Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Venetoclax

Proprietary Product Name: Venclexta

Sponsor: AbbVie Pty Ltd

April 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AE	Adverse event
AML	Acute myeloid leukaemia
AML-MRC	Acute myeloid leukaemia with myelodysplasia related changes
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
AUC_{ss}	Area under the concentration time curve at steady state
Bcl-2	B-cell lymphoma-2
CLL	Chronic lymphocytic leukaemia
CR	Complete remission
CRh	Complete remission with partial haematologic recovery
CRi	Complete remission with incomplete blood count recovery
DLP	Data lock point
DOR	Duration of response
ECOG-PS	Eastern Cooperative Oncology Group performance score
EFS	Event free survival
E-R	Exposure-response
EU	European Union
FDA	Food and Drug Administration (United States of America)
HMA	Hypomethylating agents
HR	Hazard ratio
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDAC	Low dose cytarabine

Abbreviation	Meaning
OCE	Oncology Center of Excellence (United States of America)
OS	Overall survival
PI	Product Information
PK	Pharmacokinetic(s)
PT	Preferred Term
RMP	Risk management plan
SOC	System Organ Class
TGA	Therapeutic Goods Administration
TLS	Tumour lysis syndrome
US(A)	United States of America

I. Introduction to product submission

Submission details

Type of submission:	Provisional registration to full registration
Product name:	Venclexta
Active ingredient:	Venetoclax
Decision:	Approved
Date of decision:	24 September 2021
Date of entry onto ARTG:	28 September 2021
ARTG numbers:	267441, 267442, 267443, 267444 and 267445
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	AbbVie Pty Ltd 241 O'Riordan Street Mascot NSW 2020
Dose form:	Film coated tablet
Strengths:	10 mg, 50 mg and 100 mg
Containers:	Blister pack and bottle
Pack sizes:	Starting pack: 42 tablets (comprised of 14 x 10 mg tablets, 7 x 50 mg tablets, 7 x 100 mg tablets, and 14 x 100 mg tablets) 10 mg blister packs: 2 and 14 tablets 50 mg blister packs 1 and 7 tablets 100 mg blister packs: 1, 7, 14 and 112 tablets 100 mg bottle: 120 and 180 tablets
Approved therapeutic use:	*Acute Myeloid Leukaemia* *Venclexta, in combination with azacitidine or low-dose cytarabine, is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.*

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Route of administration:	Oral
Dosage:	The dose of Venclexta depends upon the combination agent. The Venclexta dosing schedule is listed in the Product Information. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	C Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by AbbVie Pty Ltd (the sponsor) to register Venclexta (venetoclax) 10 mg, 50 mg and 100 mg, film coated tablets for the following proposed indication:

> *Acute Myeloid Leukaemia*
>
> *Venclexta is indicated, as part of combination therapy, for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.*

Venetoclax is a potent, highly selective, orally bioavailable, small molecule B-cell lymphoma-2 (Bcl-2) family inhibitor, designed to bind competitively to Bcl-2, thereby liberating pro-apoptotic proteins to trigger apoptosis in cancer cells. Anti-apoptotic Bcl-2 family members are associated with tumour initiation, disease progression, and chemotherapy resistance, as well as autoimmunity. Overexpression of Bcl-2 is a major contributor to the pathogenesis of some haematological malignancies. Antagonism of the action of these proteins may enhance response to therapy and overcome resistance, and so are potential targets for anti-tumour therapy.

Acute myeloid leukaemia (AML) is a heterogeneous group of aggressive haematological cancers that arise from clonal expansion of malignant haematopoietic precursor cells in bone marrow, peripheral blood and occasionally extramedullary tissues, leading to a disruption of normal haematopoiesis.

It is broadly categorised as one of the following:

- AML with recurrent genetic abnormalities,
- AML with myelodysplasia-related features, without a history of prior cytotoxic therapy,
- therapy-related myeloid neoplasm (AML and myelodysplastic syndromes),

- AML not otherwise specified,
- myeloid sarcoma, and
- myeloid proliferations related to Down syndrome.

The median age of patients is approximately 65 to 70 years and the incidence increases with age and is considered a life ending disease for many patients. Older patients tend to have a lower percentage of favourable cytogenetics, a higher percentage of unfavourable cytogenetics, a higher incidence of multi-drug resistance, a higher incidence of treatment resistant disease, lower complete response rates, shorter remission durations and shorter median overall survival. In addition, older adults are more likely to have co-morbidities that impact treatments that may be offered, and performance score acts independently of age in influencing prognosis.[2] Generally the prognosis is poor, with the 5-year survival rates being between 5 to 8%.

Clinical guidelines recommend a range of therapies for patients newly diagnosed with AML who are ineligible for intensive chemotherapy regimens.

This evaluation was facilitated through Project Orbis,[3] an initiative of the United States (US) Food and Drug Administration (FDA) Oncology Center of Excellence (OCE). Under this project, the FDA, Health Canada, National Health Surveillance Agency (Brazil), Swissmedic (Switzerland), and the TGA collaboratively reviewed the application. This innovative evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions.

Each regulator agency maintained its regulatory process to make independent decisions about the approval (market authorisation).

Regulatory status

The product received initial provisional registration on the Australian Register of Therapeutic Goods (ARTG) on 5 February 2020.

> *Acute Myeloid Leukaemia*
>
> *Venclexta, as part of combination therapy, is indicated for the treatment of newly diagnosed adult patients with Acute Myeloid Leukaemia (AML) who are ineligible for intensive chemotherapy.*
>
> *This medicine has provisional approval in Australia for the treatment of newly diagnosed patients with AML who are ineligible for intensive chemotherapy. The decision to approve this indication has been made on the basis of interim data (overall response rate and duration of response). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*

At the time the TGA considered this application, similar applications had been approved in the United States of America (USA), Australia, Canada, Switzerland and Brazil was reviewed under Project Orbis. Approvals for the United States, Canada, Switzerland and Brazil have been received with the approval details provided in the below Table 1. Venclexta has also approved in the European Union (EU) for a similar indication.

[2] American Society of Haematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. *Blood Adv* (2020) 4 (15): 3528-3549.
[3] Project Orbis is an initiative of the United States Food and Drug Administration's Oncology Center of Excellence that provides a framework for the collaborative review of promising new cancer treatments among international regulatory partners. It aims to give patients faster access to promising cancer treatments across the globe. Further information is available on the TGA website at https://www.tga.gov.au/project-orbis

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union via centralised procedure	23 June 2020	Approved on 19 May 2021	*Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.*
United States of America	22 May 2020	Approved 16 October 2020 (Project Orbis)	*Venclexta is indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.*
Canada	12 June 2020	4 December 2020 (Project Orbis)	*Venclexta, in combination with azacitidine or low-dose cytarabine, is indicated for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.* *Clinical effectiveness of Venclexta in combination with low-dose cytarabine is based on response rates and transfusion independence results (see Clinical trials).*
New Zealand	29 June 2020	Approved on 20 August 2020	*Venclexta is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.*

Region	Submission date	Status	Approved indications
Singapore	26 February 2019	Approved on 4 March 2021	*Venclexta is indicated, in combination with a hypomethylating agent or in combination with low-dose cytarabine, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy.*
Switzerland	29 May 2020	Approved on 16 December 2020 (Project Orbis)	*Venclyxto in combination with azacitidine or decitabine or low dose cytarabine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. Patients with acute promyelocytic leukaemia are excluded (see "clinical efficacy" and "dosage/administration").*
Brazil	8 June 2020	Approved on 11 November 2020 (Project Orbis)	*Venclexta (venetoclax) in combination with the hypomethylating agents azacitidine or decitabine, or in combination with low-dose cytarabine is indicated for newly diagnosed patients with Acute Myeloid Leukemia (AML) and who are ineligible for intensive chemotherapy, by medical criteria*

No application for the product supported by the randomised, Phase III studies (the VIALE-A and VIALE-C trials, submitted with this application) has been rejected, withdrawn or repeatedly deferred in any country.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-02543-1-6

Description	Date
Designation: Provisional;[4] Determination: Orphan;[5] Orphan extension	17 September 2019 25 September 2019 6 March 2020
Submission dossier accepted and first round evaluation commenced	30 June 2020
First round evaluation completed	30 November 2020
Sponsor provides responses on questions raised in first round evaluation	22 December 2020
Second round evaluation completed	8 February 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	7 July 2021
Sponsor's pre-Advisory Committee response	19 July 2021
Advisory Committee meeting	5 and 6 August 2021
Registration decision (Outcome)	24 September 2021
Completion of administrative activities and registration on the ARTG	28 September 2021
Number of working days from submission dossier acceptance to registration decision*	254

*Statutory timeframe for standard applications is 255 working days

[4] Provisional determination ensures that access to the Provisional approval pathway is only available to medicines that meet the eligibility criteria. Determination provides a consistent and transparent process for making this assessment.
The Provisional approval pathway allows for provisional registration of medicines on the basis of preliminary clinical data where the benefit of early availability of the medicine outweighs the risk inherent in the fact that additional data are still required. However, the TGA requires comprehensive non-clinical data on safety, quality and compliance with Good Manufacturing Practice. These requirements are the same as in the standard registration process for prescription medicines.

[5] An orphan drug is a therapeutic good developed to treat, prevent or diagnose a rare medical condition, that due to low prevalence and/or financial unviability, it would not be financially viable for a sponsor to market that good in Australia. A sponsor may apply for orphan drug designation preceding the main evaluation submission, and should the application meet the specified criteria and designation be granted, the TGA will waive the normal application and evaluation fees, thereby facilitating bring the therapeutic good to the Australian market.

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

TGA guidance at pre-submission meetings is nonbinding and without prejudice.

The following guidance documents were applicable to this submission:

- EMA/CHMP/703715/2012 Rev.2 Appendix 4: Guideline on the evaluation of anticancer medicinal products in man Condition specific guidance
- CPMP/ICH/379/95 ICH Topic E 7: Note for Guidance on Studies in Support of Special Populations: Geriatrics
- EMA/CHMP/ICH/604661/2009 ICH topic E7: Studies in Support of Special Populations: Geriatrics, Questions and Answers

Quality

No new quality data were included in this submission. Thus, there was no requirement for a quality evaluation in a submission of this type.

Nonclinical

No new non-clinical data were included in this submission. Thus, there was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical dossier comprised of:

- updated pharmacokinetic analyses,
- VIALE-A trial, a Phase III study of venetoclax in combination with azacitidine,
- VIALE-C trial, a Phase III study of venetoclax in combination with low dose cytarabine,
- updates from the two studies that supported the provisional registration of venetoclax in AML:
  - Study M14-358, a Phase Ib study of venetoclax in combination with azacitidine or decitabine.
  - Study M14-387, a Phase I/II study of venetoclax in combination with low dose cytarabine.

Pharmacology

Aspects of the pharmacology of venetoclax were reviewed in previous submissions.[6] Updated analyses and modelling were the focus of the venetoclax pharmacology component of this submission. The updated population pharmacokinetics (PK) analysis

[6] AusPAR for previous submissions of Venclexta, PM-2018-05208-1-6 and PM-2019-04393-1-6. Available at https://www.tga.gov.au

did not necessitate modification of the previous conclusions that venetoclax dosing based on age, sex, weight, mild to moderate renal impairment, or mild to moderate hepatic impairment. No dose adjustment was considered necessary based on race after a detailed consideration in the submission and evaluation.

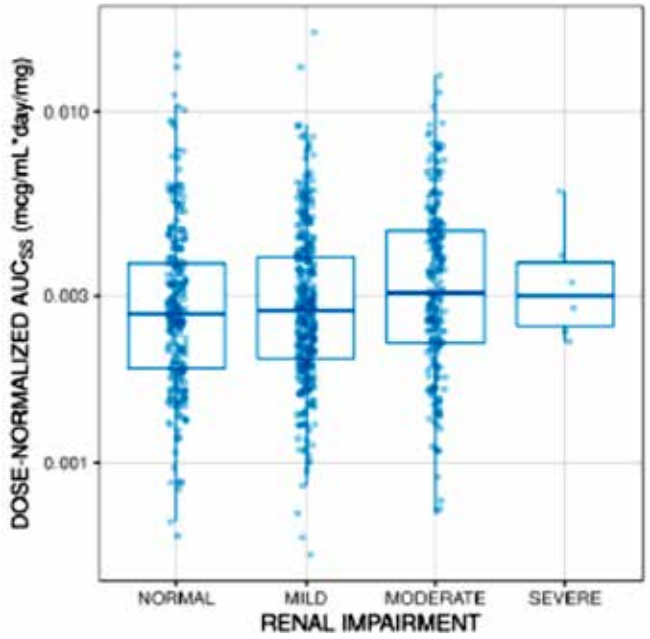
The clinical PK analyses that included information from venetoclax combined with a hypomethylating agent, from VIALE-A trial and Study M14-358 or low dose cytarabine in VIALE-C trial and Study M14-387 indicated the exposures in newly diagnosed AML were similar to those previously reported.

Within subjects receiving venetoclax in combination with hypomethylating agents or low dose cytarabine, the updated analysis did not find exposure-response relationships between area under the concentration time curve at steady state (AUC_{ss}) and the efficacy endpoints complete remission (CR), CR plus complete remission with incomplete blood count recovery (CRi), CR plus complete remission with partial haematologic recovery (CRh), overall survival (OS), event free survival (EFS), or the probabilities of conversion to post baseline transfusion independence for both platelets and red blood cells at the venetoclax dosing in the AML studies. For all efficacy variables evaluated, venetoclax AUC_{ss} quartile plots showed a clear trend of higher efficacy with venetoclax in combination with a hypomethylating agent (azacytidine or dezocitidine) or with low dose cytarabine than placebo in combination with azacytidine or cytarabine.

Consistent with previous findings of a flat or no apparent exposure-response relationship for venetoclax for safety, a shallow but not statistically significant exposure-response relationship for treatment emergent Grade ≥ 3 neutropenia in patients receiving venetoclax 400 mg to 1200 mg once per day in combination with a hypomethylating agent (Study M14-358 and VIALE-A trial).

The updated population PK analysis included data from six patients with severe renal impairment (defined as creatinine clearance ≥ 15 mL/min and < 30 mL/min). The AUS_{ss} values are summarised in the Figure 1 below.

Figure 1: Dose normalised exposure by renal function



AUC_{ss} = area under the concentration time curve at steady state

Note: Venetoclax AUC_{ss} values, normalised for designated cohort dose, are plotted versus categorical covarites.

Note: Normal (n = 224), Mild (n = 321), Moderate (n = 219), Severe (n = 6) renal impairment

Efficacy

VIALE-A trial

This is an ongoing, Phase III, multicentre, multinational, randomised (2:1), placebo controlled trial of adults with newly diagnosed AML, aged ≥ 75 years or with co-morbidities ineligible for intensive chemotherapy, that compared venetoclax in combination with azacitidine (n = 286) with placebo in combination with azacitidine (n = 145) (Table 3).

Table 3: VIALE-A trial Study design

VIALE-A study design
First patient first visit: 2 February 2017 Data cut-off date for this analysis 2: 4 January 2020, study ongoing Clinical Study Report (CSR) date: 8 May 2020 134 sites across 27 countries
Summary of study, treatment and patient flow • 433 patients randomised, 431 for the efficacy analysis VEN+AZA (n = 286), PBO+AZA (n = 145). • Treatment arms: – VEN dosing: 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, then 400 mg once daily each 28 day cycle – AZA dosing: 75 mg/m^2 once daily IV or SC on Days 1 to 7 of each 28-day cycle • Dose modification: – Reduce VEN/PBO treatment to 21 days of cycle if 2 occurrences Grade 4 neutropenia or thrombocytopenia; – Reduce AZA dose on next cycle based on bone marrow (BM) cellularity and cell count recovery time; – If ANC < 500/µL on study treatment give prophylactic anti-infectives; – If ANC < 500/µL on study treatment and BM leukaemia clearance interrupt VEN/PBO until earliest of ANC ≥ 500/µL, platelets ≥ 50x 10^3/µL. or for up to 14 days – Disease response assessed at end of Cycle 1 then every 3 cycles thereafter unless CR+CRi (see below) met on 2 consecutive BM then not repeated unless clinically indicated until final study visit (completed or discontinued). Post treatment visits performed after last study visit • At data cut: – Continued treatment:73 from VEN+AZA arm and 16 from PBO+AZA arm – Discontinued treatment 88% of PBO+AZA arm and 74.1% of VEN+AZA arm Discontinued due to morphologic relapse: 10.3% PBO+AZA arm v 22.4% VEN+AZA arm – Died: 15.9% PBO+AZA arm vs 13.6% VEN+AZA arm – Discontinued due to adverse events: 9% PBO+AZA arm vs 15% VEN+AZA arm – Discontinued due to progressive disease: 14.5% PBO+AZA arm vs 3.1% VEN+AZA arm

VIALE-A study design	
Key inclusion criteria: • Aged ≥ 75 years of age, OR Aged ≥ 18 to 74 years of age and at least one of: • History of congestive heart failure requiring treatment or ejection fraction ≤ 50% or chronic stable angina; • Diffusing Capacity of the Lung for Carbon Monoxide ≤ 65% or Forced Expiratory Volume in 1 Second ≤ 65%; • CrCl ≥ 30 mL/min to < 45 mL/min; • Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN; • Eastern Cooperative Oncology Group (ECOG) Performance Status of 2 or 3; or • Other (physician judged) comorbidity incompatible with intensive chemotherapy (reviewed and approved by Therapeutic Area Medical Director during screening).	**Key exclusion criteria:** • History of myeloproliferative neoplasm including myelofibrosis, essential thrombocythemia, polycythemia vera, chronic myeloid leukaemia with or without BCR-ABL1 translocation, and transformation to AML with BCR-ABL1 translocation; • Favourable risk cytogenetics such as t(8;21), inv(16), t(16;16) or t(15;17) per NCCN Guidelines Version 2, 2016. • Acute promyelocytic leukaemia; • Known active central nervous system (CNS) involvement with AML; • Known HIV, Hep B, or Hep C infections; • Strong ± moderate CYP3A inducers < 7 days prior to start of study treatment. • New York Heart Association Class > 2; • Prior hypomethylating agent (HMA), VEN, ± chemotherapy for MDS, CAR-T cell therapy
Endpoints	
Primary: US OS was the sole primary endpoint. For the EU, Japan and EU reference countries the dual primary endpoint of CR+CRi (by INV)+ OS. CR+CRi by IWG criteria for AML. Reference is primarily made to the US primary endpoint given the collaboration with the US in the evaluation. **Secondary**: CR + CRi rate and CR + CRh rate (US); CR + CRi at initiation of Cycle 2 (Japan, EU); CR + CRh rate by the initiation of Cycle 2 (US), CR rate; and post baseline transfusion independence rates. **Other secondary**: CR + CRi MRD response rate (Japan, EU); MRD negative remission rate (US); CR + CRi in biomarker subgroups (IDH1/IDH2 and FLT3; Japan, EU); CR + CRh rate in biomarker subgroups (IDH1/IDH2 and FLT3; US); OS in biomarker subgroups (including IDH1/IDH2 and FLT3); change from Baseline in PROMIS Cancer Fatigue SF 7a global fatigue score; change from Baseline in GHS/QoL scale from the EORTC QLQ-C3; and EFS. Baseline transfusion dependence to post-baseline transfusion independence	
Endpoint definitions	
Complete remission: ANC > 10^3/µL, platelets > 10^5/µL, RBC transfusion independence, and bone marrow with < 5% blasts. No circulating blasts and blasts with Auer rods; no extramedullary disease.	

VIALE-A study design
Complete remission with incomplete blood recovery (CRi): All criteria as CR except residual neutropenia ≤10^3/μL (1000/μL) or thrombocytopenia ≤ 10^5/μL (100,000/μL). RBC transfusion dependence also defined as CRi. Complete remission with partial haematologic recovery (CRh): BM < 5% blasts + peripheral ANC ≥ 500/μL + peripheral platelets > 50 x 10^9/L Partial remission (PR): All hematologic values for CR but with a decrease of ≥ 50% in % blasts to 5% to 25% in BM aspirate. Morphologic Leukaemia-free state (MLFS): < 5% blasts in BM aspirate sample with marrow spicules and ≥ 200 nucleated cells; no circulating blasts and extramedullary disease without peripheral blood count recovery that meet thresholds for either CR or CRi. Resistant disease (RD): Failure to achieve CR, CRi, PR, or MLFS; only for patients surviving ≥ 7 days after completion of Cycle 1, with evidence of persistent leukaemia by blood and/or bone marrow examination. Morphologic relapse (MR): Reappearance of ≥ 5% blasts after CR/CRi in peripheral blood or BM, or develop extramedullary disease. Progressive Disease (PD): 50% increase in marrow blasts > baseline (minimum 15% increase required if < 30% blasts at Baseline); or persistent marrow blast % > 70% over ≥ 3 months; without at least a 100% improvement in ANC to 500/μL, and/or platelet count to > 50 × 10^9/L (not transfused); OR 50% increase in peripheral blasts (WBC × % blasts) to > 25 × 10^9/L (> 25,000/μL); OR New extramedullary disease All patients also assessed for RBC and platelet transfusion independence and CRh
Statistics
Randomised 2:1, stratified by age (18 -≤75, 75), cytogenetics (intermediate risk, poor risk) and region (US, EU, China, Japan, ROW) **Primary endpoint:** The hierarchy of testing and alpha-spending boundary differed for US and the EU. In US had OS as the primary endpoint, in Japan and the EU a dual primary endpoint of CR+Cri (INV) and OS. Assuming a true HR of 0.7 and an interim efficacy analysis at 75% of OS events with Lan-DeMets alpha spending function with O'Brien-Fleming boundary, a total of 360 OS events were required for the study to have 88.6% power to detect statistically significant improvement in OS for the VEN + AZA arm at 2-sided alpha of 0.05. IA2 for OS planned for when 270 OS events (75% of OS events) occurred. For EU reference countries IA1 was conducted for CR + CRi (Primary Analysis for CR + CRi endpoint) at 2-sided alpha = 0.01 after 6 months follow up. Two patients were randomised on the same date 6 months prior to the data cut-off date which resulted in 226 patients included in IA1 instead of the preplanned 225 patients. IA2 was conducted for OS at 2-sided alpha = 0.02 when 270 OS events (75% of 360 total OS events) were observed. The study continued in a blinded fashion until the IDMC made the recommendation to unblind after IA2.
Protocol Amendments and Deviations
Major amendments: Seven versions of the study protocol and SAP occurred prior to unblinding of the study. Key changes: Lower the age limit for study eligibility and enrol AML patients ≥ 18 years of age instead of ≥ 60 years who are ineligible for standard induction therapies due to comorbidities

VIALE-A study design
Increase number of OS events prior to analysis increased to ensure adequate power for the OS endpoint (from 80% to 86.7% for dual endpoints with 2-sided alpha of 0.04, or 88.6% for single primary endpoint with 2-sided alpha of 0.05). CR changed to parameters, above **Important Protocol Deviations**: Incorrect dosing of study treatment in patients taking concomitant medication, incorrect dose escalation back to target after dose adjustment or incorrect dose modifications and were noted. These were not considered by the sponsor to have an impact on data integrity, or to have impacted the clinical benefit or safety of the treatment for the individual patients.

Abbreviation: CSR = clinical study report; PBO = placebo; AZA = azacitidine; VEN = venetoclax; BM = bone marrow; ANC = absolute neutrophil count; CR = complete remission; CRi = Complete remission with incomplete blood count recovery; ECOG = Eastern Cooperative Oncology Group; BCR-ABL1 = B-cell receptor-tyrosine-protein kinase ABL1; NCCN = National Comprehensive Cancer Network; CNS = central nervous system; HMA = hypomethylating agent; EU = European Union; INV = investigator; IWG = international working group; US = United States of America; MDR = minimal residual disease; IDH1 = isocitrate dehydrogenase 1; IDH2 = isocitrate dehydrogenase 2; FLT3 = fms-like tyrosine kinase 3; EFS = event free survival; RBC = red blood cell; CRh = complete remission with partial haematologic recovery; PR = partial remission; MLFS= morphologic leukaemia-free state; RD = resistant disease; MR = morphologic relapse; PD = progressive disease; OS = overall survival; HR = hazard ratio.

Demographics and baseline characteristics

Patient demographics and baseline characteristics are summarised in the tables below. Most patients were male, with a median age of 76 years.

Table 4: VIALE-A trial Study baseline demographics

Demographic parameters n (%)	Placebo + azacitidine (N = 145)	Venetoclax 400 mg once daily + azacitidine (N = 286)
Gender		
Male	87 (60.0)	172 (60.1)
Female	58 (40.0)	114 (39.9)
Age		
Mean years (SD)	75.1 (5.70)	75.6 (6.08)
Median (years)	76.0	76.0
Min, max (years)	60.0, 90.0	49.0, 91.0
Age Category		
18 to < 65 years	5 (3.4)	10 (3.5)
65 to < 75 years	53 (36.6)	102 (35.7)
≥ 75 years	87 (60.0)	174 (60.8)

Demographic parameters n (%)	Placebo + azacitidine (N = 145)	Venetoclax 400 mg once daily + azacitidine (N = 286)
Race		
White	109 (75.2)	217 (75.9)
Black or African American	2 (1.4)	3 (1.0)
Asian	33 (22.8)	66 (23.1)
American Indian or Alaskan Native	1 (0.7)	0
Region		
United States	24 (16.6)	50 (17.5)
Rest of the World*	121 (83.4)	236 (82.5)

N = sample size; n = number of patients; SD = standard deviation

*Rest of the World includes Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Norway, Poland, Portugal, Russia, South Africa, South Korea, Spain, Sweden, Taiwan and Turkey. Data cut-off date 4 January 2020.

The baseline disease characteristics of the patients are included below. Around 44% were Eastern Cooperative Oncology Group (ECOG) performance score (PS) 2 or 3,[7] and most patients had *de novo* disease, with intermediate cytogenetics. A range of mutation types were represented in both groups, and almost 50% had a high bone marrow blast count.

[7] ECOG Performance Status: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

Table 5: VIALE-A trial Baseline disease characteristics

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

FLT3 = FMS-like tyrosine kinase 3; IDH = isocitrate dehydrogenase; N = sample size; n = number of patients; NPM =nucleophosmin; PBO = placebo; TP = tumor protein; VEN = venetoclax.

Data cutoff 4 January 2020.

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

b. Number of evaluable biomarker mutation analysis specimens received at Baseline

c. Detected by Abbott RealTime IDH1 assay

d. Detected by Abbott RealTime IDH2 assay

e. Detected by LeukoStrat CDx FLT3 mutation assay f. Detected by MyAML assay

Follow up for this study was for 20.5 months. Treatment duration was 7.6 months for venetoclax in combination with azacitidine arm and 4.3 months for the placebo in combination with azacitidine arm, with 37.5% and 20.8% of venetoclax in combination with azacitidine arm and placebo in combination with azacitidine arm, respectively treated for more than 12 months.

Patients underwent a median of 7 cycles and 4.5 cycles of therapy, venetoclax in combination with azacitidine arm and placebo in combination with azacitidine arm, respectively. Around 57% and 42.4% of the venetoclax in combination with azacitidine arm arm and placebo in combination with azacitidine arm, respectively received more than 5 cycles of therapy. Median azacitidine exposure was 7 months and 3.8 months in the venetoclax in combination with azacitidine arm and placebo in combination with azacitidine arm, respectively. At least one dose interruption was experienced by 94.3% versus 77.8% of the venetoclax in combination with azacitidine arm and placebo in combination with azacitidine arm, respectively.

Overall survival

The overall survival outcome is presented below (Table 6).

Table 6: VIALE-A trial Overall survival

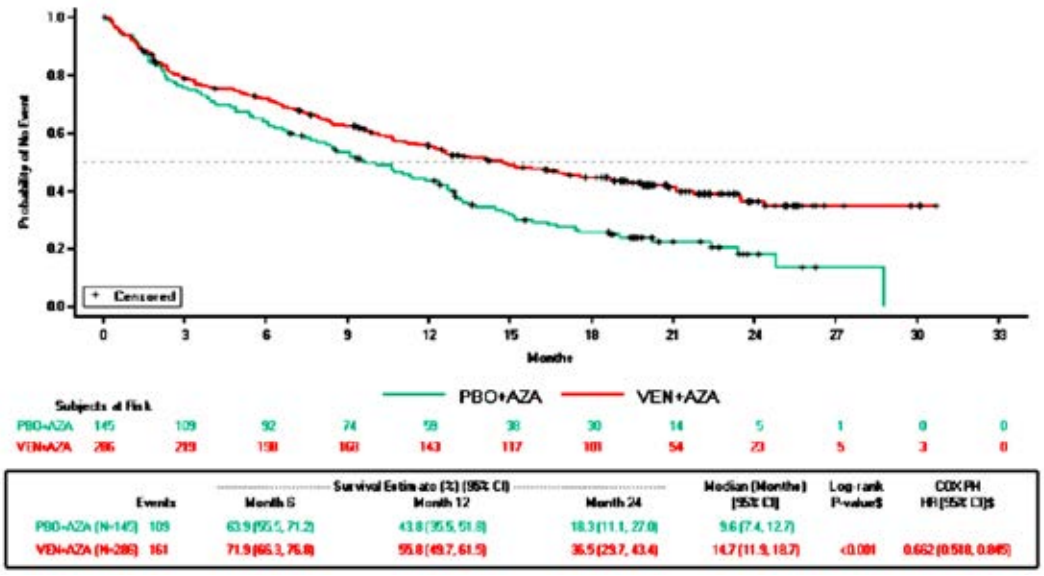
	Placebo + azacitidine (N = 145)	**Venetoclax 400 mg once daily + azacitidine (N = 286)**
Events (deaths) - n (%)	109 (75.2%)	161 (56.3%)
Duration of Overall Survival (months)		
25th (95% CI)	3.4 (2.1, 4.9)	4.8 (2.8, 6.5)
Median (95% CI)	9.6 (7.4, 12.7)	14.7 (11.9, 18.7)
75th (95% CI)	18.7 (14.7, 28.8)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

AZA = azacitidine; CI = confidence interval; IVRS = interactive voice response system; IWRS = interactive web response system; N = sample size; n = number of patients; NR = not reached; PBO = placebo; VEN = venetoclax

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

The Kaplan Meier curve for overall survival is presented below (Figure 2 and Table 7).

Figure 2: VIALE-A trial Overall survival curve

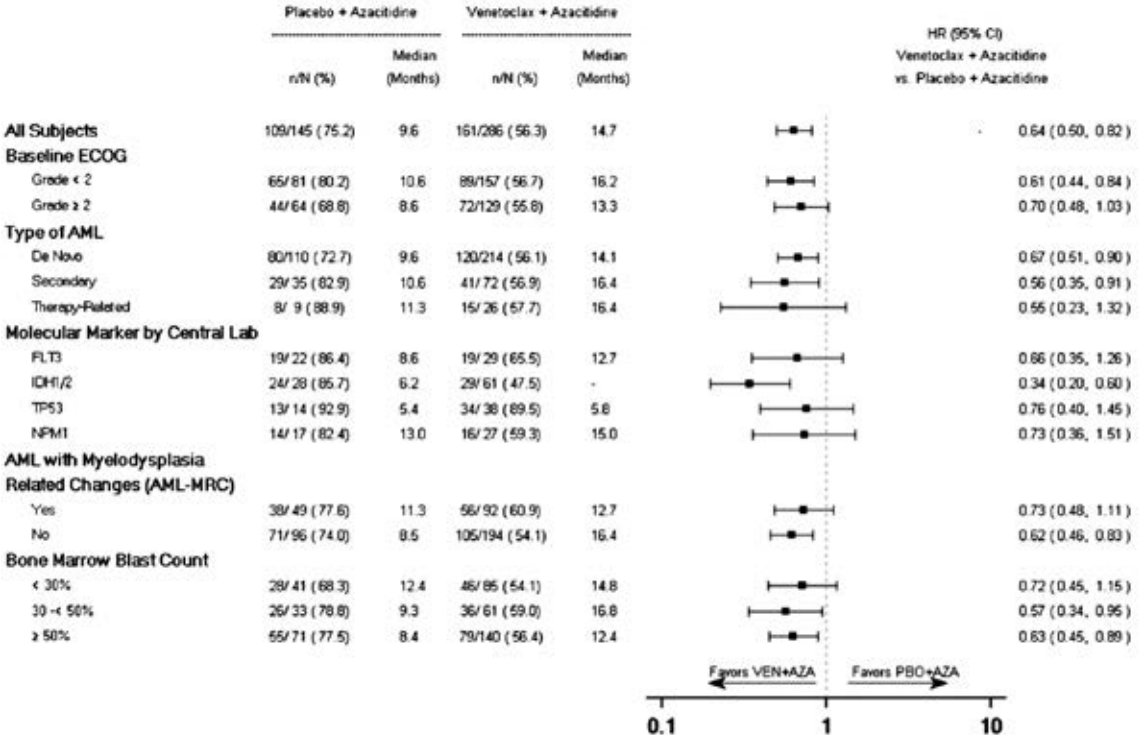


AZA = azacitidine; IVRS = interactive voice response system; IWRS = interactive web response system; PBO = placebo; VEN = venetoclax

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

Note: Data included are subjected to cutoff date 4 January 2020

Table 7: VIALE-A trial Forest plot for overall survival primary endpoint



Complete remission plus complete remission with incomplete blood count recovery

The complete remission (CR) plus complete remission with incomplete blood recovery (CRi), or the composite complete remission (CR plus CRi) was a co-primary endpoint in the EU and Japan. The results are tabulated below.

Table 8: VIALE-A trial Composite complete remission

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

AZA = azacitidine; CI = confidence interval; CR + CRi = composite complete remission; IA1 = interim analysis 1; IVRS = interactive voice response system; N = sample size; n = number of subject; Pbo = placebo; VEN = venetoclax

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

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

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

Data included are subject to a cutoff date of 1 October 2018

An analysis of CR plus CRi (investigator assessed, including Group 2 added after protocol amendment 1)(N = 431) showed venetoclax in combination with azacitidine, 66.4% (CR of 36.7% and CRi of 29.7%) versus the placebo in combination with azacitidine, 28.3% (CR of 17.9% and CRi of 10.3%) (p value < 0.001).

Secondary endpoints

A summary of secondary endpoints is included below (Table 9)

Table 9: VIALE-A trial Secondary efficacy endpoints

Parameter	Placebo + azacitidine (N = 145)	Venetoclax + azacitidine (N = 286)
CR + CRh Rate and Duration of Response		
Responders; n (%) [95% CI]	33 (22.8) [16.2, 30.5]	185 (64.7) [58.8, 70.2]
p-value (CMH test)	p < 0.001	
Duration of Response (months); median (95% CI)	13.9 (10.4, 15.7)	17.8 (15.3, NR)
CR + CRh Rate by the Initiation of Cycle 2		
Responders; n (%) [95% CI]	8 (5.5) [2.4, 10.6]	114 (39.9) [34.1, 45.8]
p-value (CMH test)	p < 0.001	
Postbaseline RBC Transfusion Independence		
Responders; n (%) [95% CI]	51 (35.2%) [27.4%, 43.5%]	171 (59.8%) [53.9%, 65.5%]

Parameter	Placebo + azacitidine (N = 145)	Venetoclax + azacitidine (N = 286)
p-value (CMH test)	p < 0.001	
CR + CRh Rate in IDH1/IDH2		
Responders; n/N (%) [95% CI]	2/28 (7.1) [0.9, 23.5]	44/61 (72.1) [59.2, 82.9]
p-value (Fisher's exact test)	p < 0.001	
CR Rate and Duration of Response		
Responders; n/N (%) [95% CI]	26 (17.9) [12.1, 25.2]	105 (36.7) [31.1, 42.6]
p-value (CMH test)	p < 0.001	
Duration of Response (months); median (95% CI)	13.3 (8.5, 17.6)	17.5 (15.3, NR)
CR + CRh Rate in FLT3		
Responders; n/N (%) [95% CI]	4/22 (18.2) [5.2, 40.3]	19/29 (65.5) [45.7, 82.1]
p-value (Fisher's exact test)	p = 0.001	
Postbaseline Platelet Transfusion Independence		
Responders; n (%) [95% CI]	72 (49.7%) [41.3%, 58.1%]	196 (68.5%) [62.8%, 73.9%]
p-value (CMH test)	p < 0.001	
Overall Survival in IDH1/IDH2		
Number of patients with events; n/N	24/28	29/61
Median OS months (95% CI)	6.2 (2.3, 12.7)	NR (12.2, NR)
HR (p-value from unstratified log-rank test)	0.345 (p < 0.0001)	
Overall Survival in FLT3		
Number of patients with events; n/N	19/22	19/29
Median OS months (95% CI)	8.6 (5.9, 14.7)	12.7 (7.3, 23.5)
HR (p-value from unstratified log-rank test)	0.664 (p = 0.2054)	

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

Data cutoff 04 January 2020.

The best haematological response data are summarised below in Table 10.

Table 10: VIALE-A trial Best overall response

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

AZA = azacitidine; CI = confidence interval; CR = complete remission; CRh = complete remission with partial haematologic recovery; IVRS = interactive voice response system; IWRS = interactive web response system; N = sample size; n = number of patients; PBO = placebo; SD = standard deviation; VEN = venetoclax

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

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

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

Note: Data included are subject to a cutoff date of 4 January 2020

Study M14-358

Study M14-358 is an ongoing Phase Ib, single arm trial multicentre, multinational, to evaluate the efficacy, PK, and safety of orally administered venetoclax combined with azacitidine or decitabine, respectively, in newly diagnosed patients with AML with intermediate or poor risk cytogenics greater or equal to 60 years of age and who are not eligible for standard induction therapy due to comorbidity or other factors. The study had a dose escalation initial stage (n = 45), followed by a dose expansion stage in two parts: Expansion 1 with patients aged greater or equal to 65 years (n = 25, each group treated with 400 mg or 800 mg of venetoclax, in combination with azacitidine or decitabine); Expansion 2 with patients aged greater or equal to 60 years, fulfilling Ferrara criteria (n = 55) taking 400 mg venetoclax, in combination of azacitidine. Those aged greater or equal to 75 years could be ECOG PS status 0 to 2,[7] and those over greater or equal to 60 years but younger than 75 years could be ECOG PS status 3.[7] All required adequate renal and liver function. This study supported the provisional registration of venetoclax in combination with chemotherapy for AML.

In the 2018 data, the complete remission (CR) rate for patients who met the modified Ferrara criteria and were treated with venetoclax in combination with azacitidine was 37% and the CR plus complete remission with partial haematologic recovery (CRh) rate

was 61.2%. For venetoclax in combination with decitabine, the CR rate was 54% and the CR plus CRh rate was 61.5%.

In updated data from the 19 July 2019 data cut-off, the CR rate for venetoclax in combination with azacitidine is 43.3% and the CR plus CRh rate is 61.2%, indicating that with additional follow up, three patients had continued count recovery meeting CR criteria from prior CRh determination. For venetoclax in combination with decitabine, the CR rate is 53.8% and CR plus CRh rate is 61.5%, unchanged from the prior data cut. The median duration of CR for the azacitidine combination was 23.8 months (95% CI: 15.4, upper bound not reached) and for the decitabine combination was 12.7 months (95% CI: 1.4, upper bound not reached).

VIALE-C trial

The Viale-C trial was a multicentre, multinational, Phase III, randomised (2:1), double blind, placebo controlled trial that compared venetoclax in combination with low dose cytarabine (n = 143) versus placebo in combination of low dose cytarabine (n = 68). Randomisation was stratified by AML status, age and region.

The VIALE-C trial was similar in design the patient populations, but the following are of note:

- VIALE-A trial excluded patients with prior exposure to hypomethylating agents (HMA) for myelodysplastic syndromes, while VIALE-C trial allowed patients treated with an HMA for this indication;
- VIALE-A trial enrolled only patients with an intermediate or poor cytogenetic risk, while VIALE-C trial also allowed patients with favourable cytogenetic risk.

The venetoclax dosing in this study was 600 mg once daily compared with 400 mg once daily in the VIALE-A trial.

Table 11: VIALE-C trial Summary of study design

VIALE-C study design
First patient first visit: 24 May 2017 Data cut-off date for this analysis: 15 February 2019, 6 month follow up 15 August 2019, ongoing. Clinical study report (CSR) date: 20 March 2020 76 sites across 20 countries
Summary of study, treatment and patient flow • 211 patients randomised, 211 for the efficacy analysis VEN+LDAC (n=143), PBO+LDAC (n=68). • Treatment arms: – VEN dosing: 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, then 600 mg once daily each 28 day cycle, matching placebo – LDAC dosing: 20mg/m^2 once daily SC on Days 1 to 10 of each 28-day cycle – VEN+ LDAC vs PBO+LDAC – Once bone marrow assessment confirmed remission, (< 5% leukaemia blasts with cytopenia) after Cycle 1 treatment, VEN or PBO was interrupted up to 14 days or until ANC ≥500/µL and platelet count ≥50 × 10^9/L. If resistant disease at the end of Cycle 1, a BM assessment was performed after Cycle 2 or 3 and as clinically indicated. LDAC resumed on the same day as VEN or PBO after interruption.

<table>
<tr><th colspan="2">VIALE-C study design</th></tr>
<tr><td colspan="2">– Continued treatment to disease progression or unacceptable toxicity
• At 15 August 2019 data cut:
– Completed treatment:103 from VEN+LDAC arm and 56 from PBO+LDAC arm
– Discontinued treatment 92.6% of PBO+LDAC arm and 81.8% of VEN+LDAC arm
– Discontinued due to morphologic relapse: 16.1% VEN+LDACarm
– Died: 11.8% PBO+LDAC arm vs 12.6% VEN+LDAC arm
– Discontinued due to adverse events: 10% PBO+LDAC arm (LDAC only) vs 10.5% VEN+LDAC arm
– Discontinued due to progressive disease: 13.7% PBO+LDAC arm vs 11.9% VEN+LDAC arm</td></tr>
<tr><td>Key inclusion criteria: Aged ≥ 75 years of age, OR Aged ≥ 18 to 74 years of age and AT LEAST ONE of:
• History of congestive heart failure requiring treatment or ejection fraction ≤ 50% or chronic stable angina;
• Diffusing Capacity of the Lung for Carbon Monoxide ≤ 65% or Forced Expiratory Volume in 1 Second ≤ 65%;
• CrCl ≥ 30 mL/min to < 45 mL/min;
• Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN;
• Eastern Cooperative Oncology Group (ECOG) Performance Status of 2 or 3; or
• Other (physician judged) comorbidity incompatible with intensive chemotherapy (reviewed and approved by Therapeutic Area Medical Director during screening).</td><td>Key exclusion criteria:
• History of myeloproliferative neoplasm including myelofibrosis, essential thrombocythemia, polycythemia vera, chronic myeloid leukaemia with or without BCR-ABL1 translocation, and transformation to AML with BCR-ABL1 translocation;
• Acute promyelocytic leukaemia;
• Known active central nervous system (CNS) involvement with AML;
• Known HIV, Hep B, or Hep C infections;
• Strong ± moderate CYP3A inducers < 7 days prior to start of study treatment.
• New York Heart Association Class > 2;
• Previously treated with VEN, ± chemotherapy for MDS, CAR-T cell therapy</td></tr>
<tr><td colspan="2">Endpoints</td></tr>
<tr><td colspan="2">Primary: Overall survival
Secondary: CR + CRh rate, CR + CRi rate; CR + CRh rate in IDH1/IDH2 subgroup; CR, CR+CRh by start of cycle 2; post baseline RBC transfusion independence; MRD and CR +CRh response rate; MRD and CR +CRi response rate; PROMIS Cancer fatigue SF-7a; EORTC QLQ=C30 GHS/QoL; OS in IDH1/IDH2 subgroup; OS in FLT3 subgroup; CR+CRh rate in FLT3 subgroups; EFS
Disease assessments performed by investigator per the IWG response criteria for AML.</td></tr>
<tr><td colspan="2">Endpoint definitions</td></tr>
<tr><td colspan="2">Same as VIALE-A trial</td></tr>
</table>

VIALE-C study design
Statistics
Randomised 2:1 stratified by AML status (de novo, secondary) and age (18 to < 75, ≥ 75 years). **Primary endpoint**: 133 OS events required for final analysis, giving 90% power to detect HR0.545 for VEN+LDAC vs LDAC, assumed median OS for VEN+LDAC increased from 6-11 months IA planned for 100 events (75% planned) OS analysis stratified by AML status (de novo, secondary) and age (stratified by age (18 -≤75, 75)) Secondary endpoints of CR + CRh rate, CR rate, CR + CRh rate by initiation of cycle 2, and postbaseline RBC and platelet transfusion independence rate were based on the CMH test stratified by AML status (de novo, secondary) and age (18 to < 75, ≥ 75 years). **Multiplicity**: Fixed sequence testing at 0.05 (two-sided) for OS then key secondary endpoints sequentially. If primary endpoint not significant no statistical significance would be claimed for secondary endpoints.
Protocol Amendments and Deviations
Major amendments: Five versions of the study protocol with the final amendment allowing unblinding of the patient assignment after the final analysis results to allow discussion of next treatment (impact uncertain).

CSR = clinical study report; PBO = placebo; LDAC = low dose cytarabine; VEN = venetoclax; BM = bone marrow; ANC = absolute neutrophil count; CR = complete remission; CRi = Complete remission with incomplete blood count recovery; ECOG = Eastern Cooperative Oncology Group; BCR-ABL1 = B-cell receptor-tyrosine-protein kinase ABL1; NCCN = National Comprehensive Cancer Network; CNS = central nervous system; HMA = hypomethylating agent; EU = European Union; INV = investigator; IWG = international working group; US = United States of America; MDR = minimal residual disease; IDH1 = isocitrate dehydrogenase 1; IDH2 = isocitrate dehydrogenase 2; FLT3 = fms-like tyrosine kinase 3; EFS = event free survival; RBC = red blood cell; CRh = complete remission with partial haematologic recovery; PR = partial remission; MLFS= morphologic leukaemia-free state; RD = resistant disease; MR = morphologic relapse; PD = progressive disease; OS = overall survival; HR = hazard ratio.

Demographics and baseline characteristics

A tabulated summary of the demographic data is included below in Table 12.

The VIALE-C trial population was predominantly White and male patients, and with a median age of 76 years.

Table 12: VIALE-C trial Baseline demographic data

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

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

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

Around 50% of the patients had an ECOG PS status of 2 or 3.[7] More patients had *de novo* AML, had intermediate or poor cytogenetics, and most had no history of AML in with myelodysplasia related changes or myelodysplastic syndrome. Most had no prior use of a hypomethylating agent. More detail is included in the table below (Table 13).

Table 13: VIALE-C trial Baseline disease characteristics

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

AML = acute myeloid leukaemia; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; FLT 3 = FMS-like tyrosine kinase; HMA = hypomethylating agent; IDH = isocitrate dehydrogenase; LDAC = low dose cytarabine; MDS = myelodydsplastic syndrome; N = sample size; n = number of patients; NPM = nucleophosmin; PBO = placebo; RBS = red blood cell; TP = tumour protein; VEN = venetoclax

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

b Number of evaluable BMA specimens received at Baseline with mutations detected by MyAML assay

Note: Data included are subject to a cut-off date of 15 February 2019

Follow-up in this study was for 12 months. Duration of treatment was 3.9 months in the venetoclax in combination of low dose cytarabine arm and 1.7 months in the placebo in combination of low dose cytarabine arm.

Overall survival

The primary endpoint was overall survival. Below is a summary of the results followed by the Kaplan Meier curves for this endpoint (Table 14).

Table 14: VIALE-C trial Overall survival

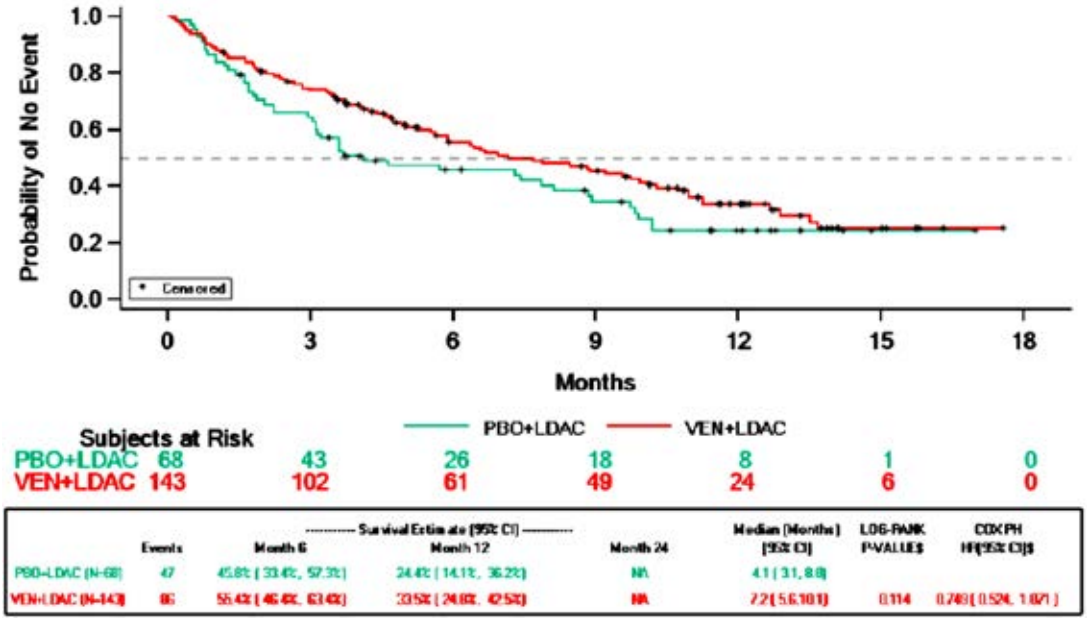
	PBO + LDAC (N = 68)	VEN 600 mg QD + LDAC (N = 143)
Events (deaths) - n (%)	47 (69.1%)	86 (60.1%)
Duration of Overall Survival (months)		
25th (95% CI)	1.7 (1.0, 3.0)	2.8 (1.8, 4.1)
Median (95% CI)	4.1 (3.1, 8.8)	7.2 (5.6,10.1)
75th (95% CI)	10.2 (8.8, NR)	NR (11.2, NR)
6-Month Survival Estimate (95%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

AML = acute myeloid leukaemia; CI = confidence interval; IVRS = interactive voice response system; IWRS = interactive web response system; LDAC = low dose cytarabine; N = sample size; n = number of patients; NA = not available; NR = not reached; PBO = placebo; VEN = venetoclax

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

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

Figure 3: VIALE-C trial Kaplan Meier curve overall survival



IVRS = interactive voice response system; IWRS = interactive web response system; LDAC = low dose cytarabine, PBO = placebo; VEN = venetoclax

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

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

Secondary endpoints

Table 15: VIALE-C trial Secondary endpoint summary

Parameter	PBO + LDAC (N = 68)	VEN + LDAC (N = 143)
CR + CRh Rate		
Primary Analysis		
Responders; n (%) [95% CI]	10 (14.7) [7.3, 25.4]	67 (46.9) [38.5, 55.4]
p-value	p < 0.001[a]	
Duration of Response (months); median (95% CI)	6.2 (1.1, -)	11.1 (5.5, -)
6-Month Follow-Up		
Responders; n (%) [95% CI]	10 (14.7) [7.3, 25.4]	69 (48.3) [39.8, 56.8]
p-value	p < 0.001[a]	
Duration of Response (months); median (95% CI)	8.3 (1.1, -)	11.7 (6.1, -)
CR + CRh by the Initiation of Cycle 2		
Primary Analysis		
Responders; n (%) [95% CI]	3 (4.4) [0.9, 12.4]	44 (30.8) [23.3, 39.0]
p-value	p < 0.001[a]	
6-Month Follow-Up		
Responders; n (%) [95% CI]	3 (4.4) [0.9, 12.4]	44 (30.8) [23.3, 39.0]
p-value	p < 0.001[a]	
CR Rate		
Primary Analysis		
Responders; n (%) [95% CI]	5 (7.4) [2.4, 16.3]	39 (27.3) [20.2, 35.3]
p-value	p < 0.001[a]	
Duration of Response (months); median (95% CI)	8.3 (3.1, 8.3)	11.1 (5.9, -)
6-Month Follow-Up		
Responders; n (%) [95% CI]	5 (7.4) [2.4, 16.3]	40 (28.0) [20.8, 36.1]
p-value	p < 0.001[a]	
Duration of Response (months); median (95% CI)	8.3 (2.8, -)	17.1 (8.2, -)
Postbaseline RBC Transfusion Independence		
Primary Analysis		
Responders; n (%) [95% CI]	12 (17.6%) [9.5%, 28.8%]	58 (40.6%) [32.4%, 49.1%]
p-value	p = 0.001[a]	
6-Month Follow-Up		
Responders; n (%) [95% CI]	13 (19.1%) [10.6%, 30.5%]	62 (43.4%) [35.1%, 51.9%]
p-value	p < 0.001[a]	
Postbaseline Platelet Transfusion Independence		
Primary Analysis		
Responders; n (%) [95% CI]	22 (32.4%) [21.5%, 44.8%]	68 (47.6%) [39.1%, 56.1%]
p-value	p = 0.040[a]	
6-Month Follow-Up		
Responders; n (%) [95% CI]	22 (32.4%) [21.5%, 44.8%]	70 (49.0%) [40.5%, 57.4%]
p-value	p = 0.024[a]	

CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; LDAC = low dose cytarabine; MRD = minimum residual disease; N = sample size; n = number of patients; PBO = placebo; RBC = red blood cell; VEN = Venetoclax

a P-value is from Cochran-Mantel-Haenszel test stratified by age (18 to < 75, ≥ 75) and AML status (*de novo*, secondary) from IVRS/IWRS. Because statistical significance was not met for the primary objective in VIALE-C trial, statistical significant cannot be declared for any of the secondary efficacy endpoints. Therefore, these p-values are only descriptive in nature.

Note: data included are subject to a cutoff date of 15 February 2019 for the primary analysis and 15 August 2019 for the 6 month follow up analysis

An analysis of the best response includes results for complete remission (CR) and the composite endpoint of complete remission including haematological response (CRh).

Table 16: VIALE-C trial Best overall response

	PBO + LDAC (N = 68)	VEN 600 mg QD + LDAC (N = 143)	p-value[a]
CR + CRh Rate (as best response) - n (%) [95% CI] [b]			
CR	5 (7.4) [2.4, 16.3]	39 (27.3) [20.2, 35.3]	<0.001***
CRh	5 (7.4) [2.4, 16.3]	28 (19.6) [13.4, 27.0]	
CR + CRh	10 (14.7) [7.3, 25.4]	67 (46.9) [38.5, 55.4]	<0.001***
Patients with Best Response of CR + CRh – Mean (SD) Median [range]			
Time to First Response (months)			
CR + CRh	2.8 (1.83) 2.8 [0.9 - 6.5]	1.8 (1.33) 1.0 [0.7 - 5.8]	
Time to Best Response (months)			
CR	3.7 (3.39) 3.7 [0.9 - 9.2]	2.3 (1.66) 1.3 [0.9 - 5.9]	
CRh	3.4 (2.19) 3.7 [1.0 - 6.5]	2.2 (1.50) 1.4 [0.8 - 5.8]	
CR + CRh	3.5 (2.70) 3.7 [0.9 - 9.2]	2.3 (1.58) 1.3 [0.8 - 5.9]	
CR + CRh Rate (as best response) by Initiation of Cycle 2 - n (%) [95% CI][b]			
CR	2 (2.9) [0.4, 10.2]	23 (16.1) [10.5, 23.1]	
CRh	1 (1.5) [0.0, 7.9]	21 (14.7) [9.3, 21.6]	
CR + CRh	3 (4.4) [0.9, 12.4]	44 (30.8) [23.3, 39.0]	<0.001***

AML = acute myeloid leukaemia; CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; IVRS = interactive voice response system; IWRS = interactive web response system; LDAC = low dose cytarabine; N = sample size; n = number of patients; SD = standard deviation

a p-value is from Cochran-Mantel-Haenszel test stratified by age (18 to < 75, ≥ 75) and AML status (*de novo*, secondary) from IVRS/IWRS.

b 95% CI is from exact binomial distribution

Note: ***. **. * statistically significant cannot be declared for any of the secondary efficacy endpoints. Therefore, these p-value are only for descriptive in nature.

Note: data included are subject to a cutoff date of 15 February 2019 for the (primary analysis)

There was a greater CR plus CRh response for venetoclax in combination with low dose cytarabine by intermediate cytogenetic risk, poor cytogenetic risk, primary AML, secondary AML, acute myeloid leukaemia with myelodysplasia related changes (AML-MRC) and with prior hypomethylating agents for myelodysplastic syndome.

At the 15 August 2019 data cutoff, 117 patients (81.8%) in venetoclax with low dose cytarabine combination arm and 63 patients (92.6%) in placebo with low dose cytarabine combination arm had discontinued treatment, and around 75% overall had discontinued the study. Death had occurred in 69.7% of the venetoclax in combination with low dose cytarabine arm and 79.4% in the placebo in combination with low dose cytarabine arm. The hazard ratio for overall survival was 0.70 (95% CI: 0.50, 0.99); nominal p-value = 0.040.

Study M14-387

Study M14-387 was a Phase I/II, multicentre, open label, single arm study of 82 adults with newly diagnosed AML ineligible for standard induction therapy. Patients received venetoclax 600 mg in combination with low dose cytarabine (20 mg/m^2). The efficacy population were 61 patients who were greater or equal to 75 years of age or who had comorbidities that precluded standard intensive induction chemotherapy. In combination with low dose cytarabine, the CR rate was 21% (95% CI: 12, 34) with a median duration of CR of 22.9 months (95% CI: 5.1 to not reached). The CRh rate was 21%.

Safety

The safety data set was derived 622 adult patients with AML exposed to at least one dose of venetoclax in the clinical studies and 212 patients exposed to a placebo combinations (See Table 17).

The sponsor has tabulated the adverse events for each study in the submission as follows in Table 17.

Table 17: Overall safety summary

SOC and PT, n (%) (MedDRA, v21.0)	VIALE-A PBO +Aza (N = 144)	VIALE-A VEN (400 mg) + AZA (N = 283)	M14-358 VEN (400 mg) + AZA (N = 84)	M14-358 VEN (400 mg) + DEC (N = 31)	VIALE-C PBO + LDAC (N = 68)	VIALE-C VEN (600 mg) + LDAC (N = 142)	M14-387 VEN (600 mg) + LDAC (N = 82)
Any AE	144 (100)	283 (100)	84 (100)	31 (100)	67 (98.5)	141 (99.3)	82 (100)
Blood and lymphatic system disorders	100 (69.4)	236 (83.4)	61 (72.6)	24 (77.4)	51 (75.0)	115 (81.0)	67 (81.7)
Anaemia	30 (20.8)	78 (27.6)	25 (29.8)	8 (25.8)	15 (22.1)	41 (28.9)	25 (30.5)
Febrile neutropenia	27 (18.8)	118 (41.7)	33 (39.3)	20 (64.5)	20 (29.4)	46 (32.4)	36 (43.9)
Leukopenia	20 (13.9)	58 (20.5)	2 (2.4)	0	5 (7.4)	14 (9.9)	2 (2.4)
Neutropenia	42 (29.2)	119 (42.0)	17 (20.2)	3 (9.7)	12 (17.6)	69 (48.6)	24 (29.3)
Thrombocytopenia	58 (40.3)	130 (45.9)	21 (25.0)	7 (22.6)	27 (39.7)	65 (45.8)	32 (39.0)
Cardiac disorders	37 (25.7)	88 (31.1)	34 (40.5)	10 (32.3)	16 (23.5)	26 (18.3)	31 (37.8)
Eye disorders	15 (10.4)	29 (10.2)	17 (20.2)	5 (16.1)	7 (10.3)	19 (13.4)	10 (12.2)
Gastrointestinal disorders	112 (77.8)	241 (85.2)	78 (92.9)	29 (93.5)	47 (69.1)	106 (74.6)	78 (95.1)
Abdominal pain	12 (8.3)	31 (11.0)	16 (19.0)	9 (29.0)	3 (4.4)	17 (12.0)	14 (17.1)
Constipation	56 (38.9)	121 (42.8)	42 (50.0)	16 (51.6)	22 (32.4)	29 (20.4)	30 (36.6)
Diarrhoea	48 (33.3)	117 (41.3)	51 (60.7)	14 (45.2)	12 (17.6)	47 (33.1)	41 (50.0)
Nausea	50 (34.7)	124 (43.8)	54 (64.3)	20 (64.5)	21 (30.9)	61 (43.0)	57 (69.5)
Vomiting	33 (22.9)	84 (29.7)	32 (38.1)	12 (38.7)	10 (14.7)	41 (28.9)	25 (30.5)
General disorders and administration site conditions	95 (66.0)	195 (68.9)	76 (90.5)	27 (87.1)	35 (51.5)	76 (53.5)	66 (80.5)
Fatigue	24 (16.7)	59 (20.8)	30 (35.7)	14 (45.2)	10 (14.7)	22 (15.5)	35 (42.7)
Oedema peripheral	26 (18.1)	69 (24.4)	34 (40.5)	10 (32.3)	14 (20.6)	20 (14.1)	15 (18.3)
Pyrexia	32 (22.2)	66 (23.3)	25 (29.8)	10 (32.3)	13 (19.1)	25 (17.6)	18 (22.0)
Infections and infestations	97 (67.4)	239 (84.5)	65 (77.4)	25 (80.6)	41 (60.3)	92 (64.8)	60 (73.2)
Bacteraemia	0	7 (2.5)	4 (4.8)	7 (22.6)	0	4 (2.8)	3 (3.7)
Pneumonia	39 (27.1)	65 (23.0)	27 (32.1)	12 (38.7)	11 (16.2)	31 (21.8)	13 (15.9)
Injury, poisoning and procedural complications	42 (29.2)	83 (29.3)	40 (47.6)	17 (54.8)	9 (13.2)	38 (26.8)	29 (35.4)
Contusion	12 (8.3)	10 (3.5)	12 (14.3)	7 (22.6)	2 (2.9)	4 (2.8)	2 (2.4)
Investigations	56 (38.9)	136 (48.1)	66 (78.6)	24 (77.4)	22 (32.4)	54 (38.0)	56 (68.3)
Blood bilirubin increased	5 (3.5)	21 (7.4)	8 (9.5)	4 (12.9)	1 (1.5)	16 (11.3)	19 (23.2)
Neutrophil count decreased	1 (0.7)	8 (2.8)	23 (27.4)	9 (29.0)	3 (4.4)	10 (7.0)	14 (17.1)
Platelet count decreased	1 (0.7)	13 (4.6)	25 (29.8)	15 (48.4)	4 (5.9)	8 (5.6)	21 (25.6)
White blood cell count decreased	2 (1.4)	11 (3.9)	28 (33.3)	14 (45.2)	4 (5.9)	10 (7.0)	28 (34.1)
Metabolism and nutrition disorders	79 (54.9)	175 (61.8)	68 (81.0)	25 (80.6)	40 (58.8)	87 (61.3)	68 (82.9)
Decreased appetite	25 (17.4)	72 (25.4)	25 (29.8)	10 (32.3)	13 (19.1)	31 (21.8)	30 (36.6)
Hypocalcaemia	8 (5.6)	17 (6.0)	7 (8.3)	2 (6.5)	8 (11.8)	13 (9.2)	23 (28.0)
Hypokalaemia	41 (28.5)	81 (28.6)	29 (34.5)	11 (35.5)	17 (25.0)	44 (31.0)	40 (48.8)
Hypomagnesaemia	5 (3.5)	21 (7.4)	12 (14.3)	8 (25.8)	6 (8.8)	13 (9.2)	28 (34.1)
Hyponatraemia	7 (4.9)	16 (5.7)	8 (9.5)	0	7 (10.3)	9 (6.3)	18 (22.0)
Hypophosphataemia	17 (11.8)	35 (12.4)	22 (26.2)	4 (12.9)	4 (5.9)	5 (3.5)	24 (29.3)
Musculoskeletal and connective tissue disorders	50 (34.7)	110 (38.9)	48 (57.1)	23 (74.2)	18 (26.5)	44 (31.0)	46 (56.1)
Back pain	13 (9.0)	24 (8.5)	13 (15.5)	6 (19.4)	5 (7.4)	9 (6.3)	17 (20.7)
Musculoskeletal pain	5 (3.5)	18 (6.4)	7 (8.3)	7 (22.6)	3 (4.4)	5 (3.5)	1 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (6.3)	18 (6.4)	1 (1.2)	8 (25.8)	4 (5.9)	6 (4.2)	6 (7.3)
Nervous system disorders	39 (27.1)	107 (37.8)	57 (67.9)	21 (67.7)	15 (22.1)	49 (34.5)	45 (54.9)
Dizziness	10 (6.9)	37 (13.1)	22 (26.2)	12 (38.7)	2 (2.9)	12 (8.5)	11 (13.4)
Headache	10 (6.9)	30 (10.6)	21 (25.0)	10 (32.3)	3 (4.4)	20 (14.1)	24 (29.3)
Psychiatric disorders	37 (25.7)	71 (25.1)	42 (50.0)	16 (51.6)	19 (27.9)	38 (26.8)	46 (56.1)
Insomnia	15 (10.4)	35 (12.4)	20 (23.8)	8 (25.8)	9 (13.2)	20 (14.1)	17 (20.7)
Renal and urinary disorders	33 (22.9)	71 (25.1)	30 (35.7)	10 (32.3)	11 (16.2)	23 (16.2)	24 (29.3)
Respiratory, thoracic and mediastinal disorders	60 (41.7)	138 (48.8)	67 (79.8)	25 (80.6)	25 (36.8)	54 (38.0)	54 (65.9)
Cough	20 (13.9)	35 (12.4)	17 (20.2)	10 (32.3)	6 (8.8)	14 (9.9)	20 (24.4)
Dyspnoea	11 (7.6)	37 (13.1)	25 (29.8)	5 (16.1)	5 (7.4)	11 (7.7)	23 (28.0)
Epistaxis	12 (8.3)	26 (9.2)	17 (20.2)	4 (12.9)	3 (4.4)	15 (10.6)	12 (14.6)
Oropharyngeal pain	6 (4.2)	25 (8.8)	9 (10.7)	8 (25.8)	3 (4.4)	6 (4.2)	8 (9.8)
Pleural effusion	8 (5.6)	28 (9.9)	17 (20.2)	4 (12.9)	5 (7.4)	5 (3.5)	11 (13.4)

AML = acute myeloid leukaemia; AZA = azacitidine; DEC = decitabine; HMA = hypomethylating agent; LDAC = low dose cytarabine; MedDRA = Medical Dictionary for Regulatory Activities; N = sample size; n = number of patients; PBO = placebo; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; VEN = venetoclax

VIALE-A trial

VIALE-A trial includes data from venetoclax 400 mg daily dose when used in combination with azacitidine. At the time of the primary analysis, the median duration of treatment was 7.6 months (range: < 0.1 to 30.7 months) in the venetoclax in combination with azacitidine arm and 4.3 months (range: 0.1 to 24.0 months) in the placebo in combination with azacitidine arm.

The most common events reported occurring in a higher proportion for venetoclax when used in combination with azacitidine included thrombocytopenia, neutropenia, nausea, febrile neutropenia, diarrhoea, vomiting, anemia, decreased appetite, peripheral oedema, leukopenia, and asthenia. Grade ≥ 3 adverse events (AE) more commonly in the venetoclax when used in combination with azacitidine arm compared to placebo when used in combination with azacitidine arm were thrombocytopenia, neutropenia, febrile neutropenia, anaemia, leukopenia, and atrial fibrillation.

Deaths occurred in 75.7% of the placebo when used in combination with azacitidine arm and 56.2% of the venetoclax when used in combination with azacitidine arm. Of those, fatal AEs events occurred in 22.6% of the venetoclax when used in combination with azacitidine arm and 20.1% of the placebo when used in combination with azacitidine arm.

Serious adverse drug reactions (ADR) in the venetoclax when used in combination with azacitidine arm were seen in 83% of patients and were most commonly febrile neutropenia (30%), pneumonia (23%), sepsis (16%) and haemorrhage (9%). Adverse events resulting in deaths due to adverse events were reported in 23% of patients who received venetoclax and azacitidine combination arm with the most frequent (≥ 2%) being pneumonia (4%), sepsis (3%) and haemorrhage (2%).

Adverse events leading to study treatment discontinuation were reported for 69 patients (24.4%) treated with venetoclax 400 mg and azacitidine combination arms and 29 patients (20.1%) treated with placebo and azacitidine. The most commonly reported adverse events leading to venetoclax/placebo discontinuation in the venetoclax and azacitidine combination arm versus placebo and azacitidine combination arm were sepsis (1.4% versus 3.5%) and pneumonia (1.4% versus 2.8%), followed by neutropenia (1.4% versus 1.4%), febrile neutropenia (1.4% versus 0.7%), and thrombocytopenia (1.1% versus 2.1%).

Tumour lysis syndrome was reported in 1% of the venetoclax in combination low dose azacitidine arm.

VIALE-C trial

This study collected safety information from the use of venetoclax 600 mg once daily with low dose cytarabine (n = 142) versus placebo in combination of low dose cytarabine (n = 68). At the time of the primary analysis, the median duration of treatment was 3.9 months (range: < 0.1 to 17.1 months) in the venetoclax in combination with low dose cytarabine and 1.7 months (range: 0.1 to 14.2 months) in the placebo with low dose cytarabine arm.

The most common events reported for any grade and reported by a higher percentage of patients (≥ 5% of patients) receiving venetoclax in combination with low dose cytarabine compared to those with placebo with low dose cytarabine arm were neutropenia, thrombocytopenia, nausea, diarrhoea, hypokalaemia, anaemia, and vomiting. The most common (≥ 5%) Grade ≥ 3 AEs reported in a higher percentage of patients (by ≥ 2%) in

the venetoclax in combination with low dose cytarabine arm compared to the placebo with low dose cytarabine arm were neutropenia, thrombocytopenia, febrile neutropenia, anaemia, and leukopenia.

Deaths occurred in 79.4% of the placebo with low dose cytarabine arm and 69.7% of the venetoclax in combination with low dose cytarabine arm. Of those, fatal AEs events occurred in 23.2% of the venetoclax in combination with low dose cytarabine arm and 20.6% of the placebo with low dose cytarabine arm.

In the VIALE-C trial, AEs leading to study treatment discontinuation were similar across treatment arms and reported for 37 patients (26.1%) treated with venetoclax 600 mg once daily with low dose cytarabine and 16 patients (23.5%) treated with placebo in combination with low dose cytarabine. Adverse events that led to venetoclax discontinuation, reported in > 1 patient (venetoclax in combination with low dose cytarabine arm) included pneumonia (7 patients, 4.9%), febrile neutropenia, lung infection, sepsis, septic shock, and tumour lysis syndrome (TLS) (2 patients each, 1.4%). AEs leading to placebo discontinuation (placebo in combination with low dose cytarabine arm) reported in > 1 patient included febrile neutropenia and tumour associated fever (2 patients each, 2.9%). Serious ADRs were reported in 67% of patients in the venetoclax in combination with low dose cytarabine arm, with the most frequent (≥ 10%) being pneumonia (20%), febrile neutropenia (17%), and sepsis (13%). In the placebo in combination with low dose cytarabine arm, serious ADRs were reported in 62% of patients. The most frequent were febrile neutropenia (18%), sepsis (18%), and pneumonia (16%).

Tumour lysis syndrome was reported in 6% of the venetoclax in combination with low dose cytarabine arm.

Risk management plan

Venclexta has been granted orphan drug designation for the AML indication by the TGA. Venclexta was provisionally approved, on 5 February 2020, for the indication of AML through submission PM-2019-04393-1-6.[6]

For the indication of AML, the most recently evaluated core-risk management plan (RMP) was version 4.1 (June 2019; data lock point (DLP) 29 May 2019) and Australian specific annex (ASA) version 3.2 (July 2019). In support of this submission, the sponsor has submitted core-RMP version 6.1 (June 2020; DLP (AML) 4 January 2020 and DLP for chronic lymphocytic leukaemia (CLL) 17 August 2018) and ASA version 4.0 (May 2020).

In response to TGA questions, the sponsor provided ASA version 4.1 (December 2020), which relates to core-RMP version 6.1.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 18.[8]

[8] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 18: Summary of safety concerns and associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Tumour lysis syndrome (TLS)	ü[1]	–	ü[3,4]	–
	Neutropenia	ü	–	ü	–
	Serious infection	ü[1]	–	ü	–
Important potential risks	Embryofetal toxicity	ü[1]	–	ü	–
	Medication error	ü	–	ü[3,4]	–
	Richter's transformation (for CLL only)	ü	ü[2]	–	–
	Second primary malignancy	ü	ü[2]	–	–
	Toxicity in patients with severe hepatic impairment	ü	–	ü	–
Missing information	Safety in severe renal impairment	ü	–	ü	–
	Safety in long-term exposure (> 12 months) (for CLL only)	ü	ü[2]	ü	–

1 Targeted follow-up questionnaire

2 Clinical trials

3 Patient Alert card as package insert in monthly starter pack for CLL indications

4 Quick start guide as package insert in monthly starter pack for CLL indications

The only change to the safety specification since it was last evaluated and accepted is the addition of 'for CLL only' to the missing information: 'Safety in long-term exposure (> 12 months)'. As this was due to the completion of clinical trial to monitor long-term safety (> 12 months) in AML patients, the summary of safety concerns is considered acceptable from an RMP perspective.

The sponsor states that routine pharmacovigilance activities for all safety concerns, which includes targeted follow-up forms for the risks of TLS, serious infections and embryonic toxicity, as previously accepted by the TGA, will continue. Additional pharmacovigilance activities, in the form of clinical trials in patients with CLL, have been evaluated and accepted in previous evaluation and continue to be acceptable. Overall, sponsor has not proposed changes to currently accepted pharmacovigilance plan for Venclexta and it continues to be acceptable.

The sponsor has proposed only routine risk minimisation to mitigate safety concerns. For the CLL indications, this includes a monthly starter pack with a quick start guide and a patient alert card in the product package. These are not required for the AML indication. This is the currently agreed risk minimisation plan for Venclexta and continues to be acceptable.

Risk-benefit analysis

Delegate's considerations

The sponsor is seeking conversion to full registration of venetoclax for use in AML for patients who are ineligible for intensive chemotherapy. These are older patients, or patients with significant co-morbidities. The patient populations included in the studies are considered sufficiently representative of the AML population who would be considered for this therapy.

The Phase Ib and Phase I/II studies were considered sufficient to support provisional registration.

- The key efficacy findings for venetoclax when used in combination with azacitidine were complete remission (CR) 40.5% with the median duration of response (DOR) > 14.6 months; CR plus complete remission with incomplete blood count recovery (CRi) 70.2% with median DOR > 8.2 months. Transfusion independence in 50% for red cells and 57.7% for platelets.
- The key efficacy findings for venetoclax when used in combination with low dose cytarabine were CR 25.6% with median DOR not reached; CR plus CRi 53.7% with median DOR 8.1 months. Transfusion independence in 43.4% for red cells and 65.2% for platelets.

The sponsor has provided two Phase III studies that compared venetoclax combined with another agent with that agent plus placebo. In this way, the sponsor has enabled an assessment of the contribution of venetoclax to the efficacy and safety of the combinations.

Efficacy evidence to support full registration of the venetoclax and azacitidine combination is from the VIALE-A trial, with data from 431 patients. The endpoints for this study were different for the USA and US-reference countries and for Japan and the EU and EU-reference countries. Overall survival events occurred in 75.2% of the placebo when used in combination with azacitidine arm and 56.3% of the venetoclax when used in combination with azacitidine arm: hazard ratio 0.66 (95% CI, 95% CI 0.52, 0.8; $p < 0.0001$). The endpoint of CR plus CRi was achieved in 65.3% of the venetoclax and azacitidine combination arm versus 25.3% of the placebo and azacitidine combination arm. Sensitivity analyses of this endpoint and the key secondary endpoints all support these findings of a benefit. These findings are considered support to the efficacy consideration for the venetoclax and azacitidine combination.

Efficacy evidence to support full registration of the venetoclax in combination with low dose cytarabine combination is less compelling and arises from the VIALE-C trial. The overall survival events occurred in 60.1% in the venetoclax in combination with low dose

cytarabine arm and 69.1% placebo in combination with low dose cytarabine arm: hazard ratio 0.75 (0.52, 1.07), p = 0.114. From a statistical perspective this is a failed study. However, the CR of 27% versus 7% with median duration of CR 11.1 months (95% CI, 6.1, upper bound not reached) versus 8.3 months (95% CI, 3.1, upper bound not reached), respectively, and there were numerical differences in favour of the venetoclax in combination with low dose cytarabine combination for haematological outcomes and for transfusion independence. It is noted the follow up in this study was shorter than for the VIALE-A trial.

This study is disadvantaged by its size. Drop outs reduced the power to detect differences and its failure to demonstrate benefit from a statistical perspective creates a regulatory challenge. While many of the other endpoints point towards a benefit in this study population and overall survival benefit has not been demonstrated. Overall survival is considered a robust endpoint. It also has assessed the efficacy and safety of a higher dose, although across the adverse events table this does not appear to have contributed significantly to the toxicity.

The sponsor provided an unplanned analysis with an additional 6 months follow up in which the overall survival hazard ratio was 0.70 (95% CI: 0.50, 0.99). The depletion of susceptible patients make this more difficult to interpret as the power of the study to robustly detect differences is diminished. The updated analysis from the provisional registration Phase I/II study adds support.

Across the VIALE-A and VIALE-C trials, safety findings are generally consistent with the findings of the early studies, and the follow up data from those early studies in this submission. The safety considerations including the risk of and mitigations strategies for tumour lysis syndrome have been taken into account and are not the main difficulty for this submission.

The safety is considered in the context of the patients in whom use is likely. Consistent with the baseline demographics in the study the patient groups, to be ineligible for intensive therapy the patients have significant comorbidities or age. Sensitivities to toxicity setting for the weighing of benefits and harms, so for more vulnerable patient groups the risk of harms must be very clearly outweighed by potential for benefits. While it is considered the sponsor has provided sufficient evidence to support its proposed venetoclax and azacitidine combination, it is less clear for the venetoclax and low dose cytarabine combination.

It is noted that internationally there are different approaches to the indication and that in the EU only the combination of venetoclax and hypomethylating agents has been approved. No Phase III data were provided for the combination of venetoclax and decitabine and decitabine is not currently registered in Australia except in combination with cedazuridine in a fixed dose combination.

Overall the clinical pharmacology analyses are supportive of the proposed venetoclax dosing regimens in combination with an hypomethylating agent or low dose cytarabine in patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

There is no apparent need for dose adjustment in patients were severe renal disease, based on the additional data from a total of 6 patients with creatinine clearance ≥ 15 mL/min and < 30 mL/min, the updated population PK analysis in this submission, and the previous findings that renal excretion accounted for < 1% of the administered dose.

Proposed action

In this preliminary consideration, it is the view of the Delegate that sufficient evidence to support the safety and efficacy of venetoclax when used in combination with azacitidine

has been provided. In this setting, the benefits of overall survival coupled with the haematological response and transfusion independence outweigh the potential harms.

For the combination of venetoclax and low dose cytarabine, the contribution of venetoclax is less clear. The overall survival did not meet statistical significance; however, haematological responses appeared favourable for venetoclax and low dose cytarabine. The magnitude of benefit for haematological responses is generally consistent with the Phase I/II study. The advice of the Advisory Committee on Medicines (ACM) is sought regarding the benefits over harms for this combination and whether based on the totality of the efficacy evidence benefits for haematological response, notwithstanding the lack of demonstrated survival benefit, are sufficient to support use in this context.

Advisory Committee considerations[9]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***Please comment on whether sufficient evidence of efficacy has been presented to support the full registration of the combination of venetoclax and low dose cytarabine in acute myeloid leukaemia for patients ineligible for intensive chemotherapy.***

The ACM advised that they support the full registration of the combination of venetoclax and low dose cytarabine in acute myeloid leukaemia for patients ineligible for intensive chemotherapy, based on a totality of evidence approach. While the level of evidence is not as robust as for the combination of venetoclax and azacitidine, the ACM advised that venetoclax and low dose cytarabine may be a reasonable combination offering to some patients, including those who cannot tolerate azacitidine. The ACM agreed that the combination of venetoclax and low dose cytarabine has an adequate safety profile, as the toxicity is understood and managed effectively in clinical practice. The ACM emphasised that AML patients who are ineligible for intensive chemotherapy are a difficult to treat group with limited treatment options.

2. ***The evidence in this submission and the provisional registration submission characterises specific venetoclax-based combinations. As a general principle, can the ACM please comment on the proposed approach of a more open indication to indicate venetoclax should be used as part of a combination in AML that does not define the components of the combination.***

While the ACM discussed the flexibility that a more open indication provides prescribers, on balance they advised that the current submission provides efficacy and safety data for the defined combination of venetoclax and azacitidine or low dose cytarabine, and therefore it is not considered appropriate for the indication to imply efficacy and safety has been established with any other second component of the combination.

The ACM noted that there are currently over 100 trials underway with venetoclax in combination with other agents and advised that the components of the combination therapy could be reconsidered at a regulatory level once further data are provided.

[9] The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm.

3. The ACM is invited to provide advice on any other matters it considers may contribute to the decision.

The ACM agreed that quality of life is an important factor in the management of AML, and that quality of life assessments are important for patients who would be considered for treatment with venetoclax and azacitidine or low dose cytarabine. The ACM emphasised that optimal care for patients with AML requires dialogue between healthcare providers and patients involving balancing goals of care and the relative risk-benefit balance of treatment.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Venclexta, in combination with azacitidine or low dose cytarabine, is indicated for the treatment of newly diagnosed adult patients with Acute Myeloid Leukaemia (AML) who are ineligible for intensive chemotherapy.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Venclexta (venetoclax) 10 mg, 50 mg and 100 mg, film coated tablets, blister pack and bottle, indicated for:

> *Acute Myeloid Leukaemia*
>
> *Venclexta, in combination with azacitidine or low-dose cytarabine, is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.*

The full indications are now:

> *Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma*
>
> *Venclexta in combination with obinutuzumab is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) who are considered unfit or unsuitable for chemo-immunotherapy.*
>
> *Venclexta in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.*
>
> *Venclexta monotherapy is indicated for the treatment of:*
>
> § *patients with relapsed or refractory CLL with 17p deletion, or*
>
> § *patients with relapsed or refractory CLL for whom there are no other suitable treatment options.*
>
> *Acute Myeloid Leukaemia*
>
> *Venclexta, in combination with azacitidine or low-dose cytarabine, is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.*

Specific conditions of registration applying to these goods

- Venclexta (Venetoclax) should remain in the Black Triangle Scheme. The PI and Consumer Medicine Information for venetoclax must include the black triangle symbol and mandatory accompanying text for five years, which started from the date the provisional indication was registered in February 2020.

- The Venclexta EU-RMP (version 8.0, dated May 2021, DLP (AML) 4 January 2020 and (CLL) 11 February 2021), with ASA (version 5.0 dated August 2021), related to submission PM-2020-02543-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Venclexta approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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