remission (CR + CRi) rate of 66.4% was achieved in the venetoclax + azacitidine arm compared to 28.3% in the placebo + azacitidine arm.

Only two patients in the venetoclax + azacitidine arm and one in the placebo+ azacitidine arm proceeded to transplant; thus, the OS data reported are considered to be unaffected by subsequent stem cell transplants. However, in real-life practice a higher proportion of a subset of patients (< 75 years) ineligible for intensive chemotherapy could become more fit and eligible for reduced intensity conditionting and allo-HSCT after achieving remission on venetoclax and azacitidine.

The analyses showed a consistent survival benefit for subjects in the venetoclax + azacitidine arm in most of the subgroups analysed. For patients with *IDH1* or *IDH2* mutations at baseline, an improved hazard ratio compared to the overall population was observed, with OS at 12 months of 66.8% in the venetoclax + azacitidine arm, compared to 35.7% in the control group (HR 0.345, 95% CI 0.20–0.60; p<0.001). This finding is consistent with the incidence of composite complete remission (CR + CRi) in this subgroup, which was 75.4% in the venetoclax + azacitidine arm and 10.7% in the control arm (p<0.001). The reliability of the subgroup analyses is somewhat hampered by the limited number of patients.

Venetoclax in combination with azacitidine improved the percentage of subjects who achieved postbaseline transfusion independence for both RBC and platelets versus azacitidine alone (58.0% vs. 33.8%).

Patient and disease characteristics, including the stratification factors, were in general well balanced between treatment arms. The study was double-blinded and the intention-to-treat population included all 431 patients who underwent randomisation. The proportions of patients who discontinued the study because of withdrawal of consent or who were lost to follow-up were low in both treatment arms (<3%).

The risk of bias for the primary endpoint of OS and complete composite remission rates and the secondary outcome of transfusion independence is considered low, and the certainty of this evidence according to GRADE is considered moderate.

PRO data collected via different HRQoL instruments were reported for VIALE-A. For the PROMIS fatigue scores and the EORTC QLQ-C30 GHS score, no clinically meaningful differences in the mean change from baseline were observed between the treatment arms. For TTD as an outcome, the results seem to support a trend for longer TTD for EORTC QLQ-C30 GHS as a measure and significantly longer TTD for EQ-5D-5L VAS for patients receiving venetoclax + azacitidine in comparison to azacitidine monotherapy. Overall, no additional deterioration in HRQoL was observed when adding venetoclax to azacitidine. Interpretation of the PRO data reported is hampered by the small number of patients still reporting beyond early treatment cycles. Furthermore, since a higher proportion of the patients in the control arm did not complete the PRO follow-up assessments, this may contribute to an attrition bias for the results reported. The certainty of the evidence according to GRADE is thus considered low.

All patients in VIALE-A experienced AEs, with comparable rates between the treatment arms of grade ≥3 AEs, deaths due to AEs and treatment discontinuations. Haematologic AEs (overall and grade ≥3) as well as infections and infestations were more frequent in the venetoclax + azacitidine group than in the placebo + azacitidine group. The incidence of SAE was approximately 10% higher in the venetoclax + azacitidine arm than in the placebo + azacitidine arm; febrile neutropenia, pneumonia and sepsis were the most common SAEs in the treatment groups. Although the incidence of deaths due to AEs was similar in the two arms, the frequency of venetoclax-related AEs was slightly higher than the frequency of placebo-related AEs. The 30-day mortality rate was similar in the two arms.

6.3.2 Results from the supportive phase 1b study (M14-358)

M14-358 was a phase 1b nonrandomised study and only descriptive statistics were used. A total of 84 subjects received venetoclax 400 mg + azacitidine, and only 31 subjects received venetoclax 400 mg + decitabine. The composite complete remission (CR + CRi) rate was 74.2% in the venetoclax + decitabine group and 71.4% in the venetoclax + azacitidine group, which is in line with the remission rate achieved with venetoclax + azacitidine in VIALE-A. Some differences between the study population in the phase 1b study and VIALE-A were observed, including a lower proportion of patients fulfilling the modified Ferrara criteria for ineligibility to intensive chemotherapy, hampering a comparison of outcomes across these studies.

Similar efficacy and safety profiles for azacitidine and decitabine in combination with venetoclax were expected owing to their similar mechanisms of action, and this is also supported by the literature. The combination of venetoclax + decitabine was also considered approvable by the EMA on these grounds (29).

6.4 Potential NMA and ITCs

In order to answer the defined PICO, the Authoring Team submitted a request for ITCs. Relevant ITC were submitted only for venetoclax in combination with azacitidine versus LDAC. Other relevant comparisons (direct or indirect) of venetoclax in combination with azacitidine versus other comparators of interest (e.g., BSC and glasdegib in combination with LDAC) were not submitted by the MAH although it was requested as missing item during formal check of completeness of the submission dossier.

- The MAH assessed the feasibility of conducting anchored ITCs of venetoclax combinations versus other relevant comparators such as BSC, LDAC and glasdegib + LDAC. The MAH stated that there are considerable differences between trials in potentially effect-modifying patient characteristics and concluded that the central similarity assumption for valid ITCs is ultimately violated.
- The MAH identified several relevant comparator studies that could be connected in a study network. The authoring team do not support the conclusion of the feasibility assessment performed by the MAH stating that the ITC analyses could not be performed. In the authors opinion, it would be of value to actually perform the potential comparisons and based on the outputs in the analysis assess the robustness (i.e. bias and direction of bias). For the comparison with glasdegib + LDAC (BRIGHT-AML population) population-adjusted methods could be applied in which differences in patient populations are to a certain degree adjusted for. If these analysis are conducted and submitted at a national level, the appropriateness of the methods should be thoroughly assessed.
- The MAH performed a propensity score weighting (PSW) analysis for indirect comparison of venetoclax + azacitidine versus LDAC based on individual patient data from VIALE-A (venetoclax + azacitidine arm) and VIALE-C (LDAC arm). The results indicate that venetoclax + azacitidine is associated with responses and time-to-event outcomes that are generally well above those reported for LDAC. The potential differences in safety profiles for comparison of these regimens are not analysed and inferences on the comparability of safety are not possible. Studies with an LDAC arm other than VIALE-C were not included in ITCs with venetoclax + azacitidine and the size of the relative efficacy estimate between the two interventions might not be generalisable.
- Since relevant comparisons (direct or indirect) are not submitted for venetoclax in combination with azacitidine versus certain comparators of interest (e.g., BSC and glasdegib in combination with LDAC) this is considered an evidence gap.

Overall, the documents submitted by the MAH are considered quite comprehensive and include complete CSRs from VIALE-A and the supportive study M14-358, a report on the systematic literature search, and protocols and reports on the feasibility assessments for NMA and the ITC performed versus LDAC. Limited PRO data from VIALE-A were submitted in the core submission dossier and additional data were extracted from the CSR by the Authoring Team. There were also some other issues with incomplete data in the core submission dossier (study design, efficacy and safety data, and statistical analyses for VIALE-A) and to meet the required completeness of the data, the CSR submitted was used by the Authoring Team as the primary data source.

7 CONCLUSION

A single double-blind phase 3 study (VIALE-A) constitutes the primary source of evidence, in which median OS was 14.7 months in the venetoclax + azacitidine arm compared to 9.6 months in the placebo + azacitidine arm. The combination of venetoclax + azacitidine was superior to azacitidine alone, with an improvement in OS of 5.1 months observed (HR 0.662, 95% CI 0.518, 0.845; p<0.001).

The safety profile of azacitidine + venetoclax is consistent with the known profiles of both agents and with expectations for an older AML population. Haematologic AEs (overall and grade ≥3) as well as infections and infestations were more frequent among subjects who received venetoclax + azacitidine than in the control arm. The SAE incidence was approximately 10% higher in the venetoclax + azacitidine arm than in the control arm; febrile neutropenia, pneumonia and sepsis were the most common SAEs in the treatment groups.

The certainty of the evidence reported for OS and safety according to GRADE is considered moderate.

PRO data from different HRQoL instruments were collected and overall no additional deterioration in HRQoL was observed when adding venetoclax to azacitidine. The certainty of the PRO data according to GRADE is considered low owing to the small number of patients still reporting beyond early treatment cycles and possible attrition bias.

Patients mentioned prolonged survival as a key expected benefit of new therapies. Reduction of side effects was also considered important, as well as limited impact on quality of life, which should ideally be enhanced.

Direct comparisons are not available for other treatment alternatives (i.e., glasdegib + LDAC, BSC or LDAC). The only indirect comparisons submitted by the MAH included a comparison of venetoclax + azacitidine versus LDAC. No firm conclusion on the comparative effectiveness versus LDAC can be drawn, although the results indicate that venetoclax + azacitidine is associated with responses and time-to event outcomes that are generally well above those reported for LDAC. Potential differences in the safety profiles in comparison to the regimens that are considered relevant were not analysed and inferences regarding the comparability of safety are not possible. No conclusion on the comparative effectiveness of venetoclax + azacitidine versus glasdegib + LDAC or BSC can be drawn.

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APPENDIX 1: GUIDELINES FOR DIAGNOSIS AND MANAGEMENT

Table A1. Overview of clinical guidelines used for this assessment

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
ESMO	March 2020	Europe	HMAs azacytidine and decitabine are currently the first choice in newly diagnosed unfit AML patients (combined with venetoclax if available). LDAC is an alternative to HMAs in first line treatment of AML patients who are ineligible for standard induction chemotherapy, except in patients with adverse-risk cytogenetics.	IIb IIIa IIb
ELN	January 2017	Europe	***Treatment option for AML patients who are not candidates for intensive chemotherapy:*** • Azacytidine • Decitabine • LDAC (not recommended in patients with adverse-risk genetics) Strong recommendation to enrol these patients in clinical trials. ***Patients who cannot tolerate or do not wish to receive any antileukemic therapy*** • Best supportive care, including hydroxyurea Strong recommendation to enrol these patients in clinical trials.	/ /

Source: (5, 8)
Abbreviations: AML=acute myeloid leukemia; ELN=European LeukemiaNet; ESMO=European Society for medical Oncology; HMA=hypomethylating agent; LDAC=low -dose cytarabine.

Table A2. Overview of cytogenetic and molecular risk stratification tools used in VIALE-A, supportive studies and comparator studies

Genetic risk group	ELN 2010 (BRIGHT-AML-1003)	NCCN 2009 (AZA-AML-001)	SWOG 2000 (DACO-016)	NCCN 2014 (M14-358,)	NCCN 2016 (VIALE C, VIALE A)[a]
Favourable/better	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Mutated *CEBPA* (normal karyotype)	t(15;17) with/without secondary aberrations; t(8;21) lacking del(9q) or complex karyotypes inv(16)/t(16;16)/del(16q)	t(8;21) inv(16) t(16;16) Normal cytogenetics with isolated *NPM1* mutation	inv(16) or t(16;16) t(8;21) t(15;17) Normal cytogenetics: *NPM1* mutation in absence of *FLT3*-ITD or isolated biallelic CEBPA mutation	Core binding factor: inv(16) or t(16;16) or t(8;21) t(15;17)
Intermediate	*Intermediate I* Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype) *Intermediate II* t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse	Normal +8 +6 -Y del(12p)	Normal +8 only, t(9;11) only Other abnormalities not listed with better risk and poor risk cytogenetics and molecular mutations C-KIT in patients with t(8;21) or inv(16)	Normal cytogenetics +8 alone T(9;11) Other non-defined t(8;21), inv(16), t(16;16): with c-KIT mutation	Normal cytogenetics +8 alone t(9;11) Other non-defined
Adverse/Poor/ Unfavourable	-5 or del(5q) -7 abnl(17p) inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *MLL* rearranged complex karyotype (≥ 3 abnormalities)	-5/ del(5q) -7/ del(7q) abn 3q, 9q, 11q, 20q, 21q, 17p, t(6;9), t(9;22) complex karyotypes (≥ 3 unrelated abn)	-5/ 5q- -7/ 7q- Abnormalities of 11q23, excluding t(9;11) Inv(3) or t(3;3) t(6;9) t(9;22) complex karyotypes (≥ 3 abnormalities) Normal cytogenetics with isolated *FLT3*-ITD mutations	Complex (≥ 3 clonal chromosomal abnormalities) Monosomal karyotype -5,5q-,-7,7q- 11q23-non t(9;11) inv(3),t(3;3) t(6;9) t(9;22) Normal cytogenetics: with *FLT3*-ITD mutation	Complex (≥ 3 clonal chromosomal abnormalities) Monosomal karyotype -5,5q-,-7,7q- 11q23-non t(9;11) inv(3),t(3;3) t(6;9) t(9;22)
Unknown	-	All other abnormalities	-		

[a] Only cytogenetic markers were evaluated in VIALE-C.
Source: (14, 58, 68-70)
Abbreviations: p=short arm of the chromosome; q=long arm of the chromosome; t(A;B)=used to denote a translocation between chromosome A and chromosome B.

APPENDIX 2: CERTAINTY OF EVIDENCE

Table A3. GRADE - Venetoclax + azacitidine compared to azacitidine + placebo for adult patients with newly-diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy (VIALE-A)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Venetoclax + azacitidine	azacitidine + placebo	Relative (95% CI)	Absolute (95% CI)		
Overall survival (follow up: median 20.5 months; assessed with: Time from date of randomization to death from any cause)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	286 participants -	145 participants 0.0%	**HR 0.66** (0.52 to 0.85) [Overall survival]	**– per 1 000** (from – to –) **– per 1 000** (from – to –)	⨁⨁⨁◯ MODERATE	
Composite Complete remission rate: CR + Cri (assessed with: CR: Absolute neutrophil count > 103/µL, platelets > 105/µL, RBC transfusion independence, and bone marrow with < 5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease. CRi:Il criteria as CR except for residual neutropenia ≤ 103/µL (1000/µL) or thrombocytopenia ≤ 105/µL (100,000/µL). RBC transfusion dependence is also defined as CRi.)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	190/286 (66.4%)	41/145 (28.3%)			⨁⨁⨁◯ MODERATE	
Transfusion independency (assessed with: The post-baseline transfusion independence was defined as a period of at least 56 days with no RBC or platelet transfusion during the evaluation period)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	166/286 (58.0%)	49/145 (33.8%)			⨁⨁⨁◯ MODERATE	
Health related quality of life (assessed with: Time to Deterioration (TTD) in the EORTC-QLQ-C30/Global Health Status)												
1	randomised trials	serious [b]	not serious	not serious	serious [a]	none	262 participants -	130 participants 0.0%	**HR 0.81** (0.55 to 1.18)	**– per 1 000** (from – to –) **– per 1 000** (from – to –)	⨁⨁◯◯ LOW	
Serious adverse events (follow up: mean 1 months; assessed with: Number of patients experiencing serious adverse events)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Venetoclax + azacitidine	azacitidine + placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [a]	none	235/283 (83.0%)	105/144 (72.9%)	**RR 1.14** (1.02 to 1.27)	**102 more per 1 000** (from 15 more to 197 more)	⨁⨁⨁◯ MODERATE	
Grade > 3 adverse events (follow up: mean 1 months)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	279/283 (98.6%)	139/144 (96.5%)	**RR 1.02** (0.99 to 1.06)	**19 more per 1 000** (from 10 fewer to 58 more)	⨁⨁⨁◯ MODERATE	
Treatment discontinuations due to AE (follow up: mean 1 months)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	69/283 (24.4%)	29/144 (20.1%)	**RR 1.21** (0.82 to 1.78)	**42 more per 1 000** (from 40 more to 124 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Only one study and/or wide confidence interval

b. Risk of bias due to different attrition rates in treatment vs control group

Table A4. RoB VIALE A

Study reference/ID Viale A. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. New England Journal of Medicine. 2020;383(7):617-29.	Description	Risk of bias judgement
Random sequence generation (selection bias)	The description of how the random sequence was generated is unclear in the article: ""We randomly assigned previously untreated patients with confirmed…". However, judged by other sources a centralized system for computer random number generation seems to have been used: P 66 CSR "Randomization and Subject (Screening) Number Assignment: Interactive Response Technology (IRT) will be utilized to register (screen and randomize) subjects on study. The site will contact the IRT to obtain a screening (subject) number only after the subject has signed the informed consent and prior to any study-specific procedures being performed (e.g. labs are drawn). Screening numbers will be a unique 5 – digit number and will begin with 10001 with the first three digits representing the investigative site, and the last two digits representing the subjects at that site. Subjects who meet all Inclusion Criteria and none of the Exclusion Criteria after Screening will proceed to being randomized. The site will contact the IRT to complete the randomization process and obtain study drug assignment. Subjects will be enrolled as described in Section 5.5.3 and will receive a separate unique 6-digit randomization number that will be automatically recorded in the eCRF through the IRT system. This randomization number will be used only by AbbVie for loading the treatment schedule into the database. Study treatment should start within 5 days after randomization."	**Low**
Allocation concealment (selection bias)	Central allocation, see above	**Low**
Blinding of participants and personnel (performance bias)	DiNardo 2020: "phase 3, multicenter, randomized, double-blind, placebo-controlled trial" S 70 CSR "This study was conducted in a double-blind fashion. All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Clinical Drug Supply Management and AbbVie Pharmacovigilance Team), the investigator, the study site personnel, and the subject remained blinded to each subject's treatment	**Low**

	with venetoclax/placebo and azacitidine throughout the course of the study."	
Blinding of outcome assessment (detection bias) For self-reported outcomes including pain, function and global assessment	Health-related quality of life: Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken: DiNardo 2020: "…double-blind…", see blinding of participants, above	**Low**
Blinding of outcome assessment (detection bias) For outcome assessor reported outcomes	Also, for other outcomes blinding of outcome assessment were ensured, and outcomes were objectively measured: • Overall survival • Transfusion independency • Composite Complete remission rate: CR + CRi • Serious AE • Grade > 3 adverse events • Treatment discontinuations due to AE	**Low**
Incomplete outcome data addressed (attrition bias)	fchmp	**Low** **High**
Selective reporting (reporting bias)	The study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.	**Low**
Other potential sources of bias	No other potential sources of bias detected, e.g. baseline demographic and clinical characteristics of the patients were generally similar (Table 1 in DiNardo 2020).	**Low**

APPENDIX 3: EVIDENCE GAPS

Table A5. Recommendations for research

Additional evidence generation needs	
Research question 1: **The aim of this EUnetHTA Joint REA of venetoclax + azacitidine is to compare the clinical effectivenes and safety of venetoclax + azacitidine for adult patients with newly-diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy with relevant comparators according to European PICO**	
Evidence	Only one RCT phase 3 study with direct evidence was identified for venetoclax in combination with azacitidine versus azacitidine alone i.e. VIALE-A. The combination of venetoclax + decitabine was approved in Europe based on limited data from the supportive study M14-358 and known similar mechanism of action and safety profile of the two HMA's. The evidence level for critical outcomes defined in the PICO was assessed as moderate for all except for health related quality of life where the evidence was rated as low. Ideally further RCT studies would be required to support exisiting evidence. RWD may be used for safety information. No studies with direct comparison of venetoclax + azacitidine vs. identified alternative therapies (glasdegib + LDAC, decitabine, LDAC or BSC) are available. Some relevant comparator studies were identified and could be connected in a network. Indirect comparision was not submitted by the MAH since they concluded that the clinical studies identified were not suitable as a basis for indirect comparisons. In the submitted ITC of venetoclax + azacitidine vs LDAC only efficacy outcomes were included (OS, EFS, CR+CRi). The potential differences in the safety profiles comparing these to regimens, are not analysed and inferences on comparability of safety cannot be drawn.
Population	Treatment naïve subjects with AML ≥18 years of age and not eligible for standard induction therapy due to age, poor health status or comorbidities.
Intervention	Venetoclax (400 mg orally once daily [QD]) in combination with hypomethylating agents (HMAs; azacitidine or decitabine)
Comparator	Azacitidine * Decitabine * Low-dose cytarabin (LDAC) Glasdegib in combination with LDAC Best Supportive Care (*national differences exists, may include: hydroxyurea, 6-mercaptopurine, 6-thyoguanine, low dose melphalan, transfusion support, anti-infective therapies etc.)*
Outcome(s)	OS, CR, Transfusion independency, HRQoL, safety: SAE, AE, discontinuation rate
Time stamp	June 2021
Study design	RCT blinded and powered to show differences, proper indirect evidence or register studies (RWE)
Ongoing studies	No studies with relevant comparators were idenfied. Several studies in AML with venetoclax in combination with new substances are ongoing. An efficacy and safety study of venetoclax and azacitidine in AML patients not eligible for induction therapy (INNOVATE) is recruting patients in Russia. NCT-04253314

**) Supplementary RCT including these comparators should ideally have been available*

APPENDIX 4: COMPARATOR AND SUPPORTIVE STUDIES

Table A6. Key Characteristics of the relevant studies

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
VIALE-A M15-656 (NCT02993523)	To compare the efficacy and safety of venetoclax plus AZA to placebo + AZA in previously untreated AML patients ineligible for intensive chemotherapy due to medical comorbidities and/or were ≥75 years old	Phase 3, randomized, double-blind, placebo-controlled, multicentre	Key inclusion criteria: Patients aged ≥18 years with previously untreated AML confirmed by WHO criteria. Patients must be considered ineligible for treatment with a standard cytarabine and anthracycline induction regimen due age or comorbidities as defined by the following: • ≥75 years of age; **or** • ≥18 to 74 years of age with at least one of the following comorbidities: – ECOG PS 2 or 3 – Cardiac history of CHF requiring treatment or ejection fraction ≤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 – Any other comorbidity that was physician judged to be incompatible with intensive chemotherapy. Patients must have a projected life expectancy of at least 12 weeks. Patients must have an ECOG PS:	• Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3 until Day 28; subsequent 28-day cycles at 400 mg plus • AZA 75 mg/m^2, SC or IV, on days 1–7 every 28-day cycle (N = 286) versus • Placebo QD plus • AZA 75 mg/m^2, SC or IV, on days 1–7 every 28-day cycle (N = 145)	Dual primary endpoint: OS (months) All patients were followed for survival information (date/cause of death) every 2 months after the last study visit or as needed until the end of the study. Composite CR rate (CR + CR with incomplete hematologic recovery; CR + CRi) Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a CR or CRi. Disease assessments were performed with the use of the modified	• CR rate • CR + CRh rate • Proportion of patients achieving composite CR by initiation of cycle 2 • Rates of RBC and platelet transfusion independence • CR rates and OS in molecular and cytogenetic subgroups • EFS • MRD response rate • HRQL • Safety Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a CR or CRi. Disease assessments were performed with the use of the modified International Working Group response criteria for AML. Patients were followed for safety and tolerability from the first dose of study drug until 30 days after the last dose of study drug.

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			• 0 to 2 for patients ≥75 years; **or** • 0 to 3 for patients ≥18 to 74 years. Patients must have adequate renal function as demonstrated by a creatinine clearance ≥30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-h urine collection. Patients must have adequate liver function as demonstrated by: • AST ≤3.0 × ULN* • ALT ≤3.0 × ULN* • bilirubin ≤1.5 × ULN* *Unless considered due to leukemic organ involvement. • Patients who are <75 years may have a bilirubin of ≤3.0 × ULN. Key exclusion criteria: Prior receipt of any hypomethylating agent, venetoclax, or chemotherapy for myelodysplastic syndrome. Patients with favourable cytogenetic risk as per the AML NCCN Guidelines.		International Working Group response criteria for AML.	PRO assessments were collected on or within 3 days prior to Cycle 1 Day 1 and then on Day 1 of every other cycle throughout the trial, including the Final Visit.
M14-358 (NCT02203773) *Supportive study*	To evaluate the safety and pharmacokinetics of orally administered venetoclax combined with DEC or AZA and the preliminary efficacy of these combinations	Phase 1b, open-label, non-randomized, multicentre study	Key inclusion criteria: • Confirmed AML by WHO criteria • Ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to comorbidity or other factors • Received no prior treatment for AML with the exception of hydroxyurea	Dose escalation: (n=45) • Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, until maximum dose is reached (400, 800, or 1,200 mg); max dose until D28; subsequent 28-day	Primary endpoints dose expansion: : • CR • CRi • CRh • OS Determined by the number of subjects who achieve a CR/CRi.	• ORR （CR + CRi + partial response) • DOR

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			• ECOG PS of 2 for subjects ≥75 years of age, or 0 to 3 for subjects ≥60 to 74 years of age • Adequate kidney and liver function as described in the protocol Key exclusion criteria: • Received treatment with an HMA and/or chemo therapeutic agent for an antecedent hematologic disorder • History of Myeloproliferative Neoplasm • Favourable risk cytogenetics as categorized by the NCCN Guidelines Version 2, 2014 for AML • t(8;21), inv(16), t(16;16) or t(15;17) karyotype abnormalities • Acute promyelocytic leukaemia. • Active CNS involvement with AML Received a strong and/or moderate CYP3A inducer within 7 days prior to the initiation of study treatment	cycles at 400 mg or 800 mg or 1,200 mg plus • AZA (75 mg/m^2, days 1–7, IV or subcutaneously) or • DEC (20 mg/m^2, days 1–5, IV) Expansion: (n=155) • Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, (600 mg Day 4, 800 mg Day 5) until Day 28; subsequent 28-day cycles at 400 mg or 800 mg plus • AZA 75 mg/m^2, SC or IV, on days 1–7 every 28-day cycle or • DEC (20 mg/m^2, days 1–5, IV) All treated patients (N = 200) • Venetoclax 400 mg (N = 115; 84 with AZA, 31 with • DEC)	Reponses were evaluated per the International Working Group criteria for AML. Time frame: Measured up to 1 year after the last subject last dose. Primary endpoint dose escalation -Safety -Pharmacokinetics: • AUC from 0 to the time of the last measurable concentration • AUC from 0 to the time of the last measurable concentration. • Half-life • Cmax • Maximum observed concentration, occurring at Tmax. • Clearance defined as the rate at which	

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
				• Venetoclax 800 mg (N = 74; 37 each AZA or DEC) • Venetoclax 1,200 mg (N = 11; 6 AZA, 5 DEC)	drug is cleared from the blood. • AUC over a 24-hour dose interval. • Time to Cmax • AUC from 0 to infinity Time frame: For approximately 5 days following a single dose of venetoclax OS: Defined as the number of days from the date of enrolment to the date of death. Time frame: Measured up to 1 year after the last subject last dose	
VIALE-C M16-043 (NCT03069352) *Supportive study*	To compare the efficacy and safety of venetoclax + LDAC to placebo + LDAC in previously untreated AML patients ineligible for intensive chemotherapy due to medical comorbidities	Phase 3, randomized, double-blind, placebo-controlled, multicentre	Key inclusion criteria: Patients aged ≥18 years with previously untreated AML confirmed by WHO criteria. Patients must be considered ineligible for treatment with a standard cytarabine and anthracycline induction regimen due age or comorbidities as defined by the following: • ≥75 years of age; **or**	• Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, 600 mg Day 4 until D28; subsequent 28-day cycles at 600 mg plus • LDAC 20 mg/m^2 SC on days 1–10 in	OS (months) All patients were followed for survival information (date/cause of death) every 2 months after the last study visit or as needed until the end of the study.	• CR rate • CR + CRi rate • CR + CRh rate • Proportion of patients with CR/CRi and CR/CRh by the initiation of therapy cycle 2 • Rate of transfusion independence • EFS • MRD response rate

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
	and/or were ≥75 years old		• ≥18 to 74 years of age with at least one of the following comorbidities: – ECOG PS 2 or 3 – Cardiac history of CHF requiring treatment or ejection fraction ≤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 – Any other comorbidity that was physician judged to be incompatible with intensive chemotherapy. Patients must have a projected life expectancy of at least 12 weeks. Patients must have an ECOG PS: • 0 to 2 for patients ≥75 years; **or** • 0 to 3 for patients ≥18 to 74 years. Patients must have adequate renal function as demonstrated by a creatinine clearance ≥30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-h urine collection. Patients must have adequate liver function as demonstrated by: • AST ≤3.0 × ULN* • ALT ≤3.0 × ULN* • bilirubin ≤1.5 × ULN*	every 28-day cycle (N = 143) versus • Placebo QD plus • LDAC 20 mg/m^2 SC on days 1–10 in every 28-day cycle (N = 68)		• CR rates and OS in molecular and cytogenetic subgroups • HRQL • Safety Disease assessments were performed at end of Cycle 1 (±3 days) and every 3 cycles starting on Cycle 4 Day 1 and continuing until disease progression as defined per ELN criteria or withdrawn consent. Patients were followed for safety and tolerability from the first dose of study drug until 30 days after the last dose of study drug. PRO assessments were collected on or within 3 days prior to Cycle 1 Day 1 and then on Day 1 of every other cycle throughout the trial, including the Final Visit.

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			*Unless considered due to leukemic organ involvement. • Patients who are <75 years may have a bilirubin of ≤3.0 × ULN. Key exclusion criteria: • Prior receipt of treatment for AML, except hydroxyurea (allowed through the first cycle of study treatment). • Prior treatment for myelodysplastic syndrome is allowed except for use of cytarabine. • Had an antecedent MPN including myelofibrosis, essential thrombocytosis, polycythaemia vera, or CML with or without BCR-ABL 1 translocation and AML with BCR-ABL 1 translocation. • Have acute promyelocytic leukaemia • Has known CNS involvement with AML • Has received strong or moderate cytochrome P450 3A4 inducers 7 days prior to the initiation of study treatment. • Patients with cardiovascular disability, chronic respiratory disease or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, history of other malignancies, any other			

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			medical condition or known hypersensitivity to any of the study medications including excipients of LDAC. • Previous treatment with venetoclax and/or current participation in any other research study with investigational products.			
AZA-AML-001 (NCT01074047)	To evaluate the efficacy and safety of AZA compared with conventional care regimens (doctor's choice of BSC only, LDAC, or standard intensive chemotherapy) in patients age ≥65 years with newly diagnosed AML and >30 % BM blasts	Phase 3, open-label, international, multicentre, randomized	Key inclusion criteria: • Aged ≥65 years with newly diagnosed, histologically confirmed de novo or secondary AML with >30 % BM blasts who were not considered eligible for hematopoietic stem cell transplantation • intermediate- or poor-risk cytogenetics (NCCN 2009 criteria) • ECOG PS ≤2 • WBC count ≤15 × 10^9/L Key exclusion criteria: • Acute promyelocytic leukaemia t(15;17)(q22;q12) and AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(8;21)(q22;q22), or t(9;22)(q34;q11.2) • AML arising from previous hematologic disorders other than MDS (e.g., myeloproliferative neoplasms) • Other malignancies • Uncontrolled systemic infection • Prior DEC, AZA, or cytarabine treatment	Treatment phase: Patients were randomly assigned (1:1) to receive AZA or conventional care regimen. AZA: N = 241 • preselected for BSC: N = 44 • preselected for LDAC: N = 154 • preselected for intensive chemotherapy: N = 43 Conventional care regimen: N = 247 • BSC: N = 45 • LDAC: N = 158 • IC: N = 44	OS (months), defined as time from randomization to death as result from any cause.	Secondary outcomes: • estimated 1 year survival rate • OS in patient subgroups defined by baseline demographic and disease characteristics: age, gender, race, geographic region, ECOG PS, baseline cytogenetic risk, WHO classification of AML, WBC count, BM blasts, and prior history of MDS.

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			• Prior AML therapy (except hydroxyurea, which was allowed up to 2 weeks before the screening haematology sample was taken) • Any experimental drug within 4 weeks of starting study treatment			
AZA-001 (NCT00071799)	To evaluate the efficacy and safety of AZA compared with conventional care regimens (doctor's choice of BSC only, LDAC, or standard IC) in patients age ≥65 years with newly diagnosed AML and ≥20 % BM blasts or peripheral blasts based on central BM review (i.e., with FAB-defined RAEB-t and WHO-defined AML).	Phase 3, international, multicentre, randomized, controlled, parallel-group, open-label trial	Key inclusion criteria: • Aged ≥18 years • Patients with ≥20% BM or peripheral blasts based on central BM review (i.e., with FAB-defined RAEB-t and WHO-defined AML) • ECOG PS 0–2 • estimated life expectancy of ≥3 months Key exclusion criteria: • Patients with therapy-related myelodysplastic syndrome, previous AZA treatment, or planned allogeneic stem-cell transplantation	Treatment phase: Patients were randomly assigned (1:1) to receive AZA or conventional care regimen. AZA: N = 55 • preselected for BSC: N = 36 • preselected for LDAC: N = 14 • preselected for IC: N = 5 Conventional care regimen: N = 58 • BSC: N = 27 • LDAC: N = 20 • IC: N = 11	OS, analysed by comparison of the AZA and combined conventional care groups. OS was defined as time from random assignment until death from any cause.	Secondary outcomes: • Morphologic CR assessed according to International Working Group AML response criteria • Transfusion independence defined as absence of RBC or platelet transfusions during 56 consecutive days • AEs (assessed using National Cancer Institute Common Toxicity Criteria, version 2.0), rate of fever requiring intravenous antibiotics, and hospitalisation rates and duration
DACO-016 (NCT00260832)	To compare the efficacy and safety of DEC with patient choice, with physician advice (BSC or LDAC)	Phase 3, open-label, international, multicentre, randomized	Key inclusion criteria: • Aged ≥65 years with newly diagnosed, histologically confirmed de novo or secondary AML (≥20 % blasts) and poor- or intermediate-risk cytogenetics	Treatment phase: Patients were randomly assigned (1:1) to receive DEC or treatment choice. • DEC: N = 242	OS (months), defined as time from randomization to death as result from any cause.	Secondary outcomes: • CR • CRp • Remission (evaluated by using modified 2003 IWG criteria) • CRi

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
	in older patients with AML		(Southwest Oncology Group categorization) • ECOG PS of 0 to 2 • WBC count ≤40,000/mm • Bilirubin ≤1.5 × ULN • AST or ALT ≤2.5 × ULN • Creatinine clearance ≥40 mL/min • Life expectancy ≥12 weeks Key exclusion criteria: • Acute promyelocytic leukaemia • t(8;21) or inv(16) karyotype abnormalities • CNS leukaemia • Active systemic malignancies • Unstable angina or New York Heart Association class 3/4 congestive heart failure • Inaspirable BM, comorbidities or organ dysfunction • Uncontrolled active infection, or HIV • Previous chemotherapy (except hydroxyurea) for any myeloid disorder or used experimental drugs for 4 weeks pre-randomization • Candidates for BM or stem-cell transplantation for 12 weeks before randomization • Received radiotherapy for extramedullary disease for 2 weeks pre-randomization	• treatment choice: N = 243 • BSC: N = 28 • LDAC: N = 215 Follow-up: Patients were followed monthly for 2 years post-randomization and then every 2 months for 3 years for OS and PD until death or loss to follow-Up.		• AEs
BRIGHT-AML 1003 (NCT01546038)	To evaluate the efficacy and safety of glasdegib plus	Phase 2, randomized, open-label, multicentre	Key inclusion criteria: • Aged ≥55 years with newly diagnosed, previously untreated	Treatment phase: • Glasdegib (100 mg once daily orally in 28-day cycles on a	OS (months), defined as duration from the date of randomization to	Secondary outcomes: • CR, defined as those with repeat BM showing ≤5 % myeloblasts,

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
	LDAC versus LDAC in patients with AML or high-risk MDS who were not eligible for intensive chemotherapy		AML according to the WHO 2008 Classification. • Known cytogenetic profile at study entry and considered not suitable for intensive chemotherapy, defined by ≥1 of the following criteria: – Age ≥75 years – Serum creatinine >1.3 mg/dL – Severe cardiac disease (e.g., left ventricular ejection fraction <45 % by multi-gated acquisition or echocardiography at screening) – ECOG PS = 2; patients with ECOG PS = 0 or 1 who met ≥1 other inclusion criteria listed above were also eligible Key exclusion criteria: • Acute promyelocytic leukaemia, • t(9;22) cytogenetic translocation • Active other malignancy • Known active uncontrolled leukaemia of the CNS • Prior treatment with Hedgehog inhibitor or other investigational agent for the treatment of an antecedent hematologic disease	continuous basis) + LDAC (20 mg SC twice daily for 10 days every 28 days) (N = 78) • LDAC (20 mg SC twice daily for 10 days every 28 days) alone (N = 38) Follow-up period: patients were followed up for post-treatment survival status for 4 years from randomization.	the date of death from any cause.	peripheral blood showing neutrophils ≥1,000/all, platelets ≥100,000/µL, 0 % blast and haemoglobin ≥11 g/dL, normal maturation of all cell lines. • Disease specific efficacy endpoints such as CRi, MLFS, PR, PRi, MR, SD, CRc, CRm • Type, incidence, severity (graded by the NCI CTCAE, Version 4.0), timing, seriousness, and relatedness of AEs. Additional outcomes: • Transfusion need: Independence from transfusion is presented in terms of absolute and relative frequencies

Source: Table adapted from Submission Dossier (22)

Table A7. Summary of baseline patient demographics and clinical characteristics – VIALE-A, supportive and comparator studies

Study name	Treatment	N of patients randomized	Age (year), median (range)	Sex (male), n (%)	ECOG/WHO PS 0/1, n (%)	ECOG/WHO PS 2, n (%)	Primary/ de novo AML, n (%)	Secondary AML, n (%)
VIALE-A	VEN + AZA	286	76 (49, 91)	172 (60)	157 (55%)	113 (40%)	214 (75%)	72 (25%)
	Placebo + AZA	145	76 (60, 90)	87 (60%)	81 (56%)	59 (41%)	110 (76%)	35 (24%)
M14-358	VEN + AZA	22	75 (65, 82)	11 (50)	18 (82)	4 (18)	16 (73)	6 (27)
	VEN + DEC	23	74 (68, 85)	9 (39)	19 (86)	4 (17)	20 (87)	3 (13)
VIALE-C	VEN+ LDAC	143	76 (36, 93)	78 (55%)	74 (52%)	63 (44%)	85 (59%)	58 (41%)
	Placebo + LDAC	68	76 (41, 88)	39 (57%)	34 (50%)	25 (37%)	45 (66%)	23 (34%)
AZA-AML-001	**AZA, combined**	241	75.0 (64, 91)	139 (58%)	186 (77%)	55 (22%)	NR	NR
	CCR, combined	247	75.0 (65, 89)	149 (60%)	189 (77%)	58 (23%)	NR	NR
	AZA, preselected BSC	44	NR	NR	NR	NR	NR	NR
	CCR, preselected BSC	45	78.0 (67, 89)	29 (64%)	30 (67%)	15 (33%)	NR	NR
	AZA, preselected LDAC[b]	154	76.0 (64, 90)	NR	NR	NR	NR	NR
	CCR, preselected LDAC	158	75.0 (65, 88)	94 (60%)	123 (78%)	35 (22%)	NR	NR
	AZA, preselected IC	43	NR	NR	NR	NR	NR	NR
	CCR, preselected IC	44	70.5 (65, 81)	26 (59%)	36 (82%)	8 (18%)	NR	NR
AZA-001	**AZA, combined**	55	70 (52, 80)	37 (67%)	51 (93%)	4 (7%)	NR	NR
	CCR, combined	58	70 (50, 83)	41 (71%)	56 (97%)	0 (0%)	NR	NR
	AZA, preselected BSC	36	70 (52, 80)	21 (58%)	32 (89%)	4 (11%)	NR	NR
	CCR, preselected BSC	27	70 (56, 81)	16 (59%)	26 (96%)	0 (0.0%)	NR	NR
	AZA, preselected LDAC	14	69 (55, 78)	13 (93%)	14 (100%)	0 (0.0%)	NR	NR
	CCR, preselected LDAC	20	71 (56, 83)	15 (75%)	19 (95%)	0 (0.0%)	NR	NR
	AZA, preselected IC	5	63 (53, 78)	3 (60%)	5 (100%)	0 (0.0%)	NR	NR

Study name	Treatment	N of patients randomized	Age (year), median (range)	Sex (male), n (%)	ECOG/WHO PS 0/1, n (%)	ECOG/WHO PS 2, n (%)	Primary/ de novo AML, n (%)	Secondary AML, n (%)
	CCR, preselected IC	11	65 (50, 76)	10 (91%)	11 (100%)	0 (0.0%)	NR	NR
DACO-016	**DEC 5d**	242	73 (64, 89)	137 (57%)	184 (76%)	58 (24%)	155 (64%)	87 (36%)
	TC	243	73 (64, 91)	151 (62%)	183 (75%)	60 (25%)	157 (65%)	84 (35%)
	TC, LDAC	215	73 (64, 91)	131 (61%)	164 (76%)	51 (24%)	140 (65%)	73 (34%)
	TC, SC	28	75 (66, 86)	20 (71%)	19 (68%)	9 (32%)	17 (61%)	11 (39%)
BRIGHT-AML 1003[a]	GLAS + LDAC	77	77 (64, 92)	59 (77%)	35 (46%)	41 (53%)	38 (49%)	39 (51%)
	LDAC	38	76 (58, 83)	23 (61%)	20 (53%)	18 (47%)	18 (47%)	20 (53%)

Source: Table adapted from Core Submission Dossier (22) Table 7.5
[a] Baseline data were reported in the FDA DAURISMO (glasdegib) label.
[b] Baseline data for AZA, preselected LDAC group, were reported in Seymour 2015 (secondary publication)
Abbreviations: AML=acute myeloid leukaemia; AZA=azacitidine; BSC=best supportive care; CCR=conventional care regimens; DEC=decitabine; ECOG=Eastern Cooperative Oncology Group; GLAS=glasdegib; IC=intensive chemotherapy; LDAC=low-dose cytarabine; NR=not reported; PS=performance status; SC=supportive care; TC=treatment choice; VEN=venetoclax; WHO=World Health Organization.

Table A8. Summary of baseline patient demographics and clinical characteristics for VIALE-A, supportive and comparator studies (cont.)

Study name	Treatment	N of patients randomized	Cytogenetic risk		WBC, 10^9/L, median (range)	Platelets, 10^9/L, median (range)	BM blasts (%), median (range)	BM blasts <30%, n (%)	BM blasts ≥30 to <50%, n (%)	BM blasts ≥50%, n (%)
			Intermediate/ good, n (%)	Poor, n (%)						
VIALE-A	VEN + AZA	286	182 (63.6%)	104 (36.4%)	NR	NR	47.0 (4.4, 100.0)	85 (29.7%)	61 (21.3%)	140 (49.0%)
	Placebo + AZA	145	89 (61.4%)	56 (38.6%)	NR	NR	47.0 (11.0, 99.0)	41 (28.3%)	33 (22.8%)	71 (49.0%)
M14-358	VEN + AZA	143	12 (55%)	10 (45%)	NR	NR	NR	6 (27%)	9 (41%)	7 (32%)
	VEN + DEC	68	15 (65%)	8 (35%)	NR	NR	NR	5 (22%)	7 (30%)	11 (48%)
VIALE-C	VEN + LDAC	143	91 (63.6%)	47 (32.9%)	NR	NR	NR	42 (29.4%)	36 (25.2%)	65 (45.5%)
	Placebo + LDAC	68	46 (67.6%)	20 (29.4%)	NR	NR	NR	18 (26.5%)	22 (32.4%)	28 (41.2%)
	AZA, combined	241	155 (64.3%)	85 (35.3%)	3.1 (0.0, 33.0)	52 (3, 585)	70.0 (2.0, 100.0)	NR	NR	173 (71.8%)

Study name	Treatment	N of patients randomized	Cytogenetic risk		WBC, 10^9/L, median (range)	Platelets, 10^9/L, median (range)	BM blasts (%), median (range)	BM blasts <30%, n (%)	BM blasts ≥30 to <50%, n (%)	BM blasts ≥50%, n (%)
			Intermediate/ good, n (%)	Poor, n (%)						
AZA-AML-001	**CCR, combined**	247	160 (64.8%)	85 (34.4%)	2.3 (0.0, 90.0)	56 (6, 327)	72.0 (2.0, 100.0)	NR	NR	193 (78.1%)
	AZA, preselected BSC	44	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected BSC	45	29 (64.4%)	16 (35.6%)	2.3 (1.0, 23.0)	52 (7, 161)	76.0 (9.0, 100.0)	NR	NR	36 (80.0%)
	AZA, preselected LDAC[b]	154	NR	NR	NR	NR	70.0 (2.0, 100.0)	NR	NR	NR
	CCR, preselected LDAC	158	104 (65.8%)	54 (34.2%)	2.3 (0.0, 73.0)	54 (6, 327)	74.0 (4.0, 100.0)	NR	NR	128 (81.0%)
	AZA, preselected IC	43	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected IC	44	27 (61.4%)	15 (34.1%)	2.2 (1.0, 90.0)	62 (9, 273)	70.0 (6.0, 100.0)	NR	NR	29 (65.9%)
AZA-001	**AZA, combined**	55	38 (69.1%)	14 (25.5%)	NR	NR	23.0 (20.0, 34.0)	NR	NR	NR
	CCR, combined	58	43 (74.1%)	13 (22.4%)	NR	NR	23.1 (13.0, 68.9)	NR	NR	NR
	AZA, preselected BSC	36	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected BSC	27	19 (70.4%)	8 (29.6%)	NR	NR	22.5 (13.0, 29.2)	NR	NR	NR
	AZA, preselected LDAC	14	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected LDAC	20	18 (90.0%)	1 (5.0%)	NR	NR	22.0 (20.0, 28.0)	NR	NR	NR
	AZA, preselected IC	5	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected IC	11	6 (54.5%)	4 (36.4%)	NR	NR	27.0 (21.0, 68.9)	NR	NR	NR
DACO-016	**DEC 5d**	242	152 (62.8%)	87 (36.0%)	3.1 (0.3, 127.0)	58 (6, 487)	NR	65 (26.9%)	67 (27.7%)	105 (43.4%)
	TC	243	154 (63.4%)	87 (35.8%)	3.7 (0.5, 80.9)	50 (6, 490)	NR	58 (23.9%)	74 (30.5%)	101 (41.6%)
	TC, LDAC	215	134 (62.3%)	79 (36.7%)	3.7 (0.5, 80.9)	NR	NR	53 (24.7%)	64 (29.8%)	90 (41.9%)

Study name	Treatment	N of patients randomized	Cytogenetic risk		WBC, 10^9/L, median (range)	Platelets, 10^9/L, median (range)	BM blasts (%), median (range)	BM blasts <30%, n (%)	BM blasts ≥30 to <50%, n (%)	BM blasts ≥50%, n (%)
			Intermediate/ good, n (%)	Poor, n (%)						
	TC, SC	28	20 (71.4%)	8 (28.6%)	2.7 (0.7, 26.5)	NR	NR	5 (17.9%)	10 (35.7%)	11 (39.3%)
BRIGHT-AML 1003[a]	GLAS + LDAC	77	48 (62.3%)	29 (37.7%)	NR	NR	NR	NR	NR	NR
	LDAC	38	21 (55.3%)	17 (44.7%)	NR	NR	NR	NR	NR	NR

Source: Table adapted from Core Submission Dossier (22) Table 7.6
[a] Baseline data were reported in the FDA DAURISMO (glasdegib) label.
[b] Baseline data for AZA, preselected LDAC group, were reported in Seymour 2015 (secondary publication).
Abbreviations: AML=acute myeloid leukaemia; AZA=azacitidine; BM=bone marrow; BSC=best supportive care; CCR=conventional care regimens; DEC=decitabine; GLAS=glasdegib; IC=intensive chemotherapy; LDAC=low-dose cytarabine; NR=not reported; SC=supportive care; TC=treatment choice; VEN=venetoclax; WBC=white blood cell.

Table A9. Overall survival for AML patients - comparator studies

Study name	Treatment	Sample size	Overall Survival (OS)		
			Median, months (95% CI)	Hazard ratio (95% CI)	Survival rates
VIALE C	VEN+LDAC	143	7.2 (5.6, 10.1)	0.75 (0.52, 1.07)	55.4%;6 months
	LDAC	68	4.1 (3.1, 8.8)		35.5%;12 months
BRIGHT AML 1003[a1-6]	GLAS + LDAC	78	8.3 (4.7, 12.2)	0.53 (0.35, 0.80)	59.7%; 6 months 28.2%; 20 months
	LDAC	38	4.3 (1.9, 5.7)	NA	33.4%; 6 months; 7.9%; 20 months
DACO 016 [7,8]	DEC 5d	242	7.7 (6.2, 9.2)	0.82 (0.68, 0.99)	NR
	TC	243	5.0 (4.3, 6.3)	NA	NR
AZA-001[10]	AZA - combined	55	24.5 (14.6, NR)	0.47 (0.28, 0.79)	50.2%; 2-year
	CCR - combined	58	16.0 (11.5, 17.5)	NA	15.9%; 2-year
	AZA - preselected BSC	36	19.1 (11.2, NR)	0.48 (0.24, 0.94)	46.3%; 2-year
	CCR - BSC	27	13.4 (5.2, 17.5)	NA	0.0%; 2-year
	AZA - preselected LDAC	14	24.5 (18.4, NR)	0.37 (0.12, 1.13)	56.3%; 2-year
	CCR - LDAC	20	17.0 (14.5, 25.8)	NA	31.8%, 2-year
	AZA - preselected IC	5	NR (2.7, NR)	0.97 (0.19, 5.10)	60.0%; 2-year
	CCR - IC	11	14.2 (10.8, 24.1)	NA	25.0%; 2-year
AZA-AML-001[11-14]	AZA - combined	241	10.4 (8.0, 12.7)	0.85 (0.69, 1.03)[b]	46.5%; 1-year
	CCR - combined	247	6.5 (5.0, 8.6)	NA	34.2%; 1-year
	AZA - preselected BSC	44	5.8 (3.6, 9.7)	0.60 (0.38, 0.95)	30.3%; 1-year
	CCR - preselected BSC	45	3.7 (2.8, 5.7)	NA	18.6%; 1-year
	AZA - preselected LDAC	154	11.2 (8.8, 13.4)	0.90 (0.70, 1.16)	48.5%; 1-year
	CCR - preselected LDAC	158	6.4 (4.8, 9.1)	NA	34.0%; 1-year
	AZA - preselected IC	43	13.3 (7.2, 19.9)	0.85 (0.52, 1.38)	55.8%; 1-year
	CCR - preselected IC	44	12.2 (7.5, 15.1)	NA	50.9%; 1-year

Source: Adapated from Core Submission Dossier (22) Table 7.18 and Appendix 8 Table 8.5

[a]Median OS was reported in Heuser 2020a (data cut: March 2019). 6-month OS was reported in Zeidan 2019 (data cut: October 11, 2018) and 20-month OS was reported in Kwon 2019 (data cut: January, 2017).

[b]When adjusted for use of subsequent AML therapy as a time-dependent variable, AZA improved OS compared with CCRs (HR, 0.75; 95% CI, 0.59-0.94; P= .0130).

Abbreviations: AML=acute myeloid leukaemia; AZA=azacitidine; BSC=best supportive care; CCR=conventional care regimens; DEC=decitabine; GLAS=glasdegib; IC=intensive chemotherapy; LDAC=low-dose cytarabine; NR=not reported; TC=treatment choice; VEN=venetoclax;

Table A10. Key efficacy outcomes VIALE-C

Outcome	Venetoclax + LDAC n = 143	Placebo + LDAC n = 68	VEN + LDAC vs LDAC HR (95% CI)	P value
Median OS (95% CI) – primary analysis *	7.2 months (5.6, 10.1)	4.1 months (3.1, 8.8)	0.75 (0.52, 1.07)	0.114
Median OS (95% CI) Post–hoc 6 months follow-up analyses of OS **	8.4 months (5.9, 10.1)	4.1 months (3.1, 8.1)	0.70 (0.50, 0.99)	0.041
CR, % patients (95% CI)	28 (21, 36)	7 (2, 16)	NA	<0.001
Composite CR (CR + CRi), % patients (95% CI) – primary analysis	48 (39, 56)	13 (6, 24)	NA	<0.001
Composite CR (CR + CRi), % patients (95% CI)	48 (40, 57)	13 (6, 24)	NA	<0.001
CR + CRh, % patients (95% CI)	48 (40, 57)	15 (7, 25)	NA	<0.001
Transfusion independence % patients (95% CI)				
RBC	43 (35, 52)	19 (11, 31)	NA	<0.001
Platelets	49 (41, 57)	32 (22, 45)	NA	0.026
Median EFS (95% CI)	4.9 months (3.7, 6.4)	2.1 months (1.5, 3.2)	0.61 (0.44, 0.84)	0.003

* Data cut-off 2nd April 2019

** Data cut-off 18th October 2019

Source: Table adapted from Sumbission Dossier (22) Table 7.18

Table A11. Overview of safety outcomes in supportive and comparator studies

Study name	Treatment	Sample size	Overall AE, n (%)	Grade ≥3, n (%)	Grade 3 or 4, n (%)	SAEs, n (%)	Deaths due to AEs, n (%)	Treatment discountinuation due to AE, n (%)
Supportive studies								
VIALE C [6-7]	VEN + LDAC	142	141 (99.3%)	138 (97.2%)	135 (95.1%)	93 (65.5%)	33 (23%)	36 (25.4%)
	Placebo + LDAC	68	67 (98.5%)	65 (95.6%)	63 (92.6%)	42 (61.8%)	14 (21%)	16 (23.5%)
M14-358 [8-9]	VEN + AZA	84	84 (100%)	82 (98%)	82 (98%)	65 (77%)	13 (15.5%)	21 (25%)
	VEN + DEC	31	31 (100%)	31 (100%)	31 (100%)	25 (81%)	6 (19.4%)	8 (26%)
Comparator studies								
BRIGHT AML 1003[a 4]	GLAS + LDAC	75	75 (100.0%)	69 (92.0%)	NR	59 (78.7%)	22 (29.3%)	23 (30.7%)
	LDAC	36	36 (100.0%)	35 (97.2%)	NR	28 (77.8%)	16 (44.4%)	17 (47.2%)
DACO-016[b] [5]	DEC	238	NR (≥ 97%)	NR	221 (92.9%)	190 (80.0%)	58 (24.4%)	14 (6%)[d]
	TC - combined	237		NR	204 (86.1%)	162 (68.0%)	NR	NR
	TC – LDAC	208	NR	NR	188 (90.4%)	150 (72.0%)	39 (18.8%)	17 (8%)[d]
	TC – SC	29	NR	NR	16 (55.2%)	12 (41.0%)	NR	NR
AZA-AML-001[c1-2]	AZA	236	234 (99.2%)	NR	207 (87.7%)	188 (79.7%)	56 (23.2%)[e]	110 (46.6%)
	CCR – combined	235	235 (100.0%)	NR	204 (88.1%)	175 (74.5%)	71 (29.8%) [e]	79 (33.6%)
AZA-001[3]	AZA	53	NR	NR	NR	NR	NR	4 (7.3%)
	CCR – combined	53	NR	NR	NR	NR	NR	3 (5.2%)

Source:[1-2](33, 41), [3](49), [4](67), [5](34), [6-7](54, 55), [8-9](53, 64)
[a] TEAE are presented for the study period.
[b] AEs are reported, except for AEs leading to treatment discontinuation w here drug-related AEs were reported. The results for 2009 cutoff are presented.
[c] Treatment-emergent AEs defined as new or w orsening AEs between the time of first dose (or randomization for BSC only) to the end of the safety follow-up period were reported. Safety population comprised 471 patients (AZA 236; CCR 235); 5 patients randomly assigned to AZA and 7 patients randomly assigned to CCR did not receive study treatment, and 5 patients in the CCR arm had no post-dose safety assessment.
[d] Drug-related AEs leading to treatment discountination w ere reported.
[e] On-treatment deaths are presented and are defined as deaths that occurred from the date of first dose of study drug through 28 days after the date of last dose of azacitidine and low-dose cytarabine, or from the date of first dose of study drug through 70 days after the date of last dose of intensive chemotherapy, or from the date of randomization through the date of treatment period discontinuation for best supportive care only. The deaths due to adverse events have been calculated in 241 subjects in azacytidine arm and 247 in CCR arm.
Abbreviations: AE=adverse event; AML=acute myeloid leukaemia; AZA=azacitidine; CCR=conventional care regimens; DEC=decitabine; GLAS=glasdegib; LDAC=low-dose cytarabine; NR=not reported; SAE=serious adverse event; SC=supportive care; TC=treatment choice; VEN=venetoclax.

Safety reported in comparator trials

BRIGHT-AML-1003

In the glasdegib + LDAC arm, the median treatment duration was 83 (3 - 972) days vs. 41 (6 – 239) days for the LDAC alone arm. Considering the entire study period, the most frequent AEs of any grade occurring in ≥ 20 % of patients were gastrointestinal disorders (77 % vs. 67 %), general disorders and administration site conditions (76 % vs. 67 %), and blood and lymphatic system disorders (71 % vs. 64 %). Regarding the AEs commonly expected for antileukaemic treatments, no relevant differences between glasdegib + LDAC and LDAC alone occurred during the entire study period (febrile neutropenia (35 % vs. 25 %), haemorrhage (48 % vs. 50 %), QT prolongation (20 % vs. 11 %), and infections including pneumonia (61 % vs. 56 %) as well as for the first 90 days of therapy. Considering the entire study period, the most frequently reported SAEs that occurred in ≥ 2 % of patients were pneumonia (21 % vs. 19 %), sepsis (4 % vs. 14 %), febrile neutropenia (28 % vs. 17 %), anaemia (7 % vs. 0), pancytopenia (0 % vs. 6 %) and disease progression (9 % vs. 11 %). During the same period, the most common AEs leading to treatment discontinuation in ≥ 2 % of patients comprised pneumonia (5 % vs. 3 %), sepsis (1 % vs. 6 %), and febrile neutropenia (3 % vs. 6 %) (67).

AZA-AML-001

Among the most frequent TEAEs in the azacitidine, LDAC, and IC groups, respectively, were pyrexia (37.7%, 39.9%, and 54.8%), nausea (39.8%, 28.1%, and 57.1%), constipation (41.9%, 27.5%, and 38.1%), febrile neutropenia (32.2%, 33.3%, and 40.5%), and diarrhea (36.9%, 22.9%, and 50.0%) (41). Grades 3 and 4 TEAEs occurring in azacitidine, BSC, LDAC or IC group were febrile neutropenia (28.0%, 27.5%, 30.1% and 31.0%, respectively), neutropenia (26.3%, 5.0%, 24.8% and 33.3%, respectively), thrombocytopenia (23.7%, 5.0%, 27.5% and 21.4%, respectively), pneumonia (19.1%, 5.0%, 19.0% and 4.8%, respectively) and anaemia (15.7%, 5.0%, 22.9% and 14.3%, respectively). The most frequent serious TEAEs were present with similar frequency in the azacitidine, LDAC, and IC arms and included febrile neutropenia (25.0%, 24.8%, and 24.3%, respectively), pneumonia (20.3%, 19.0%, and 14.9%), and pyrexia (10.6%, 10.5%, and 8.9%) (33).A 30-day mortality rates in the azacitidine and CCR arms were 6.6% and 10.1%, respectively. Drug-related TEAEs leading to study discontinuation occurred in 22 patients (9.3%) in the azacitidine arm, 20 patients (13.1%) in the LDAC arm, and 5 patients (11.9%) in the IC arm (33).

AZA-001

In total, 106 patients were included in the safety data analysis with 53 patients in azacitidine arm and 53 patient in CCR arm, consisting of BSC (n=25 (47%)), LDAC (n=18 (34%)), or intensive chemotherapy (n=10 (19%)). The most common grade 3 or 4 hematologic adverse events (determined by laboratory values) in azacitidine vs. CCR group were thrombocytopenia (90.8% vs 83.0%), neutropenia (94.3% vs 83.0%), and anaemia (56.6% vs 67.9%) (49).

DACO-016

Safety analysis was performed in 238 patients in decitabine arm and 237 patients in treatment-choice (TC) arm (receiving supportive care (SC) or cytarabine). Exposure to study medication was greater with decitabine (median, 4.4 months) than with TC (2.4 months with cytarabine) resulting in longer AE reporting period in decitabine arm (34).The most common grade 3 and 4 treatment-emergent AEs with decitabine and TC were thrombocytopenia (decitabine, 40%; cytarabine, 35%; SC, 14%) and anaemia (decitabine, 34%; cytarabine, 27%; SC, 14%. The most common serious AEs were febrile neutropenia (decitabine, 24%; cytarabine, 16%; SC, 0%), pneumonia (decitabine, 20%; cytarabine, 16%; SC, 10%), and disease progrssion (decitabine, 11%; cytarabine, 14%; SC, 7%). Within 30 days after the first treatment, 21 decitabine recipients (9%) and 17 cytarabine recipients (8%) died (34).

APPENDIX 5: DETAILS OF SAFETY VIALE-A

A summary of treatment-emerged adverse events and Grade ≥ 3 treatment-emerged adverse events for VIALE-A by system organ class (occurring in ≥5% patients overall for treatment-emerged AEs and/or occurring in ≥2% patients overall for Grade ≥ 3 treatment-emerged AEs) is given in Table A12.

Table A12. Summary of treatment-emerged adverse events and Grade ≥ 3 treatment-emerged adverse events for VIALE-A by system organ class

Study VIALE-A								
System organ class/ adverse events	All grades [a]				Grades ≥ 3 [a]			
	Ven+AZA (n = 283) n (%)	PBO+AZA (n = 144) n (%)	Relative risk (95% CI)	Risk difference (95% CI)	Ven+AZA (n = 283) n (%)	PBO+AZA (n = 144) n (%)	RR (95 % CI)	RD (95 % CI)
Overall AEs; n (%)	283 (100)	144 (100)	NA	NA	279 (98.6)	139 (96.5)	-	-
Blood and lymphatic system disorders								
All PT	236 (83.4)	100 (69.4)	1.20 (1.06, 1.35)	13.95 (5.26, 22.63)	233 (82.3)	98 (68.1)	-	-
Thrombocytopenia	130 (45.9)	58 (40.3)	1.14 (0.90, 1.44)	5.66 (-4.23, 15.55)	126 (44.5)	55 (38.2)	-	-
Neutropenia	119 (42.0)	42 (29.2)	1.44 (1.08, 1.92)	12.88 (3.49, 22.27)	119 (42.0)	41 (28.5)	-	-
Febrile neutropenia	118 (41.7)	27 (18.8)	2.22 (1.54, 3.21)	22.95 (14.36, 31.53)	118 (41.7)	27 (18.8)	-	-
Anaemia	78 (27.6)	30 (20.8)	1.32 (0.91, 1.92)	6.73 (-1.70, 15.16)	74 (26.1)	29 (20.1)	-	-
Leukopenia	58 (20.5)	20 (13.9)	1.48 (0.93, 2.35)	6.61 (-0.74, 13.96)	58 (20.5)	17 (11.8)	-	-
Cardiac disorders								
All PT	88 (31.1)	37 (25.7)	1.21 (0.87, 1.68)	5.40 (-3.54, 14.35)	44 (15.5)	20 (13.9)	-	-
Atrial fibrillation	33 (11.7)	15 (10.4)	1.12 (0.63, 1.99)	1.24 (-4.99, 7.48)	17 (6.0)	3 (2.1)	-	-
Cardiac failure	15 (5.3)	5 (3.5)	1.53 (0.57, 4.12)	1.83 (-2.14, 5.80)	9 (3.2)	5 (3.5)	-	-
Ear and labyrinth disorders								
All PT	25 (8.8)	5 (3.5)	2.54 (0.99, 6.51)	5.36 (0.90, 9.82)	1 (0.4)	0	-	-
Eye disorders								
All PT	29 (10.2)	15 (10.4)	0.98 (0.55, 1.77)	-0.17 (-6.28, 5.94)	2 (0.7)	1 (0.7)	-	-
Gastrointestinal disorders								
All PT	241 (85.2)	112 (77.8)	1.09 (0.99, 1.21)	7.38 (-0.57, 15.34)	42 (14.8)	17 (11.8)	-	-

Study VIALE-A								
System organ class/ adverse events	**All grades [a]**				**Grades ≥ 3 [a]**			
	Ven+AZA (n = 283) n (%)	**PBO+AZA (n = 144) n (%)**	**Relative risk (95% CI)**	**Risk difference (95% CI)**	**Ven+AZA (n = 283) n (%)**	**PBO+AZA (n = 144) n (%)**	**RR (95 % CI)**	**RD (95 % CI)**
Nausea	124 (43.8)	50 (34.7)	1.26 (0.97, 1.64)	9.09 (-0.60, 18.78)	5 (1.8)	1 (0.7)	-	-
Constipation	121 (42.8)	56 (38.9)	1.10 (0.86, 1.40)	3.87 (-5.96, 13.70)	2 (0.7)	2 (1.4)	-	-
Diarrhoea	117 (41.3)	48 (33.3)	1.24 (0.95, 1.62)	8.01 (-1.59, 17.61)	13 (4.6)	4 (2.8)	-	-
Vomiting	84 (29.7)	33 (22.9)	1.30 (0.91, 1.84)	6.77 (-1.92, 15.45)	6 (2.1)	1 (0.7)	-	-
Stomatitis	33 (11.7)	8 (5.6)	2.10 (1.00, 4.43)	6.11 (0.82, 11.39)	2 (0.7)	0	-	-
Abdominal pain	31 (11.0)	12 (8.3)	1.31 (0.70, 2.48)	2.62 (-3.18, 8.42)	NR	NR	-	-
Haemorrhoids	28 (9.9)	7 (4.9)	2.04 (0.91, 4.55)	5.03 (0.09, 9.98)	2 (0.7)	1 (0.7)	-	-
Dyspepsia	19 (6.7)	8 (5.6)	1.21 (0.54, 2.69)	1.16 (-3.59, 5.90)	1 (0.4)	0	-	-
General disorders and administration site conditions								
All PT	195 (68.9)	95 (66.0)	1.04 (0.91, 1.20)	2.93 (-6.50, 12.36)	38 (13.4)	22 (15.3)	-	-
Oedema peripheral	69 (24.4)	26 (18.1)	1.35 (0.90, 2.02)	6.33 (-1.70, 14.36)	1 (0.4)	0	-	-
Pyrexia	66 (23.3)	32 (22.2)	1.05 (0.72, 1.52)	1.10 (-7.29, 9.49)	5 (1.8)	2 (1.4)	-	-
Fatigue	59 (20.8)	24 (16.7)	1.25 (0.81, 1.92)	4.18 (-3.53, 11.89)	8 (2.8)	2 (1.4)	-	-
Asthenia	44 (15.5)	12 (8.3)	1.87 (1.02, 3.42)	7.21 (1.03, 13.40)	11 (3.9)	1 (0.7)	-	-
Injection site erythema	17 (6.0)	10 (6.9)	0.87 (0.41, 1.84)	-0.94 (-5.93, 4.05)	NR	NR	-	-
Injection site reaction	13 (4.6)	10 (6.9)	0.66 (0.30, 1.47)	-2.35 (-7.17, 2.46)	0	2 (1.4)	-	-
Hepatobiliary disorders								
All PT	35 (12.4)	6 (4.2)	2.97 (1.28, 6.89)	8.20 (3.16, 13.24)	10 (3.5)	1 (0.7)	-	-
Infections and infestations								

Study VIALE-A								
System organ class/ adverse events	**All grades [a]**				**Grades ≥ 3 [a]**			
	Ven+AZA (n = 283) n (%)	**PBO+AZA (n = 144) n (%)**	**Relative risk (95% CI)**	**Risk difference (95% CI)**	**Ven+AZA (n = 283) n (%)**	**PBO+AZA (n = 144) n (%)**	**RR (95 % CI)**	**RD (95 % CI)**
All PT	239 (84.5)	97 (67.4)	1.25 (1.11, 1.42)	17.09 (8.35, 25.84)	180 (63.6)	74 (51.4)	-	-
Pneumonia	65 (23.0)	39 (27.1)	0.85 (0.60, 1.19)	-4.12 (-12.87, 4.64)	56 (19.8)	36 (25.0)	-	-
Upper respiratory tract infection	26 (9.2)	13 (9.0)	1.02 (0.54, 1.92)	0.16 (-5.61, 5.92)	5 (1.8)	2 (1.4)	-	-
Urinary tract infection	26 (9.2)	11 (7.6)	1.20 (0.61, 2.36)	1.55 (-3.94, 7.04)	11 (3.9)	8 (5.6)	-	-
Lung infection	19 (6.7)	4 (2.8)	2.42 (0.84, 6.97)	3.94 (-0.03, 7.90)	14 (4.9)	3 (2.1)	-	-
Sepsis	18 (6.4)	13 (9.0)	0.70 (0.36, 1.40)	-2.67 (-8.14, 2.81)	17 (6.0)	13 (9.0)	-	-
Oral herpes	17 (6.0)	6 (4.2)	1.44 (0.58, 3.58)	1.84 (-2.44, 6.12)	2 (0.7)	0	-	-
Cellulitis	16 (5.7)	8 (5.6)	1.02 (0.45, 2.32)	0.10 (-4.51, 4.71)	8 (2.8)	3 (2.1)	-	-
Oral candidiasis	16 (5.7)	5 (3.5)	1.63 (0.61, 4.36)	2.18 (-1.84, 6.20)	1 (0.4)	1 (0.7)	-	-
Escherichia sepsis	8 (2.8)	3 (2.1)	-	-	8 (2.8)	3 (2.1)	-	-
Septic shock	8 (2.8)	2 (1.4)	-	-	8 (2.8)	2 (1.4)	-	-
Influenza	13 (4.6)	6 (4.2)	1.10 (0.43, 2.84)	0.43 (-3.65, 4.50)	7 (2.5)	2 (1.4)	-	-
Injury, poisoning and procedural complications								
All PT	83 (29.3)	42 (29.2)	1.01 (0.74, 1.37)	0.16 (-8.96, 9.29)	15 (5.3)	9 (6.3)	-	-
Fall	28 (9.9)	10 (6.9)	1.42 (0.71, 2.85)	2.95 (-2.47, 8.37)	2 (0.7)	3 (2.1)	-	-
Contusion	10 (3.5)	12 (8.3)	0.42 (0.19, 0.96)	-4.80 (-9.80, 0.20)	NR	NR	-	-
Investigations								
All PT	136 (48.1)	56 (38.9)	1.24 (0.97, 1.57)	9.17 (-0.70, 19.03)	58 (20.5)	13 (9.0)	-	-
Weight decreased	37 (13.1)	14 (9.7)	1.34 (0.75, 2.41)	3.35 (-2.88, 9.58)	4 (1.4)	2 (1.4)	-	-
Alanine aminotransferase increased	21 (7.4)	12 (8.3)	0.89 (0.45, 1.76)	-0.91 (-6.36, 4.54)	4 (1.4)	5 (3.5)	-	-

Study VIALE-A								
System organ class/ adverse events	All grades [a]				Grades ≥ 3 [a]			
	Ven+AZA (n = 283) n (%)	PBO+AZA (n = 144) n (%)	Relative risk (95% CI)	Risk difference (95% CI)	Ven+AZA (n = 283) n (%)	PBO+AZA (n = 144) n (%)	RR (95 % CI)	RD (95 % CI)
Aspartate aminotransferase increased	21 (7.4)	13 (9.0)	0.82 (0.42, 1.59)	-1.61 (-7.20, 3.98)	6 (2.1)	3 (2.1)	-	-
Blood bilirubin increased	21 (7.4)	5 (3.5)	2.14 (0.82, 5.55)	3.95 (-0.33, 8.22)	5 (1.8)	0	-	-
C-reactive protein increased	17 (6.0)	5 (3.5)	1.73 (0.65, 4.59)	2.53 (-1.54, 6.61)	4 (1.4)	1 (0.7)	-	-
Blood creatinine increased	14 (4.9)	8 (5.6)	0.89 (0.38, 2.07)	-0.61 (-5.12, 3.91)	3 (1.1)	0	-	-
Platelet count decreased	13 (4.6)	1 (0.7)	6.61 (0.87, 50.07)-	3.90 (1.11, 6.69)-	9 (3.2)	0	-	-
White blood cell count decreased	11 (3.9)	2 (1.4)	2.8 (0.63, 12.46)	2.50 (-0.46, 5.45)	9 (3.2)	1 (0.7)	-	-
Metabolism and nutrition disorders								
All PT	175 (61.8)	79 (54.9)	1.13 (0.95, 1.34)	6.98 (-2.93, 16.88)	78 (27.6)	39 (27.1)	-	-
Hypokalaemia	81 (28.6)	41 (28.5)	1.01 (0.73, 1.38)	0.15 (-8.91, 9.21)	30 (10.6)	15 (10.4)	-	-
Decreased appetite	72 (25.4)	25 (17.4)	1.47 (0.97, 2.20)	8.08 (0.08, 16.08)	12 (4.2)	1 (0.7)	-	-
Hypophosphataemia	35 (12.4)	17 (11.8)	1.05 (0.61, 1.80)	0.56 (-5.96, 7.08)	21 (7.4)	11 (7.6)	-	-
Hypoalbuminaemia	22 (7.8)	13 (9.0)	0.86 (0.45, 1.66)	-1.25 (-6.88, 4.37)	6 (2.1)	2 (1.4)	-	-
Hypomagnesaemia	21 (7.4)	5 (3.5)	2.14 (0.82, 5.55)	3.95 (-0.33, 8.22)	NR	NR	-	-
Hypocalcaemia	17 (6.0)	8 (5.6)	1.08 (0.48, 2.45)	0.45 (-4.20, 5.11)	4 (1.4)	2 (1.4)	-	-
Hyponatraemia	16 (5.7)	7 (4.9)	1.16 (0.49, 2.76)	0.79 (-3.63, 5.22)	8 (2.8)	5 (3.5)	-	-
Musculoskeletal and connective tissue disorders								
All PT	110 (38.9)	50 (34.7)	1.12 (0.86, 1.46)	4.15 (-5.48, 13.78)	13 (4.6)	3 (2.1)	-	-
Arthralgia	33 (11.7)	7 (4.9)	2.40 (1.09, 5.29)	6.80 (1.67, 11.93)	1 (0.4)	0	-	-
Back pain	24 (8.5)	13 (9.0)	0.94 (0.49, 1.79)	-0.55 (-6.24, 5.15)	3 (1.1)	1 (0.7)	-	-

Study VIALE-A								
System organ class/ adverse events	**All grades [a]**				**Grades ≥ 3 [a]**			
	Ven+AZA (n = 283) n (%)	**PBO+AZA (n = 144) n (%)**	**Relative risk (95% CI)**	**Risk difference (95% CI)**	**Ven+AZA (n = 283) n (%)**	**PBO+AZA (n = 144) n (%)**	**RR (95 % CI)**	**RD (95 % CI)**
Pain in extremity	22 (7.8)	14 (9.7)	0.80 (0.42, 1.52)	-1.95 (-7.71, 3.81)	2 (0.7)	0	-	-
Musculoskeletal pain	18 (6.4)	5 (3.5)	1.83 (0.69, 4.83)	2.89 (-1.24, 7.01)	NR	NR	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
All PT	18 (6.4)	9 (6.3)	1.02 (0.47, 2.21)	0.11 (-4.76, 4.98)	8 (2.8)	8 (5.6)	-	-
Malignant neoplasm progression	4 (1.4)	6 (4.2)	0.34 (0.10, 1.18)	-2,75 (-6.29, 0.79)	4 (1.4)	6 (4.2)	-	-
Nervous system disorders								
All PT	107 (37.8)	39 (27.1)	1.40 (1.03, 1.90)	10.73 (1.53, 19.92)	31 (11.0)	8 (5.6)	-	-
Dizziness	37 (13.1)	10 (6.9)	1.88 (0.96, 3.68)	6.13 (0.41, 11.85)	1 (0.4)	1 (0.7)	-	-
Headache	30 (10.6)	10 (6.9)	1.53 (0.77, 3.03)	3.66 (-1.83, 9.14)	1 (0.4)	1 (0.7)	-	-
Syncope	11 (3.5)	1 (0.7)	-	-	8 (2.8)	1 (0.7)	-	-
Psychiatric disorders								
All PT	71 (25.1)	37 (25.7)	0.98 (0.69, 1.38)	-0.61 (-9.35, 8.14)	7 (2.5)	6 (4.2)	-	-
Insomnia	35 (12.4)	15 (10.4)	1.19 (0.67, 2.10)	1.95 (-4.34, 8.24)	NR	NR	-	-
Renal and urinary disorders								
All PT	71 (25.1)	33 (22.9)	1.09 (0.76, 1.57)	2.17 (-6.35, 10.69)	15 (5.3)	11 (7.6)	-	-
Acute kidney injury	25 (8.8)	13 (9.0)	0.98 (0.52, 1.85)	-0.19 (-5.92, 5.54)	7 (2.5)	5 (3.5)	-	-
Reproductive system and breast disorders								
All PT	17 (6.0)	4 (2.8)	2.16 (0.74, 6.32)	3.23 (-0.63, 7.09)	1 (0.4)	0	-	-
Respiratory, thoracic and mediastinal disorders								
All PT	138 (48.8)	60 (41.7)	1.17 (0.93, 1.47)	7.10 (-2.84, 17.03)	44 (15.5)	15 (10.4)	-	-
Dyspnoea	37 (13.1)	11 (7.6)	1.71 (0.90, 3.25)	5.44 (-0.42, 11.29)	9 (3.2)	3 (2.1)	-	-
Cough	35 (12.4)	20 (13.9)	0.89 (0.53, 1.49)	-1.52 (-8.35, 5.31)	NR	NR	-	-

Study VIALE-A								
System organ class/ adverse events	**All grades [a]**				**Grades ≥ 3 [a]**			
	Ven+AZA (n = 283) n (%)	**PBO+AZA (n = 144) n (%)**	**Relative risk (95% CI)**	**Risk difference (95% CI)**	**Ven+AZA (n = 283) n (%)**	**PBO+AZA (n = 144) n (%)**	**RR (95 % CI)**	**RD (95 % CI)**
Pleural effusion	28 (9.9)	8 (5.6)	1.78 (0.83, 3.81)	4.34 (-0.77, 9.45)	7 (2.5)	4 (2.8)	-	-
Epistaxis	26 (9.2)	12 (8.3)	1.10 (0.57, 2.12)	0.85 (-4.78, 6.48)	5 (1.8)	0	-	-
Oropharyngeal pain	25 (8.8)	6 (4.2)	2.12 (0.89, 5.05)	4.67 (0.02, 9.31)	NR	NR	-	-
Skin and subcutaneous tissue disorders								
All PT	137 (48.4)	51 (35.4)	1.37 (1.06, 1.76)	12.99 (3.25, 22.74)	12 (4.2)	0	-	-
Pruritus	28 (9.9)	6 (4.2)	2.37 (1.01, 5.60)	5.73 (0.96, 10.50)	1 (0.4)	0	-	-
Rash	26 (9.2)	9 (6.3)	1.47 (0.71, 3.05)	2.94 (-2.25, 8.13)	NR	NR	-	-
Rash maculo-papular	23 (8.1)	4 (2.8)	2.93 (1.03, 8.30)	5.35 (1.19, 9.51)	1 (0.4)	0	-	-
Petechiae	17 (6.0)	8 (5.6)	1.08 (0.48, 2.45)	0.45 (-4.20, 5.11)	2 (0.7)	0	-	-
Vascular disorders								
All PT	85 (30.0)	37 (25.7)	1.17 (0.84, 1.63)	4.34 (-4.57, 13.25)	36 (12.7)	12 (8.3)	-	-
Hypotension	28 (9.9)	9 (6.3)	1.58 (0.77, 3.26)	3.64 (-1.62, 8.91)	13 (4.6)	4 (2.8)	-	-
Hypertension	26 (9.2)	12 (8.3)	1.10 (0.57, 2.12)	0.85 (-4.78, 6.48)	17 (6.0)	6 (4.2)	-	-
Haematoma	16 (5.7)	8 (5.6)	1.02 (0.45, 2.32)	0.10 (-4.51, 4.71)	NR	NR	-	-
Total serious AEs n (%)	235 (83.0)	105 (72.9)	1.14 (1.02, 1.27)	10.12 (1.65, 18.60)	NA	NA	NA	NA
Total deaths n (%)	64 (22.6)	29 (20.1)	1.12 (0.76, 1.66)	2.48 (-5.69, 10.64)	NA	NA	NA	NA
Discontinuation due to AE n (%)	231 (81.6)	92 (63.9)	1.28 (1.12, 1.46)	17.74 (8.69, 26.79)	NA	NA	NA	NA

[a] For Grade ≥3 AEs and some all grades AEs, the relative risks and risk differences were not available.
Source: (22, 47)
Abbreviations: AE=adverse event; AZA=azacytidine; CI=confidence interval; NA=not applicable; NR=not reported; PBO=placebo; PT=preferred term; RR=relative risk; RD=risk difference; SOC=system organ class; Ven=venetoclax.

APPENDIX 6: INFORMATION RETRIEVAL

Table A13. EUnetHTA Standard operating procedure: General aspects of information retrieval methodology

METHODS	
Consistency of inclusion criteria	**yes/no**
Do the inclusion criteria from the methods section match those from the appendix (list of studies excluded in full-text screening)?	The MAH inclusion criteria differ from the criteria requested by the EUnetHTA authoring team. The EUnetHTA-specific PICO is encompassed by the broader MAH global PICO, except for study design.
Search in bibliographic databases	
Did the MAH report the bibliographic databases searched?	Yes
Did the MAH search the following bibliographic databases: MEDLINE, Embase and CENTRAL?	Yes
Did the MAH apply general limitations (e.g. languages, year of publication)?	Yes – English only
Optional: If general limitations were applied, was appropriate justifications provided?	No
Search in study registries	
Did the MAH report the study registries searched?	Yes
Did the MAH search the following study registries: CT.gov, EU-CTR and the ICTRP Search Portal?	No, clinicaltrials.gov only
Did the MAH apply general limitations (e.g. languages, year of publication)?	Yes, Interventional studies with results.
Optional: If general limitations were applied, was appropriate justifications provided?	No
Study selection	
Did the MAH report that the screening step (title/abstracts and full text) were performed by 2 persons independently of one another?	Yes Submission file Figure 8.1 Study selection and data extraction process
Optional: If this was not the case, was appropriate justification provided?	Not relevant
Search strategies for bibliographic databases	
Did the MAH retrieve all search results within the last 3 months?	OK. Search October 2020, Submission file dated December 2020
Did the MAH conduct and document a search strategy for each PICOS?	The MAH searches were set up for a network meta-analysis for drugs treating acute myeloid leukemia – a much broader PICO than the scope of the EUnetHTA PTJA16 assessment.
Do the search strategies reflect the limitations mentioned in the methods section (e.g. inclusion criteria, including languages considered and year of publication?	The MAH did not include evidence synthesis or observational studies in the search as indicated in the inclusion criteria in the EUnetHTA protocol for safety outcomes.
Did the MAH document the search strategies according to the submission file template?	OK
Search strategies for study registries	
Did the MAH retrieve all search results within the last 3 months?	OK. Search October 2020, Submission file delivered December 2020
Did the MAH conduct and document a search strategy for each PICOS?	OK
Did the MAH document the search strategies according to the submission file template?	OK

Review of searches in sources mandatory according to EUnetHTA standard operating procedure for information retrieval (MEDLINE, Embase and Cochrane Central Register of Controlled Trials). The assessment was performed according to PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement (71):

Table A14. General aspects of information retrieval: Assessment of electronic strategies

1. Translation of the research question	
Does the search strategy match the research question/PICO?	No. The MAH searches were set up for a network meta-analysis for drugs treating acute myeloid leukemia (AML) – a much broader PICO than the scope of the EUnetHTA PTJA16 assessment.
Are the search concepts clear?	OK
Are there too many or too few PICO elements included?	OK
Does the search retrieve too many or too few records?	As the MAH searched for all drugs used to treat AML and not the combination of drugs of interest, the searches retrieve too many records.
Are unconventional or complex strategies explained?	Not relevant
2. Boolean and proximity operators (these vary based on search service)	
Are Boolean or proximity operators used correctly?	Yes
Is the use of nesting with brackets appropriate and effective for the search?	Yes
If NOT is used, is this likely to result in any unintended exclusions?	No
Could precision be improved by using proximity operators (eg, adjacent, near, within) or phrase searching instead of AND?	No
Is the width of proximity operators suitable (eg, might adj5 pick up more variants than adj2)?	ADJ2 in MEDLINE/Embase line 2 (AML) is not ideal. ADJ4 and ADJ3 like this would be more sensitive: (acute adj4 leuk?emia$ adj3 (myeloid [..]
3. Subject headings (database specific)	
Are the subject headings relevant?	OK
Are any relevant subject headings missing; for example, previous index terms?	Previous index terms are probably not relevant, as the search aims to retrieve articles on a drug only recently approved.
Are any subject headings too broad or too narrow?	OK
Are subject headings exploded where necessary and vice versa?	OK
Are major headings (‘‘starring” or restrict to focus) used? If so, is there adequate justification?	OK. Not relevant
Are subheadings missing?	OK. Not relevant
Are subheadings attached to subject headings? (Floating subheadings may be preferred.)	OK. Not relevant
Are floating subheadings relevant and used appropriately?	OK. Not relevant
Are both subject headings and terms in free text (see the following) used for each concept?	OK
4. Text word searching (free text)	
Does the search include all spelling variants in free text (eg, UK vs. US spelling)?	OK
Does the search include all synonyms or antonyms (eg, opposites)?	Not sure. There are entry terms in MeSH and Emtree not used as text words. Ideally the following text words should have been searched in addition to the generic drug names: (hypomethylating agent* OR HMA OR HMAs).
Does the search capture relevant truncation (ie, is truncation at the correct place)?	OK
Is the truncation too broad or too narrow?	OK
Are acronyms or abbreviations used appropriately? Do they capture irrelevant material? Are the full terms also included?	OK. Not relevant
Are the keywords specific enough or too broad? Are too many or too few keywords used? Are stop words used?	OK
Have the appropriate fields been searched; for example, is the choice of the text word fields (.tw.) or all fields (.af.) appropriate? Are there any other fields to be included or excluded (database specific)?	Used .tw throughout. Would normally searched the .kw/.kf fields. And maybe the .tn (drug trade name) as well since trade names for some of the drugs are searched. Or use .mp or .af.

Should any long strings be broken into several shorter search statements?	OK
5. Spelling, syntax, and line numbers	
Are there any spelling errors?	OK
Are there any errors in system syntax; for example, the use of a truncation symbol from a different search interface?	OK
Are there incorrect line combinations or orphan lines (ie, lines that are not referred to in the final summation that could indicate an error in an AND or OR statement)?	OK
6. Limits and filters	
Are all limits and filters used appropriately and are they relevant given the research question?	Odd choice of databases (CDSR, DARE) given the fact that SLRs and meta-analyses or review articles are listed as exclusion criteria. Fortunately, filters for study design in MEDLINE and Embase capture randomized and non-randomized trials as in the broad (global) PICO in table 7.1, and are not restricted to RCTs as in the EUnetHTA-specific PICO in table 7.2
Are all limits and filters used appropriately and are they relevant for the database?	OK
Are any potentially helpful limits or filters missing? Are the limits or filters too broad or too narrow? Can any limits or filters be added or taken away?	The EUnetHTA authoring team asked for inclusion of observational studies on safety. MAH search strategies are not set up to retrieve such articles.
Are sources cited for the filters used?	Not in the submission file. However, the AML Clinical SLR report mentions use of validated filters published by Scottish Intercollegiate Guidelines Network (SIGN).

Table A15. General aspects of information retrieval: Checking search strategies for study registries

Documentation of search strategies – Submission file Appendix 8, 8.1.1 Search strategy			
Did the MAH document a separate search strategy for each registry?	Only searched CT.gov		
Name of study registry	**CT.gov**	**ICTRP**	**EU CTR**
Date of the last search	2020-10-13	*Not searched*	*Not searched*
Did the MAH document the following items: name of study registry, internet address, date of the last search, search strategy, number of results?	Yes		
Reproducibility and comprehensiveness of search results	**CT.gov**	**ICTRP**	**EU CTR**
Is the number of hits reproducible?	Yes Submission file, Oct. '20: 474 EUnetHTA: April '21: 440		
Optional: If the above deviation is large, limit the search results to the last date of the search conducted by MAH. Is the number of hits reproducible now?			
Did the MAH list a registry entry for each study from the study pool?	Yes		
Do the search blocks for the intervention and indication contain enough synonyms?	not applicable		
Did the MAH use the basic search function on the main page?	not applicable		not applicable
Did the MAH employ Boolean operators correctly?	MAH used only one search term, acute myeloid leukemia, hence no need for Boolean operators		
Did the submitted documentation dispense with parentheses?	not applicable		not applicable
Did the MAH place phrases (e.g. XY 0071) into parentheses or quotes?	not applicable	not applicable	
Does the strategy include other search blocks than population, intervention or study type?	No		

In supplementary searches in trial registries the following number of publications were found:

Table A16. Supplementary searches

Clinicaltrials.gov	83
EU Clinical Trials Registry(EU CTR)	29
International Clinical Trials RegistryPlatform (ICTRP)	4