NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission** from AbbVie

2. **Clarification questions and company responses**
   a. Clarification response
   b. Additional Clarification response

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Leukaemia Care
   b. Royal College of Pathologists
   c. Royal College of Physicians-Association of Cancer Physicians-National Cancer Research Institute

4. **Evidence Review Group report** prepared by Aberdeen HTA Group

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Elspeth Payne – clinical expert, nominated by the Royal College of Pathologists
   b. Patient expert, nominated by Leukaemia Care

8. **Technical engagement responses from consultees and commentators:**
   a. Leukaemia Care
   b. Royal College of Pathologists
   c. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists
   d. Jazz Pharmaceuticals

9. Evidence Review Group critique of company response to technical engagement prepared by Aberdeen HTA Group

a. ERG critique
b. Addendum to ERG critique
c. ERG alternative cure timepoint scenarios

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Venetoclax with a hypomethylating agent or low-dose cytarabine for untreated acute myeloid leukaemia unsuitable for intensive chemotherapy [ID1564]

Document B

Company evidence submission

17th March 2021

File name	Version	Contains confidential information	Date
ID1564_Venetoclax AML_Company Submission_Document B_Fully Redacted	Final	No – Redacted	17th March 2020

Contents

Tables and figures

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AIC	Akaike information criterion
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukaemia
AZA	Azacitidine
Bcl-2	B-cell lymphoma 2
BIC	Bayesian information criteria
BIM	Bcl-2 interacting mediator of cell death
BSA	Body surface area
BSC	Best supportive care
CAR-T	Chimeric antigen receptor T-cells
CCR	Conventional care regimen
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CNS	Central nervous system
CPX-351	Liposomal cytarabine-daunorubicin
CR	Complete remission
CRD	Centre for Reviews and Dissemination
CRh	Complete remission with or without partial haematological recovery
CRi	Complete remission with incomplete blood count recovery
CRp	Complete remission with incomplete platelet recovery
CSR	Clinical study report
CYP3A	Cytochrome P450 3A isoform subfamily
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ELN	European LeukemiaNet
EMA	European Medicines Agency
eMIT	Drugs and Pharmaceutical Electronic Market Information Tool
EORTC	European Organisation Research and Treatment of Cancer
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
EU	European Union
FAS	Full analysis set

GHS	Global health status
HC/HU	Hydroxycarbamide/hydroxyurea
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
IA1	Interim analysis 1
IA2	Interim analysis 2
IC	Intensive chemotherapy
ICER	Incremental cost effectiveness ratio
IWRS	Interactive web response system
IPD	Individual patient data
IRT	Interactive response technology
IVRS	Interactive voice response system
JSMO	Japanese Society of Medical Oncology
LDAC	Low-dose cytarabine
LY	Life year
max	Maximum
MCT	Meaningful change threshold
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Multicolour flow cytometry
MID	Minimum important difference
MIDO	Midostaurin
MIMS	Monthly Index of Medical Supplies
min	Minimum
MLFS	Morphological leukaemia-free state
MPN	Myeloproliferative neoplasm
MR	Minor response
MRC	Myelodysplasia-related changes
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology
NHS	National Health Service
NMA	Network meta-analysis
NOS	Not otherwise specified
OR	Odds ratio
OS	Overall survival
PAS	Patient access scheme

PASLU	Patient Access Scheme Liaison Unit
PBO	Placebo
PD	Progressive disease
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSW	Propensity score weighting
PT	Preferred term
QALY	Quality-adjusted life year
QALY	Quality adjusted life year
QD	Once daily
QoL	Quality of life
RBC	Red blood cell
RCT	Randomised controlled trial
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SF-7a	Short form 7a
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	Standard of care
SUCRA	Surface under the cumulative ranking curve
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TLS	Tumour lysis syndrome
TRM	Treatment-related mortality
TSD	Technical support document
TTD	Time to deterioration
UK	United Kingdom
VBA	Visual Basic for Applications
Ven	Venetoclax
WHO	World Health Organisation

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

This submission covers the marketing authorisation (expected [redacted]) of venetoclax (Venclyxto®) [redacted] The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal with respect to the population, intervention, outcomes and comparators (with the exception of best supportive care [BSC]), and the NICE reference case. The differences between the decision problem addressed within this submission and the NICE final scope are outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated AML for whom IC is unsuitable	[redacted] This patient population is in line with the full anticipated marketing authorisation for VenAZA and VenLDAC in AML	In line with the final NICE scope.
Intervention	Venetoclax in combination with an HMA or LDAC	Venetoclax in combination with an HMA or LDAC. The decision problem addresses this by providing separate clinical and cost-effectiveness evidence for: • Venetoclax with azacitidine (VenAZA) • Venetoclax with LDAC (VenLDAC)	In line with the final NICE scope. Azacitidine (AZA) is the HMA used in UK clinical practice and hence would be the HMA used in combination with venetoclax in the UK upon a positive recommendation for this appraisal. Use of AZA as the HMA is in line with the VIALE-A trial.[1]
Comparator(s)	Established clinical management without venetoclax, for example: • LDAC • AZA for adults who are not eligible for haematopoietic stem cell transplantation (HSCT) and have AML with 20–30% blasts and multilineage dysplasia • BSC	The decision problem is split into distinct populations:[1, 2] • VenAZA comparators: o Blast cell count 20–30%: AZA o Blast cell count >30%: LDAC • VenLDAC comparators: o Blast cell count >30%: LDAC	Given that the use of AZA is only recommended by NICE for patients with a blast cell count of 20–30%, comparisons have been split into two populations: AML with 20–30% blasts and AML with >30% blasts. LDAC is not restricted by blast cell count but, in clinical practice, it is used in patients with blast cell counts of >30%, as AZA is used in patients with blast cell counts of 20–30%. Therefore, in this appraisal VenLDAC is compared only with LDAC in patients with >30% blasts. This approach has been validated by UK clinicians experienced in the treatment of AML. BSC is not considered a relevant comparator for this appraisal. Patients who receive BSC alone are not considered fit for treatment with

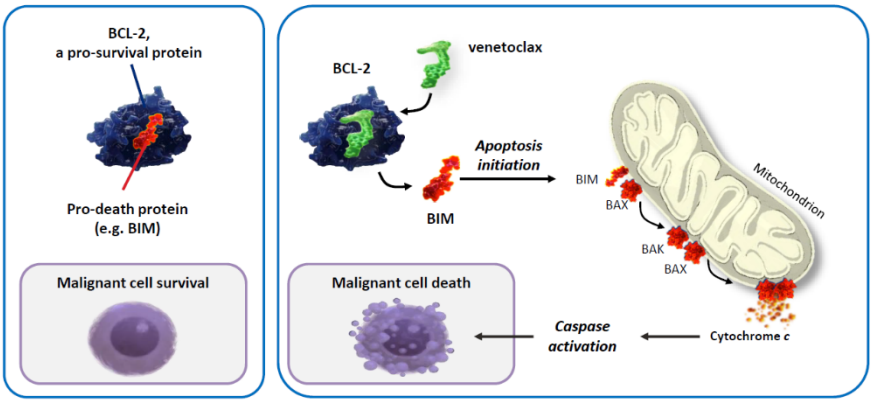
			AZA or LDAC due to being frail or elderly, or refusing treatment. This is evidenced by data from real-world clinical practice in the UK, which demonstrate that those who receive BSC comprise a different population to those who would receive VenAZA or VenLDAC (e.g. when considering age and performance status), and has been validated by UK clinicians.[3, 4]
Outcomes	The outcome measures to be considered include: • Overall survival • Event-free survival • Disease-free survival • Response rates, including remission • Blood transfusion dependence • Adverse effects of treatment • Health-related quality of life	The outcome measures considered include: • Overall survival • Event-free survival • Duration of response • Response rates, including remission • Blood transfusion dependence • Adverse effects of treatment • Health-related quality of life • Minimal residual disease (MRD)	Whilst disease-free survival data were not explicitly collected in the VIALE-A and VIALE-C trials, duration of response data were collected, which describe the time spent in a disease-free state. Whilst not specified in the NICE scope, MRD negativity has been included in the submission as it serves as a marker of the depth of response to treatment, and has been shown to be correlated with long-term disease free survival.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per final scope and NICE reference case	In line with the NICE final scope

	Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	No subgroup analyses were specified in the NICE scope	The decision problem will be split into two distinct populations according to blast cell count, since the relevant comparators differ in these subpopulations: • Blast cell count: 20–30% • Blast cell count: >30%	Economic subgroup analyses were conducted for VenAZA and VenLDAC for subgroups based on blast cell count, using patient level data from the VIALE-A and VIALE-C trials, respectively. These subgroup analyses informed the base case cost-effectiveness analysis for comparisons versus AZA (in patients with blast cell count 20–30%) and LDAC (in patients with blast cell count >30%). It should be noted that these subgroup analyses were conducted to account for the current NICE restrictions on the use of AZA only in patients with a blast count of 20–30%, and the VIALE trials were not designed to split patients by blast count.

Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; BSC: best supportive care; HMA: hypomethylating agent; HMRN; Haematological Research Network; HSCT: haematopoietic stem cell transplantation; IC: intensive chemotherapy; LDAC: low-dose cytarabine; NHS: National Health Service; QALY: quality-adjusted life year; UK: United Kingdom; Ven: venetoclax.
Source: NICE Final Scope [ID1564][5]

B.1.2 *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	Venetoclax (Venclyxto®) [in combination with AZA or LDAC]
Mechanism of action	Venetoclax is an orally bioavailable, selective small molecule inhibitor of B-cell lymphoma 2 (Bcl-2). Bcl-2 is an anti-apoptotic member of the Bcl-2 family of proteins, which regulate the intrinsic apoptosis pathway.[6-8] The overexpression of Bcl-2 can cause cells to resist apoptosis and therefore continue to survive.[8, 9] Over-expression of Bcl-2 has been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics. Additionally, malignant cells commonly display Bcl-2 dependency for survival.[10, 11] Venetoclax helps to restore the process of apoptosis in malignant cells by binding directly to Bcl-2, freeing pro-apoptotic proteins such as Bcl-2 interacting mediator of cell death (BIM), triggering mitochondrial outer membrane permeabilisation and the activation of caspases, and thereby initiating cell death. (Figure 1).[12, 13] Venetoclax, in the treatment of AML, is administered in combination with an HMA or LDAC and this combination of therapeutic agents can potentiate malignant cell death. HMAs and LDAC indirectly increase the sensitivity to Bcl-2 inhibition in AML cells by modifying the relative levels of Bcl-2 family members.[14-17] **Figure 1: Mechanism of action of venetoclax**  Venetoclax binds selectively to Bcl-2, freeing pro-death proteins that can initiate apoptosis (programmed cell death). Malignant cells can evade apoptosis through upregulation of pro survival proteins. **Source:** Adapted from Souers *et al.* (2013),[13] Leverson *et al.* (2017)[12]
Marketing authorisation/CE mark status	An application for a marketing authorisation for venetoclax for the indication of interest was submitted to the European Medicines Agency (EMA) in [redacted]. The anticipated date of positive Committee for Medicinal Products for Human Use (CHMP) opinion is [redacted]. Marketing authorisation approval for venetoclax in this indication is expected in [redacted].
Indications and any restriction(s) as described in the summary of	The anticipated EU marketing authorisation for venetoclax in the indication of interest for this submission is: [redacted]

<table>
<tr><td>product characteristics (SmPC)</td><td>Venetoclax has existing marketing authorisations from the EMA in the following indications:
Venetoclax in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)
Venetoclax in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy
Venetoclax monotherapy is indicated for the treatment of CLL either:
In the presence of del(17p) or TP53 mutation in adult patients who are unsuitable for or have failed B-cell receptor pathway inhibitor; or
In the absence of del(17p) or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell pathway inhibitor</td></tr>
<tr><td>Method of administration and dosage</td><td>Venetoclax is administered orally as a film coated tablet. The expected licensed dose of venetoclax in combination with an HMA or LDAC is:
Venetoclax orally (400 mg per day [QD]) in combination with AZA (75 mg/m^2 on days 1–7 of each 28-day cycle). Patients should receive a three day dose ramp-up to reach the target 400 mg dose (D1: 100 mg, D2: 200 mg, D3 onwards: 400 mg).
Venetoclax orally (600 mg QD) in combination with LDAC (20 mg/m^2 on days 1–10 of each 28-day cycle). Patients should receive a four day dose ramp-up increase to reach the target 600 mg dose (D1: 100 mg, D2: 200 mg, D3: 400, D4 onwards: 600 mg).
The expected licensed doses of venetoclax in combination with an HMA or LDAC are based on early phase studies which assessed the safety and pharmacokinetics of venetoclax in combination with AZA or LDAC, initial efficacy, and determined a recommended dose.[18, 19]
Venetoclax dosing may be interrupted as needed for management of haematologic toxicities and blood count recovery. Concomitant anti-microbial treatment with CYP3A inhibitors requires a reduction of venetoclax dosing. Full details of dose modifications are reported in the draft summary of product characteristics (SmPC) supplied alongside this submission.
Venetoclax, in combination with an HMA or LDAC, should be continued until disease progression or unacceptable toxicity is observed.</td></tr>
<tr><td>Additional tests or investigations</td><td>Patients receiving venetoclax should receive the following tests/investigations prior to treatment:
Patients should be assessed and have a white blood cell count <25x10^9/L prior to initiation of venetoclax
Patients should have blood chemistry assessed (potassium, uric acid, phosphorus, calcium, and creatine) and any pre-existing abnormalities should be corrected prior to initiation of venetoclax
Blood chemistries should be monitored for tumour lysis syndrome (TLS) at pre-dose, six to eight hours after each new dose during titration phase, and 24 hours after reaching final dose. For patients with risk factors for TLS, additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>Price of venetoclax (excluding VAT):<table><tr><td>Dose:</td><td>10 mg</td><td>50 mg</td><td colspan="3">100 mg</td></tr><tr><td>Pack size:</td><td>14</td><td>7</td><td>7</td><td>14</td><td>112</td></tr></table></td></tr>
</table>

	List price:	£59.87	£149.67	£299.34	£598.68	£4789.47
	PAS price:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Confirmed list price of AZA:

- 100 mg = £220.00

Confirmed list price of LDAC:
100 mg = £2.64

At list price, a 1-cycle (excluding first cycle) course of VenAZA and VenLDAC (assuming 100% treatment compliance) is £7,869.44 and £7,210.56, respectively.

Patient access scheme (if applicable)	This submission includes the confidential simple patient access scheme (PAS) for venetoclax, representing a discount to the list price of [redacted]%. A confidential PAS is also available for AZA. Since the PAS price is not available to AbbVie, all results presented in the submission include AZA at list price, including the figure for the average cost of VenAZA above.

Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; BIM: Bcl-2 interacting mediator of cell death; CHMP: Committee for Medicinal Products for Human Use; CLL: chronic lymphocytic leukaemia; D: day; EMA: European Medicines Agency; EU: European Union; HMA: hypomethylating agent; IC: intensive chemotherapy; LDAC: low-dose cytarabine; PAS: patient access scheme; PASLU: Patient Access Scheme Liaison Unit; QD: once daily; SmPC: summary of product characteristics; VAT: value-added tax.

B.1.3 *Health condition and position of the technology in the treatment pathway*

Disease overview

- AML is an aggressive, fast-growing haematological cancer that is characterised by the overproduction and accumulation of abnormal myeloblasts in the bone marrow and peripheral blood of affected patients.[20, 21]
- Despite existing treatment options, the prognosis for patients with AML who are ineligible for IC remains very poor, with a median overall survival (OS) in UK clinical practice of 9.5 and 4.6 months for patients treated with AZA and LDAC, respectively.[3]
- The signs and clinical manifestations of AML are associated with proliferation of malignant cells and the reduction of normal, functioning blood cells (causing anaemia, neutropenia, thrombocytopenia and coagulopathy), resulting in a wide range of debilitating symptoms, including bone pain, fatigue, anorexia, weight loss and enlarged organs.[21-24,]
- Due to poor prognosis and the considerable symptom burden, patients with AML have been shown to experience a substantially reduced health-related quality of life (HRQoL) and psychosocial well-being compared to the general population, which worsen as the disease progresses.[25-27]
- Treating AML is associated with a considerable economic burden on the UK healthcare system as patients require extensive use of hospital resources, such as hospitalisation and frequent blood transfusions.[28]

Current treatment pathway and position of the technology

- Treatment for AML begins with an assessment to determine patient eligibility for IC, which is based on the clinician assessed risk of treatment-related mortality (TRM) and patient preference.[3] IC is the preferred route for the treatment of AML as these treatments are

used with curative intent and are able to drive deep and lasting remission.

- In the UK approximately 40% of AML patients are ineligible for IC.[4] Patients who are ineligible for IC receive non-intensive treatment, limited to AZA or LDAC.[1, 3] No curative treatment options are currently available for this patient population.
- For the vast majority of patients who do not respond to AZA or LDAC, or who are unsuitable for/refuse treatment with these therapies due to more severe comorbidities, there are no further effective treatment options with acceptable side effect profiles. These patients therefore receive BSC, which consists of hydroxycarbamide/hydroxyurea (HC/HU) and blood transfusions. BSC aims to alleviate symptoms and complications of the disease but does not treat the underlying condition.[29] Additionally, a small minority of FLT3-positive patients subsequently are eligible to receive treatment with gilteritinib after failure of AZA or LDAC. Given this context, the current prognosis for IC-ineligible patients is therefore markedly different to those who can receive IC.
- In this submission, venetoclax, in combination with AZA or LDAC, is positioned as a first line treatment for patients with newly diagnosed AML who are ineligible for IC. Relevant comparators are therefore AZA and LDAC.
- There has been no new innovative treatment for patients in this population since the reimbursement of AZA in 2011. Venetoclax in combination with AZA or LDAC not only represents an innovative therapy in an indication with limited recent treatment advances, but also has the ability to dramatically improve treatment for patients who are ineligible for IC, bringing their outcomes closer to those afforded to older patients who are able to tolerate IC.[30-34] These therapies therefore represent a 'step-change' in treatment for patients with newly diagnosed AML who are ineligible for IC.[4]

B.1.3.1 Disease overview and epidemiology

AML is an aggressive, rapidly progressing haematological cancer that is characterised by the overproduction and accumulation of abnormal myeloblasts in the bone marrow and peripheral blood of affected patients.[20, 21] AML is a clinically heterogeneous disease characterised by many chromosomal abnormalities and genetic mutations which disrupt almost every facet of cell transformation.[20, 35]

The overexpression of Bcl-2 has been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics.[10, 11] Bcl-2 is an anti-apoptotic member of the Bcl-2 family of proteins which regulate the intrinsic apoptosis pathway.[6-8] The overexpression of Bcl-2 can therefore lead to resistance or evasion of apoptosis by malignant cells.[8, 9]

AML is the most common haematological malignancy, accounting for <1% of all new cancer cases, with an estimated 2,895 new cases reported in England and Wales (in 2017).[36, 37] Overall, the incidence rate of AML in the UK increased by 29% between 1993–2017.[36] Over this period, the incidence remained stable in people aged 0–59, but increased by 17% in those aged 60–69, 36% in those aged 70–79 and 72% in those aged ≥80.[36, 38-40] Despite accounting for <1% of all new cancer cases in the UK in 2017, AML accounted for ~2% of all cancer deaths, with mortality rates highest in those aged 85–89.[36] AML has the worst survival outcomes of any leukaemia, with an overall five-year relative survival rate of 15% in England, and just 6% in patients aged 65 and older.[36,41]

AML therefore disproportionately affects older people and older patients with AML often have a substantial comorbidity burden.[42-47] Further, many studies of older adults with AML show a relationship between greater comorbidity burden and worse outcomes, including lower remission

rates, higher risk of 30-day mortality and shorter OS. Advanced age (≥75 years) and presence of comorbidities commonly form the basis for determining ineligibility for IC.[4, 48]

Currently available non-intensive treatment options are used to control the disease but importantly do not have the capacity to deliver long term survival and, in contrast to the outcomes of older patients with IC, do not have the capacity to deliver long-term disease free survival. In clinical trials evaluating AZA and LDAC for use in this indication, median OS was 10.4–24.5 months and 6.4 months, respectively.[33, 49, 50] However, real-world data for 870 non-intensively treated patients from the Haematological Malignancy Research Network (HMRN) suggests that median OS in UK clinical practice for patients treated with AZA and LDAC is lower, 9.5 and 4.6 months, respectively.[3] The absence of effective treatments for older patients with AML who are ineligible for IC therefore represents a major unmet need. Importantly, there are no current therapies with the capacity to deliver long-term remissions and therefore there is a requirement to identify effective therapies with innovative mechanisms of action and acceptable side effect profiles.

B.1.3.2 Disease burden

The signs and clinical manifestations of AML are associated with proliferation of malignant cells and the loss of normal, functioning blood cells, resulting in a wide range of debilitating symptoms.[22] Specifically, anaemia results in fatigue and weakness; neutropenia leads to increased risk of infection; and thrombocytopenia increases the risk of bleeding complications and often leads to bruising.[21] Accumulation of myeloblasts in the medullary cavity can lead to bone pain, most commonly in the long bones of the legs and arms, and can also result in the enlargement of organs, such as the lymph nodes, liver, spleen.[23, 24] AML is also associated with anorexia and weight loss. Bleeding in the brain or lungs, and myeloid sarcoma may also be present in severe cases of AML.[24] AML often progresses rapidly and if left untreated usually causes death due to bleeding or infection within months of diagnosis.[21]

Very few studies have evaluated health-related quality of life (HRQoL) outcomes specifically in patients ineligible for IC but given their older age, the presence of comorbidities and their poorer prognosis, HRQoL outcomes are likely to be worse for these patients compared to the wider AML population. Many patients with AML report psychological stress in the form of anxiety and depression arising from uncertainty surrounding their disease.[25] Symptom burden (especially fatigue, anxiety and inability to engage in hard work) has been shown to worsen with a patient's proximity to death, with large proportions of patients being hospitalised in the last month of life or dying in intensive care units.[27] Clinical specialists and patient experts consulted as part of TA218 (azacitidine for the treatment of myelodysplastic syndromes [MDS], CMML and AML) indicated that fatigue and a reduced ability to carry out day-to-day activities are common in myelodysplastic syndromes, including AML, and can have a substantial impact on patients' quality of life.[1]

Patients ineligible for IC also typically require hospitalisation and frequent blood transfusions, adding further burden on patients' ability to live a normal life.[51] While the systematic literature review (SLR) performed to inform this submission identified no studies that assessed the impact of blood transfusions on HRQoL in patients with AML, evidence from patients with MDS suggest that blood transfusions are detrimental to HRQoL, with the number of transfusions received per month being negatively correlated with HRQoL.[52, 53] This was reflected in the views of patient groups consulted as part of TA218, who confirmed that dependence on blood transfusions has a

negative impact on quality of life.[1] Treating AML is also associated with a considerable economic burden, with patients requiring extensive use of hospital resources due to the need for frequent hospitalisation (including resource intensive emergency admissions) and blood transfusions.[28, 54]

As AML progresses, a considerable burden can be placed on caregivers due to patients becoming more dependent on their assistance and support. A study surveying caregivers of AML patients found that 80% reported significant caregiver strain.[55] This further adds to the HRQoL impact on patients, with patients reporting feelings of guilt associated with caregiver burden.[55] Patient experts consulted as part of TA399 (azacitidine for treating AML with blast count >30%) described how the high mortality rate and symptom burden of AML have a considerable emotional impact on patients' friends and family, and thus any improvements in patients' survival and HRQoL outcomes will also have a positive impact on the lives of their friends and family.[1]

In conclusion, AML has a substantial negative effect on the physical and psychosocial well-being of patients and carers. Whilst there is limited HRQoL data available for patients with AML ineligible for IC, the HRQoL for these patients is expected to be similar or worse than that of for patients eligible for IC, given the advanced age and existing comorbidities that are common in this patient population.

B.1.3.3 Current treatment pathway for patients with newly diagnosed AML

Guidelines for the treatment of patients with newly diagnosed AML are available from the European LeukemiaNet (ELN), the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) and Japanese Society of Medical Oncology Society of Medical Oncology (JSMO).[56-58] These guidelines which contain largely congruent treatment recommendations form the basis for UK treatment guidelines.

Diagnosis

Diagnostic procedures involved in AML include the analysis of morphology and immunophenotyping, plus the characterisation of the cytogenetics and molecular genetics of leukaemic cells.[58, 59] According to the World Health Organization (WHO) 2016 classification of myeloid neoplasms and acute leukaemia, AML is generally diagnosed when a patient's myeloblast cell count exceeds 20%.[60] The WHO classification recognises four clinically meaningful subcategories of AML: AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy related myeloid neoplasms and AML not otherwise specified (NOS).[60]

Treatment aims

The initial aim of treatment in patients with newly diagnosed AML is to reduce the myeloblast cell count to achieve complete remission (CR), which is defined as achieving normal absolute neutrophil count (ANC), normal platelet count, bone marrow with < 5% blasts, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease, and blood transfusion independence.[56] In patients treated with IC, acquisition of CR is considered a surrogate for long-term survival.[4] Achieving CR also results in alleviation of symptoms and improved survival and HRQoL outcomes. The ELN 2017 recommendations incorporate CR with incomplete haematological recovery (CRi), defined as CR with residual cytopenia such as ANC <1000 cells per µL or platelet count <100 000 cells per µL, into response criteria.[56] It has been demonstrated that achieving CR or CRi is associated with increased median OS in patients with

AML, and therefore CRi (in addition to CR), can be used to assess patients response to AML treatments.[61] CRi is considered particularly important for patients treated with venetoclax given that the iatrogenic and lengthy myelosuppression induced by venetoclax may hinder complete haematological recovery and prevent CR being reached.[62]

Once CR/CRi is achieved, the ultimate aim of treatment is to eradicate residual disease and aid in achieving lasting remission.[21] As a measure of residual disease; MRD negativity, defined by the ELN consensus as levels below 1 leukaemic cell per 1,000 leukocytes (MRD <0.001 or <0.1%), has been shown to be a strong prognostic indicator for OS and risk of relapse in patients who have received IC, and therefore achieving MRD negativity can be indicative of a potential curative response.[63, 64] However, improved outcomes do not necessarily require undetectable levels of MRD, whilst, inversely, a minority of MRD-negative patients may still relapse.[65-68] Currently, IC with or without allogeneic stem cell transplantation (alloSCT) is the only potentially curative treatment option for AML, with disease relapse universally observed in adults unfit for IC treated with AZA or LDAC.[64]

Assessment of eligibility for IC

IC is the preferred route for the treatment of AML as these treatments are used with curative intent and are able to drive deep and lasting remission, but are also associated with significant toxicity. Therefore, many patients with AML are ineligible for IC due to older age or other comorbidities leading to a high risk of TRM.[56] As such, an assessment of patient eligibility for IC is of critical importance prior to initiating IC. There are currently no consensus guidelines for objectively determining patient eligibility for IC and decisions are largely based on assessment of age and fitness by experienced haematologists with particular reference to previous levels of physical activity and exercise tolerance in conjunction with careful evaluation of the presence of comorbidities.[4, 48] In routine clinical practice, important predictors of TRM in patients treated with IC include pre-existing heart, kidney, lung or liver disease, cognitive impairment, an Eastern Cooperative Oncology Group (ECOG) score ≥3 and advanced age (≥75 years), and therefore these factors commonly form the basis for determining ineligibility for IC.[4, 48]

Current treatments

Intensive chemotherapy

IC consists of induction therapy (typically anthracycline, daunorubicin, or idarubicin, in combination with high-dose cytarabine) followed by 2–4 courses of consolidation therapy, typically including medium/high dose cytarabine or allogeneic haematopoietic stem cell transplants (allo-HSCT).[4, 56] Complete remission (CR) is achieved in 60–80% of younger adults and 40–60% of older adults (≥60 years) who receive IC.[32, 56, 69, 70] In patients treated with IC, the duration of first remission is positively correlated with survival.[31, 71] 5-years OS was lower in patients with a shorter duration of first CR (5% and 26% for a first duration of CR of ≤6 months and >18 months, respectively).[71] Disease relapse represents the major cause of treatment failure in adults treated with IC. The majority of patients who relapse do so within the first two years of diagnosis, and the risk of relapsing is small in those who maintain CR in the long term.[1,34, 72-75] Thus, patients who achieve a deep remission that is sustained 2–3 years after completion of IC are likely to achieve long-term disease-free survival. The specific timepoint that patients in CR can be considered cured is uncertain, but is generally considered to be between 2–3 years.[76]

The proportion of patients with AML treated with IC who can be considered to be cured is 35–40% in younger adults and 5–15% in patients who are >60 years of age.[32]

Non-intensive treatment

The only treatments currently available for adults with newly diagnosed AML deemed unfit for IC are AZA or LDAC.[56] AZA is recommended by NICE as the standard of care for adults who are not eligible for HSCT and have AML with 20–30% blasts and multilineage dysplasia, according to the WHO classification.[1] However, AZA does not have a NICE recommendation for treating AML in patients with >30% bone marrow blasts.[2] In clinical trials, AZA treatment is associated with CR rates of 18–28% and median OS of 10.4–24.5 months.[49, 50] In patients who do achieve CR, remission is often not maintained long-term and rates of relapse are high; UK real-word data for newly diagnosed patients receiving AZA demonstrate that median event-free survival (EFS), which includes relapse after CR, was 6.6 months in patients treated with AZA.[3] Real-world data have also demonstrated a median OS of 9.5 months.[3] Additionally, patients treated with AZA frequently continue to rely on blood transfusions to manage their disease, with 38–53% of patients treated with AZA in clinical trials achieving red blood cell (RBC) or platelet transfusion independence.[49, 50]

Importantly, AZA is not recommended by NICE for the treatment of AML in patients with >30% bone marrow blasts and consequently LDAC represents the standard of care for these patients.[2] The use of LDAC in AML patients is not restricted by blast count but AZA has displaced LDAC use in patients with a blast cell count of 20–30% given its modestly greater efficacy.[49] LDAC is therefore predominantly used in patients with a blast cell count >30%.[4] LDAC has a tolerable safety profile but is associated with CR rates of 18% and median OS of 6.4 months.[50, 77] UK real-world data for the use of LDAC have demonstrated a median OS of 4.6 months and a median EFS of 2.1 months for patients treated with LDAC.[3]

Best supportive care

The use of best supportive care is limited to two scenarios in which there are no remaining tolerable and effective treatment options for patients:

- First line use of BSC in patients who are ineligible for IC and are also unsuitable for or decline treatment with active treatments for AML (AZA or LDAC), due to frailty or the severity of their existing comorbidities
- Subsequent treatment with BSC in patients who have failed to respond to, or relapsed from, treatment with AZA or LDAC

It should be noted that in neither of these situation is BSC a valid comparator for VenAZA or VenLDAC. Treatment with BSC aims to alleviate the symptoms and complications of AML but does not treat the underlying condition.[29] BSC consists of treatment with HC/HU, anti-microbial prophylaxis and blood transfusions. The survival outcomes for patients receiving BSC are very poor, and UK based real-world data have shown that patients treated with BSC achieve a median OS of just 1.1 months.[3]

Gilteritinib

Gilteritinib is not currently approved as a first-line treatment for AML, and is recommended by NICE as a treatment option for a small proportion of patients with AML; those who do not respond to or relapse following first-line treatment (i.e. relapsed/refractory AML) and are positive for FLT3 mutations.[76]

Unmet need

AML incidence rates increase with age; as a result of the current demographic changes associated with an aging population, the prevalence and mortality of AML are likely to increase over the next decades, increasing the burden of disease on the NHS.[36, 78]

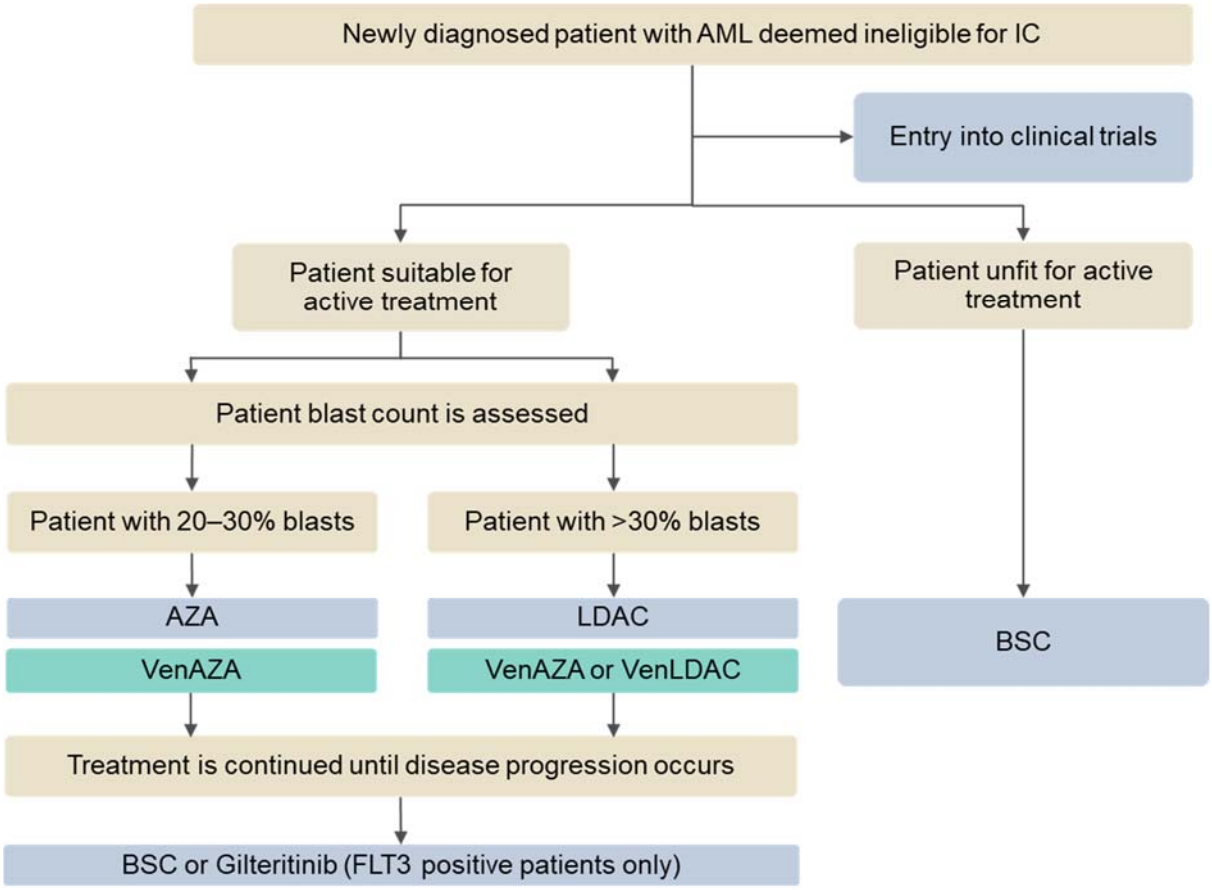
There are few treatment options for patients with untreated AML who are ineligible for IC, a population that accounts for approximately 40% of the AML population.[4] A substantial proportion of patients who are treated with current non-intensive treatment options (AZA and LDAC) fail to achieve CR, and in patients who do achieve CR with non-intensive treatment options, CR is often not maintained long-term and rates of relapse are high.[3] As such, no curative treatment options are available for this patient population. Furthermore, AZA is restricted in the UK to use in patients with 20–30% blasts and therefore, a considerable proportion of patients in the overall ineligible for IC population, who already face limited treatment options, are not able to benefit from treatment with AZA.[1, 2 77] Expected outcomes for patients ineligible for IC are therefore considerably worse than for their IC-eligible counterparts, which is demonstrated by a five-year survival rate of just 1.1% in this patient population.[3] A clinical trial will be sought for patients with AML where available, highlighting the lack of effective treatment options.[57] Furthermore, due to their low blood count patients are often reliant on blood transfusions which are burdensome not only to the patient but also to the NHS, given the extensive use of hospital resources.[28, 51, 54]

With the reimbursement of AZA in 2011 being the most recent advancement in treatment for patients in this population, and the recent termination of NICE appraisals for novel potential treatments,[79, 80] there remains an urgent unmet need for new, effective therapies which can improve survival, complete response rates and blood transfusion independence. Given that duration of CR is positively correlated with survival, new therapies for patients with AML who are ineligible for IC that can provide deep and durable remission, thereby improving long-term outcomes, have the potential to change the treatment paradigm for these patients.[71]

Proposed positioning of VenAZA and VenLDAC in clinical practice

A summary of the UK clinical pathway of care for patients with AML, including the anticipated positioning of VenAZA and VenLDAC, is presented in Figure 2. This pathway has been adapted from the ELN guidelines, based on feedback from UK clinical experts and reflects the blast count restricted usage of currently available non-intensive treatment options described above.[4, 14, 56]

Figure 2: Current treatment pathway for patients with newly diagnosed AML and proposed positioning of venetoclax in combination with AZA or LDAC



Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; BSC: best supportive care; FLT3: FMS-like tyrosine kinase 3; IC: intensive chemotherapy; LDAC: low-dose cytarabine; Ven: venetoclax.
Source: Döhner *et al.* (2017),[56] NICE TA218,[1] NICE TA399,[2] Clinical expert opinion.[3]

As a selective inhibitor of Bcl-2, venetoclax represents a first in class oral therapy with a unique targeted mechanism of action available for the treatment of AML in patients who are ineligible for IC, and has the potential to dramatically improve response rates and survival in these patients. In this submission, venetoclax, in combination with AZA or LDAC, is positioned as a first line treatment for patients with newly diagnosed AML who are ineligible for IC, but would be eligible for and accept treatment with AZA or LDAC. This is aligned with the anticipated marketing authorisation (expected [redacted]): venetoclax (Venclyxto®) [redacted].

B.1.4 *Equality considerations*

No equality issues related to the use of VenAZA and VenLDAC in this indication have been identified or are foreseen. However, if recommended, VenAZA and VenLDAC would provide effective treatment options for the elderly AML patient population that have not benefitted from recent advances in treatment.

B.2 Clinical effectiveness

The efficacy and safety of venetoclax in combination with AZA or LDAC has been demonstrated in VIALE-A and VIALE-C, two ongoing, Phase III, international, randomised, double-blind, placebo-controlled trials.[81, 82]

Efficacy

- The VIALE-A trial met its dual primary endpoints, demonstrating that VenAZA significantly improved OS and rates of CR + CR with incomplete haematological recovery (CRi) compared to AZA alone.[83]
    - VenAZA was associated with significantly longer median OS compared to AZA alone (14.7 versus 9.6 months, hazard ratio [HR]: 0.66; 95% CI: 0.52–0.85, *P* < 0.001).[81]
    - VenAZA significantly improved the proportion of patients who achieved CR + CRi compared to AZA alone (66.4% versus 28.3%, *P* < 0.001)..[71, 81]
    - VenAZA provided patients with a significantly higher rate of deep remissions (MRD <0.001 and CR + CRi) than AZA alone ([redacted] versus [redacted], *P* < [redacted]); additionally, patients treated with VenAZA achieved a lower median MRD value than those treated with AZA alone.
    - VenAZA significantly improved the proportion of patients who achieved both RBC and platelet transfusion independence compared to AZA alone ([redacted] versus [redacted], *P* = [redacted]).[83]
    - In the subgroup of patients with 20–30% blasts, median OS was higher in the VenAZA arm than in the AZA arm ([redacted] versus [redacted] months; HR: [redacted] [95% CI: [redacted]]).[81]
    - Similarly in the subgroup of patients with >30% blasts, median EFS was higher in the VenAZA arm than in the AZA arm ([redacted] versus [redacted] months; HR: [redacted] [95% CI: [redacted]]).[81]
- At the planned primary analysis of the VIALE-C trial, a non-significant improvement in the primary endpoint of OS was observed in patients treated with VenLDAC compared to LDAC alone. With an additional 6 months of follow-up, VenLDAC further improved OS and was associated with higher rates of CR + CRi compared to LDAC alone.[82, 84]
    - VenLDAC was associated with longer median OS compared to LDAC alone (8.4 versus 4.1 months, HR: 0.70; 95% CI 0.50–0.99, descriptive *P* = 0.040).[82, 84]
    - VenLDAC improved the proportion of patients who achieved CR + CRi compared to LDAC alone ([redacted]% versus [redacted]%; descriptive [redacted]).[84]
    - VenLDAC improved the proportion of patients who achieved both RBC and platelet transfusion independence compared to LDAC alone ([redacted]% versus [redacted]%; descriptive [redacted]).[84]
    - In the subgroup of patients with >30% blasts, median OS was higher in the VenLDAC arm than in the LDAC arm ([redacted] versus [redacted] months; HR: [redacted] (95% CI: [redacted]).[84]
    - Similarly in the subgroup of patients with >30% blasts, median EFS was higher in the VenLDAC arm than in the LDAC arm ([redacted] versus [redacted] months; HR: [redacted] (95% CI: [redacted]).[84]

Indirect treatment comparisons

- Given the lack of head-to-head data, indirect treatment comparisons were conducted to assess the relative efficacy of VenAZA versus LDAC.
- Network meta-analyses (NMAs) based on VIALE-A, VIALE-C and systematically identified literature demonstrated VenAZA to be associated with a statistically significantly lower risk of death and a significantly improved odds of achieving CR + CRi versus LDAC.[83-86]

- A propensity score analysis was conducted to compare patients receiving VenAZA (VIALE-A to patients receiving LDAC (VIALE-C) in the subgroup of patients with >30% blasts. After matching, this analysis found a statistically significantly lower risk of death and a significant improvement in event free survival (EFS) for patients who received VenAZA compared to LDAC.
- Individual patient data available from the HMRN dataset allows assessment of the relative efficacy of VenAZA and VenLDAC versus their relevant comparators based on real-world data in UK clinical practice. Propensity score analysis matching of the VIALE-A and VIALE C trials with the real-world HMRN dataset found statistically significant HRs for OS and EFS in favour of VenAZA versus AZA, VenAZA versus LDAC and VenLDAC versus LDAC, in the blast subgroups of relevance to the respective comparators.[3]
- In the propensity score-weighting analyses (VIALE trial data versus HMRN) the effective sample sizes for comparator arms derived from the HMRN were small, and thus the relative treatment effect estimates derived from these analyses are associated with considerable uncertainty.[3]Despite this uncertainty, all three ITC methods used to compare VenAZA and VenLDAC to relevant comparators produced results that were consistently in favour of VenAZA and VenLDAC.

Adverse reactions

- Overall, the safety profile of VenAZA and VenLDAC is consistent with the known individual safety profiles of venetoclax, LDAC, AZA, and the natural history of AML.[82, 84]

End of life criteria

- Given the short life-expectancy for patients with AML who are ineligible for IC, and the extension to life compared to current treatment that is offered by VenAZA and VenLDAC, venetoclax should be considered as meeting the end of life criteria for this patient population.

B.2.1 *Identification and selection of relevant studies*

An SLR was conducted in January 2019, with subsequent updates completed in May 2020 and October 2020, to identify efficacy and safety data of treatments for AML in treatment-naïve patients who are ineligible for IC.

The searches identified a total of 83 publications that were considered relevant for the review. Of these, 19 publications reporting on nine unique trials were included in the SLR. Of the nine trials that were identified in the SLR, four contained two or more interventions of interest and thus were included in the indirect comparisons. Two of these trials (VIALE-A and VIALE-C) included patients receiving venetoclax.

Full details of the SLR, including search strategy, study selection process and detailed results, can be found in Appendix D, along with details of the indirect comparisons conducted.

B.2.2 *List of relevant clinical effectiveness evidence*

Two separate randomised controlled trials (RCTs) were identified in the SLR that provide clinical evidence for the efficacy and safety of venetoclax [redacted]:

- VIALE-A (NCT02993523) is an ongoing, Phase III, international, randomised, double-blind, placebo-controlled trial investigating the safety and efficacy of venetoclax in combination with AZA (VenAZA) for patients with treatment naïve AML who are ineligible for IC. Data from VIALE-A have been published in the New England Journal of Medicine by DiNardo *et*

al. (2020).[81] Additional data from VIALE-A is provided in the clinical study report (CSR) located in the reference pack accompanying this submission.[83]

- VIALE-C (NCT03069352) is an ongoing, Phase III, international, randomised, double-blind, placebo-controlled trial investigating the safety and efficacy of venetoclax in combination with LDAC (VenLDAC) for patients with treatment naïve AML who are ineligible for IC. Data from VIALE-C have been published in Blood by, Wei *et al.* (2020).[82] Additional data from VIALE-C is provided in the CSR located in the reference pack accompanying this submission.[84]

The patient populations in VIALE-A and VIALE-C are aligned with the population of relevance for this submission. An overview of the clinical effectiveness evidence from the VIALE-A and VIALE-C trials is provided in Table 3.

Table 3: Clinical effectiveness evidence

Study	**VIALE-A (NCT02993523)**	**VIALE-C (NCT03069352)**
Study design	Phase III, international, randomised, double-blind, placebo-controlled trial	
Population	Newly diagnosed adult patients with AML who are treatment naïve and ineligible for standard IC due to age or comorbidities[a]	
Interventions	Venetoclax (400 mg QD[b]) + AZA (75 mg/m^2 on days 1–7 of each 28-day cycle)	Venetoclax (600 mg QD[c]) + LDAC (20 mg/m^2 on days 1–10 of each 28-day cycle)
Comparator	Placebo + AZA (75 mg/m^2 on days 1–7 of each 28-day cycle)	Placebo + LDAC (20 mg/m^2 on days 1–10 of each 28-day cycle)
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	Yes	Yes
Rationale for use/non-use in the model	Both VIALE-A and VIALE-C were included in the economic model as they provide the primary source of evidence for the clinical efficacy and safety of VenAZA and VenLDAC, respectively, are relevant to the decision problem and informed the marketing authorisation application.	
Reported outcomes specified in the decision problem[d]	• **OS** • **CR + CR with incomplete haematological recovery (CRi)** • **EFS** • Duration of response • Blood transfusion dependence • **Adverse effects of treatment** • **HRQoL outcomes**	
All other reported outcomes	AML is a heterogenous disease which lacks a simple, uniform signature to identify malignant cells capable of causing relapse. MRD is the persistence of leukaemic cells following treatment and serves as an independent, post-diagnosis, prognostic indicator in AML.[63] MRD negativity, defined by the ELN	

	guidelines as levels below 1 leukaemic cell per 1,000 leukocytes (<0.001; <0.1%), has been shown to be prognostic for OS and risk of relapse in patients who have received IC.[63]

[a]Presence of AML was confirmed using the WHO definition. [b]In cycle 1 patients received a three day dose ramp-up of venetoclax to reach the target 400 mg dose (100, 200, 400). [c]In cycle 1 patients received a four day dose ramp up of venetoclax to reach the target 600 mg dose (100, 200, 400, 600). [d]Outcomes in bold indicate those used in the cost effectiveness analysis.
Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; CR: complete remission; CRi: complete remission with incomplete haematological recovery; EFS: event-free survival; ELN: European Leukaemia Net; HRQoL: health-related quality of life; IC: intensive chemotherapy; LDAC: low-dose cytarabine; MRD: minimal residual disease; OS: overall survival; QD: once daily; Ven: venetoclax.
Source: VIALE-A Clinical Study Report,[83] DiNardo *et al.* (2020),[81] VIALE-C Clinical Study Report,[84] Wei *et al.* (2020).[82]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

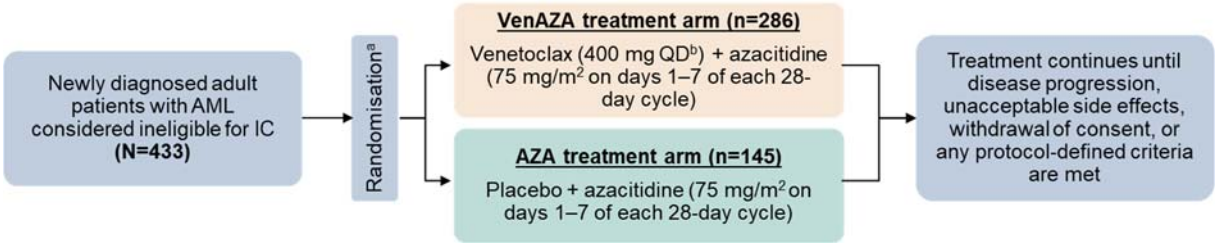
B.2.3.1 Trial design and methodology

Summaries of the trial design and methodology for VIALE-A (NCT02993523) and VIALE-C (NCT03069352) are detailed below and presented in Table 4.

VIALE-A (NCT02993523)

A summary of the trial design for VIALE-A is presented in Figure 3.

Figure 3: VIALE-A trial design



[a]Patients received a unique number via an IRT system. After meeting the eligibility criteria, patients were enrolled into a treatment arm via IRT. [b]In cycle 1 patients received a three day dose ramp-up of venetoclax to reach the target 400 mg dose (100, 200, 400).
Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; IC: intensive chemotherapy; IRT: interactive response technology; QD: once daily; Ven: venetoclax.

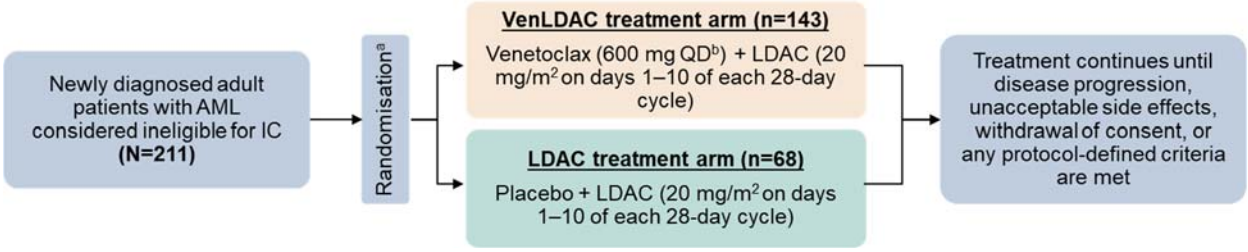
Eligible patients were assigned, in a 2:1 ratio, either to the VenAZA group or to the AZA control group. All patients were hospitalised on or before day 1 of cycle 1, and remained hospitalised during the venetoclax/placebo ramp up period (days 1–3) for the purposes of receiving prophylaxis against tumour lysis syndrome (TLS) and for monitoring.[81] All patients received an agent to reduce the level of uric acid as well as oral and/or intravenous hydration, and all patients underwent scheduled laboratory monitoring.[81] Venetoclax was administered orally, once-daily, with food. For mitigation of TLS in cycle 1, the dose of venetoclax was 100 mg on day 1 and 200 mg on day 2; on day 3, the target dose of 400 mg was reached and continued until day 28. In all subsequent 28-day cycles, the dose of venetoclax was continued at 400 mg daily.[81] Patients in the AZA group received an oral venetoclax placebo according to the same schedule. Patients in both groups received AZA at a dose of 75 mg per square meter of body surface area (BSA), subcutaneously or intravenously, on days 1 through 7 every 28-day cycle.[81] To mitigate

cytopenia and related clinical consequences, venetoclax was interrupted between cycles for recovery of blood counts after clearance of leukaemia from the bone marrow, and dose modifications related to prophylactic anti-infective agents for venetoclax dose equivalency were implemented.[81] Patients continued to receive treatment until they had disease progression or unacceptable toxic effects, until they withdrew consent, or until they met any protocol-defined criteria.[81] Except for patients who withdrew consent, all patients who discontinued a trial regimen were followed for survival.[81]

VIALE-C (NCT03069352)

A summary of the trial design for VIALE-C is presented in Figure 4.

Figure 4: VIALE-C trial design



[a]Patients received a unique number via an IRT system. After meeting the eligibility criteria, patients were enrolled into a treatment arm via IRT. [b]In cycle 1 patients received a four day dose ramp up of venetoclax to reach the target 600 mg dose (100, 200, 400, 600)
Abbreviations: AML: acute myeloid leukaemia; IC: intensive chemotherapy; IRT: interactive response technology; LDAC: low-dose cytarabine; QD: once daily; Ven: venetoclax.

Eligible patients were randomised in a 2:1 ratio, either to the VenLDAC group or to the LDAC control group.[82] All patients were hospitalised on or before day 1 of cycle 1, and remained in hospital during the venetoclax/placebo ramp up period (days 1–4) for the purposes of receiving prophylaxis against TLS.[82] All patients received an agent to reduce the level of uric acid as well as oral and/or intravenous hydration, and all patients underwent scheduled laboratory monitoring.[82] Venetoclax was administered orally, once-daily, with food. Venetoclax dosing began at 100 mg on day 1 and increased over 4 days to reach the target dose of 600 mg (100, 200, 400, and 600 mg); dosing was continued at 600 mg per day from day 4 through day 28.[82] In all subsequent 28-day cycles, the dose of venetoclax was initiated at 600 mg daily. Patients in the LDAC group received an oral venetoclax placebo according to the same schedule.[82] For patients in both arms, LDAC (20 mg/m^2) was administered subcutaneously once daily on days 1–10 of each 28-day cycle.[82] Patients continued to receive treatment until they had disease progression or unacceptable toxic effects, until they withdrew consent, or until they met any protocol-defined criteria.[82] Except for patients who withdrew consent, all patients who discontinued a trial regimen were followed for survival.[82]

Table 4: Summary of trial methodology for VIALE-A and VIALE-C

Study	VIALE-A (NCT02993523)	VIALE-C (NCT03069352)
Location	**International (134 sites across 27 countries):** Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Norway, Poland, Portugal, Russia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, and the United States.	**International (76 across 21 countries):** Australia, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Greece, Hungary, Japan, New Zealand, Norway, Puerto Rico, Russia, South Africa, South Korea, Spain, Taiwan, United Kingdom, and United States.
Trial design	Phase III, multicentre, double-blind, randomised, placebo-controlled trial	
Eligibility criteria for participants	A summary of the criteria for baseline inclusion in VIALE-A and VIALE-C are provided below. Key eligibility criteria were broadly consistent across both trials, full details of the eligibility criteria are presented in Appendix L **Key inclusion criteria:** • Aged 18 years or older with a confirmed diagnosis of AML by WHO criteria, previously untreated and be ineligible for treatment with standard IC due to age or comorbidities. • Ineligibility for IC on the basis of advanced age (≥75 years) or ≥ 18 to 75 years of age with **one or more** of the following pre-existing comorbidities: 1. A history of congestive heart failure for which treatment was warranted or an ejection fraction of 50% or less or chronic stable angina 2. A diffusing capacity of the lung for carbon monoxide of 65% or less or a forced expiratory volume in 1 second of 65% or less, 3. An ECOG performance-status score of 2 or 3 (on a 5-point scale, with higher numbers indicating greater disability). 4. Creatine clearance ≥30 to <45 mL/min 5. Moderate hepatic impairment with total bilirubin (>1.5 to ≤3.0 x upper limit of normal) • An ECOG score of 0–2 in patients aged ≥75 years or 0–3 for patients aged 18–74 years	

	Key exclusion criteria: • Prior therapy with: o An HMA, venetoclax and/or chemo therapeutic agent for MDS o CAR-T cell therapy or other experimental therapies for MDS or AML • History of myeloproliferative neoplasm (MPN) • Favourable risk cytogenetics according to the AML NCCN guidelines • Known active central nervous system (CNS) involvement with AML • Patient is HIV positive • Acute promyelocytic leukaemia (APL)	**Key exclusion criteria:** • Received prior therapy for AML, with the exception of HC/HU in cycle 1 (prior treatment for MDS allowed, except cytarabine) • Previous exposure to cytarabine for any indication • History of MPN • Known CNS involvement with AML • Patient is HIV positive • APL
Method of study drug administration	• Venetoclax was administered orally, once daily, with food. • Patients in the control group received an oral venetoclax placebo (identical tablet appearance) according to the same schedule. • Azacitidine was administered subcutaneously or intravenously once daily on days 1–7 of each 28-day cycle	• Venetoclax was administered orally, once daily, with food. • Patients in the control group received an oral venetoclax placebo (identical tablet appearance) according to the same schedule. • LDAC was administered subcutaneously once daily on days 1–10 of each 28-day cycle
Permitted and disallowed concomitant medication	• All patients received an agent to reduce the level of uric acid (e.g., allopurinol, rasburicase) as well as oral and/or intravenous hydration • Anti-infective prophylaxis for bacterial, viral and fungal infections were required for all patients with absolute neutrophil count (ANC) of < 500/μL • Venetoclax is a CYP3A and P-glycoprotein substrate, and therefore patients received protocol-recommended dose modifications for the following inhibitors: o 50% reduction in venetoclax dose if co-administered with a moderate CYP3A inhibitor P-glycoprotein inhibitor o Venetoclax dose reduced to 50 mg if co-administered with a strong CYP3A inhibitor • Excluded medications: Strong CYP3A inducers – during ramp up and throughout the study • Cautionary medications: Strong and moderate CYP3A inhibitors; moderate CYP3A inhibitors; P-gp substrates or inhibitors; Warfarin; Coumarin derivatives e.g. phenprocoumon; BCRP substrates or inhibitors; OATP1B1/1B3 substrates;	

Primary outcome	• OS • Composite CR (CR +CRi)	• OS
Secondary and other outcomes	A summary of the key secondary outcomes for VIALE-A and VIALE-C is provided below. Key secondary outcomes were broadly consistent across both trials, full details of all the secondary outcomes can be found in Appendix L. **Secondary outcomes** • Composite CR (CR + CRi)[a] • CR + CR with or without partial haematological recovery (CRh) • Proportion of patients with CR + CRi and CR + CRh by initiation of therapy cycle 2 • EFS • RBC and platelet transfusion independence • Response rates and OS in molecular subgroups • HRQoL (Fatigue/global health status [GHS]) outcomes o PROMIS and SF7a o EORTC QLQ-C30 • Minimal residual disease (MRD) response rate **Exploratory outcomes** • Exploration of biomarkers predictive of venetoclax activity and duration of response (DOR) • HRQoL impact of venetoclax based on remaining subscales from EORTC QLQ-C30 and EQ-5D-5L Safety evaluations included adverse events, serious adverse events, deaths, and changes in laboratory determinations and vital sign parameters.	
Pre-planned subgroup analyses	The primary objective was analysed by several demographic variables: • Gender (Male, Female) • Age (18–<65 years, 65–<75 years, ≥75 years) • Geographic region (US, Europe, China, Japan, rest of world) • Baseline ECOG score (grade <2, grade ≥2) • Type of AML (de novo, secondary and therapy-related AML) • Cytogenetic risk (intermediate, poor) • Molecular marker (FLT3, IDH1/IDH2, TP53, NPM1)	The primary objective was analysed by several demographic variables: • Gender (Male, Female) • Age (18–< 65 years, 65–< 75 years, ≥75 years) • Geographic region (US, Europe, China, Japan, Asia, rest of world) • Baseline ECOG score (grade <2, grade ≥2) • Type of AML (de novo, secondary) • Type of secondary AML (therapy related, post MDS/CMML) • Patients who received prior HMA for MDS (Yes, No)

	• AML with myelodysplasia-related changes (MRC) • Antecedent haematological history of MDS[b] • Bone marrow blast count (<30%, 30%-50%, ≥50%)	• Cytogenetic risk categorization (favourable, intermediate, poor) • Molecular marker (FLT3, IDH1/2, TP53, NPM1) • AML with MRC • Bone marrow blast count (<30%, 30%-50%, ≥50%)
Duration of study and follow-up	• The median duration of follow-up was 20.5 months (Range: < 0.1–30.7)	• The median duration of follow-up was [redacted] months (Range: [redacted])

[a]VIALE-C only. [b]Although planned for, subgroup analyses for OS and CR + CRi is not presented due to the small number of subjects with antecedent haematologic history of MDS.

Abbreviations: AML: acute myeloid leukaemia; ANC: absolute neutrophil count; APL: acute promyelocytic leukaemia; CAR-T: chimeric antigen receptor T-cells; CNS: central nervous system; CR: complete remission; CRh: complete remission with or without partial haematological recovery; CRi: complete remission with incomplete haematological recovery; CYP3A: cytochrome P450 3A isoform subfamily; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer core quality of life questionnaire; EQ-5D-5L: EuroQol 5 Dimensions 5 Levels Health State Instrument; GHS: global health status; HC/HU: hydroxycarbamide/hydroxyurea; HIV: human immunodeficiency virus; HMA: hypomethylating agent; HRQoL: health-related quality of life; IC: intensive chemotherapy: LDAC: low-dose cytarabine; MDS: myelodysplastic syndromes; MPN: myeloproliferative neoplasm; MRC: myelodysplasia related changes; MRD: minimal residual disease; NCCN: National Comprehensive Cancer Network; OS: overall survival; PROMIS: Patient-Reported Outcomes Measurement Information System Fatigue; QD: once daily; RBC: red blood cell; SF-7a: Short-Form 7a; WHO: World Health Organisation.

Source: VIALE-A Clinical Study Report,[83] DiNardo *et al*. (2020),[81] VIALE-C Clinical Study Report,[84] Wei *et al*. (2020).[82]

Definition of outcome measures

The definitions of the efficacy outcomes used in VIALE-A and VIALE-C are presented in Table 5.

Table 5: Outcome definitions used in VIALE-A and VIALE-C trials

Outcome Measure	Definition
OS	Number of days from the date of randomisation to the date of death or last known alive date
CR + CRi	Proportion of patients who achieve a CR or CRi at any time point during the study as per the modified IWG criteria for AML:[87] • **CR:** ANC ≥ 10^3/μL, platelets ≥ 10^5/μL, RBC transfusion independence, and bone marrow with < 5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease • **CRi:** All criteria as CR except for residual neutropenia ≤ 10^3/μL (1000/μL) or thrombocytopenia ≤ 10^5/μL (100,000/μL). RBC transfusion dependence is also defined as CRi
CR + CRi by the Initiation of Cycle 2	Proportion of patients who achieved a CR or CRi by the initiation of Cycle 2 per the modified IWG criteria for AML[87]
EFS	Number of days from randomisation to the date of progressive disease (PD), confirmed MR from CR or CRi, treatment failure defined as failure to achieve CR, CRi, or morphologic leukaemia-free state (MLFS) after at least 6 cycles of study treatment or death from any cause
Transfusion Independence Rate	The rate is defined as the proportion of patients who achieved transfusion independence post baseline. Transfusion Independence is defined as a period of at least 56-days with no RBC and platelet transfusion-while on study therapy (patients who did not receive study drug were considered transfusion dependent during the study)
MRD negativity	MRD negativity was defined as less than one leukaemic cell per 1000 leukocytes (MRD <0.001 or 0.1%) in bone marrow aspirates evaluated via a centralised, validated, multicolour flow cytometry (MFC) assay[63]
PROMIS Cancer Fatigue SF 7a	A seven-item questionnaire that assesses the impact and experience of fatigue over the prior 7 days
EORTC QLQ-C30	A 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). Patients rate items on a four-point scale, with 1 as "not at all" and 4 as "very much"

Abbreviations: AML: acute myeloid leukaemia; ANC: absolute neutrophil count; CR: complete remission; CRi: complete remission with incomplete blood count recovery: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core; ELN: European LeukemiaNet; IWG: International Working Group; MLFS: morphologic leukaemia-free state; MR: morphologic relapse; MRD: minimal residual disease; OS: overall survival; PD: progressive disease; PROMIS SF-7a: Patient Reported Outcomes Measurement Information System Short Form 7a; RBC: red blood cell;
Source: VIALE-A Clinical Study Report,[83] VIALE-C Clinical Study Report.[84]

B.2.3.2 Baseline characteristics

The baseline characteristics of patients in VIALE-A and VIALE-C are summarised in Table 6.

Baseline characteristics were broadly consistent across treatment arms in both VIALE-A and VIALE-C. Patients in both trials had a median age of 76 years, and a similar proportion of patients in both trials were aged ≥75 years.[81, 82] In both trials, there was a higher proportion of males than females, which is consistent with the higher proportion of male AML patients in the UK (56%).[36, 81, 82] The distribution of somatic mutations was also broadly similar between the treatment arms of each study and across the VIALE-A and VIALE-C trials as a whole. The proportion of patients who were dependent on RBC and/or platelet transfusions at baseline was consistent within each trial, however, patients in VIALE-C had much higher rates of transfusion dependence at baseline than patients in VIALE-A. Additionally, there was a much higher proportion of patients in VIALE-C with an antecedent history of MDS compared to patients in VIALE-A, and a greater proportion of patients with secondary AML were included in VIALE-C compared to VIALE-A.[83,84] In VIALE-C [redacted]% of patients in the VenLDAC arm, and [redacted]% of patients in the LDAC arm had received prior treatment for MDS with an HMA, whereas patients with prior HMA treatment were excluded from VIALE-A.[83,84] A large proportion of patients in both trials had a blast count ≥50% (49% and [redacted]% for VIALE-A and VIALE-C, respectively). The baseline characteristics for patients in both trials are consistent with the target population in the UK, and the generalisability of the VIALE-A and VIALE-C baseline characteristics has been validated by clinical experts.[4]

Table 6: Baseline characteristics of patients in the VIALE-A and VIALE-C trials

Characteristic	VIALE-A		VIALE-C	
	VenAZA (n=286)	AZA (n=145)	VenLDAC (n=143)	LDAC (n=68)
Age				
Median (range), years	75.6 (49.0–91.0)	75.1 (60.0–90.0)	75.1 (36.0–93.0)	74.3 (41.0–88.0)
≥75 years, n (%)	174 (60.8)	87 (60.0)	78 (54.5)	39 (57.4)
Sex, n (%)				
Male/Female	172 (60.1) / 114 (39.9)	87 (60.0) / 58 (40.0)	78 (54.5) / 65 (45.5)	39 (57.4) / 29 (42.6)
AML type, n (%)				
De novo	214 (74.8)	110 (75.9)	92 (64.3)	46 (67.6)
Secondary	72 (25.2)	35 (24.1)	[redacted]	[redacted]
Secondary AML, n/N (%)				
History of myelodysplastic syndrome or CMML	46/72 (63.9)	26/35 (74.3)	52	19
Therapy-related AML	26/72 (36.1)	9/35 (25.7)	6	4
ECOG performance status score, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow blast count, n (%)				
<30%	85 (29.7)	41 (28.3)	[redacted]	[redacted]
≥30 to <50%	61 (21.3)	33 (22.8)	[redacted]	[redacted]
≥50%	140 (49.0)	71 (49.0)	[redacted]	[redacted]
AML with MRC, n (%)	92 (32.2)	49 (33.8)	[redacted]	[redacted]
Antecedent haematologic history of MDS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Cytogenetic risk category, n (%)[a]				
Favourable	-	-	[redacted]	[redacted]

Characteristic	VIALE-A		VIALE-C	
	VenAZA (n=286)	AZA (n=145)	VenLDAC (n=143)	LDAC (n=68)
Intermediate	182 (63.6)	89 (61.4)	[redacted]	[redacted]
Poor	104 (36.4)	56 (38.6)	[redacted]	[redacted]
Somatic mutations, n/N (%)[b]				
IDH1 or *IDH2*	61/245 (25.7)	28/127 (22.9)	[redacted]	[redacted]
FLT3, ITD or TKD	29/206 (14.1)	22/108 (20.4)	[redacted]	[redacted]
NPM1	27/163 (16.6)	17/86 (19.8)	19 (17.0)	7 (13.5)
TP53	38/163 (23.3)	14/86 (16.3)	22 (19.6)	9 (17.3)
Baseline cytopenia grade ≥3, n (%)[c]				
Anaemia	88 (30.8)	52 (35.9)	[redacted]	[redacted]
Neutropenia	206/286 (72.0)	90/144[d] (62.5)	[redacted]	[redacted]
Thrombocytopaenia	145 (50.7)	73 (50.4)	[redacted]	[redacted]
≥2 Reasons for ineligibility to receive intensive therapy, n (%)	141 (49.3)	65 (44.8)	[redacted]	[redacted]
Prior HMA used (yes), n (%)	NA[g]	NA[g]	[redacted]	[redacted]
RBC or platelet infusion[f] (yes), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RBC transfusion[f] (yes), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Platelet transfusion[f] (yes), n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[a]As per the electronic data capture. [b]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. [c]Cytopenia was graded according to the Common Terminology Criteria for Adverse Events. [d]Data missing for 1 patient due to white blood cell count being too low to perform differential counts and report absolute neutrophil count. [e]Missing data for neutropenia for 12 and 6 patients in the VenLDAC and LDAC arms of VIALE-C, respectively. [f]Within 8 weeks prior to the first dose of study drug (or randomisation for non-treated patients).[g]Prior use with an HMA was part of the exclusion criteria for VIALE-A.

Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; CMML: chronic myelomonocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; FLT3: FMS-like tyrosine kinase-3; HMA: hypomethylating agent; IDH: isocitrate dehydrogenase; ITD: internal tandem duplication; LDAC: low-dose cytarabine; MDS: myelodysplastic syndrome; MRC: myelodysplasia related changes; NPM1: nucleophosmin 1; RBC: red blood cell; TKD: tyrosine kinase domain; TP52: tumour protein 53; Ven: venetoclax.

Source: VIALE-A Clinical Study Report,[83] DiNardo *et al.* (2020),[81] VIALE-C Clinical Study Report,[84] Wei *et al.* (2020).[82]

B.2.3.3 Concomitant medications

VIALE-A

Concomitant medications used by ≥20% of patients in the VIALE-A trials are presented in Table 7.

To mitigate the potential risk of TLS, all patients were to receive prophylactic uric acid reducing agents (e.g., allopurinol, rasburicase), and hydration. Anti-infective prophylaxis for bacterial, viral and fungal infections were required for all patients with ANC of < 500/µL. At the data cut-off, a similar percentage of patients had received anti-infective prophylaxis agents while receiving study treatment in the VenAZA arm (236 patients [82.5%]) and in the AZA arm (117 patients [80.7%]). In patients with CR + CRi/MLFS who had delays between treatment cycles to enable count recovery, more patients being treated with VenAZA ([redacted]) received anti-infective prophylaxis agents compared to the AZA arm ([redacted]).

Table 7: Concomitant medications used by ≥20% of patients in any treatment arm of VIALE-A

Concomitant medications, n (%)	VenAZA (N=286)	AZA (N=145)
Ondansetron	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]
Furosemide	[redacted]	[redacted]
Potassium	[redacted]	[redacted]
Levofloxacin	[redacted]	[redacted]
Piperacillin / Tazobactam	[redacted]	[redacted]
Meropenem	[redacted]	[redacted]
Pantoprazole	[redacted]	[redacted]
Acyclovir	[redacted]	[redacted]
Metoclopramide	[redacted]	[redacted]
Sodium chloride	[redacted]	[redacted]
Filgrastim	[redacted]	[redacted]
Vancomycin	[redacted]	[redacted]
Allopurinol	[redacted]	[redacted]
Lactulose	[redacted]	[redacted]
Lidocaine	[redacted]	[redacted]
Ciprofloxacin	[redacted]	[redacted]
Bactrim	[redacted]	[redacted]
Cefepime	[redacted]	[redacted]
Amlodipine	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 14.1_4.3, Page 684[83]

VIALE-C

To mitigate the potential risk of TLS, all patients were to receive prophylactic uric acid reducing agents (e.g., allopurinol, rasburicase), and hydration.

Table 8: Concomitant medications used by ≥20% of patients in any treatment arm of VIALE-C

Concomitant medications, n (%)	VenLDAC (N=143)	LDAC (N=68)
Furosemide	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]
Potassium	[redacted]	[redacted]
Ondansetron	[redacted]	[redacted]
Levofloxacin	[redacted]	[redacted]
Meropenem	[redacted]	[redacted]
Piperacillin / Tazobactam	[redacted]	[redacted]
Metoclopramide	[redacted]	[redacted]
Acyclovir	[redacted]	[redacted]
Omeprazole	[redacted]	[redacted]
Sodium chloride	[redacted]	[redacted]
Bactrim	[redacted]	[redacted]
Valaciclovir	[redacted]	[redacted]

Abbreviations: LDAC: low-dose cytarabine; Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Table 14.1_1.6.3A, Page 736[83]

B.2.3.4 Participant flow

Full CONSORT diagrams of participant flow for the VIALE-A and VIALE-C studies are provided in Appendix D. A summary for each study is provided in Section B.2.3.5 below.

B.2.3.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Trial populations

The analysis sets used in the VIALE-A and VIALE-C trials are presented in Table 9.

VIALE-A

A total of 579 patients were assessed for trial eligibility, of which 146 were excluded before randomisation (the majority [98 patients] for not meeting the eligibility criteria). Therefore, 433 patients underwent randomisation. Of these, two patients (Group 1) were randomised under the original protocol with age and region as stratification factors and were not stratified according to cytogenetic risk. The remaining 431 patients (Group 2) were randomised under protocol amendments, with cytogenetic risk as an additional stratification factor. [redacted] patients in China were enrolled directly without randomisation to receive VenAZA in an open-label safety cohort.

VIALE-C

A total of 255 patients were assessed for trial eligibility, of which 44 were excluded before randomisation (the majority [27 patients] for not meeting the eligibility criteria). Therefore, 211 patients underwent randomisation, with 143 patients randomised to VenLDAC and 68 patients randomised to LDAC. One patient in the VenLDAC arm did not receive their allocated intervention; all patients in the LDAC arm received LDAC.

Table 9: Analysis sets used in the analysis of outcomes in the VIALE-A and VIALE-C trials

Analysis set	VIALE-A	VIALE-C
Full analysis set (FAS)	• Consisted of all randomised Group 2 patients, excluding the open-label China safety cohort (n=431) • Used for efficacy analyses • Data were analysed by the treatment arm assignment given at the time of randomisation, even if the patient took the incorrect drugs that did not match the assigned treatment, did not receive any treatment, or did not follow the protocol until completion	• Consisted of all randomised patients (n=211) • Used for efficacy analyses • Data were analysed by the treatment arm assignment given at the time of randomisation, even if the patient took the incorrect drugs that did not match the assigned treatment, did not receive any treatment, or did not follow the protocol until completion
Safety analysis set (SAS)	• Consisted of all Group 1 and Group 2 patients, excluding the open-label China safety cohort, who took at least one dose of venetoclax/placebo and AZA (n=427) • Used for safety analyses • Data were analysed by the treatment the patient received	• Consisted of all patients who take at least one dose of venetoclax/placebo or LDAC (n=210) • Used for safety analyses. • Data were analysed by the actual treatment that patient received

Abbreviations: AZA: azacitidine; FAS: full analysis set; LDAC: low-dose cytarabine; SAS: safety analysis set.
Source: VIALE-A Clinical Study Report,[83] DiNardo *et al*. (2020),[81] VIALE-C Clinical Study Report,[84] Wei *et al*. (2020).[82]

VIALE-A

Primary efficacy analysis

The primary objective of the VIALE-A trial was to evaluate if VenAZA would improve OS *and* composite CR rate (CR + CRi) versus AZA, in treatment-naïve patients with AML. Full details of the statistical methods for the primary analysis of the VIALE-A trial are presented in Table 10.

Summary of clinical data cut-off dates

An initial interim analysis (IA1) was conducted for the first [redacted] randomised patients (AZA: n=[redacted]; VenAZA: n=[redacted]) with 6-months follow-up, representing a data cut-off date of 1st October 2018. Results from this interim analysis are presented in this submission for CR + CRi rate, representing the primary analysis of CR + CRi for the EU and EU reference countries. A second interim analysis (IA2) was conducted for 431 randomised patients (AZA: n=145; VenAZA: n=286) patients, once approximately [redacted] OS events (75% of the total 360 events) in the FAS had been

observed, corresponding to a data cut-off date of 4th January 2020. Results from this second interim analysis are presented in this submission for all outcomes. A final analysis is planned once approximately 360 OS events have been observed.

VIALE-C

Primary efficacy analysis

The primary objective of the VIALE-C trial was to evaluate if VenLDAC improves OS versus LDAC, in treatment naïve patients with AML. Full details of the statistical methods for the primary analysis of the VIALE-C trial are presented in Table 10.

Summary of clinical data cut-off dates

A primary interim analysis was conducted for 211 patients (LDAC: n=68; VenLDAC: n=143), corresponding to a data cut-off date of 15th February 2019. At the time of the primary analysis, there was greater censoring of patients in the VenLDAC arm than the LDAC arm, as more patients receiving VenLDAC had not yet reached median OS. As such, results for the primary endpoint, median OS, are presented from both the primary analysis and a more recent analysis with an additional 6-month follow-up, corresponding to a data cut-off date of 15th August 2019. Results for all secondary endpoints are presented from the additional 6-month data cut, with results from the primary analysis available in the CSR accompanying this submission.

Table 10: Statistical methods for the primary analyses of VIALE-A and VIALE-C

Statistical methods	VIALE-A	VIALE-C
Hypothesis objective	• The primary objective was to evaluate if VenAZA improves OS *and* composite complete remission rate (CR + CRi) versus AZA, in treatment-naïve patients with AML	• The primary objective was to evaluate if VenLDAC improves OS versus LDAC, in treatment naïve patients with AML
Statistical analysis	• The significance level of 0.05 (two sided) was split between the dual primary endpoints to give a 0.01 significance level to the CR + CRi rate analysis (based on the investigator assessment) and an overall 0.04 significance level to the OS analysis • CR + CRi rate was compared between treatment arms using Cochran-Mantel-Haenszel test stratified by age (18 – < 75, ≥ 75) and cytogenetic risk (intermediate, poor). In addition, the 95% confidence interval (CI) for CR + CRi rate based on the binomial distribution (Clopper-Pearson exact method) by treatment arms were provided. The analysis of CR + CRi rate was planned to be performed with the first 225 patients in the FAS. The 95% CI for the risk difference (exact unconditional confidence limits) were provided • The distribution of OS was estimated for each treatment arm using Kaplan–Meier methodology and compared between treatment arms using the log-rank test stratified by age (18 – < 75, ≥ 75) and cytogenetic risk (intermediate, poor). The hazard ratio between treatment arms was estimated using the Cox proportional hazards model stratified by age (18 – < 75, ≥ 75) and cytogenetic risk (intermediate, poor)	• The distribution of OS was estimated for each treatment arm using Kaplan–Meier methodology and compared between treatment arms using the log-rank test stratified by age (18 – < 75, ≥ 75) and cytogenetic risk (intermediate, poor). The hazard ratio between treatment arms was estimated using the Cox proportional hazards model stratified by age (18 – < 75, ≥ 75) and cytogenetic risk (intermediate, poor). Statistical significance was determined by a two-sided *P* value ≤ 0.05 (when rounded to three decimal places).
Sample size, power calculation	• The sample size calculation was based on the following assumptions: o The significance level (two-sided 0.05) was split to give a 0.01 significance level to the OS analysis o Median OS of 10.4 months for AZA arm o Median OS of 14.9 months for VenAZA arm (HR of 0.7) o Interim analysis of OS at 75% of death events with O'Brien-Fleming boundary	• The sample size calculation was based on the following assumptions: o Median OS of 6 months for LDAC arm o Median OS of 11 months for VenLDAC arm (HR of 0.545) o Interim analysis of OS at 75% of death events with O'Brien-Fleming boundary o 2:1 randomisation ratio to VenLDAC, and LDAC arm

	o 2:1 randomisation ratio to VenAZA and AZA arm • With the above assumptions: o A total of 225 patients (150 in VenAZA arm, and 75 in AZA arm) provide 88% power to detect statistically significant difference in CR + CRi rate between treatment arms at two-sided alpha level of 0.01 o A total of 360 death events provide 86.7% power to detect statistically significant difference in OS between treatment arms at two-sided alpha level of 0.04 o A total of ~400 patients (267 in VenAZA arm, and 133 in AZA arm) were planned to be randomised into the study to obtain 360 death events.	• With the above assumptions: o A total of 133 death events provide 90% power to detect statistically significant difference between treatment arms at two-sided alpha level of 0.05 o A total of approximately 210 patients (140 in VenLDAC arm and 70 in LDAC arm) were planned to be randomised into the study to obtain the 133 death events
Data management, patient withdrawals	• For OS, if a patient had not died, then the data were censored at the date the patient was last known to be alive on or before the cut-off date • The date patients were "last known alive" was determined by selecting the last available date of the following study procedures for a patient: adverse event start date, bone marrow collection, disease assessment, vital signs assessment, clinical laboratory collection, study drug administration, concomitant medicine start date, biospecimen sample collection, transfusion, survival follow-up, quality of life assessments, and performance status. All patients in the FAS were included in the analysis	

The primary endpoint of the VIALE-A trial differed between Japan, EU and EU reference countries and US and US reference countries: Japan, EU and EU reference countries: dual primary endpoints of composite complete remission (CR + CRi) rate (as assessed by investigator) and OS; US and US reference countries: a single primary efficacy endpoint of OS. presented in this submission is aligned with Japan, EU and EU reference countries.
Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; FAS: full analysis set; HR: hazard ratio; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax.
Source: VIALE-A Clinical Study Report,[83] VIALE-C Clinical Study Report.[84]

B.2.4 *Quality assessment of the relevant clinical effectiveness evidence*

Full details of the SLR, including methods and results of the quality assessment can be found in Appendix D.

A quality assessment of VIALE-A and VIALE-C was performed using the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs (as per recommendations in the NICE user guide), and is presented in Appendix D.[88] Overall, both VIALE-A and VIALE-C are considered to be of high quality with low risk of bias.

B.2.5 *Clinical effectiveness results of the relevant trials*

A summary of key clinical outcomes from the VIALE-A and VIALE-C trials for both the overall trial population, and the blast count restricted subgroups of interest to this submission are presented in Table 11.

In VIALE-A patients treated with VenAZA had statistically significant improvements in OS, EFS, and rate of CR + CRi compared with patients treated with AZA.[83] Additionally improvements in OS and EFS for patients treated with VenAZA compared with AZA were also demonstrated in the subgroup of patients most relevant to the decision problem (those with 20–30% blast cells).[83]

In VIALE-C no statistically significant difference was observed in OS (data cut-off date 15th February 2019). At the time of planned primary analysis there was greater administrative censoring of patients in the VenLDAC arm than the LDAC arm because trial enrolment was ongoing as recently as 3.4 months before the planned OS analysis. This administrative censoring of patients still alive at the time of analysis occurred more frequently in the VenLDAC arm than in the LDAC arm (17 [12%] versus 4 [6%] patients, respectively, within the first 6 months). This resulted in a shorter OS in patients treated with VenLDAC due to the censoring imbalance, which limited the conclusions that could be drawn from the planned primary analysis**.** At an unplanned post-hoc 6 month follow up patients treated with VenLDAC demonstrated improvements in OS, EFS, and rate of CR + CRi compared with patients treated with LDAC.[84] Additionally improvements in OS and EFS for patients treated with VenLDAC compared with LDAC were also demonstrated in the subgroup of patients most relevant to the decision problem (those with >30% blast cells).[84]

Table 11: Summary of key outcomes in the VIALE-A and VIALE-C trials

Outcome	VIALE-A				VIALE-C			
	Overall Population (B.2.5.1)		20–30% blast count (B.2.6.1)		Overall Population (B.2.5.2)		>30% blast count (B.2.6.2)	
	VenAZA (N=286)	AZA (N=145)	VenAZA (N=78)	AZA (N=36)	VenLDAC (N=143)	LDAC (N=68)	VenLDAC (N=108)	LDAC (N=52)
Rate of CR + CRi								
CR + CRi, % (95% CI)	65.4 (60.6–71.9)	28.3 (21.1–36.3)	-		48.3 (39.8–56.8)	13.2 (6.2–23.6)	-	
P	<0.001[a]				< 0.001[b,c]			
Overall Survival								
Events, n (%)	161 (56.3)	109 (75.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	14.7 (11.9–18.7)	9.6 (7.4–12.7)	[redacted]	[redacted]	8.4 (5.9–10.1)	4.1 (3.1–8.1)	[redacted]	[redacted]
HR (95% CI), *P*	0.66 (0.52–0.85), *P* < 0.001[a]		[redacted]		0.70 (0.50–0.99), *P* = 0.041[b,c]		[redacted]	
Event-free Survival								
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median EFS, months (95% CI)	9.8 (8.4–11.8)	7.0 (5.6–9.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI), *P*	0.63 (0.50–0.80), *P* < 0.001[a]		[redacted]		[redacted][b,c]		[redacted]	

[a] Stratified by age (17–<75, ≥75 years) and cytogenetics (immediate risk, poor risk).[b] Stratified by age (18–<75, ≥75 years) and AML status (de novo, secondary). [c] *P* value descriptive in nature only.
Abbreviations: AZA: azacitidine; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete haematological recovery; EFS: event-free survival; HR: hazard ratio; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax.

B.2.5.1 VIALE-A (NCT02993523)

Overview of results

The following section presents results for patients receiving venetoclax in combination with azacitidine (referred to hereafter as VenAZA) or placebo in combination with azacitidine (referred to hereafter as AZA) from the VIALE-A trial. Unless stated otherwise, the following section presents the results from the 4th January 2020 data cut of the VIALE-A trial (median 20.5 months follow-up), at which time all patients had completed a median of 7 cycles of treatment. Key results from the VIALE-A trials are presented in this section and additional results are presented in Appendix L. The dual primary endpoints were investigator-assessed OS and best response of CR + CRi, which informed the cost-effectiveness analysis presented in Section B.3. VIALE-A met its dual primary endpoints of OS and CR + CRi, and treatment with VenAZA was associated with improved survival, rapid and durable remission, and improved rates of transfusion independence compared to AZA alone.[83] The addition of venetoclax to AZA was also not associated with a detrimental effect on patients' HRQoL compared to AZA alone.[83]

Primary efficacy endpoints

Overall survival (data cut-off: 4th January 2020 [IA2])

After a median follow-up of 20.5 months, median OS was significantly longer in the VenAZA arm than in the AZA arm (14.7 months versus 9.6 months, respectively [Table 12]) with a HR of 0.66 (95% CI: 0.52–0.85; *P* < 0.001).[81]

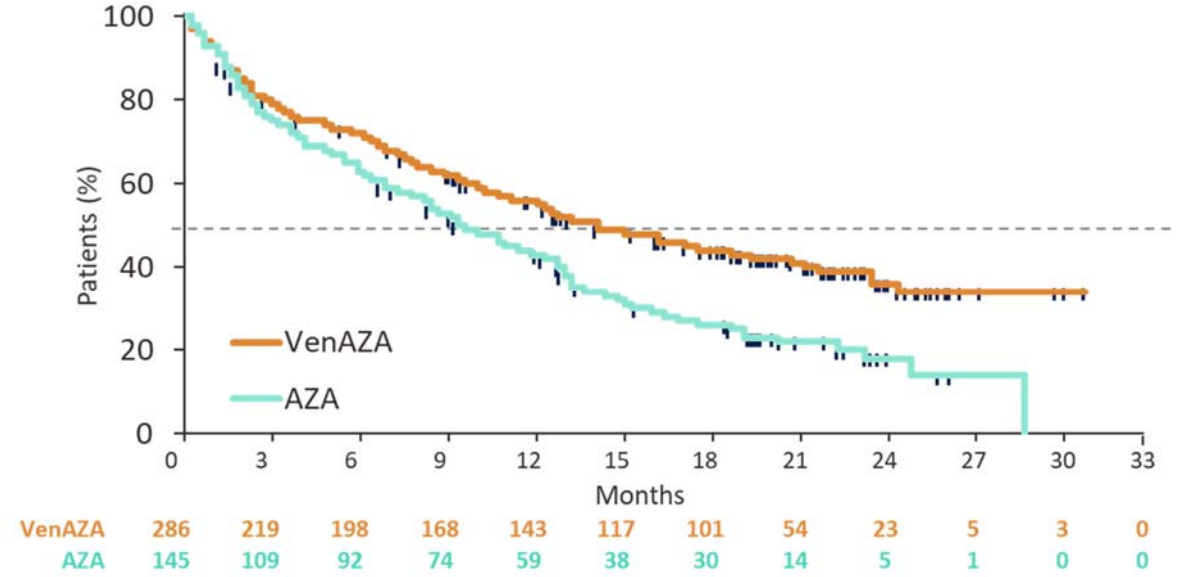
Table 12: OS in VIALE-A (FAS, IA2)

	VenAZA (N=286)	AZA (N=143)
Events (deaths), n (%)	161 (56.3)	109 (75.2)
Median OS, months (95% CI)	14.7 (11.9–18.7)	9.6 (7.4–12.7)
Rate of OS, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Treatment Comparison (Stratified[a])		
HR (95% CI)	0.66 (0.52–0.85)	
P	< 0.001	

[a]Stratified by age (18–<75, ≥75 years) and cytogenetics (intermediate risk, poor risk).
Abbreviations: AZA: azacitidine CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IA2: interim analysis 2; N: sample size; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 9, Page 140,[83] DiNardo *et al.* (2020).[81]

The Kaplan–Meier plots show rapid separation of the curves in favour of VenAZA, which was maintained over time, based on 20.5 months follow-up (Figure 5). At 24 months, a higher proportion of patients in the VenAZA treatment arm were alive than in the AZA arm ([redacted]% versus [redacted]%).

Figure 5: Kaplan–Meier plot of OS in VIALE-A (FAS, IA2)



Abbreviations: AZA: azacitidine; FAS: full analysis set; IA2: Interim Analysis 2; OS: overall survival; Ven: venetoclax.
Source: VIALE-A Clinical Study Report,[83] Figure 2, Page 141, DiNardo *et al*. (2020).[81]

Composite complete remission rate (data cut-off: 1st October 2018 [IA1])

The data presented below are from the IA1 of VIALE-A, which was conducted with the first 226 randomised patients, allowing for a 6-month follow-up, representing a cut-off date of 1st October 2018.[83] A clinically meaningful and statistically significant difference was observed in the rate of patients achieving CR + CRi, with patients in the VenAZA treatment arm achieving a higher rate of CR + CRi compared to patients in the AZA arm ([redacted]% versus [redacted]%, *P* < 0.001 [Figure 6]).[83] As discussed in Section B.1.3.3, achieving CR + CRi is a key treatment goal for patients with AML, since it is associated with considerable improvements in HRQoL and subsequent survival.

Figure 6: Best response of CR + CRi based on investigators' assessment (first 226 patients, IA1) in VIALE-A

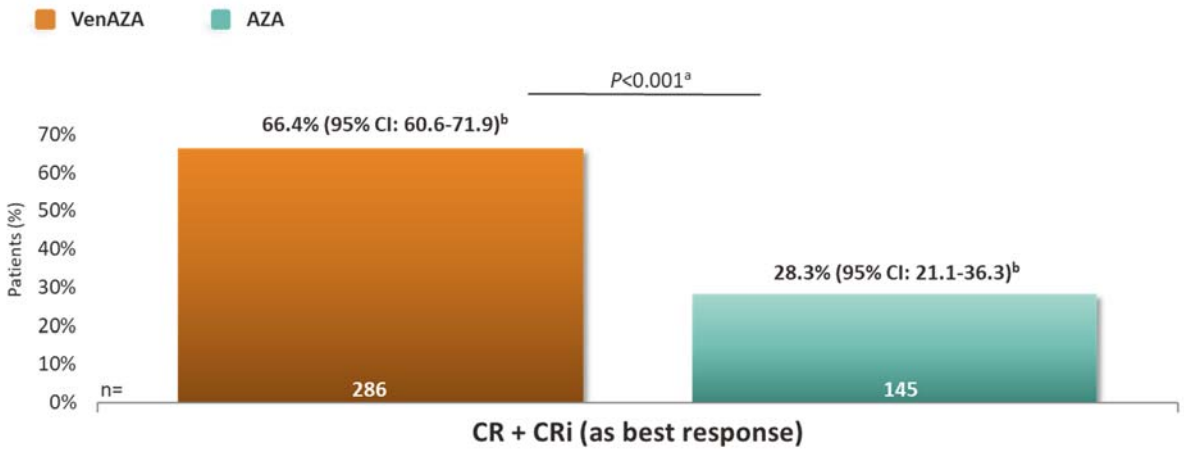
[redacted]

The cut-off date for IA1 was 1st October 2018. [a]*P* value is from Cochran-Mantel-Haenszel test stratified by age (18 to < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk). [b]95% CI from the exact binomial distribution.

Abbreviations: AZA: azacitidine; CI: confidence interval; CR + CRi: composite complete remission; IA1: Interim Analysis 1; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 7, Page 122.[83]

A sensitivity analysis was performed including data from the FAS at IA2 (data cut-off 4th January 2020). The CR + CRi rates at IA2 remained consistent with those observed at IA1 for the first 226 randomised patients (66.4% versus 28.3%, *P* < 0.001 [Figure 7]). Additionally, at IA2, the median duration of CR + CRi was 17.5 months in the VenAZA arm and 13.4 months in the AZA arm, demonstrating the improved durability of response with VenAZA.[81]

Figure 7: Best response of CR + CRi based on investigators' assessment (FAS, IA2) in VIALE-A



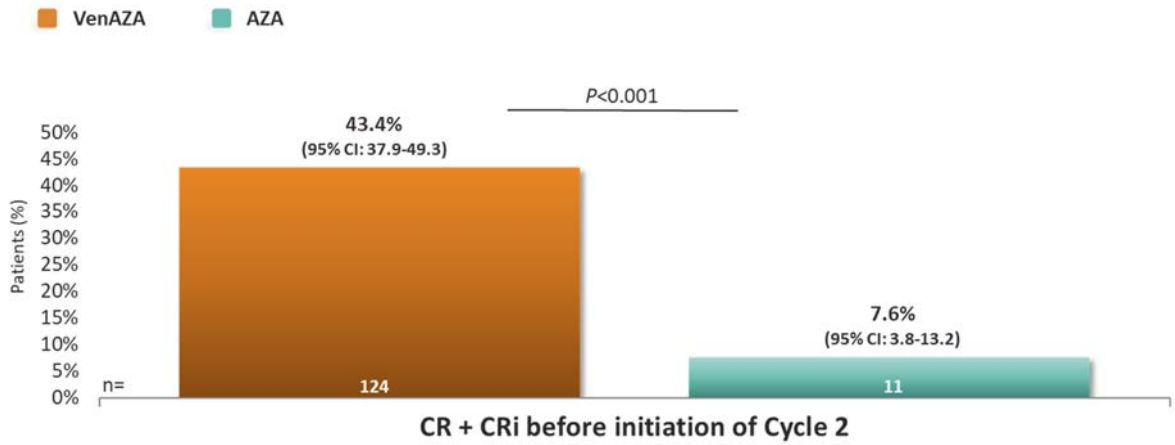
The cut-off date for IA2 was 4th January 2020. [a]*P* value is from Cochran-Mantel-Haenszel test stratified by age (18 to < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk). [b]95% CI from the exact binomial distribution.
Abbreviations: AZA: azacitidine; CI: confidence interval; CR + CRi: composite complete remission; FAS: full analysis set; IA2: Interim Analysis 2; Ven: venetoclax.
Source: DiNardo *et al*. (2020).[81]

Secondary and exploratory efficacy outcomes (data cut-off: 4th January 2020 [FAS IA2])

Early acquisition of CR: CR + CRi by initiation of Cycle 2

Achievement of CR within the first cycle of treatment has been associated with improved survival outcomes for patients with AML.[89] Patients in the VenAZA arm responded to treatment more rapidly than in the AZA arm, with a median time to first response of 1.3 months versus 2.8 months, respectively, and a considerably higher proportion of patients achieving remission by Cycle 2 (43.4% versus 7.6%; *P* < 0.001 [Figure 8]).[81]

Figure 8: CR + CRi before initiation of Cycle 2 in VIALE-A (FAS, IA2)



P value is from Cochran-Mantel-Haenszel test stratified by age (18 to <75, ≥75) and cytogenetics (intermediate risk, poor risk). 95% CI is from the exact binomial distribution.
Abbreviations: AZA: azacitidine; CI: confidence interval; CR; complete remission; CRi: complete remission with incomplete blood count recovery; FAS: full analysis set; IA2: Interim Analysis 2; Ven: venetoclax.
Source: DiNardo *et al*. (2020).[81]

Event-free survival

After a median follow-up of 20.5 months, median EFS was significantly longer in the VenAZA than the AZA arm (9.8 months versus 7.0 months, respectively [Table 13]) with a HR of 0.63 (0.50–0.80; *P* < 0.001).[81]

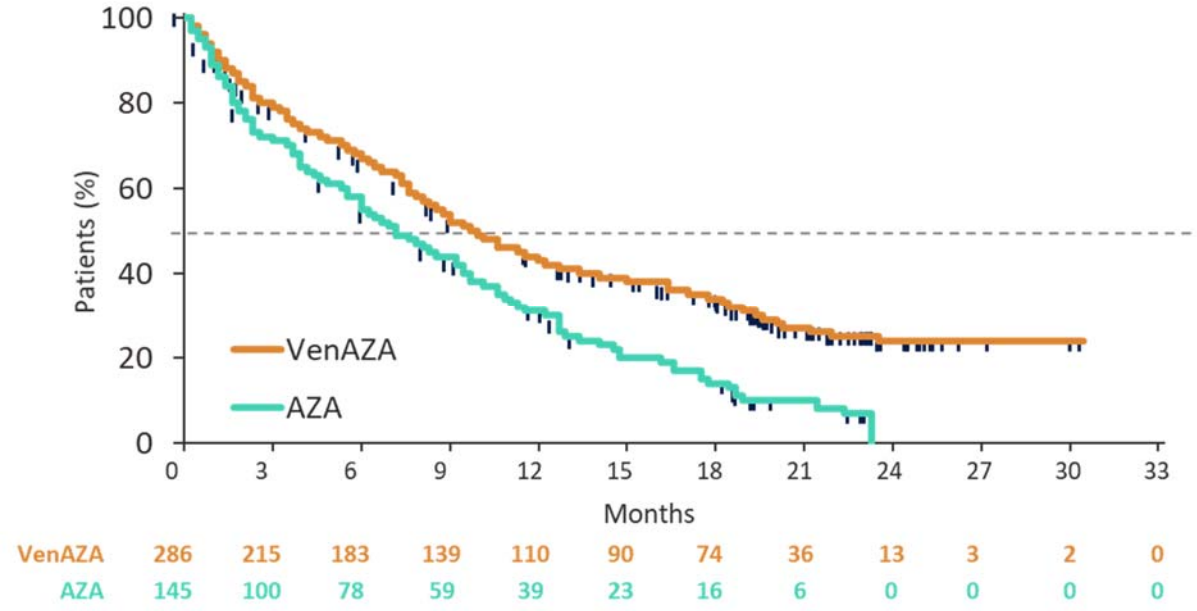
Table 13: Event-free survival in VIALE-A based on investigators' assessment (FAS, IA2)

	VenAZA (N=286)	AZA (N=145)
Number of patients with events, n (%)	[redacted]	[redacted]
Duration of event-free survival, months (95% CI)		
Median	9.8 (8.4–11.8)	7.0 (5.6–9.5)
Event-free survival rate, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Treatment Comparison (Stratified[a])		
HR (95% CI)	0.63 (0.50–0.80)	
P value	< 0.001	

The cut-off date for IA2 was 4th January 2020. [a]Stratified by age (18–<75, ≥75 years) and cytogenetics (intermediate risk, poor risk)
Abbreviations: AZA: azacitidine; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IA2: interim analysis 2; NA: not available; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 14, Page 164,[83] DiNardo *et al.* (2020).[81]

The Kaplan–Meier plots show rapid separation of the curves in favour of VenAZA, which was maintained over time, based on 20.5 months follow-up (Figure 9). A higher proportion of patients in the VenAZA treatment arm were event-free at 12 months than in the AZA arm ([redacted]% versus [redacted]%), and [redacted] of patients in the VenAZA arm remained event-free at 24 months.

Figure 9: Kaplan–Meier plot of EFS in VIALE-A (FAS, IA2)



Abbreviations: AZA: azacitidine; EFS: event free survival; FAS: full analysis set; IA2: Interim Analysis 2; Ven; venetoclax
Source: VIALE-A Clinical Study Report, Figure 3, Page 165.[83] DiNardo *et al.* (2020).[81]

Transfusion independence

As discussed in Section B.1.3.2, transfusion dependence is linked to poor HRQoL.[52, 53] Achieving transfusion independence is a key treatment goal for patients with AML, reducing the burden on patients' ability to live a normal life.

VenAZA significantly improved the percentage of patients who achieved RBC and platelet transfusion independence ($P < 0.001$, [Figure 10]).[83] For patients who were transfusion dependent at baseline, a significantly higher proportion of patients receiving VenAZA become transfusion independent during the course of treatment was compared to patients treated with AZA ($P < 0.001$, [Figure 11]). The median duration of RBC and platelet transfusion independence for VenAZA and AZA treatment arms was [redacted] and [redacted],days respectively.[83] Patients in the VenAZA arm achieved RBC and platelet transfusion independence more rapidly than those in the AZA arm, with a median time to first independence of [redacted] and [redacted] days, respectively.[83] Full details of transfusion independence rates reported for patients in VIALE-A are presented in Appendix L.

Figure 10: Post-baseline transfusion independence in VIALE-A (FAS, IA2)

P value is from Cochran-Mantel-Haenszel test stratified by age (18–<75, ≥75 years) and cytogenetics (intermediate risk, poor risk). Post-baseline transfusion evaluation period is from the first dose of study drug to the last dose of study drug + 30 days, or disease progression, or confirmed morphological relapse, or post-treatment therapy, or death, or data cut-off date, whichever occurred earlier.
Abbreviations: AZA: azacitidine; CI: confidence interval; FAS: full analysis set; IA2: Interim Analysis 2; RBC: red blood cells; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 12, Page 152.[83] DiNardo *et al.* (2020).[81]

Figure 11: Post-baseline transfusion independence conversion rate in VIALE-A (FAS, IA2)

Conversion rate of transfusion independence is the proportion of patients being post-baseline transfusion independent from baseline dependence. Post-baseline transfusion evaluation period is from the first dose of study drug to the last dose of study drug + 30 days, or disease progression, or confirmed morphological relapse, or post-treatment therapy, or death, or data cut-off date, whichever occurred earlier.
Abbreviations: AZA: azacitidine; CI: confidence interval; FAS: full analysis set; IA2: interim analysis 2; RBC: red blood cell; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 12, Page 152.[83] DiNardo *et al.* (2020).[81]

Minimal residual disease

As described in Table 3, MRD has been identified as an independent prognostic indicator in AML, with lower MRD levels indicating an improved prognosis.[63] VenAZA provided patients with a significantly higher rate of sustained deep remissions (MRD <0.001 and CR + CRi) than AZA alone ([redacted] [Table 14]). Additionally, patients treated with VenAZA achieved a lower median MRD value than those treated with AZA alone.

Table 14: MRD negativity

	VenAZA (N=286)	AZA (N=145)
Patients with MRD assessment, n	[redacted]	[redacted]
Median MRD value (range)	[redacted]	[redacted]
Patients with MRD negativity[a], n (%)	[redacted]	[redacted]
Patients with deep remission (MRD <0.001 and CR + CRi)		
n (%) [95% CI][b]	[redacted] (23.4) [18.6, 28.8]	[redacted] (7.6) [3.8, 13.2]
P value[c]	[redacted]	

[a] MRD negativity defined as MRD value of <0.001. [b]95% CI from the exact binomial distribution. [c]*P* value from Cochran-Mantel-Haenszel test stratified by age (18–<75, ≥75 years) and cytogenetic risk (intermediate, poor) from IVRS/IWRS, significance level was *P* = 0.001.
Abbreviations: AZA: azacitidine; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IVRS: interactive voice response system; IWRS: interactive web response system MRD: minimal residual disease; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 13,[83] DiNardo *et al.* (2020).[81]

In both treatment arms, patients who achieved deep remission (MRD <0.001 and CR + CRi) had longer median OS than those who achieved CR + CRi alone. In patients achieving deep remission, median OS was longer in those treated with VenAZA, with median OS not yet being reached as of the 4th January data cut-off, compared to AZA alone (Table 16). This demonstrates the ability of VenAZA to improve patients' long-term survival by providing deep and long lasting remission.

Table 15: OS among patients achieving CR + CRi stratified by MRD negativity

	VenAZA (N=286)	AZA (N=145)
Patients with deep remission (MRD <0.001 and CR + CRi)		
n, (%)	[redacted]	[redacted]
Events	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Survival estimate, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	73.6 [redacted]	63.6 [redacted]
MRD ≥0.001 and CR + CRi		
n	[redacted]	[redacted]
Events	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
Survival estimate, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; MRD: minimal residual disease; NA: not applicable; OS: overall survival; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Figure 14.2__11.4.5.1,[83] DiNardo *et al.* (2020).[81]

The Kaplan–Meier plots show rapid separation of the curves in favour of MRD negativity in both treatment arms, which was maintained over time, based on 20.5 months follow-up (Figure 5). Among those who achieved MRD negativity, the Kaplan Meier plots show separation in favour of those treated with VenAZA. Notably, only [redacted] patients ([redacted]%) in the AZA arm achieved deep remission, 6 of whom had experienced an event as of the 4th January data cut-off. This demonstrates the limited ability of AZA to provide deep and long-lasting remission, and therefore improve long-term survival outcomes.

Figure 12: Kaplan–Meier plot of OS among patients achieving CR + CRi stratified by MRD negativity

Abbreviations: MRD: minimal residual disease; OS: overall survival.
Source: VIALE-A Clinical Study Report, Figure 14.2__11.4.5.1. [83]

Patient reported outcomes

PROMIS Cancer Fatigue SF7a

Change from baseline in the PROMIS Fatigue score was compared between the VenAZA and AZA arms at each post-baseline visit; scores are presented in Figure 13. Mean baseline PROMIS scores were similar across the VenAZA and AZA arms ([redacted] and [redacted], respectively). Patients in both treatment arms experienced a [redacted] and there were [redacted] in mean change between the treatment arms. Therefore, treatment with VenAZA was [redacted] compared to AZA alone.

Figure 13: Summary of PROMIS 7a Fatigue Score in VIALE-A (FAS)

A decrease in PROMIS 7a score indicates an improvement in fatigue.
Abbreviations: AZA: azacitidine; CI: confidence interval; FAS: full analysis set; LS mean: least squares mean; PROMIS: Patient-Reported Outcomes Measurement Information System; VEN: venetoclax;
Source: VIALE-A Clinical Study Report, Table 15, Page 167.[83]

Global Health Status/Quality of Life (EORTC QLQ-C30)

Change from baseline in each EORTC QLQ-C30 GHS/QoL score was compared between the VenAZA and AZA at each post-baseline visit, scores are presented in Figure 14. Baseline EORTC QLQ-C30 GHS/QoL scores were similar between the VenAZA arm ([redacted]) and the AZA arm ([redacted]). Patients in both treatment arms experienced an improvement in HRQoL. A [redacted] in EORTC QLQ-C30 GHS/QoL scores was observed in the VenAZA arm compared to the AZA arm on Day 1 of all cycles, except Cycle 19, and between-group differences in mean change from baseline [redacted]. However, there were [redacted] in mean change from baseline in the VenAZA arm compared to the AZA arm. Therefore, no detriment to quality of life (QoL) with the addition of venetoclax to AZA was observed.

Patients treated with VenAZA experienced a longer time to deterioration (TTD) of QoL, compared to those treated with AZA alone, based on a deterioration of the within-group estimate of at least the meaningful change threshold (MCT) of 10 points. The median TTD of QoL for patients in the VenAZA arm was [redacted] months longer ([redacted] months; 95% CI: [redacted]) than the AZA arm ([redacted] months; 95% CI: [redacted]).

Figure 14: EORTC QLQ-C30 GHS/QoL Score in VIALE-A (FAS)

An increase in EORTC QLQ-C30 GHS/QoL score indicates an improvement in quality of life.
Abbreviations: AZA: azacitidine; CI: confidence interval; Diff: difference; EORTC: European Organisation for Research and Treatment of Cancer; FAS: full analysis set; GHS: Global Health Status; LS mean: least squares mean; N: sample size; QLQ C-30: Quality of Life Questionnaire Core 30; QoL: quality of life; SE: standard error; Ven: venetoclax;
Source: VIALE-A Clinical Study Report, Table 16, Page 17.[83]

B.2.5.2 VIALE-C (NCT03069352)

Overview of results

The following section presents results for patients receiving venetoclax in combination with LDAC (referred to hereafter as VenLDAC) or placebo in combination with LDAC (referred to hereafter as LDAC) from the VIALE-A trial. This section presents two analyses for the primary endpoint of OS. At the planned primary analysis, no significant difference was observed in OS (data cut-off date 15th February 2019). As previously mentioned, there was greater censoring of patients in the VenLDAC arm than the LDAC arm, as more patients treated with VenLDAC had not yet reached median OS. Results from a subsequent unplanned analysis, with an additional 6 months of follow-up, are also presented in this section (data cut-off date 15th August 2019; median [redacted] months follow-up). The secondary endpoints included in this section also correspond to the 15th August 2019 data cut, at which time all patients had completed a median of [redacted] cycles of treatment. The primary endpoint of OS and secondary endpoints of CR + CRi and EFS are utilised in the cost-effectiveness analysis presented in Section B.3

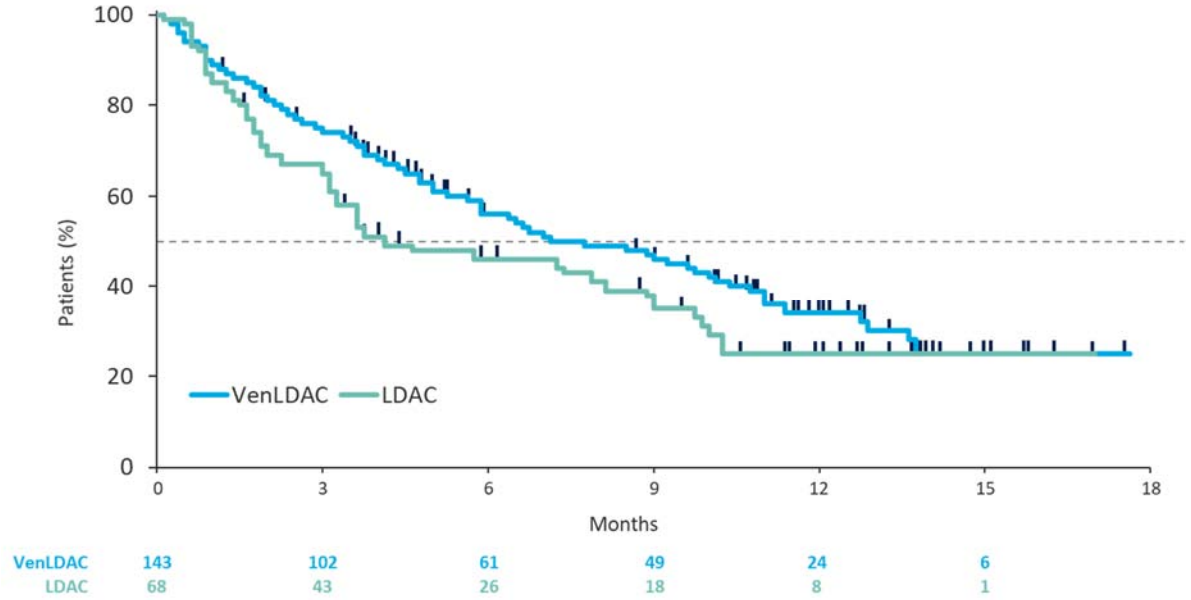
As VIALE-C did not meet its primary endpoint, all *P* values presented in this section are descriptive only.

Thus in an unplanned analysis performed with an additional 6 months follow-up, treatment with VenLDAC was associated with improved survival, rapid and durable remission, and improved rates of transfusion independence compared to LDAC alone.[84]

Primary endpoint – Overall survival (data cut-off: 15th February 2019)

At the planned primary analysis, median OS was longer in the VenLDAC arm (n=143) compared to the LDAC arm (n=68) (7.2 versus 4.1 months, respectively). Although not statistically significant, the HR was 0.75 (95% CI: 0.52–1.07; *P* = 0.11),[82] and when adjusting for baseline prognostic factors, the covariate-adjusted HR was 0.67 (95% CI: 0.47–0.96, *P* = 0.03). The Kaplan–Meier plots show separation of the curves in favour of VenLDAC, which was maintained over time, based on a median follow-up of 12.0 months (Figure 16).[84] The 12-month survival estimate was higher in the VenLDAC arm than in the LDAC arm ([redacted] versus [redacted], respectively).[84]

Figure 15: Kaplan-Meier plot of OS in VIALE-C (FAS, primary analysis)



Abbreviations: LDAC: low-dose cytarabine; PBO: placebo: Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Figure 2, Page 139.[84]

Primary endpoint – Overall survival (6-month follow-up data cut-off: 15th August 2019)

With an additional 6 months of follow-up (median follow-up of [redacted] months), a majority of patients had passed the median survival time in both arms. Median OS was longer in the VenLDAC arm compared to the LDAC arm (8.4 versus 4.1 months, respectively [Table 16]) with a HR of 0.70 (95% CI: 0.50–0.98; *P* = 0.04). Median OS in the control arm, remained unchanged between the primary analysis and the 6-month follow-up.

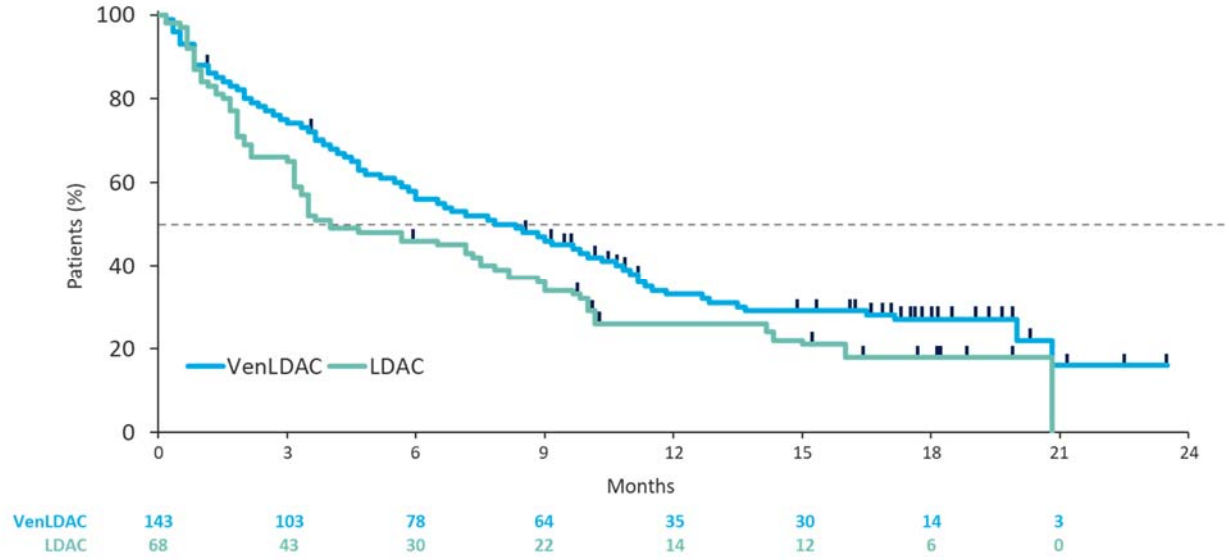
Table 16: Analysis of OS in VIALE-C (FAS – 6-month follow-up)

	VenLDAC group (N=143)	LDAC (N=68)
Events (deaths) - n (%)	[redacted]	[redacted]
Median duration of OS, months (95% CI)	8.4 (5.9–10.1)	4.1 (3.1–8.1)
Survival estimate, % (95% CI)		
6-Month	[redacted]	[redacted]
12-Month	[redacted]	[redacted]
24-Month	[redacted]	[redacted]
Treatment comparison (Stratified[a])		
HR (95% CI)	0.70 (0.50–0.99)	
P[b]	0.041	

[a] Stratified by AML status (de novo, secondary) and age (18–<75, ≥75 years).[b]*P* value descriptive only.
Abbreviations: AML: acute myeloid leukaemia; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; LDAC: low-dose cytarabine; N: sample size; n: number of patients; NA: not available; OS: overall survival; Ven: venetoclax;
Source: VIALE-C Clinical Study Report, Table 15, Page 182.[84] Wei *et al.* (2020).[82]

The Kaplan–Meier plots show separation of the curves in favour of VenLDAC, which was maintained over time, based on a median follow-up of [redacted] months (Figure 16).[84] The 12-month survival estimate was higher in the VenLDAC arm than in the LDAC arm ([redacted] versus [redacted], respectively).[84]

Figure 16: Kaplan-Meier plot of OS in VIALE-C (FAS 6-month follow-up)



Abbreviations: FAS: full analysis set; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax
Source: VIALE-C Clinical Study Report, Figure 4, Page 183.[84] Wei *et al.* (2020).[82]

Secondary and exploratory efficacy outcomes (FAS 6-month follow-up)

Composite complete remission (CR + CRi)

A clinically meaningful difference in CR + CRi was observed between treatment arms, with a higher proportion of patients achieving CR + CRi at any stage during treatment in the VenLDAC arm compared to the LDAC arm ([redacted] versus [redacted], [redacted], [Figure 17]). The median duration of remission was [redacted] months in the VenLDAC arm and [redacted] months in the LDAC arm, demonstrating the improved durability of the response with VenLDAC.

Patients in the VenLDAC arm also responded to treatment more rapidly than those in the LDAC arm, with a median time to first remission of [redacted] and [redacted] months, respectively. A higher proportion of patients in the VenLDAC arm achieved a CR + CRi response by the initiation of Cycle 2 ([redacted] versus [redacted], [redacted] [Figure 17]).

Figure 17: CR + CRi response rates in VIALE-C (FAS)

[a]*P* value is descriptive in nature only and is from Cochran-Mantel-Haenszel test stratified by age (18–<75, ≥75 years) and AML status (de novo, secondary) from IVRS/IWRS, and Fisher's exact test. 95% CI is from the exact binomial distribution.
Abbreviations: AML: acute myeloid leukaemia; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; FAS: full analysis set; LDAC: low-dose cytarabine; n: number of patients; Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Table 17, Page 186.[84]

Event-free survival

After a median follow-up of [redacted] months, median EFS was longer in the VenLDAC arm compared to the LDAC arm ([redacted] versus [redacted] months, respectively [Table 17]) with a HR of [redacted].

Table 17: Event-free survival in VIALE-C based on investigators' assessment (FAS)

	VenLDAC (N=143)	LDAC (N=68)
Number of patients with events, n (%)	[redacted]	[redacted]
Confirmed morphologic relapse/confirmed disease progression, n	[redacted]	[redacted]
Treatment failure, n	[redacted]	[redacted]
Death, n	[redacted]	[redacted]
Patients without an event, n (%)	[redacted]	[redacted]
Median duration of EFS, months (95% CI)	[redacted]	[redacted]
No event rate, % (95% CI)		
6-month	[redacted]	[redacted]
12-month	[redacted]	[redacted]
18-month	[redacted]	[redacted]
Treatment comparison (Stratified[a])		
HR (95% CI)	[redacted]	
P[b]	[redacted]	

[a]Stratified by AML status (de novo, secondary) and age (18–<75, ≥75 years).[b]*P* value is descriptive in nature only

Abbreviations: AML: acute myeloid leukaemia; CI: confidence interval; EFS: event free survival; FAS: full analysis set; LDAC: low-dose cytarabine; N: sample size; n: number of patients; Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Table 19, Page 192.[84]

The Kaplan-Meier plots show rapid separation of the curves in favour of VenLDAC, which was maintained over time, based on a median follow-up of [redacted] months (Figure 18). A higher proportion of patients in the VenLDAC arm were event-free at 18 months compared to the LDAC arm ([redacted] versus [redacted], respectively).

Figure 18: Kaplan-Meier plot of EFS in VIALE-C (FAS)

Abbreviations: FAS: full analysis set; LDAC: low-dose cytarabine; PBO: placebo; VEN; venetoclax
Source: VIALE-C Clinical Study Report, Figure 5, Page 193.[84]

Transfusion independence

VenLDAC improved the percentage of patients who achieved transfusion independence for both RBC and platelets (*P* = 0.002 [Figure 19]). Additionally, patients receiving VenLDAC who were transfusion dependent at baseline were more likely to become transfusion independent during the course of treatment than patients treated with LDAC (Figure 20). For those patients who achieved transfusion independence, the median duration of RBC and platelet transfusion independence was similar across the VenLDAC and LDAC arms ([redacted] and [redacted] days, respectively). Full details of transfusion independence rates reported for patients in VIALE-C are presented in Appendix L.

Figure 19: Post-baseline transfusion independence in VIALE-C (FAS)

[a]*P* value is description in nature only and is from Cochran-Mantel-Haenszel test stratified by age (18–<75, ≥75 years) and AML status (*de novo*, secondary) from IVRS/IWRS. [b]95% CI is from exact binomial distribution. Post-baseline transfusion evaluation period is from the first dose of study drug to the last dose of study drug + 30 days, or disease progression, or confirmed morphological relapse, or post-treatment therapy, or death, or data cut-off date, whichever occurred earlier.
Abbreviations: AML: acute myeloid leukaemia; CI: confidence interval; FAS: full analysis set; LDAC: low-dose cytarabine; RBC: red blood cells; Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Table 20, Page 195.[84]

Figure 20: Post-baseline transfusion independence conversion rate in VIALE-C (FAS)

Conversion rate of transfusion independence is the proportion of patients being post-baseline transfusion independent from baseline dependence. Post-baseline transfusion evaluation period is from the first dose of study drug to the last dose of study drug + 30 days, or disease progression, or confirmed morphological relapse, or post-treatment therapy, or death, or data cut-off date, whichever occurred earlier.
Abbreviations: CI: confidence interval; FAS: full analysis set; LDAC: low-dose cytarabine; RBC: red blood cells; Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Table 20 Page 195.[84]

Minimal residual disease

VenLDAC provided patients with a higher rate of sustained deep remissions (MRD <0.001 and CR + CRi) than LDAC alone (Table 18). Additionally, patients treated with VenLDAC achieved a lower median MRD value than those treated with LDAC alone.

Table 18: MRD negativity

	VenLDAC (N=143)	LDAC (N=68)
Number of patients with MRD assessment, n	[redacted]	[redacted]
Median MRD value (range)	[redacted]	[redacted]
Patients with MRD negativity[a], n (%)	[redacted]	[redacted]
Patients with deep remission (MRD <0.001 and CR + CRi)		
n (%) [95% CI][b]	[redacted]	[redacted]
P value[c]	[redacted]	

[a]MRD negativity defined as MRD value of <0.001. [b]95% CI from the exact binomial distribution. [c]*P* value from Cochran-Mantel-Haenszel test stratified by age (18–<75, ≥75 years) and AML status (*de novo*, secondary) from IVRS/IWRS.
Abbreviations: AML: acute myeloid leukaemia; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; IVRS: interactive voice response system; IWRS: interactive web response system; LDAC: low-dose cytarabine; MRD: minimal residual disease; Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Table 23.

Patient reported outcomes

PROMIS Cancer Fatigue SF7a

Change from baseline in the PROMIS Fatigue score was compared between two treatment arms at each post-baseline visit. PROMIS Cancer Fatigue SF7a scores from VIALE-C are presented Figure 21

Mean baseline PROMIS fatigue score was similar between patients in the VenLDAC and LDAC arms ([redacted] and [redacted], respectively). Patients in the VenLDAC arm experienced a greater improvement in fatigue than those in the LDAC arm. By Day 1 of Cycles 3, 5, 7, and 9, the change from baseline was greater in the VenLDAC arm vs the LDAC arm, with Cycles 3 and 5 meeting the threshold for MID (3 points).

Figure 21: PROMIS 7a Fatigue Score in VIALE-C (FAS)

A decrease in PROMIS 7a score indicates an improvement in fatigue.
MID was 3 points; estimated from the literature and confirmed by analysis of meaningful change using both anchor and distribution-based approaches
Abbreviations: CI: confidence interval; LDAC: low-dose cytarabine; Diff: difference; FAS: full analysis set; LS mean: least squares mean; PROMIS: Patient-Reported Outcomes Measurement Information System; VEN: venetoclax.
Source: VIALE-C Clinical Study Report, Table 21, Page 199.[84]

Global Health Status/Quality of Life (EORTC QLQ-C30)

Change from baseline in each EORTC QLQ-C30 GHS/QoL score was compared between the VenLDAC and LDAC at each post-baseline visit, scores are presented in Figure 22.

Figure 22: EORTC QLQ-C30 GHS/QoL Score in VIALE-C (FAS)

An increase in EORTC QLQ-C30 GHS/QoL score indicates an improvement in quality of life.

Abbreviations: CI: confidence interval; LDAC: low-dose cytarabine EORTC: European Organisation for Research and Treatment of Cancer; FAS: full analysis set; LS mean: least squares mean; N: sample size; QLQ C-30: Quality of Life Questionnaire Core 30; Ven: venetoclax;
Source: VIALE-C Clinical Study Report, Table 22, Page 202.[84]

B.2.6 *Subgroup analysis*

B.2.6.1 VIALE-A (NCT02993523)

Predictors of response

In order to identify any variation in the efficacy of VenAZA, the primary endpoints (OS and CR + CRi) were analysed by several demographic and disease subgroups. The subgroups included gender, age group, region, baseline ECOG score, type of AML (primary or secondary), cytogenetic risk group at diagnosis, molecular mutational status at diagnosis, antecedent haematologic history of MDS, and AML-MRC. Subgroup analyses for CR, CR + CRi by initiation of Cycle 2, and CR + CRh are presented in Appendix L.

Patients treated with VenAZA had increased OS compared with those treated with AZA alone for the majority of subgroups evaluated. A forest-plot for OS by all included subgroups is presented in Figure 23.

Figure 23: OS by subgroup in VIALE-A (FAS, IA2)

Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EDC: electronic data capture; FAS: full analysis set; HR: hazard ratio.
Source: VIALE-A Clinical Study Report, Figure 4, Page 184.[83] DiNardo *et al.* 2020.[81]

In the subgroup analysis of CR + CRi, the incidence of CR + CRi was improved across all AML genomic risk groups, including patients with adverse cytogenetic risk, secondary AML, and across all molecular subgroups including those with high-risk mutations. A forest plot of the rate of CR + CRi by all included subgroups is presented in Figure 24.

Figure 24: CR + CRi rate by subgroup based on investigators' assessment in VIALE-A (FAS, IA2)

Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EDC: electronic data capture; FAS: full analysis set; HR: hazard ratio.
Source: VIALE-A Clinical Study Report, Figure 6, Page 186.[83]

Impact of blast count restriction: 20–30% blast count subgroup

As discussed in Section B.1.1, the use of AZA is restricted by NICE for the treatment of patients with a blast count of 20–30% and, therefore, AZA is only considered a relevant comparator in this subpopulation. As such, post-hoc subgroup analyses were conducted for OS and EFS for patients in VIALE-A with 20–30% blasts at diagnosis, to provide efficacy data for this population in the cost-effectiveness model. This analysis confirmed that patients in this subgroup treated with VenAZA had improved OS and EFS outcomes compared to those treated with AZA alone. However, given the small number of patients in this subgroup, there is some uncertainty associated with the results presented below.

Overall Survival in patients with 20–30% blasts (data cut-off: 4th January 2020 [IA2])

Median OS was higher in the VenAZA arm than in the AZA arm (months versus months, respectively [Table 19]) with a HR of (95% CI:).[81] In the VenAZA arm, median OS was higher in the 20–30% blast count subpopulation compared to the overall population (months versus 14.7 months, respectively [Table 12]) .

Table 19: OS in the 20–30% blast subgroup VIALE-A (FAS, IA2)

	VenAZA (N=)	AZA (N=)

Events (deaths), n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
Rate of OS, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Treatment Comparison		
HR (95% CI)	[redacted]	
P	[redacted]	

Abbreviations: AZA: azacitidine CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IA2: interim analysis 2; N: sample size; n: number of patients; OS: overall survival; Ven: venetoclax.

The Kaplan–Meier plots generally show separation of the curves in favour of VenAZA (Figure 25). At 24 months, a higher proportion of patients in the VenAZA treatment arm were alive than in the AZA arm ([redacted]% versus [redacted]%).

Figure 25: Kaplan–Meier plot of OS in the 20–30% blast subgroup in VIALE-A (FAS, IA2)

[redacted]

Abbreviations: AZA: azacitidine; FAS: full analysis set; IA2: Interim Analysis 2; OS: overall survival; PBO: placebo; VEN: venetoclax.

Event free survival in patients with 20–30% blasts (data cut-off: 4th January 2020 [IA2])

Median EFS was higher in the VenAZA arm than in the AZA arm ([redacted] months versus [redacted] months, respectively [Table 20]) with a HR of [redacted][81] Median EFS was higher in the 20–30% blast count subpopulation compared to the overall population in both the VenAZA ([redacted] months and 9.8 months, respectively [Table 13]) and AZA ([redacted] months and 7.0 months, respectively) treatment arms.

Table 20: EFS in the 20–30% blast subgroup VIALE-A (FAS, IA2)]

	VenAZA (N=[redacted])	AZA (N=[redacted])
Events, n (%)	[redacted]	[redacted]
Median EFS, months (95% CI)	[redacted]	[redacted]
Event free survival rate, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]

24 months	[redacted]	[redacted]
Treatment Comparison		
HR (95% CI)	[redacted]	
P	[redacted]	

Abbreviations: AZA: azacitidine CI: confidence interval; EFS: event free survival; FAS: full analysis set; HR: hazard ratio; IA2: interim analysis 2; N: sample size; n: number of patients; NA: not available; Ven: venetoclax.

The Kaplan–Meier plots show separation of the curves in favour of VenAZA, which was maintained over time (Figure 26). A higher proportion of patients in the VenAZA treatment arm were event-free at 12 months than in the AZA arm ([redacted]% versus [redacted]%), and [redacted] of patients in the VenAZA arm remained event-free at 24 months.

Figure 26: Kaplan–Meier plot of EFS in the 20–30% blast subgroup in VIALE-A (FAS, IA2)

[redacted]

Abbreviations: AZA: azacitidine; EFS: event free survival; FAS: full analysis set; IA2: Interim Analysis 2; PBO: placebo; VEN: venetoclax.

B.2.6.2 VIALE-C (NCT03069352)

Predictors of response

To identify any variation in the efficacy of VenLDAC, the primary endpoint and key secondary endpoint (OS and CR + CRi rate, respectively) were analysed by several demographic and disease subgroups. The subgroups included gender, age group, region, baseline ECOG score, type of AML (primary or secondary), cytogenetic risk group at diagnosis, molecular mutational status at diagnosis, antecedent haematologic history of MDS, and AML-MRC. Subgroup analyses for CR, CR + CRi by initiation of Cycle 2, CR + CRh, and CR + CRh by initiation of Cycle 2 are presented in Appendix L.

Across most patient subgroups, those treated with VenLDAC showed a trend towards longer OS compared with those treated with LDAC alone. A forest plot for OS across all included subgroups in VIALE-C is presented in Figure 27.

Figure 27: OS by subgroup in VIALE-C (FAS)

HR calculated from unstratified Cox proportional hazards model. Arrow indicates CI extended more than current range.
Abbreviations: AML: acute myeloid leukaemia; CI: confidence interval; CMML: chronic myelomonocytic leukaemia; ECOG: Eastern Oncology Cooperative Group; EU: Europe; HMA: hypomethylating agent; HR: hazard ratio; LDAC: low-dose cytarabine; MDS: myelodysplastic syndromes; MRC: myelodysplasia related changes; OS: overall survival; PBO: placebo; US: United States; VEN: venetoclax.
Source: VIALE-C Clinical Study Report, Figure 14.2_1.3.1A, Page 1127.[84]

CR + CRi was increased across all patient subgroups patients in the VenLDAC treatment arm compared to the LDAC arm. A forest plot of the rate of CR + CRi by all included subgroups in VIALE-C is presented in Figure 28.

Figure 28: CR + CRi based on investigators' assessment by subgroup in VIALE-C (FAS)

95% CI is exact unconditional confidence limits. Arrow indicates CI extended more than current range.
Abbreviations: AML: acute myeloid leukaemia; CI: confidence interval; CMML: chronic myelomonocytic leukaemia; CR: complete remission; CRi: complete remission with incomplete blood count recovery; ECOG: Eastern Oncology Cooperative Group; EU: Europe; HMA: hypomethylating agent; LDAC: low-dose cytarabine; MDS: myelodysplastic syndromes; PBO: placebo; US: United States; VEN: venetoclax.
Source: VIALE-C Clinical Study Report, Figure 14.2_2.4A, Page 1147.[84]

Impact of blast count restriction: >30% blast count subgroup

As described in Section B.1.1, LDAC is not restricted by blast count but, in clinical practice is used to treat patients with a blast count of >30%, as AZA is used to treat patients with blast counts of 20–30%. Therefore, in the context of this appraisal, LDAC is considered a relevant comparator only in the >30% blast count population. As such, post-hoc subgroup analyses were conducted for OS and EFS to provide efficacy data for this population in the cost-effectiveness model. Given the small number of patients in this subgroup, there is some uncertainty associated with the results presented below.

Overall survival in patients with >30% blasts (FAS 6-month follow-up)

Median OS was higher in the VenLDAC arm than in the LDAC arm (months versus months, respectively [Table 21]) with a HR of (95% CI: .[84] Median OS was higher in the overall population compared to the >30% blast count subpopulation in both the VenLDAC (8.4 months and months, respectively [Table 16]) and LDAC (4.1 months and months, respectively) treatment arms.

Table 21: OS in the >30% blast subgroup VIALE-C (FAS 6-month Follow-Up)

	VenLDAC (N=)	LDAC (N=)

Events (deaths), n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
Rate of OS, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Treatment Comparison		
HR (95% CI)	[redacted]	
P	[redacted]	

Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; LDAC: low-dose cytarabine; N: sample size; n: number of patients; NA: not available; OS: overall survival; Ven: venetoclax.

The Kaplan–Meier plots show separation of the curves in favour of VenLDAC which is maintained over time (Figure 29). At 12 months, a higher proportion of patients in the VenAZA treatment arm were alive ([redacted]% versus [redacted]%).[84]

Figure 29: Kaplan–Meier plot of OS in the >30% blast subgroup in VIALE-C (FAS 6-month follow-up)

[redacted]

Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax.

Event free survival in patients with >30% blasts (FAS 6-month follow-up)

Median EFS was higher in the VenLDAC arm than in the LDAC arm ([redacted] months versus [redacted] months, respectively [Table 22]) with a HR of [redacted][84] In the VenLDAC arm, median EFS was higher in the overall population compared to the >30% blast count subpopulation ([redacted] months versus [redacted] months, respectively [Table 17]) whilst no change was seen in the LDAC arm ([redacted] months for both populations).

Table 22: EFS in the >30% blast subgroup VIALE-C (FAS 6-month Follow-Up)

	VenLDAC (N=[redacted])	LDAC (N=[redacted])
Events, n (%)	[redacted]	[redacted]
Median EFS, months (95% CI)	[redacted]	[redacted]
Event free survival rate, % (95% CI)		

6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Treatment Comparison		
HR (95% CI)	[redacted]	
P	[redacted]	

Abbreviations: CI: confidence interval; EFS: event free survival; FAS: full analysis set; HR: hazard ratio; LDAC: low-dose cytarabine; N: sample size; n: number of patients; NA: not available; Ven: venetoclax.

The Kaplan–Meier plots show separation of the curves in favour of VenLDAC, which was maintained over time (Figure 30). A higher proportion of patients in the VenLDAC treatment arm were event-free at 12 months ([redacted]% versus [redacted]%).[84]

Figure 30: Kaplan–Meier plot of EFS in the >30% blast subgroup in VIALE-C (FAS 6-month follow-up)

Abbreviations: EFS: event free survival; FAS: full analysis set; HR: hazard ratio; LDAC: low-dose cytarabine; Ven: venetoclax.

B.2.7 *Meta-analysis*

As the VIALE-A and VIALE-C trials investigated different venetoclax combinations for patients with AML, a meta-analysis was not performed.

B.2.8 *Indirect and mixed treatment comparisons*

The VIALE-A and VIALE-C trials provided direct head-to-head comparisons for VenAZA versus AZA and VenLDAC versus LDAC, respectively. However, no direct head-to-head comparison is available for VenAZA versus LDAC, which also forms part of the decision problem. Indirect treatment comparison methods were therefore required for this comparison. It should be noted that indirect comparison of VenLDAC to AZA is not relevant to the decision problem (Section B.1.1), as it is expected that patients currently considered for AZA treatment would receive VenAZA and not VenLDAC.

Two forms of indirect comparison based on VIALE-A and VIALE-C were explored:

- Network meta-analysis (NMA), comparing the VenAZA arm of VIALE-A to the LDAC arm of VIALE-C via a connected network (Section B.2.8.1). This approach was explored to align to the NICE methods guide recommendations that submitting manufacturers should conduct a SLR and subsequent NMA for indirect comparisons where feasible.

- Propensity score analysis, which utilises individual patient data (IPD) to compare the VenAZA arm of VIALE-A to the LDAC arm of VIALE-C. This approach applies propensity score weighting methods to reduce bias of the indirect comparison by adjusting for the observed baseline differences between the two cohorts (Section B.2.8.2). This approach to indirect comparison was explored based on the availability of IPD to permit such a comparison and following from the identified limitations with the NMA (see Section B.2.8.1).

The above methods were used to provide indirect comparison based on available clinical trial data from VIALE-A and VIALE-C. In addition to the evidence for AZA and LDAC available from the VIALE-A and VIALE-C clinical trials and published literature, real-world evidence for these comparators is available from the haematological malignancy research network (HMRN – See section B.2.8.3). Indirect comparison via propensity score weighting was therefore also conducted to generate comparisons of VenAZA (from VIALE-A) and VenLDAC (from VIALE-C) with real-world data for AZA and LDAC from the HMRN, using individual patient data from these sources. This propensity score analysis utilising real-world evidence is reported in Section B.2.8.3.

B.2.8.1 Network meta-analysis

Evidence sources

As reported in Section B.2.1 and in line with the NICE methods guide, an SLR was conducted to identify efficacy data of treatments for AML in treatment naïve patients who are ineligible for IC. The SLR did not restrict by blast cell count subgroup. Aside from the VIALE-A and VIALE-C trials, the SLR identified the following trials containing two or more interventions of interest, which were considered for inclusion in the NMA:

- **AZA-AML-001 (NCT01074047)** – A multi-centre, randomised, open-label, phase III trial evaluating azacitidine versus BSC in patients aged ≥65 years with newly diagnosed AML and a blast count of >30%.[50]
- **AZA-001 (NCT00071799)** – A multi-centre, randomised, open-label, parallel-group, phase III trial evaluating azacitidine versus conventional care regimens (IC, LDAC, or BSC) in patients with intermediate-2- and high-risk myelodysplastic syndromes, including patients with AML and a blast count of 20–30%.[49]

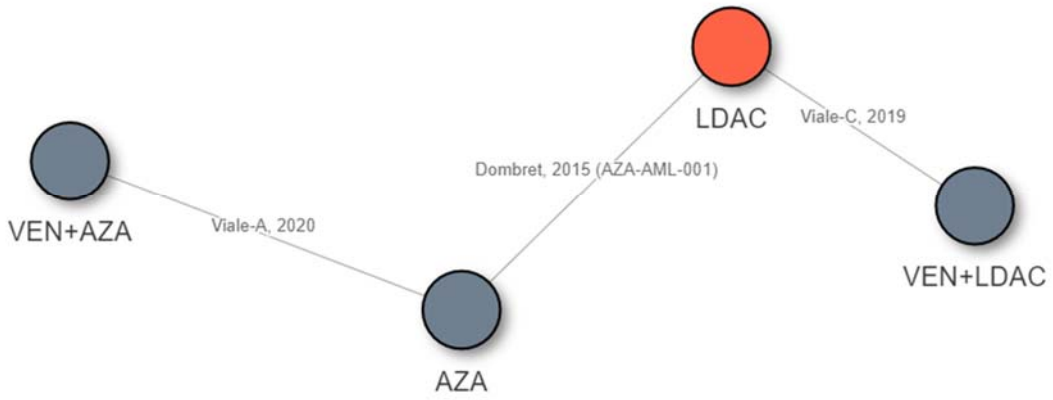
LDAC is not restricted by blast cell count but, in clinical practice, it is used in patients with blast cell counts of >30%, as AZA is only prescribed in patients with blast cell counts of 20–30%. Therefore, an NMA was conducted in the subgroup of patients with >30% blasts, since this is the relevant population for the comparison of VenAZA versus LDAC. An NMA was also conducted in the overall population (i.e. not restricted by blast), and is presented in Appendix D. Additionally, further details on the study characteristics and outcomes of interest for these trials are also presented in Appendix D.

NMA for >30% blast count subgroup

Feasibility assessment for NMA

The comparability of study characteristics and outcomes of the four studies (VIALE-A, VIALE-C, AZA-AML-001 and AZA-001) was assessed to determine feasibility of conducting NMAs for OS and CR + CRi. For the NMA of both outcomes, three of the trials identified were deemed suitable and included within the analysis (VIALE-A, VIALE-C, and AZA-AML-001), AZA-001 was not deemed suitable as this trial was conducted in AML patients with 20–30% bone marrow blasts. On the other hand, AZA-AML-001 was deemed suitable for inclusion in the network as this study was conducted exclusively in patients with >30% bone marrow blasts. The resulting network evidence diagram for the NMA of both OS and CR + CRi is presented in Figure 31.

Figure 31: Evidence network diagram for the NMA of OS and CR + CRi (>30% blast count subgroup)



[a] Included in the network for OS only.
Abbreviations: AZA: azacitidine; CR: complete remission; CRi: complete remission with incomplete blood count recovery; LDAC: low-dose cytarabine; NMA: network meta-analysis; OS: overall survival; VEN: venetoclax.

Methodology

In accordance with the most recent guidance from the NICE decision support unit (DSU) and the best practices for indirect comparisons of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the Bayesian approach to NMA was used.[90-92] The comparative estimates were summarised using posterior medians and their associated 95% credible intervals. The nature of the NMA also allowed for the relative rankings for each treatment.

In order to adjust for any differences in the distribution of baseline characteristics including: age, AML type (primary or secondary), blast count (20–30% or >30%), cytogenic risk (poor, intermediate, or normal) and ECOG status between trials, meta-regression analyses that included covariates representing the baseline characteristics in each trial were considered. Finally, key NMA assumptions such as homogeneity, transitivity, and consistency were tested to ensure that the final network and results were as robust as possible.

Full details of the NMA methodology are provided in Appendix D.

Results

Of the indirect comparisons provided via the networks outlined above, the comparison of interest to the decision problem was that of VenAZA versus LDAC. However, the full set of pairwise comparisons arising from the NMA is presented in the results tables below for completeness.

Overall survival (OS)

The NMA for OS demonstrated that VenAZA was associated with a significantly lower risk of death than LDAC (HR: [redacted]; 95% CrI: [redacted]). The HRs for each pairwise treatment comparison are shown in Table 23.

Table 23: Pairwise treatment comparisons for OS (>30% blast count subgroup)

	Treatment comparison for OS, HR (95% Credible Interval)			
	VenAZA	**VenLDAC**	**AZA**	**LDAC**
VenAZA		[redacted]	[redacted]	[redacted]
VenLDAC	[redacted]		[redacted]	[redacted]
AZA	[redacted]	[redacted]		[redacted]
LDAC	[redacted]	[redacted]	[redacted]	

Comparisons between treatments should be read as the hazard ratio for the row-defining treatment versus the column-defining treatment. A hazard ratio below one favours the row-defining treatment. Green cell highlights hazard ratio of relevance to the decision problem.
[a]Significant results: the 95% credible interval does not contain one.
Abbreviations: AZA: azacitidine; HR: hazard ratio; LDAC: low-dose cytarabine; OS: overall survival; VEN: venetoclax.

The cumulative ranking curves for each treatment included in the NMA for OS are presented in Figure 32. The cumulative probability on the y-axis indicates the likelihood that each therapy is at least the rank shown on the x-axis in terms of OS. The higher the surface under the cumulative ranking curve (SUCRA) value, and the closer to 100%, the higher the likelihood that a therapy is in the top rank or one of the top ranks in terms of OS. VenAZA and VenLDAC had the highest SUCRA values, which means that these treatments performed best with respect to OS.

Figure 32: SUCRA plots for each treatment included in the NMA for OS (>30% blast count subgroup)

Abbreviations: AZA: azacitidine; LDAC: low-dose cytarabine; NMA: network meta-analysis; OS: overall survival; SUCRA: surface under the cumulative ranking curve; VEN: venetoclax.

Composite complete remission rate (CR + CRi)

The NMA for CR + CRi demonstrated that patients receiving VenAZA were significantly more likely to achieve CR + CRi than patients receiving LDAC (odds ratio [OR]: [redacted] (95% CrI: [redacted]). The odds ratios (ORs) for each pairwise treatment comparison are shown in Table 24

Table 24: Pairwise treatment comparisons for CR + CRi (>30% blast count subgroup)

	Treatment comparison for CR + CRi, OR (95% Credible Interval)			
	VenAZA	**VenLDAC**	**AZA**	**LDAC**
VenAZA		[redacted]	[redacted]	[redacted]
VenLDAC	[redacted]		[redacted]	[redacted]
AZA	[redacted]	[redacted]		[redacted]
LDAC	[redacted]	[redacted]	[redacted]	

Comparisons between treatments should be read as the odds ratio for the row-defining treatment versus the column-defining treatment. An odds ratio above one favours the row-defining treatment. Green cell highlights hazard ratio of relevance to the decision problem.
[a]Significant results: the 95% credible interval does not contain one.
Abbreviations: AZA: azacitidine; CR: complete remission; CRi: complete remission with incomplete blood count recovery; LDAC: low-dose cytarabine; OR: odds ratio; VEN: venetoclax.

VenAZA and VenLDAC had the highest SUCRA values, which means that these treatments performed best with respect to achievement of CR + CRi. The cumulative ranking curves for each treatment included in the NMA for CR + CRi are presented in Figure 33.

Figure 33: SUCRA plots for each treatment included in the NMA for CR + CRi (>30% blast count subgroup)

Abbreviations: AZA: azacitidine; CR: complete remission; CRi: complete remission with incomplete blood count recovery; LDAC: low-dose cytarabine; NMA: network meta-analysis; SUCRA: surface under the cumulative ranking curve; VEN: venetoclax.

B.2.8.2 Propensity score analysis (VIALE-A to VIALE-C cross-trial comparison)

As an alternative to the anchored indirect treatment comparison provided by the NMA, propensity score analysis methods using individual patient data allow an unanchored, population-adjusted indirect treatment comparison of VenAZA (from VIALE-A) with LDAC (from VIALE-C). Propensity score weighting aims to reduce bias by adjusting for the observed baseline differences between the two cohorts by increasing or decreasing the relative contributions of individual patients within the two cohorts so that, after weighting, the two cohorts have similar average baseline characteristics.

Methodology

The methodology for the propensity score analysis is outlined in Appendix D. Briefly, this analysis estimated the propensity score (i.e. the probability of treatment assignment) for each patient via a logistic regression model with the enrolment of the VenAZA arm versus the LDAC arm as the outcome, conditional on a set of observed baseline covariates. The baseline covariates were selected based on prior research on prognostic factors and potential confounders and the eligibility criteria for the VIALE-A and VIALE-C trials. These variables were age, race, gender,

geographic region, AML status, MRC status, history of MDS status, ECOG score, cytogenetic risk category, bone marrow blasts, and prior systemic therapy use.

In line with the decision problem addressed in this submission (Section B.1.1), the most relevant population for indirect comparison of VenAZA with LDAC is the subgroup of patients with >30% blasts[1, 3]. The propensity score analysis was conducted both on the full population and on the subgroup of patients with bone marrow blast count >30%. Results for the relevant subgroup with >30% blasts are presented in the main submission; results for the full population are provided in Appendix D.

Results – VenAZA versus LDAC (>30% blasts)

Baseline characteristics

To examine the balance in baseline characteristics between treatment arms, standardised mean differences were calculated. Absolute values of standardised differences < 0.1 were indicative of sufficient balance. A propensity score density plot was also used to check visually if the common support condition was satisfied, i.e. if there was sufficient overlap between the two groups.

Patient baseline characteristics of the >30% blasts subgroup before and after weighting in the propensity score analysis of VIALE-A VenAZA versus VIALE-C LDAC are presented in Table 25. Before weighting, baseline characteristics were generally well-balanced across the treatment arms. However, standardised differences for variables such as age and ECOG performance status <2 were fairly large, and these differences may lead to bias given the prognostic importance of these variables. After weighting, standardised mean differences in all characteristics [redacted], indicating that the treatment arms were sufficiently well- balanced.

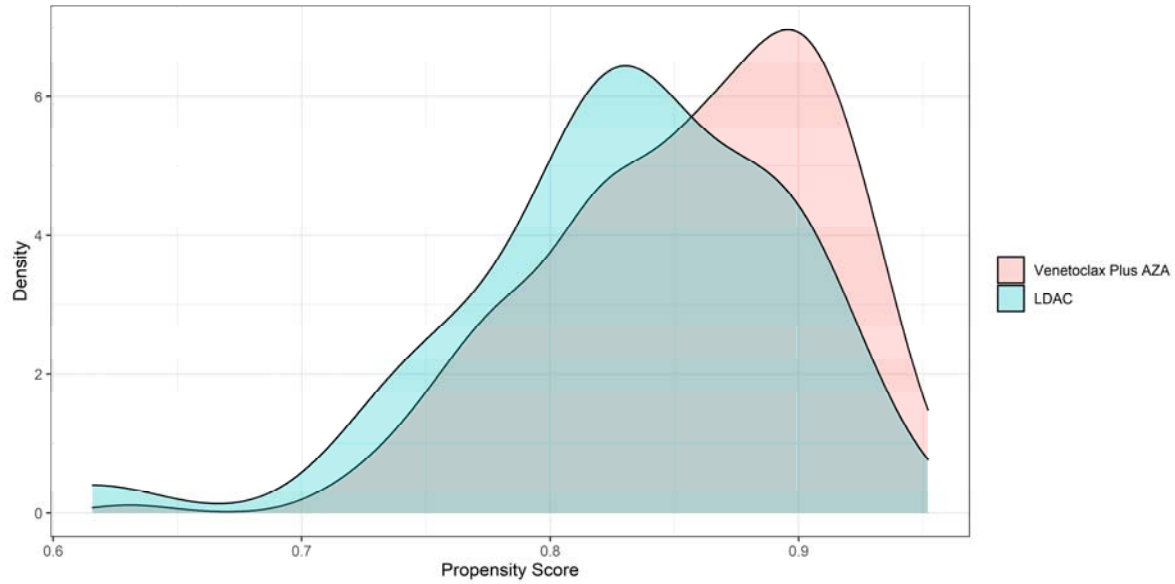
Table 25: Baseline characteristics before and after weighting – VenAZA versus LDAC (>30% blasts)

	Before weighting				After weighting			
	LDAC[a] (N=36)	VenAZA (N=206)	Standardised mean difference	*P*[b]	LDAC[a] (N eff=31.89)	VenAZA (N eff=204.99)	Standardised mean difference	*P*[b]
Age <75 years, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary AML, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AML with MRC, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antecedent haematological history of MDS, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status <2, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVRS cytogenetic risk: Poor, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow blast count, % mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]One patient was removed from the analysis due to missing cytogenetic risk. [b]Before weighting, categorical outcomes were compared using chi-squared tests, and continuous outcomes with ANOVAs. After weighting, categorical outcomes were compared using weighted chi-squared tests, and continuous outcomes with weighted ANOVAs.
Abbreviations: AML: acute myeloid leukaemia; ANOVA: analysis of variance; AZA: azacitidine; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EU: European Union; IVRS: interactive voice response system; LDAC: low-dose cytarabine; MDS: myelodysplastic syndrome; MRC: myelodysplasia related changes.

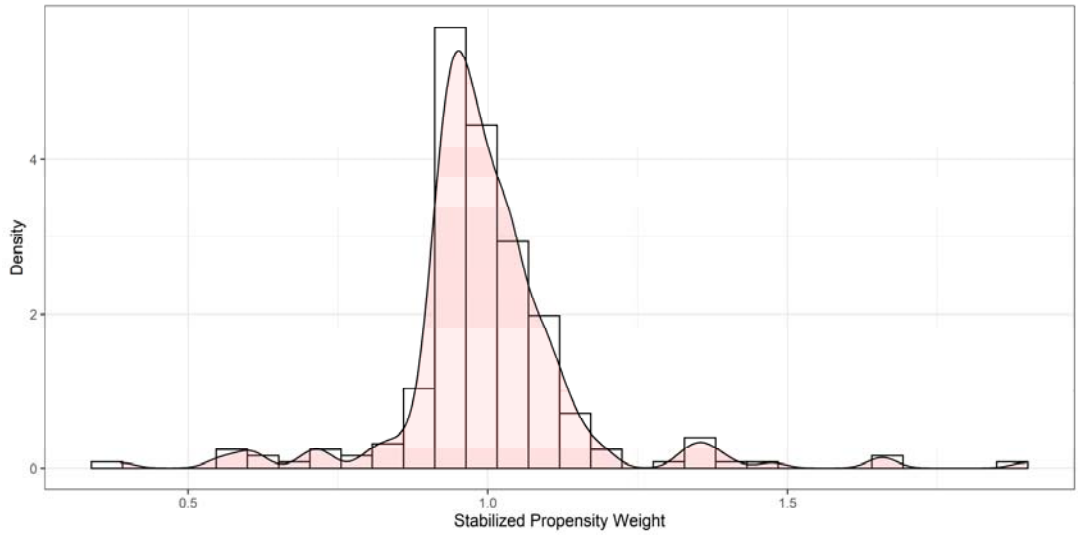
The propensity score density plot for VIALE-A VenAza versus VIALE-C LDAC in the >30% blast subgroup is presented in Figure 34, showing significant overlap between the treatment arms. Similarly, propensity score distribution presented in Figure 35 demonstrates a lack of extreme weights.

Figure 34: Propensity score density plot – VenAZA versus LDAC (>30% blasts)



Abbreviations: AZA: azacitidine; LDAC: low-dose cytarabine.

Figure 35: Distribution of weights – VenAZA versus LDAC (>30% blasts)



Abbreviations: AZA: azacitidine; LDAC: low-dose cytarabine.

Overall survival and event-free survival

Hazard ratios for OS and EFS in the >30% blasts subgroup were similar before and after weighting, and indicated that treatment with VenAZA was associated with a significant reduction in risk of death and risk of progression compared with LDAC (Table 26). Median OS and EFS were also similar before and after weighting, and substantially higher for VenAZA than LDAC. Kaplan–Meier curves and OS and EFS are presented in Figure 36 and Figure 37, respectively, showing rapid separation of the curves in favour of VenAZA, which was maintained over time.

Table 26: OS and EFS before and after weighting – VenAZA versus LDAC (>30% blasts)

	N	Events	Before weighting		After weighting	
			Median, months (95% CI)	HR (95% CI)	Median, months (95% CI)	HR (95% CI)
Overall survival						
VenAZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDAC	[redacted]	[redacted]	[redacted]		[redacted]	
Event-free survival						
VenAZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDAC	[redacted]	[redacted]	[redacted]		[redacted]	

[a]Denotes statistical significance at the level of 0.05.
Abbreviations: AZA: azacitidine; CI: confidence interval; EFS: event-free survival; LDAC: low-dose cytarabine; OS: overall survival.

Figure 36: Kaplan-Meier curves for OS before (left) and after (right) weighting – VenAZA versus LDAC (>30% blasts)

Abbreviations: AZA: azacitidine; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax.

Figure 37: Kaplan-Meier curves for EFS before (left) and after (right) weighting – VenAZA versus LDAC (>30% blasts)

Abbreviations: AZA: azacitidine; CI: confidence interval; EFS: event-free survival; LDAC: low-dose cytarabine.

Composite complete remission (CR + CRi)

The odds ratio (OR) for CR + CRi in the >30% blasts subgroup was similar before and after weighting (VIALE-A VenAZA versus VIALE-C LDAC), and indicates that a significantly greater proportion of patients treated with VenAZA achieve composite complete remission compared with LDAC (Table 27).

Table 27: CR + CRi before and after weighting – VenAZA versus LDAC (>30% blasts)

Outcome	Before weighting				After weighting			
	VenAZA, proportion (95% CI)	LDAC, proportion (95% CI)	OR	*P*	VenAZA, proportion (95% CI)	LDAC, proportion (95% CI)	OR	*P*
CR + CRi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Denotes statistical significance at the level of 0.05
Abbreviations: AZA: azacitidine; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete haematological recovery; LDAC: low-dose cytarabine.

B.2.8.3 Propensity score analysis (VIALE trials versus HMRN)

Real-world evidence for comparators from the Haematological Malignancy Research Network (HMRN)

The HMRN is an ongoing population-based cohort study which was established in 2004 with the aim of providing robust and generalisable data to inform clinical practice.[3] The HMRN region covers two former adjacent UK Cancer Networks (Yorkshire and the Humber and Yorkshire Coast Cancer Networks) and has a total population of ~3.8M.[3] The HMRN has an emphasis on primary-source data, and prognostic factors, sequential treatment/response history, and socio-demographic details are all recorded to clinical trial standards.[3] The HMRN provides real-world evidence on current UK clinical practice for patients with AML who are ineligible for IC.[3] Using propensity score weighting methods, a population-adjusted indirect comparison can be conducted to provide comparison of the efficacy of VenAZA and VenLDAC observed in the VIALE-A and VIALE-C clinical trials with real-world effectiveness data for AZA and LDAC from HMRN.

HMRN data were collected for [redacted] patients (1st September 2004–31st August 2017) with AML, [redacted] of whom received non-intensive treatment. Of those treated with non-intensive treatment, [redacted] patients received LDAC, [redacted] received azacitidine ([redacted] of whom had a blast count of 20–30%), [redacted] received HC/HU and [redacted] received other chemotherapy. Median follow-up was [redacted] years (95% CI: [redacted]).[3] As discussed in Section B.1.1, BSC is not considered a relevant comparator for this appraisal, since those who receive BSC comprise a different population to those who would receive VenAZA or VenLDAC (e.g. when considering age and performance status).

Methodology

The propensity score weighting method was applied to compare the efficacy outcomes from the VenAZA and VenLDAC arms of the VIALE-A and VIALE-C trials, respectively, to real-world data from the HMRN. The trial patients (VIALE-A and VIALE-C) were considered as the “treated” group and propensity score matching was used to pair the “control” HMRN group to make the

populations as comparable as possible. There was longer follow-up of HMRN patients, so these were censored at 20.7 months to mirror the trial follow-up. Full details of the propensity score weighting analytic approach are provided in Appendix D.

The baseline covariates informing this propensity score analysis were sex, age, secondary AML status, ECOG performance status and blast cell count, which were selected on the basis of being considered potential prognostic factors, effect modifiers or confounders.

In line with the decision problem, comparisons versus AZA and LDAC were conducted in subgroups of patients with 20–30% and >30% blasts, respectively. Table 28 summarises the comparisons explored in the propensity score analysis of the VIALE trials versus HMRN. Rate of CR + CRi was not an outcome that was investigated in the HMRN analysis and as such, CR + CRi was not included in the propensity score analysis.

Table 28: Summary of comparisons explored in the propensity score analysis (VIALE trials versus HMRN)

Population	Intervention	Comparator	Outcome
Subgroup with 20–30% blasts	VenAZA (VIALE-A)	AZA (HMRN)	• OS • EFS
Subgroup with >30% blasts	VenAZA (VIALE-A)	LDAC (HMRN)	• OS • EFS
	VenLDAC (VIALE-C)	LDAC (HMRN)	• OS • EFS

Abbreviations: AZA: azacitidine; CR: complete remission; CRi: complete remission with incomplete blood count recovery; EFS: event-free survival; OS: overall survival; LDAC: low-dose cytarabine.

Results

Baseline characteristics

Baseline characteristics for all propensity score weighting analyses before and after weighting are presented in Table 29.

Table 29: Baseline characteristics before and after weighting

Intervention/ comparator	Before weighting						After weighting						
	N	Characteristics					Remaining patients,[a] N	N, eff.[b]	Characteristics				
		Female, %	Age, mean (years)	Secondary AML, %	ECOG score ≥2, %	Blast count			Female, %	Age, mean (years)	Secondary AML, %	ECOG score ≥2, %	Blast count
20–30% blasts													
VenAZA	[redacted]												
AZA	[redacted]												
P	[redacted]												
>30% blasts													
VenAZA	[redacted]												
LDAC	[redacted]												
P	[redacted]												
VenLDAC	[redacted]												
LDAC	[redacted]												
P	[redacted]												

[a] Patients within the common support of propensity scores (where the distributions overlap).
[b] Kish's effective sample size calculated after matching and weighting.
Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; ECOG: Eastern Oncology Cooperative Group; LDAC: low-dose cytarabine; Ven: venetoclax;

Overall survival and event-free survival

A summary of OS and EFS results for all comparisons is presented in Table 30, and Kaplan-Meier plots of OS and EFS before and after weighting are presented in Figure 38 to Figure 40.

In the comparison of VenAZA versus AZA in the subgroup with 20–30% blasts, the adjusted HRs for both OS and EFS after weighting demonstrated a statistically significant reduction in the risk of death/an EFS event. In the comparisons of VenAZA and VenLDAC versus LDAC in the subgroup with >30% blasts, all HRs (unadjusted and adjusted) for OS and EFS before and after weighting found a statistically significant reduction in the risk of death/an EFS event.

Taken together, the results of the propensity score analysis weighting the VIALE-A and VIALE-C intervention arms to HMRN evidence for relevant comparators from real-world practice demonstrate support for statistically significantly improved OS and EFS with VenAZA and VenLDAC versus their comparators in the relevant blast subgroups.

Table 30: HRs for OS and EFS before and after weighting

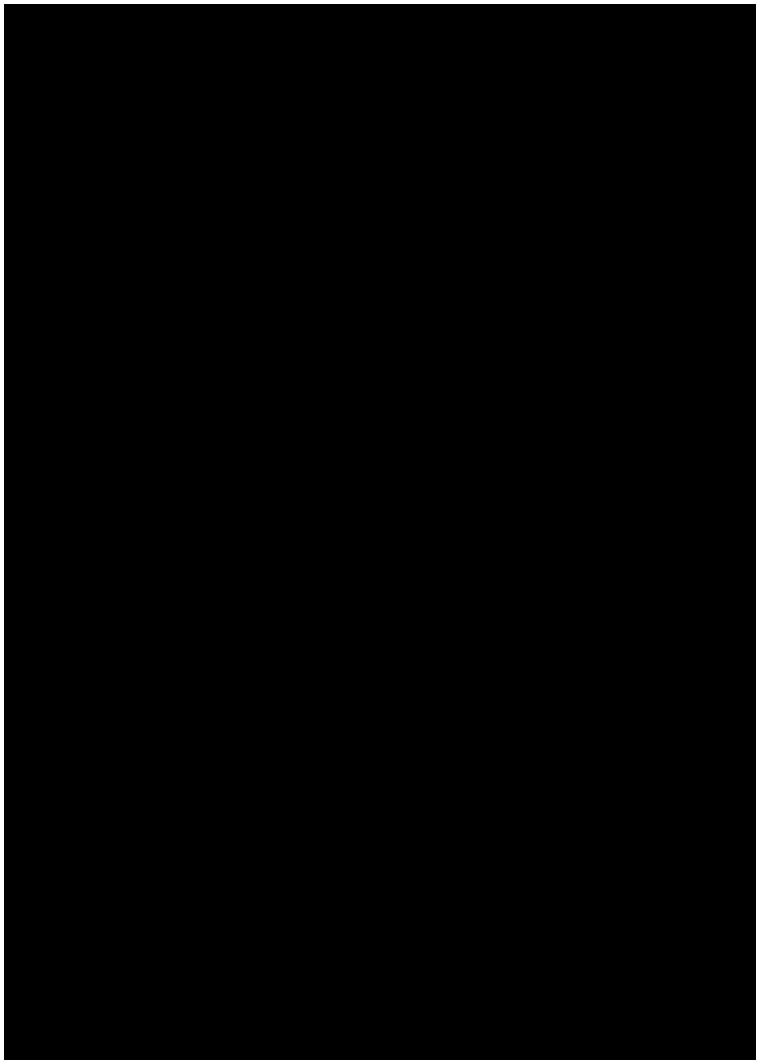
		Before weighting			After weighting		
		Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
20–30% blasts							
VenAZA vs AZA	OS						
	P						
	EFS						
	P						
>30% blasts							
VenAZA vs LDAC	OS						
	P						
	EFS						
	P						
VenLDAC vs LDAC	OS						
	P						
	EFS						
	P						

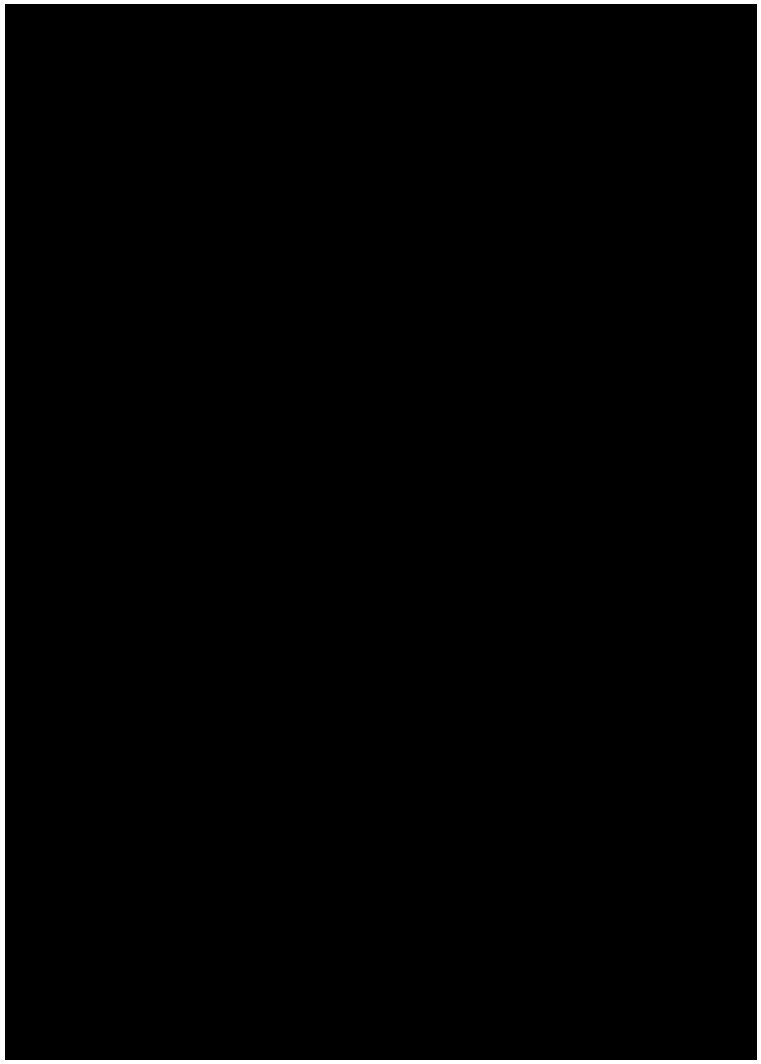
[a] HR and 95% Confidence Intervals (95% CI) estimated using Cox's regression.
[b] Adjusted for age, sex
[c]Adjusted for age, sex, secondary AML, ECOG (0-1 vs >=2) and blast count as a continuous variable.
Abbreviations: AZA: azacitidine; CI: confidence interval; EFS: event-free survival; HR: hazard ratio; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax.

Figure 38: Kaplan-Meier curves for OS and EFS before (left) and after (right) weighting – VenAZA versus AZA (20–30% blasts)

OS

EFS



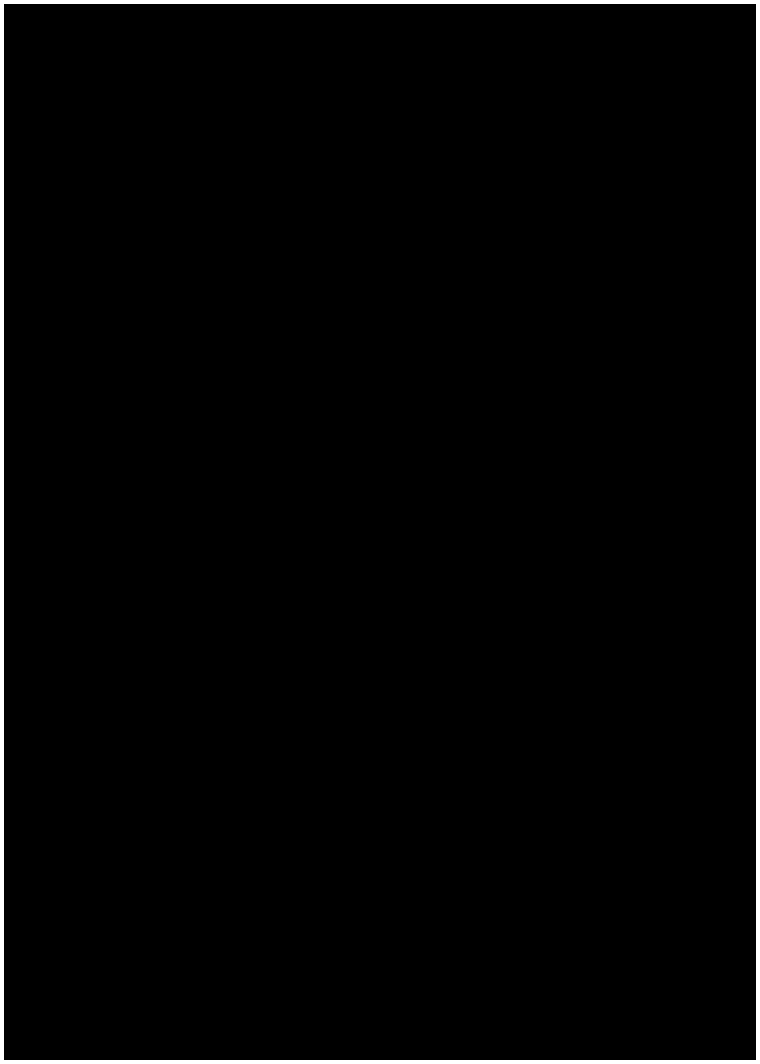


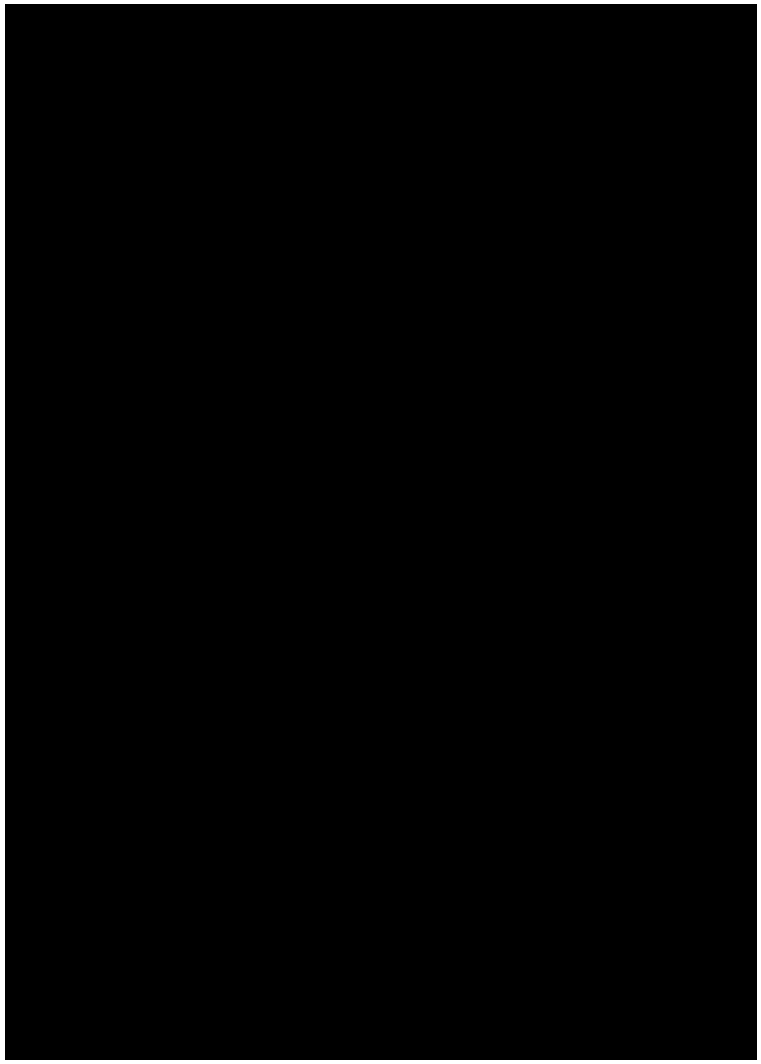
Abbreviations: AZA: azacitidine; EFS: event-free survival; HMRN: Haematological Malignancy Research Network; OS: overall survival; Ven: venetoclax.

Figure 39: KM curves for OS and EFS before (left) and after (right) weighting – VenAZA versus LDAC (>30% blasts)

OS

EFS



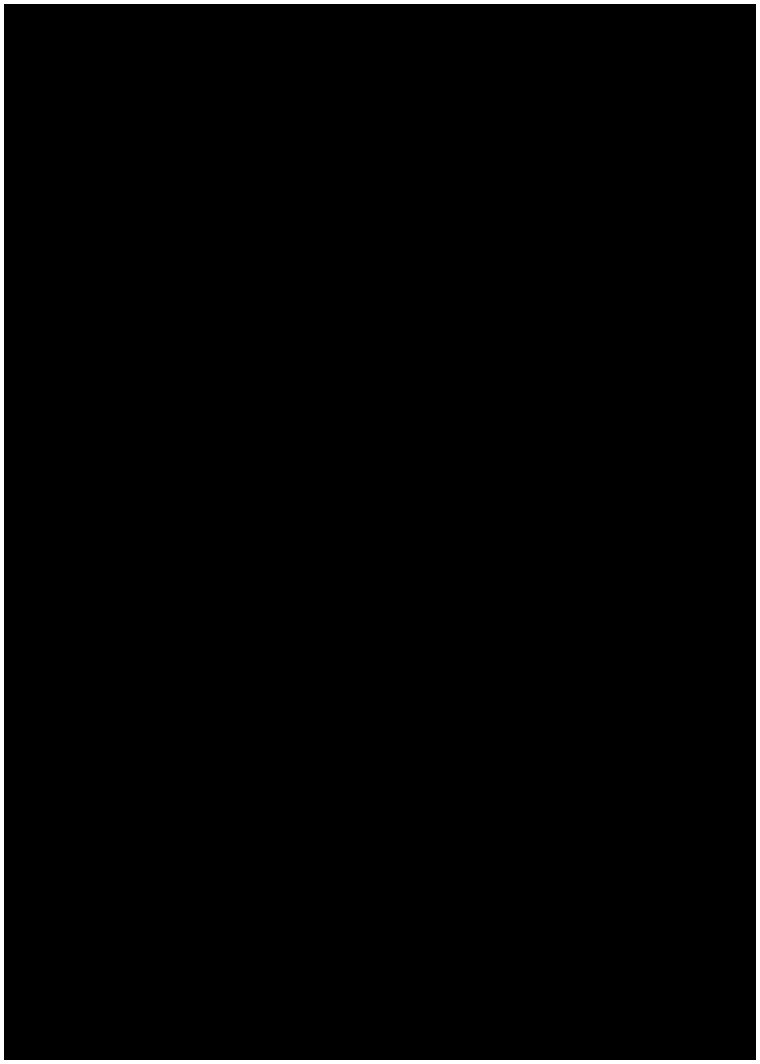


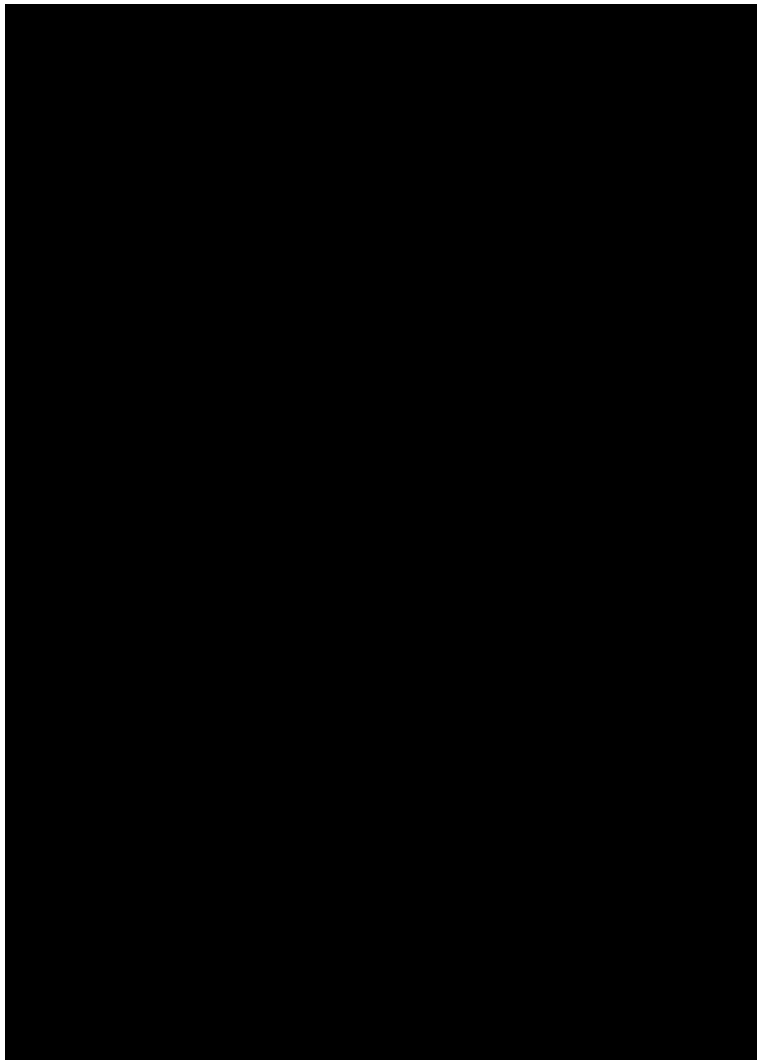
Abbreviations: AZA: azacitidine; EFS: event-free survival; HMRN: Haematological Malignancy Research Network; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax.

Figure 40: KM curves for OS and EFS before (left) and after (right) weighting – VenLDAC versus LDAC (>30% blasts)

OS

EFS





Abbreviations: EFS: event-free survival; HMRN: Haematological Malignancy Research Network; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax.

B.2.8.4 Uncertainties in the indirect and mixed treatment comparisons

Across the NMA and the propensity score analysis of the VIALE trials versus HMRN, only known baseline prognostic factors that were consistently reported across the relevant data sources could be adjusted for (or matched for, in the case of the propensity score analyses). Consequently, potential prognostic factors and effect modifiers that were not consistently reported could not be accounted for in the analyses. This was not a limitation of the propensity score analysis on the VIALE trials, since baseline prognostic factors were consistently reported across the VIALE-A and VIALE-C trials and thus all known potential prognostic factors and effect modifiers should have been accounted for in the analyses.

As is the case with any comparison of non-randomised treatment groups, all three indirect treatment comparisons (NMA and both sets of propensity score analysis) are subject to potential bias due to unobserved or unmeasurable confounding. In addition, within trial randomisation is not preserved within the indirect treatment comparisons, since the NMA comparison was conducted within blast cell count subgroups and the propensity score analysis was based on unanchored comparison.

In the propensity score-weighting analyses where data from the VIALE trials was compared to the HMRN, effective sample sizes for comparator arms derived from the HMRN were small, and thus relative treatment effect estimates derived from these analyses are associated with considerable uncertainty. Despite this uncertainty, three different ITCs have been used to compare VenAZA and VenLDAC to relevant comparators with all three comparisons producing results consistently in favour of VenAZA and VenLDAC.

Clinical evidence used in the cost-effectiveness analysis

The various estimates for the relative efficacy of VenAZA and VenLDAC versus the relevant comparators (AZA and LDAC) that are available from the VIALE-A and VIALE-C RCTs (Section B.2.6) and the indirect comparisons (Section B.2.8) are summarised in Table 31. The data selected to inform clinical efficacy for the various comparisons forming the decision problem was based on consideration of the consistency in relative efficacy estimates across analyses and the (effective) sample sizes informing the analyses.

VenAZA versus AZA (20–30% blast count subgroup)

The in-trial subgroup data for OS and EFS from the VIALE trials have been used as the primary source of efficacy data to inform the model. The point estimates of the HRs from the VIALE-A RCT subgroup analysis and VIALE-A versus HMRN PSW both indicated a reduction in risk for VenAZA (Table 31) in terms of both OS and EFS. However there was some inconsistency, with a greater treatment effect observed in the HMRN PSW than the VIALE-A RCT subgroup analysis. As previously mentioned, the effective sample sizes for comparator arms derived from the HMRN were small, and thus relative efficacy estimates are associated with uncertainty. Given the VIALE-A RCT subgroup analysis was considered to be a more robust comparison, and was associated with more conservative HRs, the VIALE-A subgroup data were used directly in the model to inform the efficacy of VenAZA and AZA. However, it should be noted that the treatment effect for VenAZA versus AZA may in fact be larger in real-world practice.

VenLDAC versus LDAC (>30% blast count subgroup)

The point estimates of the HRs for the VIALE-C RCT subgroup analysis and VIALE-C versus HMRN PSW both indicated a benefit for VenLDAC, but were not entirely consistent (Table 31). As such, the VIALE-C RCT subgroup data were used directly in the model to inform the efficacy of VenLDAC and LDAC, but again it should be noted that the treatment effect for VenLDAC versus LDAC may in fact be larger in real-world practice.

VenAZA versus LDAC (>30% blast count subgroup)

For the comparison of VenAZA versus LDAC, unadjusted subgroup data from VIALE-A and VIALE-C, respectively, have been used within the model. The VIALE-C trial is considered to be more generalisable to UK clinical practice than AZA-AML-001 (which facilitates the comparison of VenAZA versus LDAC in the NMA), with greater similarity in median OS observed between patients treated with LDAC in the VIALE-C trial (>30% blast subgroup; [redacted] months) and the HMRN (4.6 months) compared with AZA-AML-001 (6.4 months). This can also be seen in the greater similarity of the HRs for OS for the comparison of VenAZA and LDAC derived from the VIALE-A/C PSW and the HMRN PSW analysis (HR: [redacted] in both analyses), compared with the NMA (HR: [redacted]) (Table 31). As such, the results of the NMA were not used to inform this comparison in the economic model. In the VIALE-A/C cross-comparison, there were very minimal changes in the baseline characteristics and the HR for OS/EFS before and after weighting (see Table 25 and Table 26).Therefore, adjusted (i.e. after weighting) trial data were not used directly in the model to compare VenAZA with LDAC. Instead, for consistency with the VenAZA versus AZA, and VenLDAC versus LDAC comparisons, the unadjusted subgroup data were used to inform the efficacy of VenAZA and LDAC across all comparisons.

Relative efficacy estimates as presented in Table 31 were not used directly in the economic model, given that the selected model structure was not based on OS and EFS endpoints. Full details of the approaches used to derive clinical parameters for the model from the unadjusted VIALE-A and VIALE-C subgroup data are provided in Section B.3.3.

Table 31: Summary of relative efficacy estimates for OS and EFS across the analyses presented in this submission

Source	Population	HR for OS (95% CI/CrI)	HR for EFS (95% CI/CrI)	Relevant section of Submission
VenAZA vs AZA				
VIALE-A RCT subgroup analysis	20–30% blast subgroup	[redacted]	[redacted]	Section B.2.6.1
VIALE-A vs HMRN PSW	20–30% blast subgroup	[redacted]	[redacted]	Section B.2.8.3
VenAZA vs LDAC				
NMA	>30% blast subgroup	[redacted]	-	Section B.2.8.1
VIALE-A vs VIALE-C PSW	>30% blast subgroup	[redacted]	[redacted]	Section B.2.8.2

VIALE-A vs HMRN PSW	>30% blast subgroup	[redacted]	[redacted]	Section B.2.8.3
VenLDAC vs LDAC				
VIALE-C RCT subgroup analysis	>30% blast subgroup	[redacted]	[redacted]	Section B.2.6.2
VIALE-C vs HMRN PSW	>30% blast subgroup	[redacted]	[redacted]	Section B.2.8.3

Results are significant if the 95% CI/CrI dose not contain one.
[a]Stratified by age (18–<75, ≥75 years) and cytogenetics (intermediate risk, poor risk). [b]Unstratified Cox model. [c]Crude HR estimated after matching using Cox's regression. [d]Fitted Cox proportional hazards model, after PS weighting. [e]Stratified by AML status (de novo, secondary) and age (18–<75, ≥75 years). [f]15th August 2019 data cut. [g]p-value descriptive in nature.
Abbreviations: AZA: azacitidine; CI: confidence interval; CrI: credible interval; EFS: event-free survival; HMRN: Haematological Malignancy Research Network; LDAC: low-dose cytarabine; NMA: network meta-analysis; OS: overall survival; PSW: propensity score weighting; RCT: randomised controlled trial.

B.2.9 *Adverse reactions*

B.2.9.1 VIALE-A (NCT02993523)

A total of 427 patients enrolled in the study received at least one dose of venetoclax/placebo and/or AZA and are included in the safety analyses.[83] Within this section details of treatment exposure, and a summary of AEs for patients in VIALE-A are provided. Further details are also provided for Grade ≥3 TEAEs and AEs leading to death.

Treatment exposure

Patients who received VenAZA had a longer median duration of exposure compared with patients receiving matching placebo ([redacted] months [range: < [redacted]] versus [redacted] months [range: [redacted]]). This corresponded to a median of 7.0 treatment cycles (range: 1.0–30.0) for patients receiving VenAZA, and 4.5 treatment cycles (range: [redacted]) for patients receiving matching placebo.[83] [redacted] of patients in the VenAZA arm received venetoclax for more than 5 cycles compared to [redacted] of patients receiving matching placebo.[83] Median duration of AZA exposure was also longer in patients in the VenAZA treatment arm, compared with patients receiving matching placebo ([redacted] months [range: [redacted]] versus [redacted] months [range: [redacted]]).[83]

In VIALE-A, the observed dose intensity was based on the planned dose to be received by patients, taking into consideration any dose reductions or interruptions, rather than the full expected licensed dose of venetoclax (400 mg) (see Table 32).[83] As a result, this dose intensity does not take into consideration dose reductions due to co-prescribing or cycle length reductions. Data from VIALE-A and clinical expert opinion indicate that neutropenia and infections are common in patients with AML, and as such patients often receive antimicrobial prophylaxis using agents that are strong/moderate CYP3A inhibitors.[4, 83] The use of concomitant strong/moderate CYP3A inhibitors requires dose reduction of venetoclax, but not AZA.[93] Furthermore, many patients who respond to VenAZA also require dose modifications to manage cytopenia, which include delays between treatment cycles or within-cycle reduction of the venetoclax dosing days.[93] For these reasons, a post-hoc analyses was carried out to determine the dose intensity measured against the expected licenced dose of venetoclax (Table 33).

Clinical expert feedback indicated that the dose intensity for the Ven component of VenAZA in VIALE-A ([redacted]%) was higher than expected, and a dose intensity of 50% was more in line with anticipated clinical practice in the UK.[4]

Table 32: Summary of dose intensity of venetoclax/placebo in VIALE-A

	AZA (N=144)	VenAZA (N=283)	Total (N=427)
Dose Intensity Accounting for Dose Reduction, n (%) (All patients)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Dose Intensity Accounting for Dose Reduction and Interruption, n (%) (All patients)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: Azacitidine; max: maximum; min: minimum; SD: standard deviation; Ven: venetoclax;
Source: VIALE-A Clinical Study Report, Table 6, Page 128[83]

Table 33: Post-hoc analysis of VIALE-A dose intensity

Treatment arm	Component	Mean (%)	SD
VenAZA	Ven	[redacted]	[redacted]
	AZA	[redacted]	[redacted]
AZA	AZA	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; SD: standard deviation; Ven: venetoclax.

Summary of adverse events

[redacted] patients included in the safety analysis reported at least 1 adverse event (AE).[83] The rate of AEs that led to discontinuation of venetoclax or placebo were similar in both treatment arms (Table 34).[81]

Table 34: Overview of Patients with AEs (Safety Analysis Set)

Type of AE, n (%)	AZA (N=144)	VenAZA (N=283)	Total (N=427)
Any AE	[redacted]	[redacted]	[redacted]
Any AE with NCI-CTCAE toxicity Grade ≥ 3	[redacted]	[redacted]	[redacted]
Any reasonable possibility venetoclax/placebo-related AE[a]	[redacted]	[redacted]	[redacted]
Any reasonable possibility azacitidine-related AE[a]	[redacted]	[redacted]	[redacted]
Any AE leading to venetoclax/placebo discontinuation	[redacted]	[redacted]	[redacted]
Any AE leading to azacitidine discontinuation	[redacted]	[redacted]	[redacted]
Fatal AE (AE leading to death)	[redacted]	[redacted]	[redacted]

[a]As assessed by investigator.
Abbreviations: AE: adverse event; AZA: azacitidine; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; QD: once daily; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 26, Page 225[83]

Grade ≥3 treatment emergent adverse events

Grade ≥3 TEAEs were reported in almost all patients in both the VenAZA and AZA treatment arms.[81] The most common Grade ≥3 TEAEs, that were reported in a higher proportion of patients in the VenAZA arm compared to the AZA arm (an increase of ≥2%), were thrombocytopenia, neutropenia, febrile neutropenia, anaemia, leukopenia, and atrial fibrillation.[81] Common Grade ≥3 AEs reported in a similar percentage of patients between the VenAZA and AZA arms, included hypokalaemia, hypophosphatemia, hypertension, and urinary tract infection.[83] A lower percentage of patients in the VenAZA arm versus AZA arm reported Grade ≥3 AEs of pneumonia and sepsis.[83] Grade ≥3 TEAEs reported for ≥5% of patients in the VIALE-A trial, which are used to inform the cost effectiveness analysis, are presented in Table 35.[83]

Table 35: TEAEs Grade ≥3 reported for ≥5% of patients in VIALE-A

AE, n (%)	AZA (N=144)	VenAZA (N=283)	Total (N=427)
Any AEs	139 (96.5)	279 (98.6)	418 (97.9)
Blood and lymphatic system disorders	98 (68.1)	233 (82.3)	331 (77.5)
Thrombocytopenia	55 (38.2)	126 (44.5)	181 (42.4)
Neutropenia	41 (28.5)	119 (42.0)	160 (37.5)
Febrile neutropenia	27 (18.8)	118 (41.7)	145 (34.0)
Anaemia	29 (20.1)	74 (26.1)	103 (24.1)
Leukopenia	17 (11.8)	58 (20.5)	75 (17.6)
Cardiac disorders	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Infections and infestations	74 (51.4)	180 (63.6)	254 (59.5)
Pneumonia	36 (25.0)	56 (19.8)	92 (21.5)
Sepsis	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Hypokalaemia	15 (10.4)	30 (10.6)	45 (10.5)
Hypophosphatemia	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified	[redacted]	[redacted]	[redacted]

Nervous system disorders	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; AZA: azaciticine; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; QD: once daily; SOC: system organ class; Ven: venetoclax
Source: DiNardo *et al*. (2020),[81] Table 2; VIALE-A Clinical Study Report, Table 28, Page 233[83]

Gastrointestinal disorders

Grade ≥3 gastrointestinal disorders were reported in a higher proportion of subjects in the VenAZA arm compared to the AZA arm.[83]

Table 36: Grade ≥3 gastrointestinal disorders reported in >1% of patients in VIALE-A

AE, n (%)	AZA (N=144),	VenAZA (N=283)	Total (N=427)
Any AE	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; AZA: azacitidine; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 14.3_1.4.1.1, Page 1437[83]

Deaths

Overall There was a higher proportion of deaths in the AZA arm compared to the VenAZA arm (Table 37). A similar incidence of deaths between the VenAZA and AZA arms had occurred 30 and 60 days after the first dose of study drug, and a higher proportion of deaths in the AZA treatment arm were attributed to disease progression compared to the VenAZA treatment arm, consistent with the increased clinical response rates observed in the VenAZA arm.[83] There was a similar number of deaths not attributed to disease progression in both the VenAZA and AZA treatment arms.[83]

Table 37: Summary of patient deaths in VIALE-A

Deaths, n (%)	VenAZA (N=283)	AZA (N=144)	Total (N=427)
All deaths	[redacted]	[redacted]	[redacted]
Due to disease progression	[redacted]	[redacted]	[redacted]
Not due to disease progression	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]

Death occurring after first dose of study drug			
≤30 days	[redacted]	[redacted]	[redacted]
≤60 days	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 14.3_2.6.1.1, Page 4286[83]

A similar proportion of patients in both the VenAZA and AZA arms had AEs leading to death. (Table 38). Infections and Infestations was the most common type of AE leading to death in both treatment arms and occurred with a similar incidence across both treatment arms.[83]

Table 38: AEs leading to death that occurred in >1% of patients in VIALE-A

AE, n (%)	VenAZA (N=283)	AZA (N=144)	Total (N=427)
Any AE	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Death not specified	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]
Intracranial haemorrhage	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse events; AZA: azacitidine; Ven: venetoclax.
Source: VIALE-A Clinical Study Report, Table 33, Page 254[83]

Conclusions of the safety analysis

Overall, there were similar incidences of AEs and Grade ≥3 TEAEs in both the VenAZA and AZA treatment arms. The increased incidences of thrombocytopenia, neutropenia, anaemia, febrile neutropenia, nausea, diarrhoea, vomiting, infections in general, and haemorrhage in the VenAZA arm are consistent with the known safety profile of venetoclax, AZA, and the natural history of AML.[83, 86] In some cases, the longer exposure time on the VenAZA treatment arm compared to the AZA treatment arm may have been a contributing factor. Most patients who experienced nausea, vomiting, and diarrhoea had Grade 1–2 events that responded to standard medical treatment and did not require discontinuation or dose reduction.[83]

B.2.9.2 VIALE-C (NCT03069352)

A total of 210 patients enrolled in the study received at least one dose of venetoclax/placebo and/or LDAC and are therefore included in the safety analyses.[84] Within this section details of treatment exposure, and a summary of AEs for patients in VIALE-C are provided. Further details are also provided for Grade ≥3 TEAEs and AEs leading to death.

Treatment exposure

Patients who received VenLDAC had a longer median duration of exposure compared with patients receiving matching placebo ([redacted] months [range: [redacted]] versus [redacted] months [range: [redacted]]). This corresponded to a median of [redacted] treatment cycles (range: [redacted]) for patients receiving venetoclax, and [redacted] treatment cycles (range: [redacted]) for patients receiving matching

placebo. [redacted] of patients in the VenLDAC arm received venetoclax for ≥4 cycles compared to [redacted] of patients receiving matching placebo.[84] Similarly, the median duration of LDAC exposure was longer in the VenLDAC treatment arm compared with patients receiving LDAC with matching placebo ([redacted] months [range: [redacted]] versus [redacted] months [range: [redacted]]).[84]

As for VIALE-A, the observed dose intensity in VIALE-C was based on the planned dose to be received by patients, taking into consideration any dose reductions or interruptions, rather than the full expected licenced dose of venetoclax (600 mg) (see Table 39).[84] As a result, this dose intensity does not take into consideration dose reductions due to co-prescribing or cycle length reductions. A post-hoc analyses was carried out to determine the dose intensity measured against the expected licenced dose of venetoclax, as shown in Table 40.

Table 39: Summary of dose intensity of venetoclax/placebo in VIALE-C

	LDAC (N=68),	VenLDAC (N=142),	Total (N=210)
Dose intensity accounting for dose reduction (%) (All patients)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min - max	[redacted]	[redacted]	[redacted]
Dose intensity accounting for dose reduction and interruption (%) (All patients)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min - max	[redacted]	[redacted]	[redacted]

Abbreviations: LDAC: low-dose cytarabine; max: maximum; min: minimum; SD: standard deviation; Ven: venetoclax;
Source: VIALE-C Clinical Study Report, Table 14.1_2.4, Page 728[84]

Table 40: Post-hoc analysis of VIALE-C dose intensity

Treatment arm	Component	Mean (%)	SD
VenLDAC	Ven	[redacted]	[redacted]
	LDAC	[redacted]	[redacted]
LDAC	LDAC	[redacted]	[redacted]

Abbreviations: LDAC: low-dose cytarabine; SD: standard deviation; Ven: venetoclax.

Summary of adverse events

[redacted] patients included in the safety analysis reported at least 1 AE. The rate of AEs that led to discontinuation of venetoclax or placebo were similar in both treatment arms (Table 41).[82]

Table 41: Overview of Patients with TEAEs in VIALE-C

AE, n (%)	LDAC (N=68)	VenLDAC (N=142)
Any AE	[redacted]	[redacted]
Any AE with NCI CTCAE toxicity Grade ≥ 3	[redacted]	[redacted]

Any reasonable possibility venetoclax/placebo-related AE	[redacted]	[redacted]
Any reasonable possibility LDAC-related AE	[redacted]	[redacted]
Any AE leading to venetoclax/placebo discontinuation	[redacted]	[redacted]
Any AE leading to LDAC discontinuation	[redacted]	[redacted]
Fatal AE (AE leading to death)	[redacted]	[redacted]

Abbreviations: AE; adverse event; LDAC; low-dose cytarabine; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Table 30, Page 233[84]

Grade ≥3 treatment emergent adverse events

Grade ≥ 3 TEAEs were reported in [redacted] patients in the VenLDAC and LDAC arm.[82] The most common Grade ≥ 3 AEs (occurring in ≥ 10% of patients) that were reported in a higher proportion of patients in the VenLDAC arm compared with the LDAC arm were neutropenia, thrombocytopenia, and anaemia. Common Grade ≥ 3 AEs reported in a similar percentage of patients between the VenLDAC and LDAC arms included febrile neutropenia and pneumonia.[84] TEAEs Grade ≥3 reported for ≥5% of patients in VIALE-C, which are used to inform the cost effectiveness analysis, are presented in Table 42.

Table 42: TEAEs Grade ≥3 reported for ≥5% of patients in either arm of VIALE-C

AE, n (%)	LDAC (N=68)	VenLDAC (N=142)
Any AE	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Leukocytosis	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]

Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Abbreviations: AE: adverse event; LDAC: low dose cytarabine; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; QD: once daily; SOC: system organ class; Ven: venetoclax.
Source: Wei *et al*. (2020);[82] VIALE-C Clinical Study Report, Table 32, Page 240[84]

Gastrointestinal disorders

Grade ≥3 gastrointestinal disorders reported in ≥2 patients in either treatment arm of VIALE-C are reported in Table 43.

Table 43: Grade ≥3 gastrointestinal disorders reported in ≥2 patients in either treatment arm of VIALE-C

AE	LDAC (n=68), n (%)	VenLDAC (n=142), n (%)
Diarrhoea	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]
Nausea	[redacted]	[redacted]

Abbreviations: AE: adverse event; LDAC: low-dose cytarabine; Ven: venetoclax.
Source: Wei *et al*. (2020);[82] VIALE-C Clinical Study Report, Table 32, Page 238[84]

Deaths

There was a higher proportion of deaths in the LDAC arm compared to the VenLDAC arm, and there was a higher incidence of deaths that occurred in the LDAC arm compared to the VenLDAC arm 30 and 60 days after the first dose of study drug. A higher proportion of deaths in the LDAC arm were attributed to disease progression compared to the VenLDAC arm, consistent with the increased clinical response rates observed in the VenLDAC arm. There was a similar number of deaths not attributed to disease progression in both the VenLDAC and LDAC treatment arms.[84]

Table 44: Summary of patient deaths in VIALE-C

Deaths, n (%)	VenLDAC (N=142)	LDAC (N=68)
All deaths	[redacted]	[redacted]
Due to disease progression	[redacted]	[redacted]

Not due to disease progression	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Death occurring after first dose of study drug		
≤30 days	[redacted]	[redacted]
≤60 days	[redacted]	[redacted]

Abbreviations: LDAC: low-dose cytarabine; Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Table 14.3_2.6.1A, Page 3174

Overall, a similar proportion of patients in both the VenLDAC and LDAC arms had AEs leading to death. Infections and Infestations was the most common classification of AE leading to death which, occurred with a similar percentage across both treatment arms.

Table 45: AEs leading to death that occurred in >1% of patients in VIALE-C

AE, n (%)	VenLDAC (N=283)	LDAC (N=144)
Acute cardiac failure	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
TLS	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Staphylococcal sepsis	[redacted]	[redacted]
Candida sepsis	[redacted]	[redacted]
Lung infection pseudomonal	[redacted]	[redacted]
Pneumonia staphylococcal	[redacted]	[redacted]
Intracranial haemorrhage	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]

Abbreviations: AE: adverse events; LDAC: low-dose cytarabine; TLS: tumour lysis syndrome; Ven: venetoclax.
Source: VIALE-C Clinical Study Report, Table 37, Page 275[84]

Conclusions of the safety analysis

Overall, there was a similar incidence of AEs and Grade ≥ 3 AEs between both the VenLDAC and LDAC arms. The increased incidence of neutropenia, thrombocytopenia, anaemia, nausea, vomiting, diarrhoea, and haemorrhage in the VenLDAC arm are consistent with the known safety profile of venetoclax, LDAC and the natural history of AML.[84] Most patients with nausea, vomiting, and diarrhoea had Grade 1–2 events which responded to standard medical treatment and did not require discontinuation or dose reduction.[84] Patients in the VenLDAC and LDAC arms had similar incidences of both infection and febrile neutropenia, and patients who received venetoclax had lower incidences of cardiac and respiratory AEs.[84]

B.2.10 *Ongoing studies*

The VIALE-A and VIALE-C trials are ongoing, however, there are no additional survival data expected from either trial during the course of this appraisal.

B.2.11 *Innovation*

AML is an aggressive heterogenous disease with one of the poorest survival rates of all haematologic malignancies.[3] Treatment options, particularly for patients with AML who are ineligible for IC are limited and, as a consequence, this population has a particularly poor prognosis. AZA and LDAC represent the only treatment options, and the current SOC used to control the disease, however, a substantial proportion of patients who are treated with current non-intensive treatment options (AZA and LDAC) fail to achieve CR. In patients who do achieve CR with non-intensive treatment options, CR is often not maintained long-term and rates of relapse are high.[3] The recent termination of NICE appraisals for novel potential treatments,[79, 80] means that there remains no curative treatment options available for this patient population, and as such an urgent unmet need exists for novel, efficacious and tolerable treatments for patients across all blast counts.[1, 2]

Venetoclax is a first-in-class, oral, highly selective inhibitor of Bcl-2, with a unique targeted mechanism of action that distinguishes it from other available therapies.[82, 86] The innovative potential of VenAZA and VenLDAC, as demonstrated in the VIALE clinical trials, can be summarised as follows:

- VenAZA would provide patients with significantly prolonged OS, rapid and more durable remissions, and reduction in transfusion dependence (versus AZA alone).[86]
    - VenAZA prolonged patients' OS by a median of 5.1 months compared with AZA alone, with a higher proportion of patients in the VenAZA treatment arm remaining alive in the long term (>24 months) and a plateau in the Kaplan–Meier curves which is observed at ~24 months of treatment for VenAZA.[86]
    - A significantly higher proportion of patients treated with VenAZA achieved CR + CRi, compared to those treated with AZA alone. Remission is associated with alleviation of symptoms and improved survival and HRQoL outcomes.[86]
    - A significantly higher proportion of patients treated with VenAZA also achieved deep remissions (defined as MRD <0.001 and CR + CRi) compared to those treated with AZA alone. Deep and durable remissions have been shown to be positively correlated with increased survival in patients treated with IC.[71] As of a median follow-up of 20.5 months, patients in the VenAZA arm who experienced deep remissions had not yet reached median OS.[86]
    - As described in Section B.1.3.2, evidence collected from patients with AML and MDS suggests that frequent blood transfusions are detrimental to patient HRQoL.[1, 52, 53] Treatment with VenAZA leads to increased rates of transfusion independence compared to treatment with AZA.[86]
    - Patients treated with VenAZA experienced a longer time to deterioration (TTD) of QoL, compared to those treated with AZA alone, based on a deterioration of the within-group estimate of at least the MCT of 10 points.[86]

- VenLDAC would provide an alternative treatment option, offering prolonged OS (based on an unplanned post-hoc 6-month follow-up analysis) and improvements in remission and, transfusion dependence (versus LDAC alone).[82]
    - VenLDAC prolonged patients' OS by a median of 4.3 months compared with LDAC alone with a higher proportion of patients in the VenAZA treatment arm remaining alive in the longer term (>12 months).[82]
    - A higher proportion of patients treated with VenLDAC achieved CR + CRi compared to those treated with LDAC alone.[82]
    - Treatment with VenLDAC leads to increased rates of transfusion independence compared to treatment with LDAC alone, which demonstrates the potential of VenLDAC to further improve patients' HRQoL.[82]
    - It should be noted that VenLDAC failed to meet its primary endpoint of OS at the planned primary analysis. This was due to greater censoring of patients in the VenLDAC arm than the LDAC arm, as more patients treated with VenLDAC had not yet reached median OS (for further details see Section B.2.5.2).
- The rapid and durable remission and transfusion independence demonstrated across the VIALE trials for VenAZA and VenLDAC has the potential to improve patients' and carers' lives by allowing patients to return to their daily lives, and spend less time in hospital. Furthermore, blood transfusions have a substantial burden on the NHS and therefore treatments which allow for a reduction in transfusions are highly desirable.[54, 52, 53]
- The side-effect profile of both combinations is manageable and consistent with the known side effect profiles of the individual agents.[82, 86]

In summary, the results of the VIALE trials demonstrate the efficacy of VenAZA and VenLDAC in the treatment of patients with AML who are ineligible for IC. Considering the benefits described above, coupled with their unique mechanism of action, VenAZA and VenLDAC have the potential to bring about a significant step-change in the treatment of patients in this population, who otherwise face limited treatment options and a very poor prognosis. VenAZA in particular has demonstrated the potential to provide patients in this population with positive long-term outcomes, bringing their prognosis closer to that of patients who are eligible for IC. Consultations with clinical experts have suggested that VenAZA and VenLDAC are highly anticipated by the clinical and patient communities and if recommended, VenAZA and VenLDAC are expected to replace the current first-line treatments (AZA and LDAC alone) in this patient population.[4]

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

Principal findings of the clinical evidence base

The VIALE-A and VIALE-C trials are the primary sources of data for the efficacy and safety of VenAZA and VenLDAC, respectively, in patients with AML who are ineligible for IC.

VIALE-A demonstrated that VenAZA was effective in significantly improving the length of survival of patients with AML compared with AZA alone.[81] Patients receiving treatment with VenAZA in VIALE-A had a median OS of 14.7 months compared with 9.6 months in the AZA treatment arm ($P < 0.001$).[81] Patients treated with VenAZA also demonstrated a significantly improved rate of CR + CRi compared to patients treated with AZA alone. In VIALE-A 66.4% of patients treated

with VenAZA achieved CR + CRi compared with just 28.3% of patients treated with AZA (*P* < 0.001) (see Section B.2.5.1).[81]

The response observed in patients treated with VenAZA was both rapid and durable when compared with AZA alone. This was demonstrated by the fact that significantly more patients treated with VenAZA achieved CR + CRi by cycle 2 compared with patients treated with AZA alone (43.4% versus 7.9%; *P* < 0.001).[81] Additionally, the median DOR of CR + CRi for patients treated with VenAZA was 17.5 months compared with 13.4 months for patients treated with AZA alone [81] VenAZA also performed significantly better than AZA alone across a range of other secondary endpoints including EFS, MRD, CR, and CR + CRh (*P* < 0.001 for all comparisons) (see Section B.2.5.1 and Appendix L).[81] Clinical expert feedback has indicated that the rates of remission observed in patients treated with VenAZA have historically only been associated with IC.[32, 56, 69, 70] This is despite the poorer prognosis for this patient population compared with patients eligible for IC. Given that sustained deep remissions are positively correlated with improved long-term survival,[31, 71] VenAZA has the potential to provide positive long-term outcomes in a patient population who would otherwise face a very poor prognosis. This treatment effect can be observed in the plateau in the Kaplan–Meier curves which is observed at ~24 months of treatment for VenAZA (Section B.2.6).

Similarly, VIALE-C with 6-months of additional follow-up demonstrated that VenLDAC was effective in demonstrating clinically meaningful improvements in the length of survival for patients with AML compared with LDAC alone.[82] Patients receiving treatment with LDAC had a median OS of 8.4 months compared with 4.1 months in the LDAC treatment arm (descriptive *P* = 0.04).[82] Patients treated with VenLDAC demonstrated an improved rate of response compared to patients treated with LDAC alone. In VIALE-C [redacted] of patients treated with VenLDAC achieved CR + CRi compared with just [redacted] (of patients treated with LDAC (descriptive [redacted]) (see Section B.2.5.2).

The response observed in patients treated with VenLDAC was both rapid and durable when compared with LDAC alone. This was demonstrated by the fact that more patients treated with VenLDAC achieved CR + CRi by cycle 2 compared with patients treated with LDAC alone ([redacted] versus [redacted]; descriptive *P* < 0.001). Additionally, the median DOR for CR + CRi for patients treated with VenLDAC was [redacted] months compared with [redacted] months for patients treated with LDAC.[82]

The VIALE-A and VIALE-C trials found venetoclax combinations to have an acceptable and predictable safety profile, that was consistent with the known safety profile of venetoclax, AZA, and LDAC (See Section B.2.9).[81,82]

Patients with AML who are ineligible for IC are often reliant on blood transfusions to manage the symptoms of disease, and this is associated with decreased HRQoL and inconvenience for patients, as well as a substantial burden for the NHS.[52-54] In VIALE-A and VIALE-C patients treated with VenAZA or VenLDAC were more likely to achieve post-baseline RBC/platelet transfusion independence compared with patients receiving AZA or LDAC alone (See Section B.2.5).[81,82]

The VIALE-A and VIALE-C trials provide head-to-head evidence for comparison of VenAZA versus AZA and VenLDAC versus LDAC. However, they do not provide evidence for the relative effectiveness of VenAZA versus LDAC, which is also of relevance to the decision problem. An

NMA based on clinical trials identified via a systematic review of the literature has demonstrated that VenAZA is associated with a significantly lower risk of death and a significantly improved odds of achieving CR + CRi, compared with LDAC.

Availability of IPD from the VIALE-A and VIALE-C trials additionally allows a propensity score analysis to be conducted to compare patients who received VenAZA in VIALE-A to those who received LDAC in VIALE-C in the subgroup of patients with >30% blasts in whom LDAC is predominately used in practice. After matching, this analysis found a statistically significantly lower risk of death and of an EFS event for patients who receive VenAZA compared to LDAC.

Finally, IPD available from the HMRN allows assessment of the relative efficacy of VenAZA and VenLDAC versus their relevant comparators based on real-world data for comparator effectiveness in UK clinical practice. Propensity score analysis matching the VIALE-A and VIALE C trials with the real-world HMRN dataset found statistically significant HRs for OS and EFS in favour of VenAZA versus AZA, VenAZA versus LDAC and VenLDAC versus LDAC, in the blast subgroups of relevance to the respective comparators.

Strengths and limitations of the clinical evidence base

The clinical evidence within this submission has been derived from an SLR of clinical trials investigating the efficacy and safety of a variety of treatment options, including venetoclax, in patients with AML who are ineligible for IC (see Section B.2.1). Evidence for VenAZA and VenLDAC are provided by the VIALE-A and VIALE-C trials.[81, 82] Both of these trials are of high quality (randomised, double-blind, placebo-controlled), and the trials have been used as the basis of the submitted EMA marketing authorisation application.

The trial populations of VIALE-A and VIALE-C are consistent with the anticipated licenced indication for venetoclax and the population specified in the NICE final scope (see Section B.1). The baseline characteristics for the patients in both trials are consistent to the target patient population in the UK, and the generalisability of VIALE-A and VIALE-C baseline characteristics has been validated by clinical experts.[14] The patient population in VIALE-A and VIALE-C are comparable to the HMRN, a UK population-based cohort study.[3]

A further strength of the evidence base is that the OS data for VIALE-A and VIALE-C are reasonably mature. At the most recent data cut in VIALE-A (4 January 2020), 56.3% of patients in the VenAZA arm, and 75.2% of patients in the AZA arm had died.[81] Similarly, in VIALE-C at the most recent data-cut (15th August 2019) 69.2% of patients in the VenLDAC arm and 79.4% of patients in the LDAC arm had died.[82]

A key limitation of the evidence base was the lack of a head-to-head comparison for VenAZA to LDAC, and to address this a propensity score analysis was conducted. In this comparison, VenAZA was found to be associated with significantly longer OS and EFS compared to LDAC.

Additionally, VIALE-C did not meet its primary endpoint, with no significant difference observed in OS at the planned primary analysis. However, at the time of the primary analysis, there was greater censoring of patients in the VenLDAC arm than the LDAC arm, because more patients had not yet reached median OS. Results from a subsequent unplanned analysis with an additional 6 months of follow-up (data cut off 15th August 2019) demonstrated a significant difference in OS between the VenLDAC arm and the LDAC arm.[84]

Finally, due to the restriction of AZA for use in patients with 20–30% blast count, the decision problem necessitated blast-restricted comparisons (VenAZA versus AZA in 20–30% blasts; VenAZA versus LDAC in >30% blasts; VenLDAC versus LDAC in >30% blasts). However, VIALE-A and VIALE-C were not designed to detect differences between the blast restricted subgroups (blast count at baseline was not a stratification factor), and this is therefore an area of uncertainty.

End-of-life criteria

Venetoclax should be considered as an end-of-life treatment [redacted], given that (a) these patients have a short life expectancy, normally less than 2 years and (b) there is sufficient evidence to indicate that the venetoclax offers an extension to life of at least an additional 3 months, compared with current NHS treatment.

The treatment is indicated for patients with a short life expectancy, normally less than 24 months

Median OS data are available for patients in the 20–30% and >30% blast count subgroups from post-hoc analyses of the VIALE trials.[83, 84] In both populations, patients receiving comparator treatments had median OS substantially lower than 24 months (Table 46). Results from the economic model predicted mean undiscounted life years for both populations to be below two years. As such, VenAZA and VenLDAC should meet the NICE end of life criteria for these subgroups of the licensed indication under review.

There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment

The post-hoc analyses of the VIALE trials by blast count subgroups also demonstrated that VenAZA and VenLDAC provided an extension in median OS of greater than three months, compared to their relevant comparators (Table 46). Results from the economic model also predicted that VenAZA and VenLDAC would provide incremental undiscounted life year gains of substantially more than three months. Therefore, the end-of-life criteria apply to these subgroups of the licensed indication under review.

Table 46: End-of-life criteria

Criterion	Data available			
	AZA (20–30% blast count)	**LDAC (>30% blast count)**	**Source**	**Reference in submission**
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS: [redacted] months	Median OS: [redacted] months	Post-hoc SGA of VIALE trial data[83, 84]	Section B.2.6
	Mean undiscounted life years: 1.833	Mean undiscounted life years: 0.832–0.839	Economic model prediction, based on VIALE trial data[83, 84]	Section B.3.7
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Difference in median OS, months: **vs VenAZA** [redacted]	Difference in median OS, months: **vs VenAZA:** [redacted] **vs VenLDAC:** [redacted]	Post-hoc SGA of VIALE trial data[83, 84]	Section B.2.6
	Incremental life years gained: **vs VenAZA**: 2.609 (31.308 months)	Incremental life years gained: **vs VenAZA:** 2.926 (35.112 months) **vs VenLDAC** 1.606 (19.272 months)	Economic model prediction, based on VIALE trial data[83, 84]	Section B.3.7

Abbreviations: AZA: azacitidine; LDAC: low-dose cytarabine; NHS: National Health Service; OS: overall survival; SGA: sub-group analysis; Ven: venetoclax.

B.2.12.1 Conclusion

Considerable unmet need exists for patients with newly diagnosed AML who are ineligible for IC. The current standard of care treatment options available for these patients are limited to AZA and LDAC. However, a substantial proportion of patients who are treated with these options fail to achieve remission. In patients who do achieve remission, remission is often not maintained long-term and rates of relapse are high.

VenAZA leads to prolonged OS, rapid and durable remissions (CR + CRi), and increased rates of transfusion independence in patients newly diagnosed with AML and ineligible for IC, including hard-to-treat subgroups. This increased OS and rate of CR + CRi will improve patients HRQoL and allow them to spend more time with their family and friends, whilst reductions in transfusion dependence further improve HRQoL and reduce NHS burden.[1, 52, 53, 85, 86] Additionally, clinical expert feedback has indicated that the remission rates observed in patients treated with VenAZA have historically only been seen in patients treated with IC,[32, 56, 69, 70] despite the poorer prognosis of patients unsuitable for IC. VenLDAC has also shown increased OS, CR + CRi rates, and transfusion independence rates. Therefore, a positive recommendation from NICE would lead to a significant step-change and dramatically improve the prognosis for patients with AML who are ineligible for IC, bringing their outcomes closer to those afforded to older patients who are able to tolerate IC.[30-34]

B.3 Cost effectiveness

VenAZA and VenLDAC represent a cost-effective use of NHS resources when considered at the venetoclax PAS price, with ICERs below the £50,000 per QALY willingness-to-pay threshold for all comparisons considered in the base-case analysis

Summary of cost-effectiveness results

De novo cost-effectiveness model

- A de novo cost-utility model was developed to evaluate the cost-effectiveness of VenAZA and VenLDAC for the treatment of newly diagnosed adult patients with AML who are ineligible for IC
- The economic analyses focused on two distinct populations based on blast cell count: (i) patients with a bone marrow blast count of 20–30%, and, (ii) patients with a bone marrow blast count >30%
- The model adopted a discrete time, cohort-level Markov model with five health states: 'Remission', 'Non-remission', 'Progressive disease/relapse', 'Cure', and 'Death'
- Data from the VIALE-A and VIALE-C trials were used to compare VenAZA and VenLDAC to AZA and LDAC[85, 86]
- There is no direct clinical trial data comparing VenAZA to LDAC and therefore a propensity score analysis was conducted to compare the VenAZA arm of VIALE-A to the LDAC arm of VIALE-C. However, given the similarity of results, unadjusted trial subgroup data were used to inform the efficacy of VenAZA and LDAC across all comparisons, for consistency
- Standard parametric distributions were used to extrapolate time-to-event data (time to relapse/progressive disease; time to death) for patients in the model, stratified by treatment arm and blast cell count cohort
- Utility values for the 'Remission' (CR + CRi), 'Non remission', and ' Progressive disease/relapse' health states were derived from pooled EQ-5D data from the VIALE-A and VIALE C trials, whereas patients in the 'Cure' health state were assumed to have the utility of the general population
- Resource use and costs included in the model were based on information from the VIALE-A and VIALE-C trials, previous technology appraisals (TA642[76] and TA451[94]) and appropriate published sources including the NHS national costs collection[95], NHS national tariff system,[96] eMIT,[97] and MIMS[98]
- Feedback from UK clinicians was sought in order to validate assumptions and inputs included in the model

Base case cost-effectiveness results

- Compared to AZA, VenAZA was associated with an increased number of life years (2.609) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for VenAZA versus AZA in the 20–30% blast cell count subgroup was £38,866.
- Compared to LDAC, VenAZA was associated with an increased number of life years (2.926) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for VenAZA versus LDAC in the >30% blast cell count subgroup was £39,449.
- Compared to LDAC, VenLDAC was associated with an increased number of life years (1.606) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for VenLDAC versus LDAC in the >30% blast cell count subgroup was £31,291

Sensitivity and scenario analyses

- The DSA results identified a small number of key influential parameters (treatment costs, patient age, and time horizon) with the model being largely robust to uncertainty in the majority of parameters
- Scenario analyses conducted to address sources of uncertainty in the model (extrapolations, cure time point, dose intensity, time-on-treatment, utilities) demonstrated that whilst there was variation in the ICER, the cost-effectiveness conclusions remain the same and the majority of ICERs are considered cost-effective at a willingness-to-pay threshold of £50,000 per QALY

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify all relevant economic evaluations for the treatment of adult patients with newly diagnosed AML receiving established first-line treatment, including those ineligible for IC. Searches were performed in August 2020, and full details of the SLR search strategy, study selection process and results of included studies are reported in Appendix G.

In total, 12 records were identified which met the inclusion criteria. Of these, five publications (presented in Table 47), including four previous NICE technology appraisals (TAs) and one journal article, were used to inform the model structure and inputs for the economic analysis presented in this submission. The NICE appraisal of gilteritinib for treating relapsed or refractory AML (TA642) was published after the date of the original SLR and was added retrospectively and also informed the model structure and inputs.[76] A prior appraisal of azacitidine (TA218) which included patients with AML was identified by the SLR, but was excluded on the basis that AML patients were pooled with patients with CMML and MDS, and no subgroup analyses of the AML population only were performed.[1] Therefore, the SLR did not identify any economic evaluations or prior TAs which considered the specific population of interest to this submission.

Table 47: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	Intervention (QALYs, costs)	Comparator (QALYs, costs)	ICER (per QALY gained)
Tremblay[99]	2018	Partition survival model based on OS and CR with a lifetime time horizon	Adult patients with newly diagnosed AML (aged 18–59)	**MIDO + SOC** QALYs: 7.79 Costs: £267,325	**SOC alone** QALYS: 6.32 Costs: £213,253	£36,926
TA552[100]	2018	Decision tree and partitioned survival model based on OS and EFS with a lifetime time horizon	Patients with untreated AML aged ≥60 years	**Liposomal cytarabine-daunorubicin (CPX-351)** QALYs: Redacted Costs: Redacted	**Standard cytarabine and daunorubicin chemotherapy** QALYs: Redacted Costs: Redacted	£46,631
TA523[101]	2018	Partitioned survival model based on OS and CR with a lifetime time horizon	Patients with untreated AML aged 18–60 years (mean: 45.2, median: 47.0)	**MIDO + standard chemotherapy** QALYs: Redacted Costs: Redacted	**Standard chemotherapy alone** QALYs: Redacted Costs: Redacted	£34,327
TA545[102]	2018	Cohort state-transition model based on CR/CRp with a lifetime time horizon	Patients with untreated AML aged ≥15 years	**Gemtuzumab ozogamicin** QALYs: Redacted Costs: Redacted	**Standard chemotherapy** QALYs: Redacted Costs: Redacted	All patients: £20,457 Cytogenetic risk profile subpopulation:[a] £12,251
TA399[2]	2016	Semi-Markov model based on OS and EFS with a 10-year time horizon	Patients with AML with >30% bone marrow blasts (Patients aged 75 years at model initiation)	**Azacitidine** QALYs: Redacted Costs: Redacted	**CCR:** QALYs: 0.64 Costs: £40,608	£20,648
TA642[76]	2020	Decision-tree followed by partitioned survival models based on OS and EFS with a lifetime time horizon	Adult patients with relapsed or refractory FLT3 mutation positive AML	**Gilteritinib** QALYs: Redacted Costs: Redacted	**Weighted comparator**[b] QALYs: Redacted Costs: Redacted	£47,695

[a]Favourable and intermediate cytogenetic risk. [b]Weighted comparator included azacitidine, FLAG_IDA (combination of fludarabine, cytarabine, granulocype colony stimulating factor and idarubicin), MEC (combination of mitoxantrone, etoposide and cytarabine), LDAC and BSC. [b]Favourable and intermediate cytogenetic risk.
Abbreviations: AML: acute myeloid leukaemia; BSC: best supportive care; CCR: conventional care regimen (consisted of standard chemotherapy, LDAC and BSC); CPX-351: liposomal cytarabine-daunorubicin; CR: complete remission; CRp: complete remission with incomplete platelet recovery; EFS: event-free survival; ICER: incremental cost-effectiveness ratio; LDAC: low-dose cytarabine; MIDO: midostaurin; OS: overall survival; QALY: quality-adjusted life year; SOC: standard of care.

B.3.2 *Economic analysis*

A *de novo* cost-effectiveness analysis has been conducted for the purpose of this appraisal and is described below. The cost-effectiveness model employed for this economic analysis was built in Microsoft Excel® with the core calculations being conducted in Visual Basic for Applications (VBA).

The objective of this economic analysis was to assess the cost effectiveness of VenAZA compared to AZA and LDAC, and VenLDAC compared with LDAC for the treatment of [redacted].

In line with the NICE reference case, this analysis was conducted from the perspective of the NHS, including direct medical costs and Personal Social Services (PSS) over a lifetime time horizon.

B.3.2.1 Patient population

In line with the decision problem addressed in this submission, and the anticipated licenced indication for VenAZA and VenLDAC, the patient population considered in this economic evaluation was [redacted].

As set out in the decision problem in Section B.1.1 (Table 1), AZA is restricted by NICE in current clinical practice to patients with a blast cell count of 20–30%. Whilst LDAC is not restricted by blast cell count, it is predominantly used in clinical practice in patients with blast cell counts of >30%, since AZA is used in patients with blast cell counts of 20–30%. The decision problem was therefore split into two distinct populations based on blast cell count:

- Patients with a bone marrow blast count of 20–30%
- Patients with a bone marrow blast count >30%

Scenarios have also been explored in the overall population.

B.3.2.2 Model structure

As noted in Section B.3.1, no prior health economic evaluations for VenAZA or VenLDAC in patients with newly diagnosed AML for whom IC is unsuitable were identified by an SLR for published economic evaluations in this indication.

Therefore, a *de novo* health economic model was constructed in Microsoft Excel to evaluate the cost-effectiveness of VenAZA and VenLDAC versus relevant comparators in the indication of interest. The developed model is a discrete time, cohort-level five-state Markov model. For oncology modelling, most model structures revolve between a partitioned survival model (PSM) and a state-transition model, such as a Markov model. Whilst a PSM does offer the advantage of simplifying the modelling of patients, it has inherent limitations, which are described in further detail in Table 48.

Table 48 Summary of strengths of the Markov modelling approach

Component	PSM	Markov model	Justification for choosing Markov model

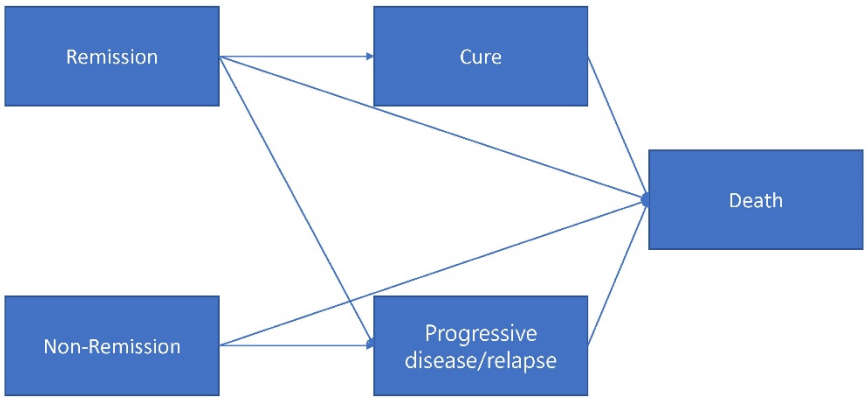
State occupancy	The proportion of patients residing in a health state is determined by a set of non-mutually exclusive survival curves	The probability of residing in a set of mutually exclusive health states is determined by transition probabilities	Allows the model to capture response-stratified health states where efficacy, costs, and utilities can be independently captured. Including a health state for patients in cure allows the application of different survival to be used (such as general population mortality)
Extrapolation	Relies on prior mortality trends to inform long-term extrapolation from baseline	Links mortality with intermediate prognostic events, such as progressive disease or relapse	Permits modelling of time to death for patients in progressive disease/relapse
Treatment sequencing	Difficult to capture subsequent treatment lines	Allows for subsequent treatment lines to be captured	Allows for the impact of subsequent treatments to be captured and reflected during the patient's lifetime
Decision making	More difficult to assess the plausibility of long-term extrapolations and provide structural sensitivity analyses	Easier to assess the plausibility of long-term extrapolations and provide structural sensitivity analyses	Allows the model to explore the impact of alternative extrapolations for individual endpoints as well as alternative assumptions around cure

Abbreviations: PSM: partitioned survival model.

A Markov model was deemed the most appropriate modelling approach to robustly and transparently capture the benefits of patients who achieve CR + CRi. A 'Cure', in which patients have outcomes in line with the general population is included in the model for patients who maintain CR + CRi – this is described in full in Section B.3.3.5. This modelling approach ensures that only patients who maintain CR + CRi can transition to the 'Cure' health state. In contrast, a PSM approach would require application of a fixed cure point whereby all patients who survive up to a given timepoint are assumed to be cured, irrespective of whether they have previously relapsed/progressed. This is not clinically realistic, as highlighted by the Evidence Review Group (ERG) in TA642.[16] The Markov modelling approach provides the flexibility to specify mortality risk separately for those patients who maintain CR + CRi and transition to the 'Cure' state, and thus can more accurately and transparently reflect clinical reality. The proportions of modelled patients who are estimated to achieve cure can also be more easily clinically validated using a Markov approach compared to a PSM. Of note, it is reasonable to assume that transition to cure can apply to both CR/CRi patients as incomplete count recovery in CRi can be a direct result of the myelosuppressive nature of the treatment combination in some patients.[62]

A graphical depiction of the Markov model approach is presented in Figure 41, and a summary of the health state transitions that are possible for patients in the model is presented in Table 49.

Figure 41: Markov model structure overview



The model is comprised of five health states, which reflect the disease progression pathway for patients with AML and are consistent with previous economic evaluations submitted to NICE in the IC-eligible AML population.[76] The health states in the model include:

- (i) 'Remission': patients who achieved CR or CRi
- (ii) 'Non-remission': patients who did not achieve CR or CRi
- (iii) 'Progressive disease (PD)/relapse': patients who have PD from non-remission or relapsed after remission
- (iv) 'Cure': patients who are considered to be cured from AML (i.e. patients with long term CR + CRi and have outcomes in line with the general population)
- (v) 'Death' (an absorbing state): patients who have died

As discussed in Section B.3.2.1, the decision problem was split into two distinct populations based on blast cell count, and therefore two separate Markov models with identical structures were developed to consider the interventions and comparators of relevance to these subpopulations:

- Patients with blast counts 20–30% for whom the intervention was VenAZA and the comparator was AZA
- Patients with blast counts > 30% for whom the intervention was VenLDAC and the comparator was LDAC'

At initiation, patients were distributed into either the 'Remission' or 'Non-remission' health states according to the CR + CRi rate for each treatment observed in the VIALE-A and VIALE-C trials. The proportion of patients remaining in each heath state or transitioning to the 'PD/relapse' state at each monthly model cycle was then determined for each therapy, based on cyclical hazards derived from parametric survival functions of time to event data for patients who either did, or did not, achieved CR + CRi in the VIALE-A and VIALE-C trials (time-to-relapse and time-to-PD for the transitions from 'Remission' and 'Non-remission' health states, respectively). Patients could also transition to the absorbing 'death' health state from any other health state in the model, based on parametric survival functions of time-to-death data from the VIALE-A and VIALE-C trials. These transitions are discussed in more detail in Section B.3.3.3. The model applies a

general population mortality in addition to disease specific mortality, which is informed by age- and sex-specific UK life tables.[103]

Due to the ability of venetoclax to facilitate sustained deep remission, the model contains a 'Cure' health state.[104] Patients in this state are assumed to be cured, and thus have general population mortality (based on UK life tables) and accrue the utility of the age-adjusted general population. Based on feedback from clinical experts, in the base-case analysis it is assumed that all patients who are receiving VenAZA or VenLDAC and are residing in the 'Remission' health state at two years (27 model cycles) are assumed to be cured and thus these patients transition to the cure health state. The cure assumption is discussed further in Section B.3.3.4.

Features of the *de novo* analysis

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. The following costs were considered in the model: initial treatment costs (acquisition and administration), subsequent treatment costs, costs associated with the management of AEs, monitoring costs for interventions and comparators, and end-of-life palliative care costs. Effectiveness measures included life years (LYs) and quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) of VenAZA/VenLDAC versus each comparator was evaluated in terms of the incremental cost per QALY gained and the incremental costs per LY gained.

The analysis was conducted from the perspective of the NHS in England, including direct medical costs and PSS costs over a lifetime time horizon of the patient cohort from the initiation of treatment. A lifetime horizon was considered in order to comprehensively capture the expected costs and health outcomes of patients over their remaining lifetime from the initiation of their treatment. A 28-day cycle length was used to align with the length of a treatment cycle and appropriately capture the incidence of modelled events and associated outcomes. An annual discount rate of 3.5% was applied to both costs and benefits, in line with the NICE reference case.[105]

Table 49: Summary of the features of the economic analysis

Factor	Current appraisal	
	Chosen values	**Justification**
Model structure	Cohort level Markov model	Accurately reflects the clinical reality for patients treated with VenAZA/LDAC and comparator therapies, particularly with respect to achieving a cure
Time horizon	Lifetime (40 years)	A lifetime horizon was chosen to fully capture the expected costs and health outcomes of patients over their remaining lifetime from the initiation of their treatment
Cycle length	1 month (28 days) with a half-cycle correction applied to state occupancy traces	Aligned with the length of a treatment cycle and appropriate to capture the incidence of modelled events and associated outcomes
Discount rate	3.5% for both costs and benefits	In line with the NICE reference case[105]
Perspective	NHS/PSS in England	In line with the NICE reference case[105]

Source of utilities	Health state utility values are derived by cross-walking EQ-5D-5L scores collected in the VIALE trials to EQ-5D-3L index scores, using the algorithm presented in van Hout *et al*. 2012, with preference weights based on the UK value set by Dolan *et al.* 1997, in line with the NICE reference case.[106, 107]	In line with the NICE reference case[105]
Source of costs	• MIMS[98] • eMIT[97] • NHS National Cost Collection 2018–19[95] • National Tariff System 2016–17[108] and 2020–2021[96] • NICE TA642[76] • NICE TA451[94]	Established sources of costs within the NHS. In line with the NICE reference case and previous appraisals
Resource use	Resource use in each health state was assumed to be the same as that reported in TA642[16]	Resource use was not captured within the VIALE trials but TA642 was considered a relevant source for resource use data for patients with AML.
Measure of health effects	QALYs	In line with the NICE reference case[105]

Abbreviations: AZA: azacitidine; eMIT: Drugs and Pharmaceutical Electronic Market Information Tool; LDAC: low-dose cytarabine; NHS: National Health Service; MIMS: Monthly Index of Medical Supplies; NICE: National Institute for Health and Care Excellence; PSS: personal social services; QALY: quality-adjusted life year; TA: technology appraisal; UK: United Kingdom; Ven: venetoclax.

B.3.2.3 Intervention technology and comparators

Cohort: 20–30% blasts

Interventions

As described in Section B.1.1, VenAZA is the intervention of interest for the cohort of patients with 20–30% blasts. In the cost-effectiveness model, VenAZA consisted of venetoclax orally (400 mg QD) in combination with AZA (75 mg/m^2) on days 1–7 of each 28-day cycle. Patients received a dose increase of venetoclax over the first three days of Cycle 1 to reach the target 400 mg dose (Day 1: 100 mg, Day 2: 200 mg, Day 3: onwards: 400 mg). This is in line with the dosing regimen in the VIALE-A trial and the suggested posology in the draft SmPC for venetoclax.[82, 86, 93] Data from the subgroup of patients with 20–30% blasts from the VenAZA arm of VIALE-A were used to inform the inputs for VenAZA in the economic analysis.[83, 86]

VenLDAC was not considered a relevant intervention for this cohort of patients, as it is expected that patients currently considered for AZA treatment would receive VenAZA and not VenLDAC (see Section B.1.3.3).

Comparators

As described in Section B.1.1, the comparators of relevance to this submission are AZA and LDAC, in line with the NICE final scope for this submission. AZA is recommended by NICE as the standard of care for adults who are not eligible for HSCT and have AML with 20–30% blasts and multilineage dysplasia, according to the WHO classification.[1, 60] The use of LDAC in AML patients is not restricted by blast count but, in clinical practice, it is used in patients with blast cell counts of >30%, as AZA is used in patients with blast cell counts of 20–30%. Therefore, AZA represents the relevant comparator in the cohort of patients with 20–30% blasts. In the cost-effectiveness model, azacitidine was administered in the AZA arm according to the same regimen as in the VenAZA arm described above.

Data from the subgroup of patients with 20–30% blasts from the comparator arm of VIALE-A were used to inform the inputs for the AZA arm in the economic analysis.[83, 86]

Cohort: >30% blasts

Interventions

VenAZA and VenLDAC are both relevant interventions for the cohort of patients with >30% blasts. In the cost-effectiveness model, VenLDAC consisted of venetoclax orally (600 mg QD) in combination with LDAC (20 mg/m^2) on days 1–10 of each 28-day cycle. Patients received a dose increase of venetoclax over the first four days of Cycle 1 to reach the target 600 mg dose (Day 1: 100 mg, Day 2: 200 mg, Day 3: 400 mg, Day 4 onwards: 600 mg). This is in line with the dosing regimen in the VIALE-C trial and the suggested posology in the draft SmPC for venetoclax.[82, 86, 93] The dosing regimen for VenAZA was the same for both 20–30% and >30% blast cohorts.

Data from the subgroup of patients with >30% blasts from the VenAZA and VenLDAC arms of VIALE-A and VIALE-C trials, respectively, were used to inform the inputs for VenAZA and VenLDAC in the economic analysis.[83, 86]

Comparators

AZA is not recommended by NICE for treating AML patients with a >30% bone marrow blast count, and therefore AZA does not represent a relevant comparator in the cohort of patients with >30% blasts.[2] Since AZA has generally displaced LDAC used in patients with a blast cell count of 20–30%, LDAC is predominantly used in patients with a blast cell count >30% and therefore represents the relevant comparator for this cohort of patients.[4] In the cost-effectiveness model, LDAC was administered in the LDAC arm according to the same regimen in the VenLDAC arm described above.

Data from the subgroup of patients with >30% blasts from the comparator arm of VIALE-C were used to inform the inputs for the LDAC in the economic analysis.[84, 85]

Scenarios were also conducted where data from the overall populations from the VIALE-A and VIALE-C trials were used to inform the inputs for interventions and comparators, respectively. A summary of all comparisons which were explored in the model is provided in Table 50.

Table 50: Summary of intervention comparisons in the model

Intervention	AZA	LDAC
20–30% blast count cohort		
VenAZA	✓	×
>30% blast count cohort		
VenAZA	×	✓
VenLDAC	×	✓

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; Ven: venetoclax

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The patient baseline characteristics which were used in the model are summarised in Table 51. These demographics are used alongside UK life tables to calculate the natural mortality of the general population within the model, as discussed in Section B.3.2.2.

These inputs were based on the baseline characteristics for all patients pooled across the VIALE-A and VIALE-C clinical trials. As noted in Section B.2.12, the baseline characteristics for the patients in both trials are consistent with the target patient population in the UK, and the generalisability of VIALE-A and VIALE-C baseline characteristics has been validated by clinical experts.[14]

Table 51: Patient characteristics in the model

Model parameter	Value, mean (SE)	Source
Age, years	[redacted]	VIALE-A,[83] VIALE-C[84]
Proportion male	[redacted]	
Weight, kg	[redacted]	
Height, m	[redacted]	
BSA, m/kg	[redacted]	

Weight, heights and BSA are used for calculating dosing in derivation of treatment costs and are not model inputs. BSA calculated using the Mostellar formula.[109]
Abbreviations: BSA: body surface area; SE: standard error.

B.3.3.2 Initial health state occupancy

At the start of the model, patients are distributed into either the 'Remission' or 'Non-remission' health states. This was considered to be an appropriate approach given that in VIALE-A and VIALE-C patients generally achieved remission (CR + CRi) quickly after treatment initiation (see Section B.2.5). The distribution of patients across these health states is dependent on the treatment received and is based on the rate of CR + CRi observed for patients in the VIALE-A and VIALE-C trials (See Section B.2.5).

A summary of the baseline health state occupancy for patients by blast count subgroup and treatment arm is presented in Table 52. The baseline health state occupancy for the overall population (by treatment arm) is presented in Appendix M.

Table 52: Base case distribution of patients into 'Non-remission' and 'Remission' health states by intervention and blast count subgroup

Intervention	Health state	Distribution at initiation		Source
		n/N	Proportion, mean (SE)	
20–30% blast count cohort				
VenAZA	Non-remission	[redacted]	[redacted]	VIALE-A[83]
	Remission	[redacted]	[redacted]	
AZA	Non-remission	[redacted]	[redacted]	
	Remission	[redacted]	[redacted]	
>30% blast count cohort				
VenAZA	Non-remission	[redacted]	[redacted]	VIALE-A[83]
	Remission	[redacted]	[redacted]	
VenLDAC	Non-remission	[redacted]	[redacted]	VIALE-C[84]
	Remission	[redacted]	[redacted]	
LDAC	Non-remission	[redacted]	[redacted]	
	Remission	[redacted]	[redacted]	

Abbreviations: AZA: azacitidine; CR: complete remission; CR + CRi: composite complete remission; LDAC: low dose cytarabine; SD: stable disease; SE: standard error; VEN: venetoclax.

B.3.3.3 Time-to-event data informing health state transitions

As described in Section B.3.2.2, the proportion of patients remaining in the 'Remission' or 'Non-remission' heath states, or transitioning to the 'PD/relapse' or 'Death' state at each monthly model cycle are based on time-dependent hazards derived from time-to-event data from the VIALE-A and VIALE-C trials.[83, 84] The hazard at any one time point is calculated using the following formula:

$$h_{(t)} = \frac{S_{(t-1)} - S_{(t)}}{S_{(t-1)}}$$

The EFS outcome collected in the trials does not distinguish between events of progression, relapse or death. In order to isolate the risk of PD/relapse and death independently, events were defined separately for the transitions to the 'PD/relapse' and 'Death' health states to capture the specific hazard reflected in each transition. Definitions of events were complementary, such that events included in one transition were censored in the other and vice versa, in order to avoid double counting. Time-to-relapse and time-to-PD were used to define transitions from 'Remission' and 'Non-remission' to 'PD/relapse', respectively. Relapse and PD were captured as events for time-to-relapse and time-to-PD, respectively, and patients who experienced death events or who were lost to follow-up were censored. Time-to-death data were used to inform transitions from 'Remission' and 'Non-remission' to 'PD/relapse' health states to 'Death'. For time-to-death, death was captured as an event, and patients who experienced PD, relapse or who were lost to follow-up were censored. The time-to-event data used to inform health state transitions in the model are presented in Table 53.

Table 53: Summary of time-to-event data informing health state transitions

Transition	Eligible patient population	Index time	Event	Censor[a]
Non-remission to PD	Patients who did not achieve CR + CRi	Randomisation	Confirmed MR/PD or treatment failure	Death or last follow-up
Non-remission to Death			Death	Confirmed MR/PD, treatment failure or last follow-up
Remission to relapse	Patients who achieved CR + CRi	First date of CR + CRi	Confirmed MR/PD or treatment failure	Death or last follow-up
Remission to Death			Death	Confirmed MR/PD, treatment failure or last follow-up
PD/relapse to Death	Patients who had confirmed morphologic relapse (MR)[b], progressed disease (PR), or treatment failure	Time of confirmed MR/PD or treatment failure	Death	Last follow-up

[a]Censoring occurs when patients who experience an event not captured by the transition are censored, this allows the model to capture the risk of PD and death independently of each other without double counting.
[b]Morphologic relapse is defined by the IWG as reappearance of ≥5 blasts after CR + CRi in the peripheral blood or bone marrow or development of extramedullary disease.
Abbreviations: CR: complete remission; CRi: complete remission with incomplete recovery; MR: morphologic relapse; PD: progressed disease.

20–30% blast cell count cohort

A summary of the patient numbers used to derive survival curves for the VenAZA and AZA treatment arms in the 20–30% blast cell count cohort is presented in Table 54.

When considering the clinical plausibility of the survival curves, it is important to bear in mind that patients can transition out of the 'Non-remission' and 'Remission' states due to PD/treatment failure, relapse *or* due to death events, but these events are captured by independent transitions (as described in Table 53) that are not reflected in the survival curves of the individual events. Collectively, these two transitions determine the overall rate of transition out of the 'Remission' and 'Non-remission' states, which in turn determines the health state distribution over time, but the presented survival curves (Figure 42 to Figure 46) correspond to the individual events in isolation.

For example, in the 20–30% blast cell subgroup of the VIALE-A trial, 60 patients receiving VenAZA achieved remission, of whom 24 (40%) experienced relapse over the trial follow-up. In contrast, 18 patients did not achieve remission, of whom two (11%) experienced PD/treatment failure event. Counterintuitively, this might suggest that patients in the "Remission" state are at a greater risk of PD/relapse than those in the "Non-remission" state; indeed, the resulting Kaplan–Meier curves (Figure 42 and Figure 44) reflect this. However, these patients are also at risk of death, which is captured independently by the transition to the 'Death state'. Of those patients

who achieved remission, only 12 (20%) died, compared with 15 (83%) of those patients who did not achieve remission. Since patients in the 'Non-remission' state are at a higher risk of death, fewer patients remain alive to be at risk of experiencing PD/treatment failure. In contrast, patients in the 'Remission' state are at lower risk of death, and therefore remain alive for longer periods of time where they are at risk of relapse events. When transitions to the 'PD/Relapse' and 'Death' states are taken together, it is clear that patients transition out of the 'Non-remission' state at a faster rate than those in the 'Remission' health state, which aligns with the trial outcomes and align with clinical expectations. The accuracy of model predictions with respect to the proportions of patients in the 'Remission' and 'Non-remission' health states is explored further in B.3.10.

Table 54: Time-to-event data used to derive survival curves in the 20–30% blast cell count cohort

Transition	Event type	N	Events	Censors	Kaplan–Meier curve	Source
VenAZA						
Non-remission to PD/relapse	PD	[redacted]	[redacted]	[redacted]	Figure 42	VIALE-A trial[83]
Non-remission to death	Death	[redacted]	[redacted]	[redacted]	Figure 43	
Remission to PD/relapse	Relapse	[redacted]	[redacted]	[redacted]	Figure 44	
Remission to Death	Death	[redacted]	[redacted]	[redacted]	Figure 45	
PD/relapse to Death	Death	[redacted]	[redacted]	[redacted]	Figure 46	
AZA						
Non-remission to PD/relapse	PD	[redacted]	[redacted]	[redacted]	Figure 42	VIALE-A trial[83]
Non-remission to death	Death	[redacted]	[redacted]	[redacted]	Figure 43	
Remission to PD/relapse	Relapse	[redacted]	[redacted]	[redacted]	Figure 44	
Remission to Death	Death	[redacted]	[redacted]	[redacted]	Figure 45	
PD/relapse to Death	Death	[redacted]	[redacted]	[redacted]	Figure 46	

Abbreviations: AZA: azacitidine; N: number of patients; Ven: venetoclax.

Figure 42: Kaplan–Meier curve for time-to-PD in 'Non-remission' patients (20–30% blast cell count cohort; VIALE-A)

Abbreviations: AZA: azacitidine; PD: progressive disease.

Figure 43: Kaplan–Meier curve for time-to-death in 'Non-remission' patients (20–30% blast cell count cohort; VIALE-A)

Abbreviations: AZA: azacitidine.

Figure 44: Kaplan–Meier curve for time-to-relapse in 'Remission' patients (20–30% blast cell count cohort; VIALE-A)

Abbreviations: AZA: azacitidine.

Figure 45: Kaplan–Meier curve for time-to-death in 'Remission' patients (20–30% blast cell count cohort; VIALE-A)

Abbreviations: AZA: azacitidine.

Figure 46: Kaplan–Meier curve for time-to-death in 'PD/relapse' patients (20–30% blast cell count cohort; VIALE-A)

Abbreviations: AZA: azacitidine; PD: progressive disease.

>30% blast cell count cohort

A summary of the patient numbers used to derive survival curves for the VenAZA, VenLDAC and LDAC treatment arms in the >30% blast cell count cohort is presented in Table 55. As noted above, when interpreting the resulting Kaplan–Meier curves, it is important to bear in mind that patients can transition out of the 'Non-remission' and 'Remission' states due to PD/treatment failure, relapse *or* due to death events, but these events are captured by independent transitions (as described in Table 53). Collectively, these two transitions determine the overall rate of transition out of the 'Remission' and 'Non-remission' states, which in turn determines the health state distribution over time.

Table 55: Summary of patient numbers used to derive survival curves in the >30% blast cell count cohort

Transition	N	Events	Censors	Kaplan–Meier curve	Source
VenAZA					
Non-remission to PD/relapse	[redacted]	[redacted]	[redacted]	Figure 47	VIALE-A trial[83]
Non-remission to Death	[redacted]	[redacted]	[redacted]	Figure 48	
Remission to PD/relapse	[redacted]	[redacted]	[redacted]	Figure 49	
Remission to Death	[redacted]	[redacted]	[redacted]	Figure 50	
PD/relapse to Death	[redacted]	[redacted]	[redacted]	Figure 51	
VenLDAC					
Non-remission to PD/relapse	[redacted]	[redacted]	[redacted]	Figure 52	VIALE-C trial[84]
Non-remission to Death	[redacted]	[redacted]	[redacted]	Figure 53	

Remission to PD/relapse	[redacted]	[redacted]	[redacted]	Figure 54	
Remission to Death	[redacted]	[redacted]	[redacted]	Figure 55	
PD/relapse to Death	[redacted]	[redacted]	[redacted]	Figure 56	
LDAC					
Non-remission to PD/relapse	[redacted]	[redacted]	[redacted]	Figure 52	VIALE-C trial[84]
Non-remission to Death	[redacted]	[redacted]	[redacted]	Figure 53	
Remission to PD/relapse	[redacted]	[redacted]	[redacted]	Figure 54	
Remission to Death	[redacted]	[redacted]	[redacted]	Figure 55	
PD/relapse to Death	[redacted]	[redacted]	[redacted]	Figure 56	

[a]As no events occurred in the >30% blast cohort, the curve selected for the overall population was used.
Abbreviations: AZA: azacitidine; LDAC:low dose cytrabine; N: number of patients; Ven: venetoclax.

Figure 47: Kaplan–Meier curve for time-to-PD in 'Non-remission' patients (>30% blast cell count cohort; VIALE-A)

Placebo plus AZA arm is not used in the model.
Abbreviations: AZA: azacitidine; PD: progressive disease.

Figure 48: Kaplan–Meier curve for time-to-death in 'Non-remission' patients (>30% blast cell count cohort; VIALE-A)

Placebo plus AZA arm is not used in the model.
Abbreviations: AZA: azacitidine.

Figure 49: Kaplan–Meier curve for time-to-relapse in 'Remission' patients (>30% blast cell count cohort; VIALE-A)

Placebo plus AZA arm is not used in the model.
Abbreviations: AZA: azacitidine.

Figure 50: Kaplan–Meier curve for time-to-death in 'Remission' patients (>30% blast cell count cohort; VIALE-A)

Placebo plus AZA arm is not used in the model.
Abbreviations: AZA: azacitidine.

Figure 51: Kaplan–Meier curve for time-to-death in 'PD/relapse' patients (>30% blast cell count cohort; VIALE-A)

Placebo plus AZA arm is not used in the model.
Abbreviations: AZA: azacitidine; PD: progressive disease.

Figure 52: Kaplan–Meier curve for time-to-PD in 'Non-remission' patients (>30% blast cell count cohort; VIALE-C)

Abbreviations: LDAC: low-dose cytarabine; PD: progressive disease.

Figure 53: Kaplan–Meier curve for time-to-death in 'Non-remission' patients (>30% blast cell count cohort; VIALE-C)

Abbreviations: LDAC: low-dose cytarabine.

Figure 54: Kaplan–Meier curve for time-to-death in 'Remission' patients (>30% blast cell count cohort; VIALE-C)

Abbreviations: LDAC: low-dose cytarabine.

Figure 55: Kaplan–Meier curve for time-to-death in 'Remission' patients (>30% blast cell count cohort; VIALE-C)

Abbreviations: LDAC: low-dose cytarabine.

Figure 56: Kaplan–Meier curve for time-to-death in 'PD/relapse' patients (>30% blast cell count cohort; VIALE-C)

Abbreviations: LDAC: low-dose cytarabine; PD: progressive disease.

B.3.3.4 Extrapolation of health state transitions

As the follow-up periods for the VIALE-A and VIALE-C trials (see Section B.2.5) were shorter than the model time horizon, extrapolation from the observed time-to-event data was required. In accordance with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance on survival analyses, a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were explored for extrapolation.[110] The choice of parametric survival curves were deemed sufficient to capture the long-term survival of patients beyond the follow up of the trials. More advanced statistical techniques (e.g. spline) outlined in the NICE DSU 21 were deemed unnecessary and inappropriate due to the large degree of uncertainty associated with small sample sizes in the blast count subgroups and were therefore not considered.[111] The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) were then estimated for each parametric function. In determining the choice of survival model used for extrapolation in the base case analysis, consideration was given to the following, as per the recommendations provided in NICE DSU TSD14 and TSD21:[110, 111]

- **Akaike information criterion (AIC)/Bayesian information criteria (BIC) tests:** the AIC and the BIC provide useful statistical tests of the relative fit of different parametric survival models. These tests weight the improved fit of models with the potentially inefficient use of additional parameters. Lower AIC and BIC values indicate better fit of the selected model.
- **Visual inspection:** the visual inspection can evaluate how well a parametric survival model fits with the observed Kaplan–Meier curves. The parametric survival model that most closely follows the Kaplan–Meier curve could be considered the best fit.
- **Cumulative hazard plots:** the parametric curves which best capture the hazard profile of the survival endpoint could be considered the best fit.
- **Clinical plausibility for both short-term and long-term estimates of survival.**

A summary of the selected base case extrapolation methods for patients by cohort treatment arm and health state transition is presented in Table 56. Parametric curve goodness-of-fit statistics, extrapolated curves, and log cumulative hazard plots are presented for each transition below. These extrapolations are subject to considerable uncertainty given the small sample sizes informing each transition (see Section B.3.3.3), but extensive scenario analyses have been conducted which suggest that the results are robust to alternative approaches for extrapolation (Section B.3.8.3).

Table 56: Summary of health state transition data sources and base-case extrapolation approach

Intervention	Health state transition	Survival figure	Cumulative hazard figure	Extrapolation methods
20–30% blast count cohort				
VenAZA	Non-remission to PD/relapse	Figure 57	Figure 58	Log-normal
	Non-remission to Death	Figure 59	Figure 60	Log-normal
	Remission to PD/relapse	Figure 61	Figure 62	Log-normal
	Remission to Death	Figure 63	Figure 64	Generalised gamma

	PD/relapse to Death	Figure 65	Figure 66	Log-normal
AZA	Non-remission to PD/relapse	Figure 67	Figure 68	Gompertz
	Non-remission to Death	Figure 69	Figure 70	Weibull
	Remission to PD/relapse	Figure 71	Figure 72	Weibull
	Remission to Death	Figure 73	Figure 74	Log-normal
	PD/relapse to Death	Figure 75	Figure 76	Log-normal
>30% blast count cohort				
VenAZA	Non-remission to PD/relapse	Figure 77	Figure 78	Exponential
	Non-remission to Death	Figure 79	Figure 80	Log-normal
	Remission to PD/relapse	Figure 81	Figure 82	Generalised gamma
	Remission to Death	Figure 83	Figure 84	Log-logistic
	PD/relapse to Death	Figure 85	Figure 86	Log-normal
VenLDAC	Non-remission to PD/relapse	Figure 87	Figure 88	Log-normal
	Non-remission to Death	Figure 89	Figure 90	Log-normal
	Remission to PD/relapse	Figure 91	Figure 92	Generalised gamma
	Remission to Death	Figure 93	Figure 94	Log-normal
	PD/relapse to Death	Figure 95	Figure 96	Generalised gamma
LDAC	Non-remission to PD/relapse	Figure 97	Figure 98	Generalised gamma
	Non-remission to Death	Figure 99	Figure 100	Log-normal
	Remission to PD/relapse	Figure 101	Figure 102	Exponential
	Remission to Death	NE[a] (Figure 103)		Exponential
	PD/relapse to Death	Figure 104	Figure 105	Log-normal

[a]As no events occurred in the >30% blast cohort, the curve selected for the overall population was used.
Abbreviations: AZA: azacitidine; EFS: event-free survival; LDAC: low-dose cytarabine; Ven: venetoclax.

The model has taken a relative survival approach, in which simulated patients are assumed to be subject to the risk of disease-specific events due to two independent mechanisms:[111]

- Disease-specific hazard (as determined by the disease-specific survival curves reported in Table 56)
- General population background mortality hazard

In the base case this general population hazard is applied as a product with the disease-specific survival curves after the maximum follow-up of the VIALE-A and VIALE-C trials**.** The general population background mortality hazard component is informed by age- and sex-specific national life tables.

20–30% blast cell count cohort

VenAZA

'Non-remission' to 'PD/relapse': A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-PD in 'Non-remission' patients in the VenAZA arm. The exponential curve provided the lowest AIC/BIC values. However, the distribution provided a poor visual fit to the data, failing to capture the tail observed in the Kaplan–Meier curve. During

clinician consultation, it was noted that the exponential distribution provided the most likely observed survival for long-term extrapolations. However, the poor visual fit and unlikely hazard profile meant it was disregarded. None of the parametric curves could adequately capture the cumulative hazard, and therefore the log-normal curve was selected as it had the next lowest AIC/BIC and a much better visual fit than any of the other distributions.

'Non-remission' to 'Death': A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-death in 'Non-remission' patients in the VenAZA arm. The exponential curve provided the lowest AIC/BIC values. However, this distribution was unable to capture the flex in hazard over time observed in the cumulative hazard plot and was therefore disregarded. The log-normal model was selected as it had the next lowest AIC/BIC and was able to capture the decreasing hazard observed in the data. During clinician consultation, it was suggested that the long-term survival predicted by this model at 10 years (0.1%) was unlikely, but this would be reduced to a more plausible estimate upon application of general population mortality.

'Remission' to 'PD/relapse': A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-relapse in 'Remission' patients in the VenAZA arm. The Weibull curve provided the lowest AIC/BIC values. However, this distribution provided a poor visual fit to the observed data, failing to capture the tail observed in the Kaplan–Meier curve. The log-normal model had the next lowest AIC/BIC, was supported by the cumulative hazard plot, and captured the general shape of the observed data. Upon clinician consultation, the preferred choice of survival curve was the log-logistic model. Given the lognormal model provides lower AIC/BIC and the long-term survival predicted by the log-normal and log-logistic extrapolations were similar, the log-normal distribution was selected.

'Remission' to 'Death': A generalised gamma distribution was selected in the base-case analysis for extrapolation of time-to-death in 'Remission' patients in the VenAZA arm. The generalised gamma distribution was selected as it provided the lowest AIC/BIC values, and was supported by the cumulative hazard plot, which captured the severe change in hazard observed over the trial period. The high predicted mean survival is supported by the observed plateau in the Kaplan-Meier data, and reflects the fact that patients can be considered cured after approximately two years.

'PD/relapse' to 'Death': A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-death in 'PD/relapse' patients in the VenAZA arm. The exponential curve provided the lowest AIC/BIC values. However, this distribution was a poor fit to the cumulative hazard and Kaplan–Meier curve, and was therefore disregarded. The log-normal model was selected as it had the next lowest AIC/BIC and was able to capture the decreasing hazard observed in the data.

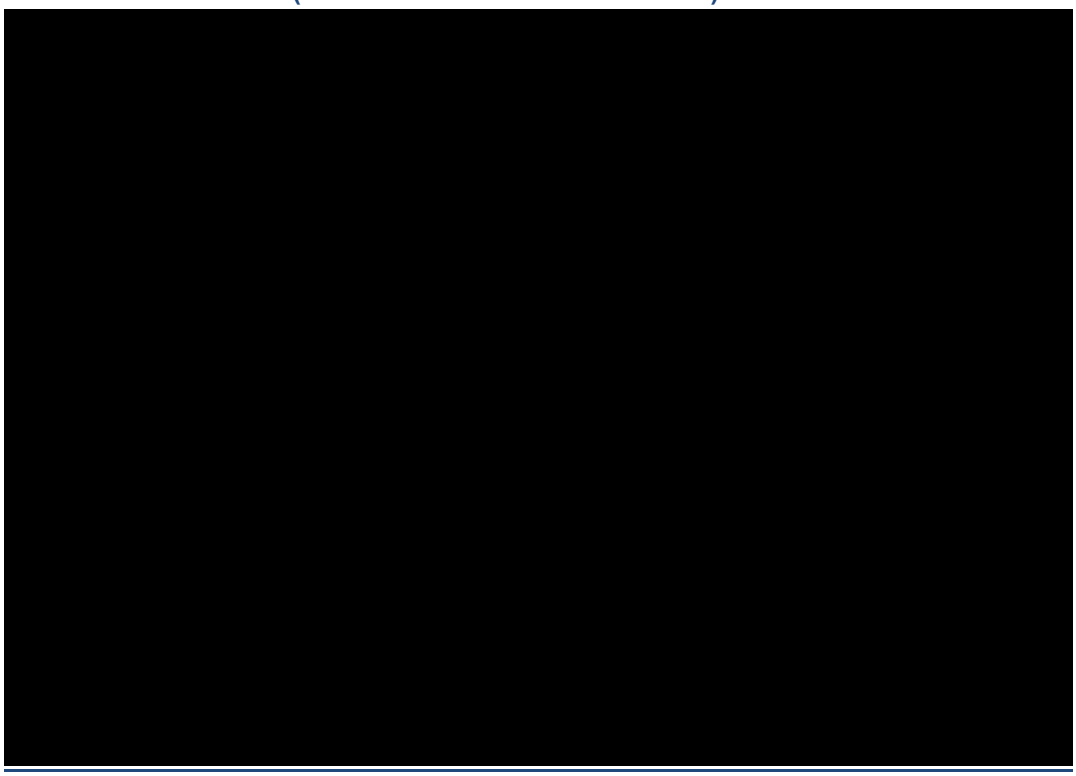
Figure 57: Parametric survival extrapolations of time-to-PD for patients in 'Non-remission' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; PD: progressive disease; Ven: venetoclax.

Figure 58: Log cumulative hazard plots of time-to-PD for patients in 'Non-remission' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine; PD: progressive disease; Ven: venetoclax.

Figure 59: Parametric survival extrapolations of time-to-death for patients in 'Non-remission' – VenAZA (20–30% blast cell count cohort)



Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 60: Log cumulative hazard plots of time-to-death for patients in 'Non-remission' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 61: Parametric survival extrapolations of time-to-relapse for patients in 'Remission' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 62: Log cumulative hazard plots of time-to-relapse for patients in 'Remission' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 63: Parametric survival extrapolations of time-to-death for patients in 'Remission' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 64: Log cumulative hazard plots of time-to-death for patients in 'Remission' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 65: Parametric survival extrapolations of time-to-death for patients in 'Remission' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 66: Log cumulative hazard plots of time-to-death for patients in 'PD/Relapse' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine; PD: progressive disease; Ven: venetoclax.

AZA

'Non-remission' to 'PD/relapse': A Gompertz distribution was selected in the base-case analysis for extrapolation of time-to-PD in 'Non-remission' patients in the AZA arm. The exponential curve provided the lowest AIC/BIC values. However, the distribution provided a poor fit to the cumulative hazard data, and was unable to capture the late increasing hazard and was therefore disregarded. The Gompertz distribution was selected as it provided the next lowest AIC/BIC values and was able to capture the increasing hazard observed in the data.

'Non-remission' to 'Death: A Weibull distribution was selected in the base-case analysis for extrapolation of time-to-death in 'Non-remission' patients in the AZA arm. The exponential curve provided the lowest AIC/BIC values. However, this distribution was a poor fit to the cumulative hazard data and was therefore disregarded. The Weibull distribution was selected as whilst the cumulative hazard did not fully capture the changes in hazard, particularly the increase seen in the early section, it was deemed a conservative choice of curve given the uncertainty in the changing hazard. A mean survival time of 24.1 months was deemed plausible and it provided a reasonable visual fit. During clinician consultation, it was suggested that the Weibull distribution was a conservative choice as it was likely to overestimate patient survival.

'Remission' to 'PD/relapse': A Weibull distribution was selected in the base-case analysis for extrapolation of time-to-relapse in 'Remission' patients in the AZA arm. The Weibull curve provided the lowest AIC/BIC values and whilst it is acknowledged that the Weibull distribution did not provide a particularly strong fit to the cumulative hazard data, none of the parametric fits were deemed more representative. Upon visual inspection the Weibull distribution provided a good fit to the Kaplan–Meier and so therefore was selected.

'Remission' to 'Death': A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-death in 'Remission' patients in the AZA arm. The Gompertz curve provided the lowest AIC/BIC values. However, this model was associated with an implausible median and mean survival time and thus was ruled out. The distribution providing the next lowest AIC/BIC values was the log-normal distribution. Whilst the mean survival could be deemed implausible at over 150 months, the log-normal distribution provides a more conservative prediction compared with the Gompertz curve, and the Kaplan–Meier does suggest a large plateau in the data. Similarly, when inspecting the cumulative hazard data, the Gompertz curve suggests a total elimination of any disease-specific hazard, whereas the log-normal curve does capture some of the shaping hazard over the trial period.

'PD/relapse' to 'Death': A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-death in 'PD/relapse' patients in the AZA arm. The exponential curve provided the lowest AIC/BIC values. However, this distribution provided a poor fit to the cumulative hazard, and was therefore disregarded. The log-normal model was selected as it had the next lowest AIC/BIC whilst also providing a more suitable fit to the cumulative hazard profile. The use of a log-normal distribution may also be considered conservative given the predicted mean survival time of 14.5 months.

Figure 67: Parametric survival extrapolations of time-to-PD for patients in 'Non-remission' – (AZA 20–30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; PD: progressive disease; BIC: Bayesian information criterion.

Figure 68: Log cumulative hazard plots of time-to-PD for patients in 'Non-remission' – VenAZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine; PD: progressive disease.

Figure 69: Parametric survival extrapolations of time-to-death for patients in 'Non-remission' – AZA (20–30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion.

Figure 70: Log cumulative hazard plots of time-to-death for patients in 'Non-remission' – AZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine.

Figure 71: Parametric survival extrapolations of time-to-relapse for patients in 'Remission' – AZA (20–30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion.

Figure 72: Log cumulative hazard plots of time-to-relapse for patients in 'Remission' – AZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine.

Figure 73: Parametric survival extrapolations of time-to-death for patients in 'Remission' – AZA (20–30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion.

Figure 74: Log cumulative hazard plots of time-to-death for patients in 'Remission' – AZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine.

Figure 75: Parametric survival extrapolations of time-to-death for patients in 'Remission' – AZA (20–30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion.

Figure 76: Log cumulative hazard plots of time-to-death for patients in 'PD/Relapse' – AZA (20–30% blast cell count cohort)

Abbreviations: AZA: azacitidine; PD: progressive disease.

>30% blast cell count cohort

Company evidence submission template for venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia unsuitable for intensive chemotherapy ID1564

VenAZA

'Non-remission' to 'PD/relapse': An exponential distribution was selected in the base-case analysis for extrapolation of time-to-PD in 'Non-remission' patients in the VenAZA arm. The Gompetz curve provided the lowest AIC/BIC values and was supported during clinician consultation. However, when considering the fit to cumulative hazard data this curve incorrectly identified an increasing hazard and was inconsistent with the data. The exponential distribution provided the next lowest AIC/BIC, and whilst this distribution did not provide an adequate fit to the cumulative hazard profile observed, it was deemed a conservative choice for extrapolation, given the inadequacy of all other curves.

'Non-remission' to 'Death': A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-death in 'Non-remission' patients in the VenAZA arm. The generalised gamma curve provided the lowest AIC/BIC values; however, the mean survival was predicted to be 56.3 months, which was deemed implausible. Log-normal was selected as it had the next lowest AIC/BIC and yielded a more conservative estimate for the mean survival at 7.4 months. The choice of a log-normal curve was also supported by the cumulative hazard, which showed an excellent fit to the data and captured the changed in hazard over the trial period. The predicted survival was also considered to be the most plausible.

'Remission' to 'PD/relapse': A generalised gamma distribution was selected in the base-case analysis for extrapolation of time-to-relapse in 'Remission' patients in the VenAZA arm. The generalised gamma provided the lowest AIC/BIC values, was a good fit to the cumulative hazard data, and captured the decreasing hazard observed in the data.

'Remission' to 'Death': A log-logistic distribution was selected in the base-case analysis for extrapolation of time-to-death in 'Remission' patients in the VenAZA arm. Whilst it was acknowledged that the log-normal distribution provided the lowest AIC/BIC values, it was deemed that the log-logistic was a more conservative choice of extrapolation, with a lower median survival estimate. The log-logistic distribution also provided a similar visual fit to the cumulative hazard as the log-normal distribution.

'PD/relapse' to 'Death': A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-death in 'PD/relapse' patients in the VenAZA arm. The log-normal curve provided the lowest AIC/BIC values, was a good fit to the cumulative hazard data, and captured the decreasing hazard seen in the data.

Figure 77: Parametric survival extrapolations of time-to-PD for patients in 'Non-remission' – VenAZA (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; PD: progressive disease; Ven: venetoclax.

Figure 78: Log cumulative hazard plots of time-to-PD for patients in 'Non-remission' – VenAZA (>30% blast cell count cohort)

Abbreviations: AZA: azacitidine; PD: progressive disease; Ven: venetoclax.

Figure 79: Parametric survival extrapolations of time-to-death for patients in 'Non-remission' – VenAZA (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 80: Log cumulative hazard plots of time-to-death for patients in 'Non-remission' – VenAZA (>30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 81: Parametric survival extrapolations of time-to-relapse for patients in 'Remission' – VenAZA (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 82: Log cumulative hazard plots of time-to-relapse for patients in 'Remission' – VenAZA (>30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 83: Parametric survival extrapolations of time-to-death for patients in 'Remission' – VenAZA (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 84: Log cumulative hazard plots of time-to-death for patients in 'Remission' – VenAZA (>30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 85: Parametric survival extrapolations of time-to-death for patients in 'Remission' – VenAZA (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 86: Log cumulative hazard plots of time-to-death for patients in 'PD/Relapse' – VenAZA >30% blast cell count cohort)

Abbreviations: AZA: azacitidine; PD: progressive disease; Ven: venetoclax.

VenLDAC

Company evidence submission template for venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia unsuitable for intensive chemotherapy ID1564

‘Non-remission’ to ‘PD/relapse’: A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-PD in ‘Non-remission’ patients in the VenLDAC arm. The log-normal curve provided the lowest AIC/BIC values, whilst also providing a good visual fit to the data in the cumulative hazard plot. The log-normal distribution was able to capture the decreasing hazard over time and therefore was deemed suitable to extrapolate time-to-PD for patients in ‘Non-remission’.

‘Non-remission’ to ‘Death’: A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-death in ‘Non-remission’ patients in the VenLDAC arm. The log-normal curve provided the lowest AIC/BIC values and a good visual fit to the cumulative hazard.

‘Remission’ to ‘PD/relapse’: A generalised gamma distribution was selected in the base-case analysis for extrapolation of time-to-PD in ‘Remission’ patients in the VenLDAC arm. The generalised gamma curve provided the lowest AIC/BIC, and this was also supported by a visually good fit to the cumulative hazard plot. The generalised gamma distribution captured the change in hazard seen in the data and was therefore selected as an appropriate distribution to extrapolate. During the clinician consultation it was suggested that the exponential distribution would be the most likely to represent the time to relapse in patients with remission. However, upon inspection of the hazard and the clear decrease in hazard over time, it was deemed unsuitable to chose an exponential distribution, given the violation of the constant hazard assumption.

‘Remission’ to ‘Death’: A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-death in ‘Remission’ patients in the VenLDAC arm. The generalised gamma curve provided the lowest AIC/BIC values, however, the implausible predicted mean made it inappropriate for selection. The log-normal distribution provided the next lowest AIC/BIC values and provided a more plausible mean survival of 65.2 months, aligning to the plateau observed in the Kaplan–Meier curve. The log-normal distribution did not fully capture the change in hazard over time, however, it was noted that none of the parametric distributions were able to fully capture the change in hazard observed over the trial period. During clinician consultation, it was suggested that the log-logistic would be the most suitable to extrapolate time to death from remission. However, given that the predicted mean survival associated with log-logistic (71.6 months) versus log-normal (66.2 months) was lower, the log-normal curve can be considered a conservative choice.

‘PD/relapse’ to ‘Death’: A generalised gamma distribution was selected in the base-case analysis for extrapolation of time-to-death in ‘PD/relapse patients’ in the VenLDAC arm. The Gompertz curve provided the lowest AIC/BIC. However, given the implausible mean survival it was deemed an inappropriate choice of curve for extrapolation. The distribution providing the next lowest AIC/BIC values was the log-logistic distribution. However, similar to the Gompertz distribution, the mean survival of 8.4 months for patients’ PD/relapse was deemed implausible and it was again ruled out. The distribution with the next lowest AIC/BIC values was the generalised gamma distribution, providing a more plausible mean survival time of 4.1 months. The generalised gamma distribution was deemed to provide a good fit to the cumulative hazard and was able to adequately capture the late hazard in observed in the data. However, it was acknowledged that the early hazard was not appropriately captured.

Figure 87: Parametric survival extrapolations of time-to-PD for patients in 'Non-remission' – VenLDAC (30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine; PD: progressive disease; Ven: venetoclax.

Figure 88: Log cumulative hazard plots of time-to-PD for patients in 'Non-remission' – VenLDAC (>30% blast cell count cohort)

Abbreviations: LDAC: low dose cytarabine; PD: progressive disease; Ven: venetoclax.

Figure 89: Parametric survival extrapolations of time-to-death for patients in 'Non-remission' – VenLDAC (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine; Ven: venetoclax.

Figure 90: Log cumulative hazard plots of time-to-death for patients in 'Non-remission' – VenLDAC (>30% blast cell count cohort)

Abbreviations: LDAC: low dose cytarabine; Ven: venetoclax.

Figure 91: Parametric survival extrapolations of time-to-relapse for patients in 'Remission' – VenLDAC (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine; Ven: venetoclax.

Figure 92: Log cumulative hazard plots of time-to-relapse for patients in 'Remission' – VenLDAC (>30% blast cell count cohort)

Abbreviations: LDAC: low dose cytarabine; Ven: venetoclax.

Figure 93: Parametric survival extrapolations of time-to-death for patients in 'Remission' – VenLDAC (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; LDAC: low dose cytarabine; Ven: venetoclax.

Figure 94: Log cumulative hazard plots of time-to-death for patients in 'Remission' – VenLDAC (>30% blast cell count cohort)

Abbreviations: LDAC: low dose cytarabine; Ven: venetoclax.

Figure 95: Parametric survival extrapolations of time-to-death for patients in 'Remission' – VenLDAC (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine; Ven: venetoclax.

Figure 96: Log cumulative hazard plots of time-to-death for patients in 'PD/Relapse' – VenLDAC (>30% blast cell count cohort)

Abbreviations: LDAC: low dose cytarabine; PD: progressive disease; Ven: venetoclax.

LDAC

‘Non-remission’ to ‘PD/relapse’: A generalised gamma distribution was selected in the base-case analysis for extrapolation of time-to-PD in ‘Non-remission’ patients in the LDAC arm. The generalised gamma curve provided the lowest AIC/BIC values, and whilst it was acknowledged that the mean survival could be deemed implausible, it is consistent with the observed plateau in the data from 9 months. The cumulative hazard of the generalised gamma distribution also fit to the observed data well and it was therefore deemed an appropriate distribution to extrapolate time-to-PD in ‘Non-remission’ patients. During clinician consultation it was suggested that the log-normal distribution was the most likely to represent long-term hazard. As such, given its similarity to the log-normal distribution, the generalised gamma was considered a suitable choice for capturing the hazard profile of ‘Non-remission’ patients.

‘Non-remission’ to ‘Death’: A log-normal distribution was selected in the base-case analysis for extrapolation of OS in non-remission patients in the VenLDAC arm. The generalised gamma curve provided the lowest AIC/BIC values; however, an implausible mean survival time suggests the curve is inappropriate for extrapolation. The distribution providing the next lowest AIC/BIC values was the log-normal distribution which also provided a more plausible mean survival of 11.5 months and captured the changing shape in the hazard well. During clinician consultation, it was suggested that the exponential distribution would be the best predictor of long-term survival. However, given that the exponential distribution provided a poor fit to the changing hazard observed in the data, the log-normal distribution was deemed the most suitable choice.

‘Remission’ to ‘PD/relapse’: An exponential distribution was selected in the base-case analysis for extrapolation of EFS in Remission patients in the VenLDAC arm. The exponential curve provided the lowest AIC/BIC, and captured the constant hazard observed in the data, and was therefore selected as an appropriate distribution to extrapolate.

‘Remission’ to ‘Death’: No ‘Remission’ to ‘Death’ events occurred in the LDAC >30% blast cell count cohort, and therefore no Kaplan–Meier curve was generated. Given that only one event occurred in the overall population it was assumed that this would be representative of patients in the 30% blast cell count cohort and therefore the curves for the overall population were used. The exponential curve provided the lowest AIC/BIC values for extrapolating OS in remission patients in the LDAC arm, only one event was observed in the trial period and therefore there is considerable uncertainty surrounding the Kaplan–Meier curve. Given this uncertainty, it was deemed inappropriate to select more flexible curves to extrapolate the data and therefore the exponential curve was deemed appropriate. As only one event was observed, no cumulative hazard plots were able to be generated.

‘PD/relapse’ to ‘Death’: A log-normal distribution was selected in the base-case analysis for extrapolation of time-to-death in ‘PD/relapse’ patients in the LDAC arm. The Gompertz curve provided the lowest AIC/BIC values; however, an implausible mean ruled out this choice of curve for extrapolation. The exponential distribution provided the next lowest AIC/BIC values, however, whilst it provided a more plausible mean survival of 3.1 months, this curve did not fit well to the cumulative hazard observed in the data and was also disregarded. The log-normal distribution provided the next lowest AIC/BIC values, whilst also providing a plausible mean survival of 4.5 months and a good fit to the cumulative hazard. During the clinician consultation, it was suggested that the exponential survival rates were too low, whilst the log-normal rates were too high. As such, the choice of log-normal can be viewed as a conservative choice of curve.

Figure 97: Parametric survival extrapolations of time-to-PD for patients in 'Non-remission' – LDAC (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PD: progressive disease; LDAC: low dose cytarabine.

Figure 98: Log cumulative hazard plots of time-to-PD for patients in 'Non-remission' – LDAC (>30% blast cell count cohort)

Abbreviations: PD: progressive disease; LDAC: low dose cytarabine.

Figure 99: Parametric survival extrapolations of time-to-death for patients in 'Non-remission' – LDAC (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine.

Figure 100: Log cumulative hazard plots of time-to-death for patients in 'Non-remission' – LDAC (>30% blast cell count cohort)

Abbreviations: LDAC: low dose cytarabine,

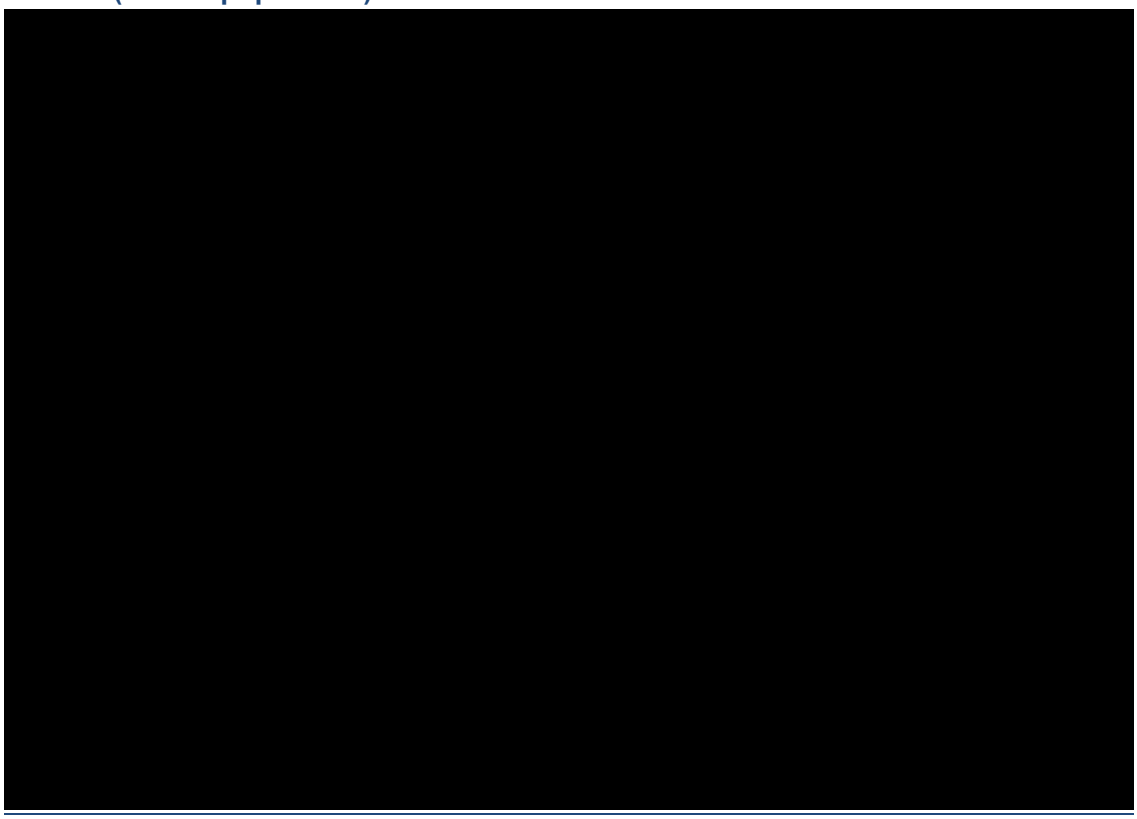
Figure 101: Parametric survival extrapolations of time-to-relapse for patients in 'Remission' – LDAC (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine.

Figure 102: Log cumulative hazard plots of time-to-relapse for patients in 'Remission' – LDAC (>30% blast cell count cohort)

Abbreviations: LDAC: low dose cytarabine.

Figure 103: Parametric survival extrapolations of time-to-death for patients in 'Remission' – LDAC (overall population)[a]



[a]As no events occurred in the >30% blast cohort, the curve selected for the overall population was used.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine.

Figure 104: Parametric survival extrapolations of time-to-death for patients in 'Remission' – LDAC (>30% blast cell count cohort)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine.

Figure 105: Log cumulative hazard plots of time-to-death for patients in 'PD/Relapse' – LDAC (>30% blast cell count cohort)

Abbreviations: LDAC: low dose cytarabine; PD: progressive disease.

B.3.3.5 Cure assumption

As previously discussed in Section B.3.2.2, the model contains a 'Cure' health state in which patients are assumed to have age- and sex-matched population mortality (based on UK life tables) and accrue the utility of the general population.[39] Clinical experts consulted explained that patients treated with venetoclax combinations who achieve a sustained deep remission have the potential to achieve long-term survivorship, whereby their outcomes are in line with those of the general population. VenAZA provides deep and durable complete remission rates (CR/CRi with/without MRD) that have historically only been associated with IC.[32, 56, 69, 70]Depth and duration of remission has been positively correlated with length of survival in patients who receive IC.[31, 71] Furthermore, rate of relapse after two years is low (based on experience of patients treated with IC).[1,34, 72-75] This feedback corroborates the plateau in the Kaplan–Meier curves which is observed at ~24 months of treatment for VenAZA (in 20–30% and >30% blast populations; B.2.6.1 and B.2.8.2, respectively). Additionally, clinicians noted that the proportion of patients in CR/CRi for whom cure is assumed at year 2 will be enriched with those with no/low MRD. Such deep and durable remissions have been shown to be positively correlated with increased survival in patients treated with IC.[71] However improved outcomes do not necessarily require undetectable levels of MRD, whilst, inversely, a minority of MRD-negative patients may still relapse.[65-68] Feedback from clinical experts suggested that there was no additional mortality risk for these patients compared with the general population. As such, patients in the 'Cure' state are assumed have age- and sex-matched general population mortality (based on UK life tables) and accrue the utility of the general population.[39]

For the base case analysis, it is assumed that all patients receiving VenAZA or VenLDAC who are in the 'Remission' health state after 2 years (27 model cycles) are cured and thus transition to the 'Cure' health state. Alternative timepoints (2.5 and 3 years) have been explored in scenario analyses. Cure assumptions were included in the previous NICE TAs for gilteritinib (TA642) and gemtuzumab ozogamicin (TA545).[76, 102] However, in contrast to the model presented in this submission, these cure assumptions were applied to all patients who remained alive after a certain timepoint, whereas only patients in 'Remission' were permitted to transition to the 'Cure' state in this model.

As discussed in Section B.1.3, current non-intensive treatments are not used with curative intent in clinical practice, and therefore it is not clinically plausible to include a cure assumption for patients receiving AZA and LDAC in the model.[3, 50] Venetoclax on the other hand has an innovative mechanism of action that can drive sustained deep remission in combination with these therapies,[104] as shown by the significantly higher proportion of patients treated with VenAZA achieving sustained deep remissions compared to AZA alone (Section B.2.5). In addition, only a small proportion of patients in the AZA (3.5% of patients) and LDAC (0.9% of patients) arms were in the 'Remission' health state at 2 years. Therefore, it is assumed that patients in the AZA and LDAC arms cannot transition to the cure state, irrespective of whether these patients are in the 'Remission' health state after 2 years.

B.3.3.6 Discontinuation

Patients receiving active treatment in the model are assumed to be at risk of treatment discontinuation. The rate at which patients discontinue treatment is dependent on treatment arm and is determined by fully parametric time on treatment curves. In the same manner as for time-to-PD/relapse (see Section B.3.3.4), six standard parametric survival functions were explored.

Time on treatment is modelled independently of the model health states, with the model containing functionality to prevent time on treatment from surpassing OS. Once patients have discontinued treatment, they are assumed to move on to subsequent treatment, and receive the costs of subsequent treatment until death or the modelled time horizon has been reached (See section B.3.5.1).

For patients treated with VenAZA and AZA in the 20–30% blast count cohort, and patients treated with VenAZA in the >30% blast count cohort, the log-normal distribution was selected as it provided the lowest AIC/BIC for extrapolating time on treatment, whilst also providing a reasonable fit to the data.

For patients treated with VenLDAC in the >30% blast count cohort the log-normal distribution was selected. Whilst the Gompertz curve provided the lowest AIC/BIC values for extrapolating time on treatment in patients in the VenLDAC arm; however, due to the implausible mean time on treatment, it was deemed an inappropriate survival curve. The log-logistic distribution provided the next lowest AIC/BIC values; however, similar to the Gompertz distribution, an inappropriate mean time on treatment of 59.1 months was predicted. The log-normal distribution provided the next lowest AIC/BIC values, whilst offering a more conservative estimate of the mean time on treatment.

For patients treated with LDAC in the >30% blast count cohort the log-normal distribution was selected. The generalised gamma curve provided the lowest AIC/BIC values for extrapolating time on treatment in patients in the LDAC arm; however, due to the implausible mean time on treatment of 8.6 months, it was deemed an inappropriate survival curve. The log-normal distribution provided the next lowest AIC/BIC values whilst also offering the more conservative mean time on treatment.

A summary of the selected base case extrapolation methods for patients treatment arm is presented in Table 57.

Table 57: Summary of discontinuation data sources and base-case extrapolation approach

Treatment arm	Extrapolation methods	Data sources
20–30% blast count cohort		
VenAZA	Log-normal	VIALE-A trial[83]
AZA	Log-normal	
>30% blast count cohort		
VenAZA	Log-normal	VIALE-A trial[83]
VenLDAC	Log-normal	VIALE-C trial[84]
LDAC	Log-normal	

Abbreviations: AZA: azacitidine; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax.

Parametric curve goodness-of-fit statistics and extrapolated curves for time-on-treatment are presented below.

Figure 106: Extrapolated time-on-treatment curves for patients treated with VenAZA in the 20–30% blast count cohort

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 107: Extrapolated time-on-treatment curves for patients treated with AZA in the 20–30% blast count cohort

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion.

Figure 108: Extrapolated time-on-treatment curves for patients treated with VenAZA in the >30% blast count cohort

Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; Ven: venetoclax.

Figure 109: Extrapolated time-on-treatment curves for patients treated with VenLDAC in the >30% blast count cohort

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine; Ven: venetoclax.

Figure 110: Extrapolated time-on-treatment curves for patients treated with LDAC in the >30% blast count cohort

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LDAC: low dose cytarabine.

B.3.3.7 Adverse events

AEs were evaluated for the modelled cohort at treatment initiation (Cycle 1). AEs included in the model were those of Grade 3 or 4 severity that occurred in >5% patients (see Table 58). AE frequencies were treatment-arm specific and based on the rate of AEs observed in the overall populations of the VIALE trials.[83, 84] Utility decrements and costs associated with AEs are presented in Section B.3.4.3 and Section B.3.5.3, respectively.

Table 58: Rate of AEs in the economic analysis

AE, mean (SE)	Treatment arm			
	VenAZA	AZA	VenLDAC	LDAC
Anaemia	0.261 (0.026)	0.201 (0.033)	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropaenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]
Leucocytosis	[redacted]	[redacted]	[redacted]	[redacted]
Leukopaenia	0.205 (0.024)	0.118 (0.027)	[redacted]	[redacted]

Neutropenia	0.420 (0.029)	0.285 (0.038)	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count Decreased	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	0.177 (0.023)	0.250 (0.036)	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	0.445 (0.030)	0.382 (0.040)	[redacted]	[redacted]
Urinary tract Infection	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; AZA: azacitidine; LDAC: low-dose cytarabine; SE: standard error; Ven: venetoclax.
Source: VIALE-A Clinical Study Report,[83] VIALE-C Clinical Study Report.[84]

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials and mapping

The VIALE trials assessed HRQoL via the EQ-5D-5L health utilities instrument.[83, 84] For use in the model, health state utility values were derived in line with the NICE reference case: pooled EQ-5D-5L scores collected in the VIALE trials were cross-walked to EQ-5D-3L utility index scores using the algorithm presented in van Hout *et al*. (2012), which is based on the UK value set by Dolan *et al*. (1997).[106, 107] Therefore, the utility values presented in Section B.3.4.4 are representative of the population of interest in UK clinical practice.

B.3.4.2 Health-related quality-of-life studies

An SLR was conducted to identify all relevant utilities in patients with AML. The SLR was performed in August 2020. In total, 16 records were identified that included primary utility data. Full details of the SLR search strategy, study selection process and the results of included studies are reported in Appendix H.

The SLR yielded no utility data for patients with AML who are ineligible for IC treated with VenAZA or VenLDAC. In line with the NICE reference case, health state utility values applied in the base case were derived from EQ-5D-5L data collected in the VIALE trials.[112] The SLR did identify one study, Wehler *et al.* (2018), describing a health state utility model, which estimated the impact of ivosidenib on HRQoL in patients with relapsed or refractory AML.[113] AE utility decrement values presented in Wehler *et al.* (2018) were applied in the base case economic analysis.[113]

B.3.4.3 Adverse reactions

Utility decrements were applied as a one off decrement during Cycle 1, to estimate the reduction in quality of life associated with short-term AEs. All AE utility decrements were sourced from Wehler *et al.* (2018).[113] This was deemed to be an appropriate source of inputs for the AE

decrement values as this study represents a recent source of utility data from a patient population similar to the population of interest in this submission. AE decrement values used in the base case economic analysis are presented in Table 59.

Table 59: AE utility decrement values

AE	Mean	SE	Source
Anaemia	0.090	0.018	Wehler *et al.* (2018)[113]
Atrial fibrillation	0.121	0.024	
Dyspnoea	0.219	0.044	
Fatigue	0.073	0.015	
Febrile neutropaenia	0.090	0.018	
Hypertension	0.020	0.004	
Hypokalaemia	0.121	0.024	
Hyponatraemia	0.121	0.024	
Hypophosphataemia	0.121	0.024	
Leucocytosis	0.090	0.018	
Leukopaenia	0.090	0.018	
Neutropaenia	0.090	0.018	
Neutrophil count decreased	0.090	0.018	
Platelet count decreased	0.090	0.018	
Pneumonia	0.218	0.044	
Pyrexia	0.110	0.022	
Sepsis	0.218	0.044	
Thrombocytopaenia	0.090	0.018	
Urinary tract infection	0.218	0.044	
White blood cell count Decreased	0.090	0.018	

Abbreviations: AE: adverse event; SE: standard error.

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utilities

EQ-5D data pooled from the VIALE-A and VIALE-C trials were used to derive health state utility values. The data were pooled to maximise overall sample sizes, thereby reducing the uncertainty in the utility estimates. EQ-5D data were collected initially on Day 1 of Cycle 1 then on Day 1 of alternating subsequent cycles (Cycle 3, Cycle 5 etc.). Data were also collected on the final visit of each patient, defined as the last assessment on or after the date of disease progression, relapse from CR + CRi, or treatment failure. The numbers of patients who provided EQ-5D scores at each cycle are presented in Table 60.

Table 60: Number of patients who provided EQ-5D scores at each treatment cycle (data pooled across VIALE-A and VIALE-C trials)

Cycle	Number of Patients

1	[redacted]
3	[redacted]
5	[redacted]
7	[redacted]
9	[redacted]
11	[redacted]
13	[redacted]
15	[redacted]
17	[redacted]
19	[redacted]
21	[redacted]
23	[redacted]
25	[redacted]
Final visit	[redacted]

Source: VIALE-A Clinical Study Report, Table 14.2 6.3.[83] VIALE-C Clinical Study Report, Table 14.2__8.3.[84]

Descriptive statistics (presented in Table 61) for the utility values were calculated using pooled patient-level EQ-5D data stratified by the following categories, corresponding to model health states:

- **EQ-5D measures for 'Non-remission':** Any EQ-5D assessments for patients in the EFS state without remission, i.e. any assessment before the date of CR + CRi
- **EQ-5D measures for 'Remission':** any EQ-5D assessments for patients in the EFS state with remission, i.e. any assessment on or after the date of CR + CRi
- **EQ-5D measures for PD/relapse:** Any EQ-5D assessment for patients in "PD" or "relapsed disease". This was defined as any assessments on or after the date of disease progression, relapse from CR + CRi, or treatment failure

Patient-level EQ-5D data from all treatment arms were used to generate utility values, with utility assumed to be health-state dependent only, not treatment-dependent.

Table 61: Descriptive statistics for EQ-5D health state utility values (data pooled across VIALE-A and VIALE-C trials)

Health state	Number of patients	Number of assessments	Mean (SD)
Before treatment	[redacted]	[redacted]	[redacted]
EFS without CR/CRi (Non-remission)	[redacted]	[redacted]	[redacted]
EFS with CR/CRi (Remission)		[redacted]	[redacted]
PD/relapse	[redacted]	[redacted]	[redacted]

The same patient could have been in multiple health states at different visits. The statistics presented here reflect the number of patients with at least one assessment with the specified health state
Abbreviations: SD: standard deviation.

Health state utility values were derived in line with the NICE reference case: pooled EQ-5D-5L scores collected in the VIALE trials were cross-walked to EQ-5D-3L utility index scores using the

algorithm presented in van Hout *et al*. (2012), which is based on the UK value set by Dolan *et al*. (1997).[106, 107]

The utility index scores were measured repeatedly over time, which resulted in correlation of observations between different time points. To account for the repeated and longitudinal nature of the data, a linear mixed-effects (LMM) regression model was developed to estimate patient utility scores with a robust variance estimator to account for correlation within patients' repeated assessments. Assuming data were missing at random, the LMM model would yield unbiased estimates of the health state utilities. The dependent variable of the model was EQ-5D utility score, and the independent variables were the health state status (EFS with CR/CRi, EFS without CR/CRi, PD/relapse). Utility values for “before treatment” were used as the reference group. In the LMM model, the patient effects were included as random effects to account for unobserved, patient-specific characteristics and multiple observations per patient. Both random intercepts and slopes were considered in the analysis.

Since utilities estimated were treatment-independent, the impact of AEs on utility estimates were considered and were adjusted for in the model. Grade 3 or 4 AEs that occurred in ≥5% in the VIALE-A and VIALE-C trials were included as covariates. Specifically, selected AEs included neutropenia (including neutropenia, neutrophil count decreased and febrile neutropenia), thrombocytopenia (including thrombocytopenia, and platelet count decreased), anaemia, leukopenia (including leukopenia and white blood cell count decreased), hypokalaemia (including hypokalaemia, hyponatraemia and hypophosphatemia), pneumonia, hypertension. The LMM regression analysis was conducted using the SAS PROC GLIMMIX procedure with an identity link function and normal error term distribution. The resulting EQ-5D health state utilities used in the base case economic analysis are presented in Table 62.

Table 62: EQ-5D health state utilities

Health state	Mean	SE	Source
Remission	[redacted]	[redacted]	Pooled VIALE-A/C data[83, 84]
Non-remission	[redacted]	[redacted]	
PD/relapse	[redacted]	[redacted]	

Abbreviations: SE: standard error.

In oncology modelling, the utility of patients is well characterised as a function of time to death, with a lower QoL expected for patients as they approach end-of-life. The majority of patients receiving AZA and LDAC in VIALE-A and VIALE-C died during the trial follow-up, with [redacted]/143 ([redacted]) of patients receiving AZA and [redacted]/68 ([redacted]) patients receiving LDAC experiencing a death event. Since patient-level EQ-5D data from all treatment arms were used to generate these utility values, any changes in the HRQoL as patients approached death are likely to have been captured and the utility values presented in Table 62 were deemed appropriate to reflect the utility of patients in these health states.

Cure utility

Based on feedback from clinical experts, patients who reside within the cure state are assumed to receive the utility of the general population. This assumption was considered plausible by clinical experts given that only patients in ‘Remission’ were permitted to transition to the ‘Cure’ state, and the difference between utility associated with remission and the utility of the general

population is small (0.74 versus 0.79). With increasing age, health utility is expected to decline. In the base case, age-dependent utilities are based on the formula outlined in Ara *et al.* (2010),[114] which calculates the utility as a function of age and sex.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An SLR was conducted to identify all relevant cost and resource use in treatment naïve patients with AML. The SLR was performed in August 2020. In total, 7 records were identified which featured relevant cost and resource use data associated with treatment naïve patients with AML. Full details of the SLR search strategy, study selection process and results are reported in Appendix H.

The following cost categories are included in the model:

- Drug acquisition costs for interventions and comparators (Section B.3.5.1)
- Costs associated with subsequent treatments (Section B.3.5.1)
- Monitoring costs for intervention and comparators (Section B.3.5.2)
- Cost of end-of-life palliative care (Section B.3.5.2)
- Costs associated with the management of AEs (Section B.3.5.3)

The economic analysis was conducted from the perspective of the NHS and PSS and therefore only included direct medical costs that would be incurred by the NHS and PSS. Cost inputs were based on the Monthly Index of Medical Specialities (MIMS),[98] Personal Social Service Research Unit (PSSRU),[115] NHS National Cost Collection 2018–19,[95] NHS National Tariff System 2016–17,[108] and electronic Market Information Tool (eMIT).[97] Relevant resource use and costs were also extracted from TA642 and TA451.[76, 94]

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition and administration costs

For drug acquisition costs for interventions and comparators, presented in Table 63, the dosing regimen and dose intensity were sourced from the VIALE-A and VIALE-C clinical study reports.[83, 84] The mean BSA of patients in the VIALE-A and VIALE-C trials was used to calculate the mean dose of AZA and LDAC, respectively (see Section B.3.3.1). Per cycle treatment acquisition costs were based on the cost per 100 mg and the total per cycle dose of each treatment. The treatment acquisition cost for venetoclax including a patient access scheme (PAS) discount of [redacted]% is also presented in Table 63.

The administration costs associated with azacitidine and LDAC treatment were derived from NHS National Tariff (2020/21).[96] Given that venetoclax is an oral therapy, it was assumed that there were no administration costs associated with venetoclax treatment.

Table 63: Treatment acquisition and administration costs for venetoclax, azacitidine and LDAC

Treatment arm	Dosing schedule[a]	Price per 100 mg (list price)	Acquisition cost per treatment cycle[b,c]		Cost per administration	Administrations per cycle	Total administration cost per treatment cycle
			List price	PAS price			
VenAZA							
Ven [Cycle 1: treatment initiation]	Orally, QD, three-day dose ramp-up: D1: 100 mg, D2: 200 mg, D3: 400 mg	£42.76	£299.34	[redacted]	£0.00	3	£0.00
Ven [Cycle 1: post treatment initiation]	400 mg, orally, QD		£4,276.29	[redacted]		25	£0.00
Ven [Subsequent cycles]	400 mg, orally, QD		£4,789.44	[redacted]		28	£0.00
AZA	(All cycles) 75 mg per m^2 BSA on days 1–7 of each cycle	£220.00[c]	£ 3,080.00[c,d]		£159.00[e]	7	£1,113.00
VenLDAC							
Ven [Cycle 1: treatment initiation]	Orally, QD, four-day dose ramp-up: D1: 100 mg, D2: 200 mg, D3: 400 mg, D4: 600 mg	£42.76	£555.88	[redacted]	£0.00	4	£0.00
Ven [Cycle 1: post treatment initiation]	600 mg, orally, QD		£6,157.85	[redacted]		24	£0.00
Ven [Subsequent cycles]	600 mg, orally, QD		£7,184.16	[redacted]		28	£0.00
LDAC	(All cycles) 20 mg per m^2 BSA on days 1–10 of each cycle	£2.64	£26.40[c,f]		£159.00[e]	10	£1,590.00

Comparators						
AZA	(All cycles) 75 mg per m^2 BSA on days 1–7 of each cycle	£220.00[c]	£3,080.00 [c,d]	£159.00[e]	7	£1,113.00
LDAC	(All cycles) 20 mg per m^2 BSA on days 1–10 of each cycle	£2.64	£26.40[c,f]	£159.00[e]	10	£1,590.00

[a]Each treatment cycle was 28 days. [b]List prices for Ven and AZA were sourced from the MIMS,[98] the list price for LDAC was sourced from the eMIT database.[28] [c]List prices were used for AZA and LDAC as it was not possible to determine PAS prices. [d]Per cycle acquisition costs based on 138.57 mg of AZA per day on days 1–7 (assuming a BSA of 1.85 m^2 and wastage of the remainder of the vial) [e]National Tariff 2020/21;[96] SB12Z; deliver simple parenteral chemotherapy at first attendance. [f]Per cycle acquisition costs based on 36.02 mg of LDAC per day on days 1–10 (assuming a BSA of 1.80m^2 and wastage of the remainder of the vial).
Abbreviations: AZA: azacitidine; BSA: body surface area; D: day; LDAC: low-dose cytarabine; eMIT: Drugs and Pharmaceutical Electronic Market Information Tool; MIMS: Monthly Index of Medical Supplies; PAS: patient access scheme; QD: once daily; Ven: venetoclax.

Dose intensity

Data from the VIALE trials and clinical expert opinion indicate that neutropenia and infections are common in patients with AML, and as such patients often receive antimicrobial prophylaxis using agents that are strong/moderate CYP3A inhibitors.[4, 83, 84] The use of concomitant strong/moderate CYP3A inhibitors requires dose reduction of venetoclax.[93] Furthermore, many patients who respond to VenAZA also require dose modifications to manage cytopenia, which include delays between treatment cycles or within-cycle reduction of the venetoclax dosing days.[93] In order to account for dose reductions and interruptions in each treatment arm a relative dose intensity was applied to each component of treatment.

In the base case analysis, dose intensity estimates for VenLDAC, AZA and LDAC were based on the post-hoc analyses of VIALE-A and VIALE-C trial data (measured against the expected licenced dose of venetoclax, as reported in Table 33 and Table 40), which were subsequently validated by clinical experts as being reflective of dose intensities seen in UK clinical practice (Table 64).[4, 83, 84] The dose intensity of the Ven component of VenAZA was based on expert clinical opinion as clinicians indicated that the dose intensity for the Ven component of VenAZA in VIALE-A ([redacted]%) was higher than expected, and a dose intensity of 50% was more in line with clinical practice in the UK.[4] Evidence suggests that there is no dose-response relationship associated with Ven dose reductions when CYP3A inhibitors are prescribed concomitantly, so it was assumed that the efficacy of VenAZA remains unchanged in the model.[116]

Given the uncertainty surrounding the assumption for Ven dose intensity, and the subsequent impact on cost-effectiveness, a scenario analysis assessed the impact of increasing the dose intensity to 60% for venetoclax, in line with the dose intensity observed in the VIALE-A trial (See Section B.3.8.3).

Table 64: Treatment arm dependant dose intensity

Treatment arm	Component	Mean	SE	Source
VenAZA	Ven	0.500	0.100[a]	Clinical expert opinion
	AZA	[redacted]	[redacted]	VIALE-A[83]
VenLDAC	Ven	[redacted]	[redacted]	VIALE-C[84]
	LDAC	[redacted]	[redacted]	
AZA	AZA	[redacted]	[redacted]	VIALE-A[83]
LDAC	LDAC	[redacted]	[redacted]	VIALE-C[84]

[a]SE for the Ven component of VenAZA assumed to be 20% of the mean value.
Abbreviations: AZA: azacitidine; LDAC: low-dose cytarabine; SE: standard error; Ven: venetoclax.

Subsequent treatments

As described in Section B.3.3.6, patients receiving active treatment in the model were assumed to be at risk of treatment discontinuation. Once patients discontinued treatment, they were assumed to stop accruing the treatment-related costs and incur costs associated with subsequent treatment.

Based on expert clinical opinion, 3% of patients receive gilteritinib after receiving VenAZA and VenLDAC, with all remaining patients receiving hydroxycarbamide. Patients receiving AZA or LDAC all go on to receive hydroxycarbamide. Given the uncertainty surrounding the composition

of subsequent treatments, a scenario analysis was used to determine the impact of assuming 15% of patients receiving VenAZA and VenLDAC go on to receive subsequent gilteritinib (see Section B.3.8.3). The dosing schedule and drug acquisition and administration costs of subsequent treatments are presented in Table 65. The proportion of patients receiving subsequent treatments and the mean total cost in each first line treatment arm are presented in Table 66.

Table 65: Dosing schedule and drug acquisition and administration costs of subsequent treatments

Subsequent treatment	Dosing schedule[a]	Price/pack[b]	Pack size (mg)	Acquisition cost per cycle	Cost per administration	Administrations/ cycle	Administration cost per cycle
Gilteritinib	120 mg QD	£14,188.00	84 x 40 mg	£14,188.00	£127.00[c]	1	£127.00
HC/HU	20–30 mg per kg QD (assumed to be 25 mg per kg)	£9.59[d]	100 x 500 mg	£10.74	£127.00[c]	1	£127.00

[a]Each treatment cycle was 28 days. [b]List price for gilterinib was sourced from the MIMS,[98] the list price for HC/HU was sourced from the eMIT database.[28] [c]National Tariff 2020/21;[96] SB11Z; deliver exclusively oral chemotherapy. [d]Per cycle acquisition costs based on 1847.50 mg of HC/HU per day (assuming a weight of 73.90 kg; VIALE-A) and 1775.00 mg of HC/HU per day (assuming a weight of 71.00 kg; VIALE-C).
Abbreviations: BSA: body surface area; HC/HU: hydroxycarbamide/hydroxyurea; LDAC: low-dose cytarabine; QD: once daily.

Table 66: Subsequent treatment costs

Treatment	Proportion receiving subsequent treatment	Total cost per cycle	Weighted cost per cycle	Mean total cost	SE total cost
VenAZA					
Gilteritinib	3.0%	£14,315.00	£429.45	£563.06	£112.61
HC/HU	97.0%	£137.74	£133.61		
VenLDAC					
Gilteritinib	3.0%	£14,315.00	£429.45	£563.06	£112.61
HC/HU	97.0%	£137.74	£133.61		
AZA					
HC/HU	100.0%	£137.74	£137.74	£137.74	£27.55
LDAC					
HC/HU	100.0%	£137.74	£137.74	£137.74	£27.55

[a]All SEs were assumed to be 20% of the mean value.
Abbreviations: AZA: azacitidine; HC/HU: hydroxycarbamide/hydroxyurea; LDAC: low-dose cytarabine; SE: standard error; Ven: venetoclax.

B.3.5.2 Health-state unit costs and resource use

The mean total health state costs per cycle in the 'Remission', 'Non-remission', and PD/relapse health states are presented in Table 67. Health state resource use was assumed to be the same as that modelled in TA642, and included outpatient and emergency department visits, diagnostic procedures and tests, blood transfusion, and hospitalisations.[76]Health state costs in TA642 are reported for patients 'alive and event-free', 'alive and post-event' and 'death'.[76] The model presented within this submission adds an additional level of granularity on the 'alive and event-free' health state by stratifying patients by achievement of CR + CRi. The corresponding health states in TA642 which were used to heath state costs for this model are presented in Table 67.

Patients in the cure health state were assumed to have a health state cost which was the same as patients in the remission health state, in alignment with the approach taken in TA642.[76]

One-off costs were incurred by those entering the 'Death' health state to capture the additional resource use associated with end of life care. The cost incurred by patients entering the 'Death' health state was derived from data presented by Georghio and Bardsley (2014).[117]

Table 67: Mean total health state costs used in the base case economic analysis

Health state	Corresponding Health State in TA642	Justification	Mean total costs per cycle (SE)[a]	Source
Non-remission[b]	EFS without HSCT (Azacitidine/LDAC)	Deemed to appropriately represent patients in the non-remission health state	£2,432.86 (484.77)	TA642[d,f,76]
Remission[b]	EFS with HSCT/Long-term survivors	Deemed to appropriately represent the lower resource use associated with achieving CR + CRi for patients in the remission health state	£163.55 (32.71)	
PD/relapse[b]	Post-event without HSCT	Deemed to appropriately represent the resource use associated with patients in the PD/relapse health state	£2,638.21 (527.64)	
Cure[b]	NA		£163.55 (32.71)	Assumption
Death[c]			£2,603.40 (520.68)	Georghio and Bardsley (2014)[e,f,117]

[a]All SEs were assumed to be 20% of the mean value.[b] Per cycle cost. [c] One-off cost. [d] Costs from TA642 were inflated from 2018 to 2019 costs using an inflation factor of 1.023. [e]Costs from Georghiou and Bardsley were adjusted to a 28-day cost be multiplying by a ratio of 28/90. Costs were inflated from 2011 costs to 2020 costs using an inflation factor of 1.148. [f] All inflation factors were calculated using data from the PSSRU Unit Costs of Health and Social Care (2019).[115]
Abbreviations: NA: not applicable; SE: standard error.

B.3.5.3 Adverse reaction unit costs and resource use

AE management costs were modelled via a one-off cost, applied on treatment initiation (Cycle 1). The mean cost of each AE (per occurrence) in the economic analysis is presented in Table 68.

Table 68: AE costs used in the economic analysis

AE	Mean cost per occurrence (SE)[a]	Currency code	Source
Anaemia[f]	£350.04 (70.01)	SA08G, SA08H, SA08J	NHS National Cost Collection 2018–19[b,95]
Atrial Fibrillation[f]	£731.32 (146.26)	EB07A, EB07B, EB07C, EB07D, EB07E	
Dyspnoea[f]	£459.87 (91.97)	DZ27N, DZ27Q, DZ27R, DZ27S, DZ27T, DZ27U	
Fatigue[f]	£303.57 (60.71)	KC05J, KC05K, KC05L, KC05M, KC05N	
Febrile Neutropenia[f]	£350.04 (70.01)	SA08G, SA08H, SA08J	
Hypertension[g]	£331.74 (66.35)	EB04Z	
Hypokalaemia[h]	£303.57 (60.71)	PA48B	
Hyponatremia[h]	£1,026.11 (205.22)	PA48B	NHS National Tariff System 2016–17[c,e,108]
Hypophosphatemia	£827.96 (165.59)	NA	NICE TA451[d,f,94]
Leucocytosis[h]	£1,026.11 (205.22)	PA48B	NHS National Tariff System 2016–17[c,e,108]
Leukopenia[h]	£1,026.11 (205.22)	PA48B	
Neutropenia[f]	£350.04 (70.01)	SA08G, SA08H, SA08J	NHS National Cost Collection 2018–19[95]
Neutrophil Count Decreased[h]	£1,026.11 (205.22)	PA48B	NHS National Tariff System 2016–17[c,e,108]
Platelet Count Decreased[h]	£1,026.11 (205.22)	PA48B	
Pneumonia[h]	£179.96 (35.99)	WF01A	NHS National Cost Collection 2018–19[b,95]
Pyrexia[f]	£496.78 (99.36)	WJ07B, WJ07C, WJ07D	
Sepsis[f]	£298.68 (59.74)	WJ06G, WJ06H, WJ06J	
Thrombocytopenia[f]	£322.01 (64.40)	SA12G, SA12H, SA12J, SA12K	
Urinary Tract Infection[f]	£278.85 (55.77)	LA04P, LA04Q, LA04R, LA04S	
White Blood Cell Count Decreased[h]	£1,026.11 (205.22)	PA48B	NHS National Tariff System 2016–17[b,d,108]

[a]All SEs were assumed to be 20% of the mean value.
[b]All costs from the National Cost Collection 2018/19 inflated from 2019 costs to 2020 costs using an inflation factor of 1.022.
[c]Costs from the National Tariff System 2016/17 were inflated from 2017 to 2020 using an inflation factor of 1.058.
[d]All costs from NICE TA451 were inflated from 2011 to 2020 costs using an inflation factor of 1.148.

[e]All inflation factors were calculated using data from the PSSRU Unit Costs of Health and Social Care (2020).[115] [f]Costs derived using a weighted average of day cases. [g]Costs derived using a consultant led. [h]Costs derived using a non-elective.
Abbreviations: AE: adverse event; NA: not applicable; SE: standard error.

B.3.5.4 Miscellaneous unit costs and resource use

There were no further unit costs or resource use included in the model.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

A summary of the variables applied in the base case economic analysis is presented in Table 57.

Table 69: Summary of variables applied in the cost effectiveness analysis

Variable	Inputs	Reference to section in submission
Model settings		
Discount rate costs, %	3.5	Section B.3.2.2
Discount rate benefits, %	3.5	
Time horizon	Lifetime (40 years)	
Perspective	NHS and PSS	
Patient characteristics		
Starting age, years (SE)	[redacted]	Section B.3.3.1
Proportion male	[redacted]	
Weight, kg	[redacted]	
Height, m	[redacted]	
BSA, m/kg	[redacted]	
Clinical inputs		
Initial health state occupancy	Rate of CR + CRi from the relevant cohorts of the VIALE-A and VIALE-C	Section B.3.3.2
Health state transitions	Time-to-event data from the relevant cohorts of the VIALE-A and VIALE-C: • Non-remission to PD/relapse: Time-to-PD • Non-remission to Death: Time-to-death • Remission to PD/relapse: Time-to-relapse • Remission to Death: Time-to-death • PD/relapse to Death: Time-to-death	Sections B.3.3.3 and B.3.3.4
Discontinuation	Time on treatment data from the relevant cohorts of the VIALE-A and VIALE-C	Section B.3.3.6
AEs	AE frequencies from the overall populations of the VIALE trials	Section B.3.3.7
Utility inputs		

Complete remission, mean (SE)	[redacted]		Section B.3.4.4
Stable disease, mean (SE)	[redacted]		
Relapse, mean (SE)	[redacted]		
Cure	*Same as general population* (sourced from Ara et al. [2010][114])		
AE decrement	*Various* (sourced from Wehler *et al* [2018][113])		
Cost inputs			
Intervention and comparator costs per cycle	**Acquisition**	**Administration**	Section B.3.5.1
VenAZA			
Venetoclax: Cycle 1	List: £4,575.63 PAS: [redacted]	£0.00	Section B.3.5.1
Venetoclax: Subsequent cycles	List: £4,789.44 PAS: [redacted]		
Azacitidine: All cycles	£3,080.00	£1,113.00	
VenLDAC			
Venetoclax: Cycle 1	List: £6,713.73 PAS: [redacted]	£0.00	Section B.3.5.1
Venetoclax: Subsequent cycles	List: £7,184.16 PAS: [redacted]		
LDAC: All cycles	£26.40	£1,590.00	
AZA			
Azacitidine: All cycles	£3,080.00	£1,113.00	Section B.3.5.1
LDAC			
LDAC: All cycles	£26.40	£1,590.00	Section B.3.5.1
Health state costs per cycle, mean (SE)			
Non-remission	£2,432.86 (484.77)		Section B.3.5.2
Remission	£163.55 (32.71)		
PD/Relapse	£2,638.21 (527.64)		
Cure	£163.55 (32.71)		
Death	£2,603.40 (520.68)		
Adverse events	*Various*		Section B.3.5.3

Abbreviations: AE: adverse event; AZA: azacitidine; CR: complete remission; CRi: complete remission with incomplete haematological recovery; EFS: event-free survival; LDAC: low-dose cytarabine; NHS: National Health Service; OS: overall survival; PSS: personal social services; SE: standard error; Ven: venetoclax.

B.3.6.2 Assumptions

A list of the key assumptions made in the base case economic analysis and their justifications is provided in Table 70 Where appropriate, the exploration of the potential impact of these assumptions via scenario analyses is noted.

Table 70: Key assumptions of the cost effectiveness analysis

Parameter	Assumption	Justification	Addressed in scenario analysis
Health states	At the start of each cycle, patients were redistributed among the five health states, with death being the absorbing state.	In the treatment pathway, patients are assumed to enter in either the 'Remission' state or in the 'Non-remission' state. In VIALE-A, the time to response ranged between 1.3 and 2.8 months, therefore it was deemed acceptable to assume patients could achieve response from baseline.	Deterministic sensitivity analysis were conducted investigating a ±20% variation on the proportion of patients entering 'Remission' at baseline.
Efficacy	Time-to-PD/relapse and time-to-death were separately estimated for VenAZA, VenLDAC, AZA and LDAC. Time-to-PD/relapse was stratified into patients who have achieved 'Non-remission' and 'Remission'; time-to-death was stratified into patients in 'Non-remission', 'Remission' and 'PD/relapse'.	Extensive analyses have been undertaken to identify appropriate and conservative survival curves describing VenAZA, VenLDAC, AZA and LDAC efficacy, with reference to the guidance from NICE DSU and Bagust and Beale.[111, 118] The approach and identified survival extrapolations have been validated by clinical and health economic experts.	Scenario analyses are conducted to address the uncertainty around the survival extrapolations by applying alternative assumptions around extrapolations.
Cure	Patients receiving VenAZA or VenLDAC who remained in remission at year 2 were considered to be cured; these patients were associated with a risk of death equivalent to the general population mortality. After year 2, all patients receiving VenAZA or VenLDAC who were in remission were assumed to incur health state costs the same as patients in remission and utilities associated with the general population.	Cure assumptions were included in the previous NICE TAs for gilteritinib (TA642) and gemtuzumab ozogamicin (TA545).[76, 102] However, in contrast to the model presented in this submission, these cure assumptions were applied to all patients who remained alive after a certain timepoint, whereas only patients in 'Remission' were permitted to transition to the 'Cure' state in this model. Clinical experts consulted explained that patients treated with venetoclax combinations who achieve a sustained deep remission have the potential to achieve long-term survivorship, whereby their	A scenario analysis was conducted exploring alternative cure points.

Parameter	Assumption	Justification	Addressed in scenario analysis
		outcomes are in line with those of the general population. VenAZA provides deep and durable complete remission rates (CR/CRi with/without MRD) that have historically only been associated with IC.[32, 56, 69, 70] Depth and duration of remission has been positively correlated with length of survival in patients who receive IC. [31, 71] Furthermore, rate of relapse after two years is low (based on experience of patients treated with IC).[1,34, 72-75] This feedback corroborates the plateau in the Kaplan-Meier curves which is observed at ~24 months of treatment for VenAZA (20-30%, >30%) and VenLDAC (>30%) (B.2.6 and B.2.8, respectively). Additionally, clinicians noted that the proportion of patients in CR/CRi for whom cure is assumed at year 2 will be enriched with those with no/low MRD, but this would not account for all who achieve cure.[65, 66] As discussed in Section B.1.3, current non-intensive treatments are not used with curative intent in clinical practice, and therefore it is not clinically plausible to include a cure assumption for patients receiving AZA and LDAC in the model. In addition, only a small proportion of patients in the AZA (3.5% of patients) and LDAC (0.9% of patients) arms were in the 'Remission' health state at 2 years. Therefore, it is assumed that patients in the AZA and LDAC arms cannot transition to the cure state, irrespective of whether these patients are in the 'Remission' health state after 2 years.	
Treatment duration	The time on treatment was based on patient-level data observed in the VIALE-A and VIALE-C trials.	In clinical practice, treatment cessation may be caused be a loss of clinical benefit or may be	A scenario analysis was conducted to explore

Parameter	Assumption	Justification	Addressed in scenario analysis
		related to other factors, such as adverse events. Clinicians may choose to cease treatment on progression or treat beyond progression. Hence, the proportion of patients on initial or subsequent treatment lines is based on the time on treatment, as opposed to time to discontinuation.	alternative extrapolations for time on treatment.
Subsequent treatment	Subsequent pharmacological treatments after the initial treatment were considered in the model for patients who had either progressive or relapsed disease to reflect the natural treatment course patients experienced. It was assumed that 3% of patients receive gilteritinib after receiving VenAZA and only 1% after VenLDAC, with all remaining patients receiving HC/HU. Effectiveness of subsequent treatments on efficacy are assumed to be reflected in the clinical trial results and therefore only costs were considered.	The subsequent therapies considered in the model were informed by clinical experts are in line with the treatment pathway in the UK.	Deterministic sensitivity analysis was conducted to explore the impact of a ±20% variation on subsequent treatment costs in each arm.
Treatment costs	Patients were treated based on the treatment schedule specified in the VIALE-A trial and VIALE-C trial.	Treatment duration and costs from the VIALE-A and VIALE-C trials are assumed to be representative of UK clinical practice.	Deterministic sensitivity analysis was conducted to explore the impact of a ±20% variation on treatment costs.
Dose intensity	Patients in the VenAZA treatment arm have a dose intensity of 0.500 applied to the Ven component of treatment based on clinical expert opinion. All other dose intensity values are based on data recorded during the VIALE-A and VIALE-C trials.	Clinician feedback indicated that the dose intensity for the Ven component of VenAZA in VIALE-A ([redacted]%) was higher than expected, and a dose intensity of 50% was more in line with clinical practice in the UK.[4] For VenLDAC, AZA and LDAC, the dose intensities calculated in the post-hoc analyses of the VIALE-A and VIALE-C trials were deemed reflective of the dose intensity observed UK clinical practice, and therefore these values were used in the base case analysis.[4]	A scenario analysis was conducted exploring an alternative dose intensity of 60% for the Ven component of VenAZA, in line with the dose intensity observed in the VIALE-A trial.
Medical and AE costs	All patients incur one-time terminal care costs before death.	Patients are assumed to incur different medical costs for each health state, with increasing cost for health states requiring additional medical care.	Deterministic sensitivity analysis was conducted to explore the impact of a ±20%

Parameter	Assumption	Justification	Addressed in scenario analysis
	The model considered medical costs including hospitalisation, blood transfusion and other monitoring costs associated with each health state (i.e., non-remission, remission, progressive disease/relapse and cure) and terminal care costs. All patients incur one-time terminal care costs in the cycle of death. Costs of grades 3 or 4 AEs were considered in the model. Only AEs with a prevalence rate greater than 5% in any of the arms were considered. AE costs were added as one-time costs in the model for all treatment arms.	The cost of death and adverse events are reflective of the burden of care on the NHS, with only the key AEs selected for application in the model.	variation on health state costs, cost of terminal care and AE costs.
AE utility decrements	The model considered the utility decrements associated with grade 3/4 AEs with a prevalence greater than 5%. AE utility decrements were added as one-time utility decrements in the model for all treatment arms.	The quality-of-life associated with adverse events are reflective of the burden of disease on patients, with only the key AEs selected for application in the model.	Deterministic sensitivity analysis was conducted to explore the impact of a ±20% variation on AE utility decrements.

Abbreviations: AE: adverse event; AZA: azacitidine; DSU: Decision Support Unit; HC/HU: hydroxycarbamide/hydroxyurea; LDAC: low-dose cytarabine; NICE: National Institute for Health and Care Excellence; PD: progressive disease; Ven: venetoclax.

B.3.7 *Base-case results*

Base case results for the cost-effectiveness analysis are presented in the following subsections for both patients in the 20–30% blast count and >30% blast count populations. Base case results are presented as follows:

- PAS price of venetoclax only (AZA/LDAC remain at list price) versus list price of all comparators (AZA and LDAC)

The Evidence Review Group (ERG) will undertake similar comparisons using the confidential discounted prices for AZA and share these with the appraisal committee.

As discussed in Section B.2.12, venetoclax should be considered as an end-of-life treatment for [redacted], given that (a) these patients have a short life expectancy, normally less than 2 years and (b) there is sufficient evidence to indicate that the venetoclax offers an extension to life of at least an additional 3 months, compared with current NHS treatment. Therefore, the higher willingness-to-pay threshold of £50,000 per QALY gained applies to these populations.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

20–30% blast cell count cohort

The base case deterministic cost-effectiveness results for patients in the 20–30% blast cell count cohort are provided with venetoclax PAS price in Table 71. Compared to AZA, VenAZA was associated with an increased number of life years (2.609) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for VenAZA versus AZA in the 20–30% blast cell count subgroup was £38,866.

>30% blast cell count cohort

The base case deterministic cost-effectiveness results for patients in the >30% blast cell count cohort are provided with venetoclax PAS price in Table 72, respectively. Compared to LDAC, VenAZA was associated with an increased number of life years (2.926) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for VenAZA versus LDAC in the >30% blast cell count subgroup was £39,449.

Compared to LDAC, VenLDAC was associated with an increased number of life years (1.606) and QALYs gained ([redacted]), but also higher total costs ([redacted]). In the base case analysis the ICER for VenLDAC versus LDAC in the >30% blast cell count subgroup was £31,291. Therefore, the base case ICERs for all comparisons investigated fall below a £50,000 per QALYs willingness-to-pay threshold and VenAZA and VenLDAC can be considered a cost-effective use of NHS resources.

Table 71: Base-case results for 20–30% blasts at Ven PAS price (deterministic)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER inc. (£/QALY)
AZA	£103,749	1.833	1.139	-	-	-	-
VenAZA	[redacted]	4.442	[redacted]	[redacted]	2.609	[redacted]	£38,866

[a] Undiscounted.
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; PAS: patient access scheme; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 72: Base-case results for >30% blasts at Ven PAS price (deterministic)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
VenAZA versus LDAC							
LDAC	£33,828	0.839	0.523				
VenAZA	[redacted]	3.765	[redacted]	[redacted]	2.926	[redacted]	£39,449
VenLDAC versus LDAC							
LDAC	£33,617	0.832	0.518				
VenLDAC	[redacted]	2.438	[redacted]	[redacted]	1.606	[redacted]	£31,291

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; LYG, life years gained; QALYs, quality-adjusted life years; Ven: venetoclax.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 1,000 iterations, in order to assess the impact of the uncertainty in costs and outcomes with respect to the model results. For inputs which did not have a standard error value, a variation of ±20% of the mean value was used in the PSA. A full summary of the PSA inputs used is provided in Appendix J.

20–30% blast cell count subgroup

The base case probabilistic results for patients in the 20–30% blast cell count subgroup are provided with venetoclax at PAS price in Table 73. Based on this analysis, the probability that VenAZA is cost-effective versus AZA in the 20-30% blasts subgroup is estimated to be 82.6% at a willingness-to-pay threshold of £50,000 per QALY.

Table 73: Base-case results for 20–30% blasts at Ven PAS price (probabilistic)

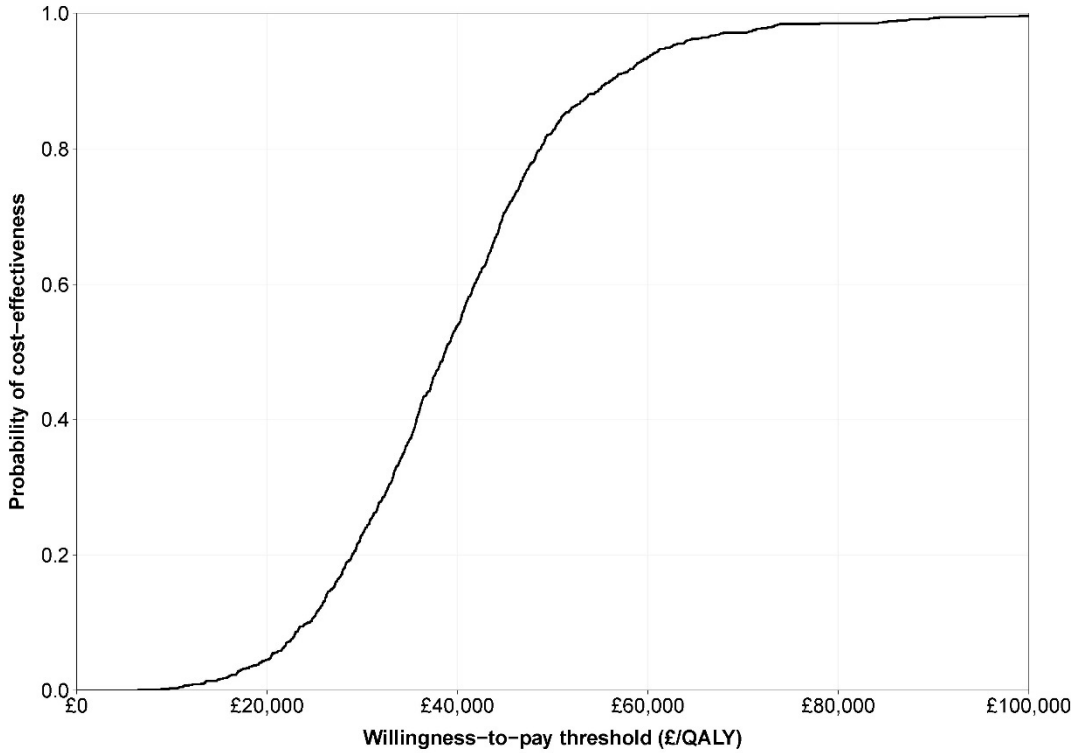
Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
AZA	£106,833	2.017	1.216				
VenAZA	[redacted]	4.469	[redacted]	[redacted]	2.452	[redacted]	£39,758

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; PAS: patient access scheme; QALYs, quality-adjusted life years; Ven: venetoclax.

Figure 111: Scatter plot of probabilistic results on the cost-effectiveness plane for 20–30% blasts at venetoclax PAS price

Abbreviations: PAS: patient access scheme; QALYs, quality-adjusted life years.

Figure 112: Cost-effectiveness acceptability curves for 20–30% blasts at venetoclax PAS price



Abbreviations: PAS: patient access scheme; QALYs, quality-adjusted life years.

>30% blast cell count subgroup

The base case probabilistic results for patients in the >30% blast cell count subgroup are provided with venetoclax at PAS price in Table 74. In the >30% blasts subgroup, the probability that VenAZA is cost-effective versus LDAC is estimated to be 90.4% and for VenLDAC versus LDAC it is estimated to be 86.1% at a willingness-to-pay threshold of £50,000 per QALY.

Table 74: Base-case results for >30% blasts at venetoclax PAS price (probabilistic)

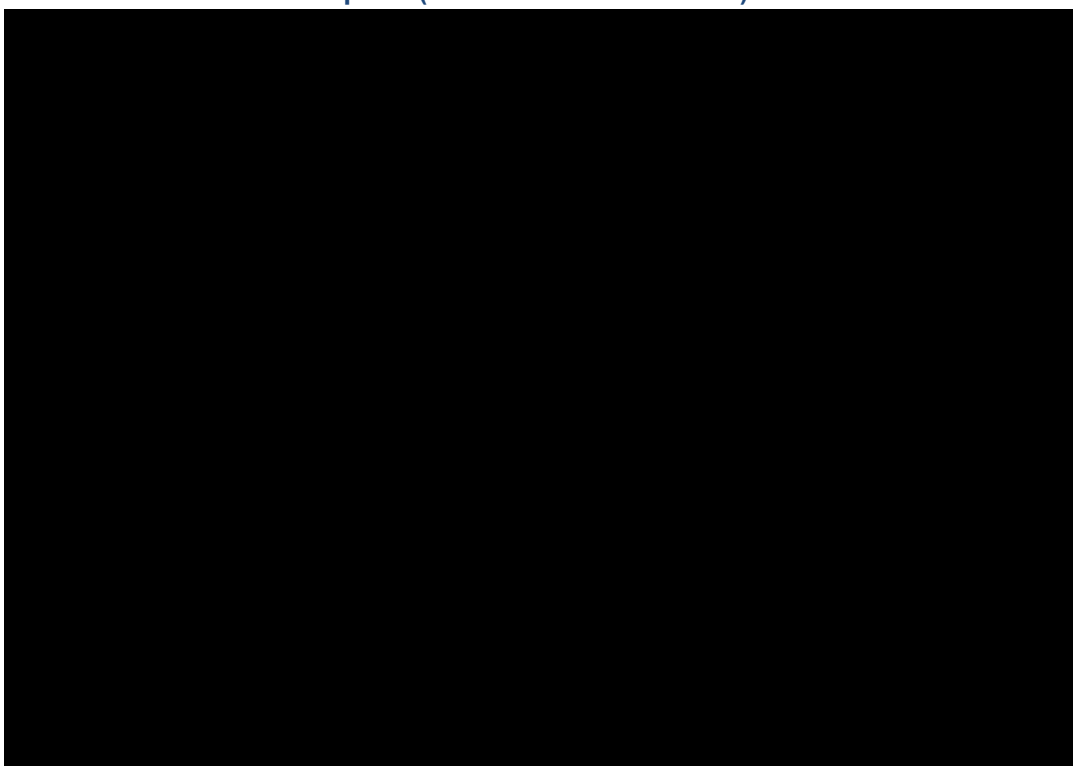
Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
VenAZA versus LDAC							
LDAC	£35,782	0.908	0.559				
VenAZA	[redacted]	3.730	[redacted]	[redacted]	2.822	[redacted]	£40,329
VenLDAC versus LDAC							
LDAC	£35,478	0.898	0.553				
VenLDAC	[redacted]	2.331	[redacted]	[redacted]	1.433	[redacted]	£36,319

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; LYG, life years gained; QALYs, quality-adjusted life years; Ven: venetoclax.

Figure 113: Scatter plot of probabilistic results on the cost-effectiveness plane for >30% blasts at venetoclax PAS price (VenAZA versus LDAC)

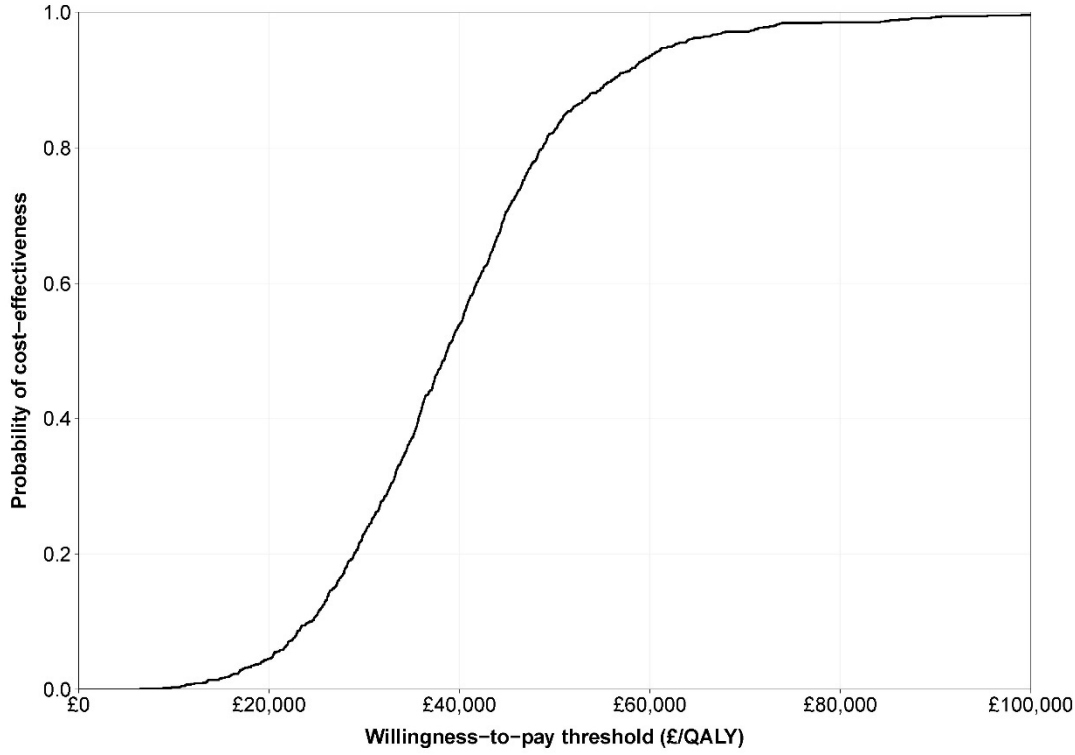
Abbreviations: PAS: patient access scheme; QALYs, quality-adjusted life years.

Figure 114: Scatter plot of probabilistic results on the cost-effectiveness plane for >30% blasts at venetoclax PAS price (VenLDAC versus LDAC)



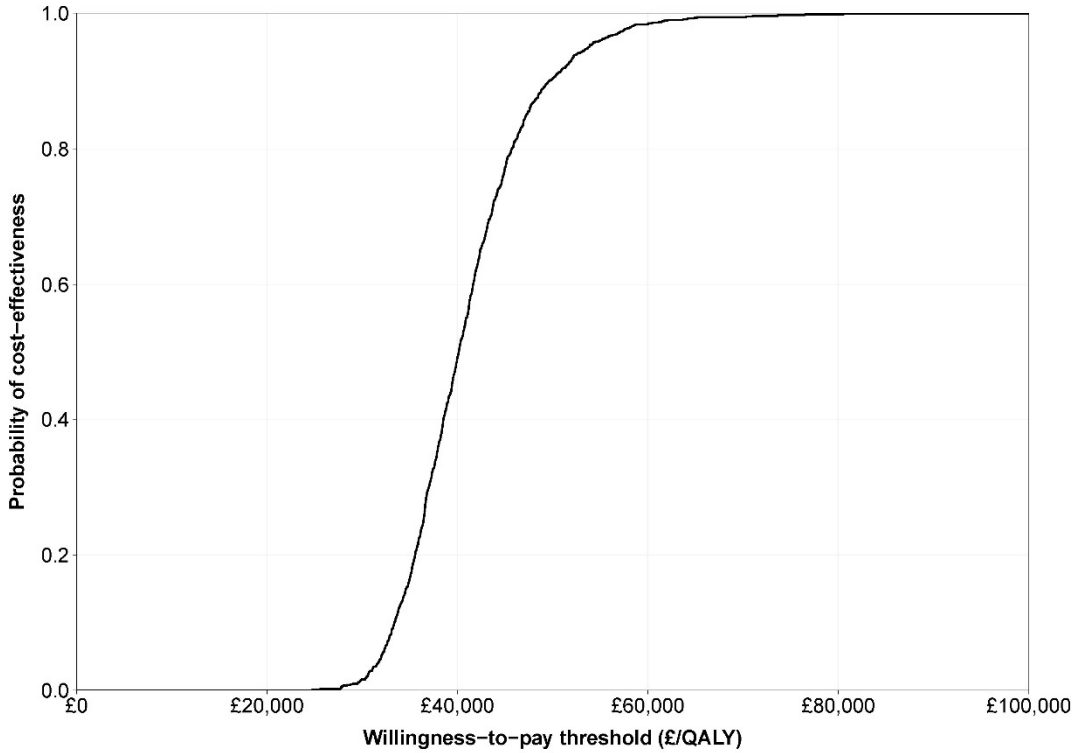
Abbreviations: PAS: patient access scheme; QALYs, quality-adjusted life years.

Figure 115: Cost-effectiveness acceptability curves for >30% blasts at venetoclax PAS price (VenAZA versus LDAC)



Abbreviations: PAS: patient access scheme; QALYs, quality-adjusted life years.

Figure 116: Cost-effectiveness acceptability curves for >30% blasts at venetoclax PAS price (VenAZA versus LDAC)



Abbreviations: PAS: patient access scheme; QALYs, quality-adjusted life years.

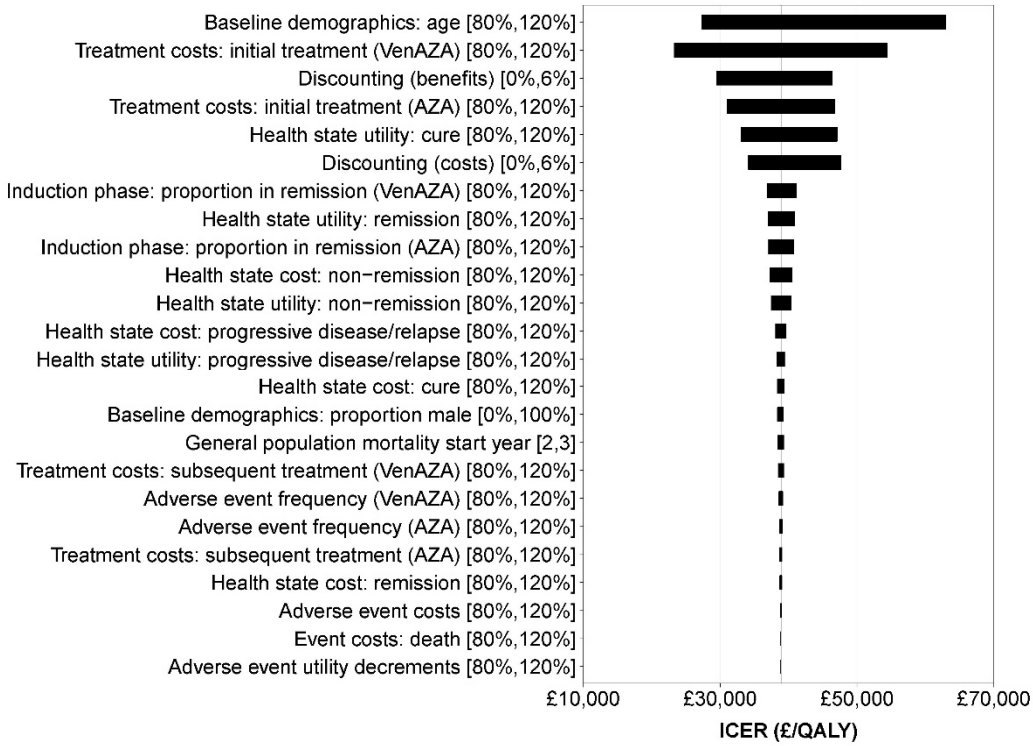
B.3.8.2 Deterministic sensitivity analysis

20–30% blast cell count cohort

Figure 117 presents the tornado plot for the one-way deterministic sensitivity analysis (DSA) for VenAZA versus AZA at PAS price. A summary of the DSA inputs is provided in Appendix J.

The parameter with the greatest impact on the ICER for VenAZA versus AZA are related to treatment costs, with patient age also being influential.

Figure 117: Tornado plot (ICER) of deterministic sensitivity analysis: VenAZA versus AZA for 20–30% blasts at venetoclax PAS price

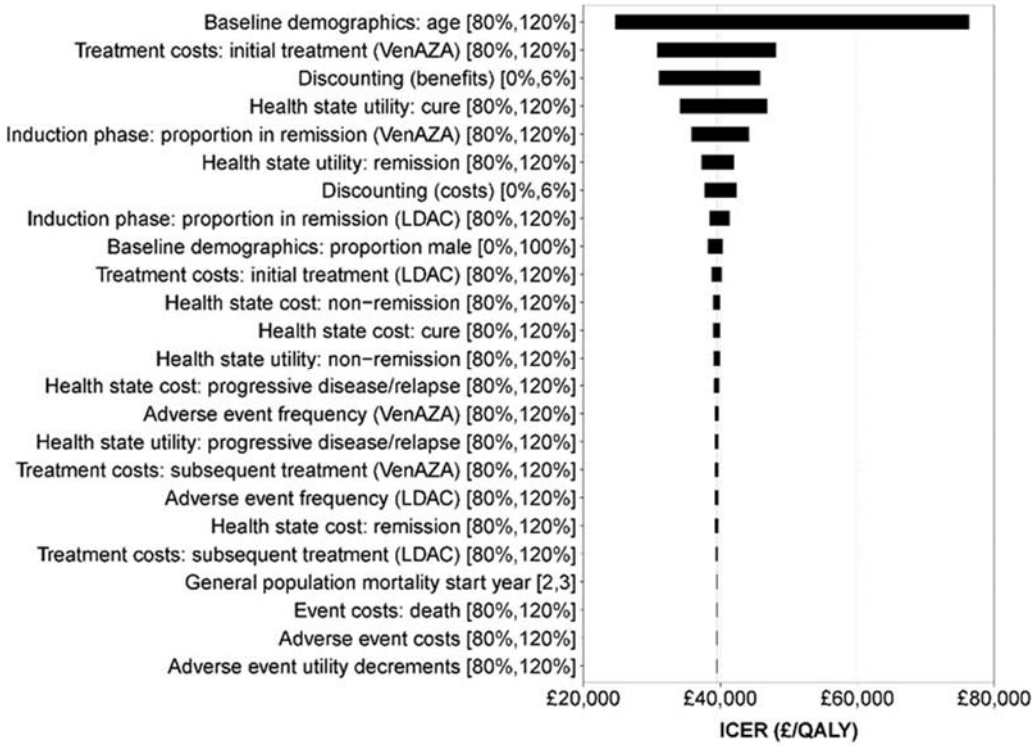


Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; Ven: venetoclax.

>30% blast cell count subgroup

Figure 118 presents the tornado plot for the one-way deterministic sensitivity analysis (DSA) for VenAZA versus LDAC at PAS price. The parameter with the greatest impact on the ICER for VenAZA versus LDAC are patient age, with treatment cost also being influential.

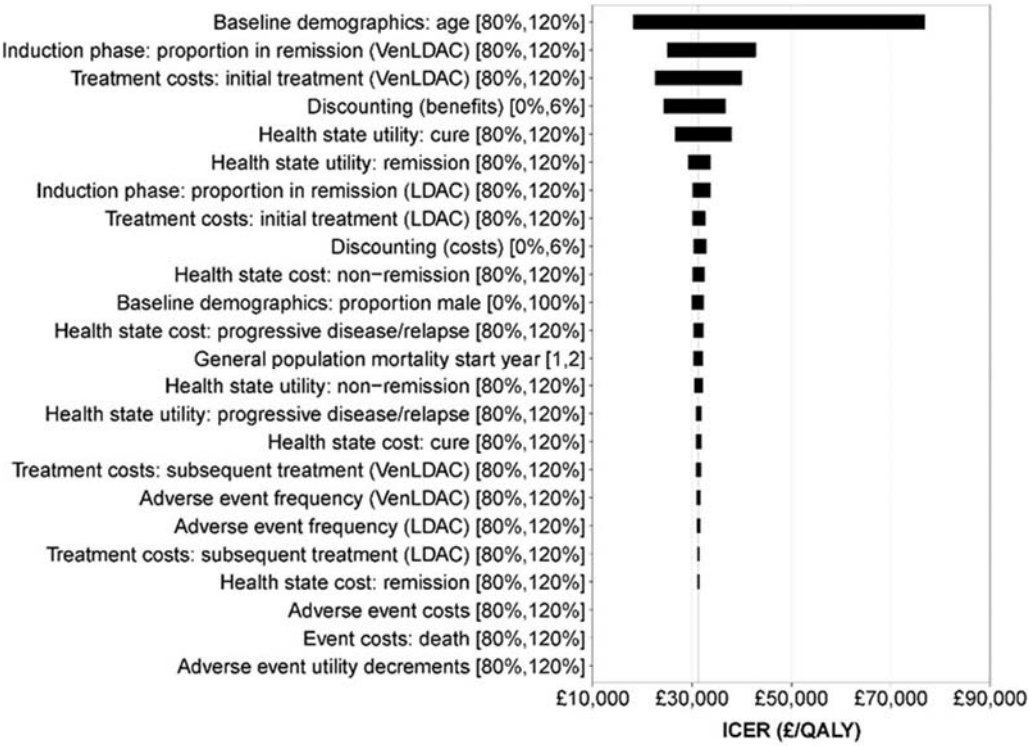
Figure 118: Tornado plot (ICER) of deterministic sensitivity analysis: VenAZA versus LDAC for >30% blasts at venetoclax PAS price



Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; LDAC: low dose cytarabine; QALYs, quality-adjusted life years; Ven: venetoclax

Figure 119 presents the tornado plot for the one-way deterministic sensitivity analysis (DSA) for VenLDAC versus LDAC at PAS price. The parameter with the greatest impact on the ICER for VenLDAC versus LDAC are patient age, with proportion of patients in remission also being influential.

Figure 119: Tornado plot (ICER) of deterministic sensitivity analysis: VenLDAC versus LDAC for >30% blasts at venetoclax PAS price



Abbreviations: ICER, incremental cost-effectiveness ratio; LDAC: low dose cytarabine; QALYs, quality-adjusted life years; Ven: venetoclax

B.3.8.3 Scenario analysis

Alternative extrapolation of survival

Survival modelling using long-term extrapolation of parametric functions is subject to uncertainty despite efforts to robustly and transparently provide survival curves that best represent patients in clinical practice. In order to assess the impact of alternative parametric fittings on cost-effectiveness, survival curves described in Section B.3.3.4 have been applied within the model as scenario analyses.

Results of the scenario analysis are presented in Table 75 to Table 77. In the 20-30% blasts subgroup, predicted ICERs ranged between dominates (exponential distribution for modelling time to death from progressive disease/relapse in the VenAZA) to £45,789 (Gompertz distribution for modelling time to death from progressive disease/relapse in the VenAZA arm). In the >30% blasts subgroup for VenAZA versus LDAC, predicted ICERs ranged between £27,042 (Gompertz distribution for modelling time to death from progressive disease/relapse in the LDAC arm) to £41,283 (log-logistic distribution for modelling time to relapse from remission in the VenAZA arm). In the >30% blasts subgroup for VenLDAC versus LDAC, predicted ICERs ranged between dominates (Gompertz distribution for modelling time to death from progressive disease/relapse in the LDAC arm) to £43,425 (Gompertz distribution for modelling time to death from progressive disease/relapse in the VenLDAC arm). In all scenarios, the ICERs ranged below the £50,000 per QALY threshold.

Table 75: Results from scenario analyses – impact of alternative extrapolations in the 20–30% VenAZA vs AZA comparison

Outcome	Arm	Distribution	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Time-to-PD from 'Non-remission'	VenAZA	Exponential	[redacted]	[redacted]	£38,887
		Generalised gamma	[redacted]	[redacted]	£38,852
		Gompertz	[redacted]	[redacted]	£38,827
		Log-logistic	[redacted]	[redacted]	£38,875
		Log-normal	[redacted]	[redacted]	£38,866
		Weibull	[redacted]	[redacted]	£38,877
	AZA	Exponential	[redacted]	[redacted]	£38,969
		Generalised gamma	[redacted]	[redacted]	£38,989
		Gompertz	[redacted]	[redacted]	£38,866
		Log-logistic	[redacted]	[redacted]	£39,055
		Log-normal	[redacted]	[redacted]	£39,086
		Weibull	[redacted]	[redacted]	£38,925
Time-to-relapse from remission	VenAZA	Exponential	[redacted]	[redacted]	£33,527
		Generalised gamma	[redacted]	[redacted]	£42,219
		Gompertz	[redacted]	[redacted]	£46,883
		Log-logistic	[redacted]	[redacted]	£40,184
		Log-normal	[redacted]	[redacted]	£38,866
		Weibull	[redacted]	[redacted]	£44,231
	AZA	Exponential	[redacted]	[redacted]	£40,395
		Generalised gamma	[redacted]	[redacted]	£38,817
		Gompertz	[redacted]	[redacted]	£38,629
		Log-logistic	[redacted]	[redacted]	£39,919
		Log-normal	[redacted]	[redacted]	£39,844
		Weibull	[redacted]	[redacted]	£38,866
Time-to-death from non-remission	VenAZA	Exponential	[redacted]	[redacted]	£38,805
		Generalised gamma	[redacted]	[redacted]	£38,810
		Gompertz	[redacted]	[redacted]	£38,805
		Log-logistic	[redacted]	[redacted]	£38,990
		Log-normal	[redacted]	[redacted]	£38,866
		Weibull	[redacted]	[redacted]	£38,805
	AZA	Exponential	[redacted]	[redacted]	£39,051
		Generalised gamma	[redacted]	[redacted]	£39,189
		Gompertz	[redacted]	[redacted]	£38,888
		Log-logistic	[redacted]	[redacted]	£38,548

		Log-normal	[redacted]	[redacted]	£38,566
		Weibull	[redacted]	[redacted]	£38,866
Time-to-death from remission	VenAZA	Exponential	[redacted]	[redacted]	£42,673
		Generalised gamma	[redacted]	[redacted]	£38,866
		Gompertz	[redacted]	[redacted]	£38,222
		Log-logistic	[redacted]	[redacted]	£41,090
		Log-normal	[redacted]	[redacted]	£40,861
		Weibull	[redacted]	[redacted]	£40,986
	AZA	Exponential	[redacted]	[redacted]	£39,070
		Gompertz	[redacted]	[redacted]	£38,638
		Log-logistic	[redacted]	[redacted]	£38,858
		Log-normal	[redacted]	[redacted]	£38,866
		Weibull	[redacted]	[redacted]	£38,909
Time-to-death from PD/relapse	VenAZA	Exponential	[redacted]	[redacted]	Dominates
		Generalised gamma	[redacted]	[redacted]	£45,910
		Gompertz	[redacted]	[redacted]	£51,254
		Log-logistic	[redacted]	[redacted]	£39,212
		Log-normal	[redacted]	[redacted]	£38,866
		Weibull	[redacted]	[redacted]	£4,786
	AZA	Exponential	[redacted]	[redacted]	£41,720
		Gompertz	[redacted]	[redacted]	£26,705
		Log-logistic	[redacted]	[redacted]	£37,590
		Log-normal	[redacted]	[redacted]	£38,866
		Weibull	[redacted]	[redacted]	£41,801
Time-on-treatment	VenAZA	Exponential	[redacted]	[redacted]	£21,082
		Generalised gamma	[redacted]	[redacted]	£40,870
		Gompertz	[redacted]	[redacted]	£41,256
		Log-logistic	[redacted]	[redacted]	£40,480
		Log-normal	[redacted]	[redacted]	£38,866
		Weibull	[redacted]	[redacted]	£25,050
	AZA	Exponential	[redacted]	[redacted]	£38,866
		Generalised gamma	[redacted]	[redacted]	£34,710
		Gompertz	[redacted]	[redacted]	£27,826
		Log-logistic	[redacted]	[redacted]	£24,390
		Log-normal	[redacted]	[redacted]	£24,284
		Weibull	[redacted]	[redacted]	£35,433

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax.

Table 76: Results from scenario analyses – impact of alternative extrapolations in the >30% VenAZA vs LDAC comparison

Outcome	Arm	Distribution	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Time-to-PD from 'Non-remission'	VenAZA	Exponential	[redacted]	[redacted]	£39,449
		Generalised gamma	[redacted]	[redacted]	£39,383
		Gompertz	[redacted]	[redacted]	£39,371
		Log-logistic	[redacted]	[redacted]	£39,416
		Log-normal	[redacted]	[redacted]	£39,440
		Weibull	[redacted]	[redacted]	£39,396
	LDAC	Exponential	[redacted]	[redacted]	£39,322
		Generalised gamma	[redacted]	[redacted]	£39,449
		Gompertz	[redacted]	[redacted]	£39,522
		Log-logistic	[redacted]	[redacted]	£39,350
		Log-normal	[redacted]	[redacted]	£39,347
		Weibull	[redacted]	[redacted]	£39,346
Time-to-relapse from remission	VenAZA	Exponential	[redacted]	[redacted]	£41,802
		Generalised gamma	[redacted]	[redacted]	£39,449
		Gompertz	[redacted]	[redacted]	£41,395
		Log-logistic	[redacted]	[redacted]	£46,451
		Log-normal	[redacted]	[redacted]	£44,997
		Weibull	[redacted]	[redacted]	£46,419
	LDAC	Exponential	[redacted]	[redacted]	£39,449
		Gompertz	[redacted]	[redacted]	£40,262
		Log-logistic	[redacted]	[redacted]	£39,676
		Log-normal	[redacted]	[redacted]	£39,660
		Weibull	[redacted]	[redacted]	£39,465
Time-to-death from non-remission	VenAZA	Exponential	[redacted]	[redacted]	£38,542
		Generalised gamma	[redacted]	[redacted]	£40,666
		Gompertz	[redacted]	[redacted]	£41,708
		Log-logistic	[redacted]	[redacted]	£39,696
		Log-normal	[redacted]	[redacted]	£39,449
		Weibull	[redacted]	[redacted]	£38,816
	LDAC	Exponential	[redacted]	[redacted]	£39,428
		Generalised gamma	[redacted]	[redacted]	£39,140
		Gompertz	[redacted]	[redacted]	£39,351
		Log-logistic	[redacted]	[redacted]	£39,444
		Log-normal	[redacted]	[redacted]	£39,449

		Weibull	[redacted]	[redacted]	£39,430
Time-to-death from remission	VenAZA	Exponential	[redacted]	[redacted]	£40,713
		Generalised gamma	[redacted]	[redacted]	£39,073
		Gompertz	[redacted]	[redacted]	£38,940
		Log-logistic	[redacted]	[redacted]	£39,449
		Log-normal	[redacted]	[redacted]	£39,206
		Weibull	[redacted]	[redacted]	£39,499
	LDAC	Exponential	[redacted]	[redacted]	£39,449
		Generalised gamma	[redacted]	[redacted]	£39,456
		Gompertz	[redacted]	[redacted]	£39,450
		Log-logistic	[redacted]	[redacted]	£39,451
		Log-normal	[redacted]	[redacted]	£39,452
		Weibull	[redacted]	[redacted]	£39,453
Time-to-death from PD/relapse	VenAZA	Exponential	[redacted]	[redacted]	£32,407
		Generalised gamma	[redacted]	[redacted]	£40,894
		Gompertz	[redacted]	[redacted]	£33,971
		Log-logistic	[redacted]	[redacted]	£44,686
		Log-normal	[redacted]	[redacted]	£39,449
		Weibull	[redacted]	[redacted]	£32,178
	LDAC	Exponential	[redacted]	[redacted]	£41,056
		Generalised gamma	[redacted]	[redacted]	£40,286
		Gompertz	[redacted]	[redacted]	£33,039
		Log-logistic	[redacted]	[redacted]	£38,559
		Log-normal	[redacted]	[redacted]	£39,449
		Weibull	[redacted]	[redacted]	£40,824
Time on treatment	VenAZA	Exponential	[redacted]	[redacted]	£39,574
		Generalised gamma	[redacted]	[redacted]	£39,448
		Gompertz	[redacted]	[redacted]	£39,337
		Log-logistic	[redacted]	[redacted]	£39,417
		Log-normal	[redacted]	[redacted]	£39,449
		Weibull	[redacted]	[redacted]	£40,033
	LDAC	Exponential	[redacted]	[redacted]	£39,290
		Generalised gamma	[redacted]	[redacted]	£38,375
		Gompertz	[redacted]	[redacted]	£38,014
		Log-logistic	[redacted]	[redacted]	£39,430
		Log-normal	[redacted]	[redacted]	£39,449
		Weibull	[redacted]	[redacted]	£39,290

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax.

Table 77: Results from scenario analyses – impact of alternative extrapolations in the >30% VenLDAC vs LDAC comparison

Outcome	Arm	Distribution	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Time-to-PD from 'Non-remission'	VenLDAC	Exponential	[redacted]	[redacted]	£31,406
		Generalised gamma	[redacted]	[redacted]	£31,478
		Gompertz	[redacted]	[redacted]	£31,292
		Log-logistic	[redacted]	[redacted]	£31,279
		Log-normal	[redacted]	[redacted]	£31,291
		Weibull	[redacted]	[redacted]	£31,281
	LDAC	Exponential	[redacted]	[redacted]	£31,041
		Generalised gamma	[redacted]	[redacted]	£31,291
		Gompertz	[redacted]	[redacted]	£31,394
		Log-logistic	[redacted]	[redacted]	£31,174
		Log-normal	[redacted]	[redacted]	£31,131
		Weibull	[redacted]	[redacted]	£31,096
Time-to-relapse from remission	VenLDAC	Exponential	[redacted]	[redacted]	£40,088
		Generalised gamma	[redacted]	[redacted]	£31,291
		Gompertz	[redacted]	[redacted]	£32,557
		Log-logistic	[redacted]	[redacted]	£38,421
		Log-normal	[redacted]	[redacted]	£37,438
		Weibull	[redacted]	[redacted]	£39,560
	LDAC	Exponential	[redacted]	[redacted]	£31,291
		Gompertz	[redacted]	[redacted]	£32,516
		Log-logistic	[redacted]	[redacted]	£31,631
		Log-normal	[redacted]	[redacted]	£31,600
		Weibull	[redacted]	[redacted]	£31,315
Time-to-death from non-remission	VenLDAC	Exponential	[redacted]	[redacted]	£31,100
		Generalised gamma	[redacted]	[redacted]	£31,482
		Gompertz	[redacted]	[redacted]	£31,446
		Log-logistic	[redacted]	[redacted]	£31,195
		Log-normal	[redacted]	[redacted]	£31,291
		Weibull	[redacted]	[redacted]	£31,230
	LDAC	Exponential	[redacted]	[redacted]	£31,246
		Generalised gamma	[redacted]	[redacted]	£30,236
		Gompertz	[redacted]	[redacted]	£30,975

		Log-logistic	[redacted]	[redacted]	£31,271
		Log-normal	[redacted]	[redacted]	£31,291
		Weibull	[redacted]	[redacted]	£31,243
Time-to-death from remission	VenLDAC	Exponential	[redacted]	[redacted]	£28,908
		Generalised gamma	[redacted]	[redacted]	£27,801
		Gompertz	[redacted]	[redacted]	£29,283
		Log-logistic	[redacted]	[redacted]	£31,828
		Log-normal	[redacted]	[redacted]	£31,291
		Weibull	[redacted]	[redacted]	£31,883
	LDAC	Exponential	[redacted]	[redacted]	£31,291
		Generalised gamma	[redacted]	[redacted]	£31,328
		Gompertz	[redacted]	[redacted]	£31,309
		Log-logistic	[redacted]	[redacted]	£31,337
		Log-normal	[redacted]	[redacted]	£31,336
		Weibull	[redacted]	[redacted]	£31,344
Time-to-death from PD/relapse	VenLDAC	Exponential	[redacted]	[redacted]	£24,378
		Generalised gamma	[redacted]	[redacted]	£31,291
		Gompertz	[redacted]	[redacted]	£53,002
		Log-logistic	[redacted]	[redacted]	£44,383
		Log-normal	[redacted]	[redacted]	£39,193
		Weibull	[redacted]	[redacted]	£26,631
	LDAC	Exponential	[redacted]	[redacted]	£35,212
		Generalised gamma	[redacted]	[redacted]	£33,390
		Gompertz	[redacted]	[redacted]	£8,561
		Log-logistic	[redacted]	[redacted]	£28,904
		Log-normal	[redacted]	[redacted]	£31,291
		Weibull	[redacted]	[redacted]	£34,672
Time on treatment	VenLDAC	Exponential	[redacted]	[redacted]	£28,032
		Generalised gamma	[redacted]	[redacted]	£31,134
		Gompertz	[redacted]	[redacted]	£31,476
		Log-logistic	[redacted]	[redacted]	£30,568
		Log-normal	[redacted]	[redacted]	£31,291
		Weibull	[redacted]	[redacted]	£30,689
	LDAC	Exponential	[redacted]	[redacted]	£30,996
		Generalised gamma	[redacted]	[redacted]	£29,380
		Gompertz	[redacted]	[redacted]	£28,742
		Log-logistic	[redacted]	[redacted]	£31,267

		Log-normal	[redacted]	[redacted]	£31,291
		Weibull	[redacted]	[redacted]	£30,997

Abbreviations: ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax.

Alternative cure time

The uncertainty around the time in which patients in remission are assumed to be cured has been explored in scenario analyses. In the base case analysis, patients in remission at two years, whilst receiving either VenAZA or VenLDAC were assumed to be cured.

Table 78 and Table 79 present the results of the analysis exploring alternative cure points. ICERs ranged between £39,261 (2.5-year cure point; >30% blasts subgroup; VenLDAC versus LDAC) to £59,053 (3-year cure point; 20–30% blasts subgroup; VenAZA versus LDAC). When exploring the 2.5-year cure point, ICERs remained below the £50,000 per QALY threshold.

Table 78: Results from scenario analyses – impact of alternative cure points in the 20-30% VenAZA vs AZA comparison

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
2.5-year cure point	[redacted]	[redacted]	£48,262
3-year cure point	[redacted]	[redacted]	£59,053

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax.

Table 79: Results from scenario analyses – impact of alternative cure points in the >30% blast cell count cohort

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
2.5-year cure point	[redacted]	[redacted]	£46,648
3-year cure point	[redacted]	[redacted]	£55,278
VenLDAC versus LDAC			
2.5-year cure point	[redacted]	[redacted]	£39,261
3-year cure point	[redacted]	[redacted]	£48,481

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax.

Alternative dose intensity

In the base case, dose intensity for the Ven component of VenAZA was based upon clinical expert opinion. Given the uncertainty surrounding this assumption and the subsequent impact on cost-effectiveness, scenario analyses assessed the impact of increasing the dose intensity to 60% for venetoclax.

Results are presented in Table 80 and Table 81. The ICERs ranged between £41,755 (>30% blasts subgroup; VenAZA versus LDAC) to £43,027 (>30% blasts subgroup; VenAZA versus AZA). In all scenarios the ICERs remained below the £50,000 per QALY threshold.

Table 80: Results from scenario analyses – impact of alternative dose intensity in the 20–30% VenAZA vs AZA comparison

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
60% DI for Ven	[redacted]	[redacted]	£43,027

Abbreviations: AZA: azacitidine; DI: dose intensity; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax.

Table 81: Results from scenario analyses – impact of alternative dose intensity in the >30% blast cell count cohort

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
60% DI for Ven	[redacted]	[redacted]	£41,755

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax.

Alternative time on treatment

In the base case analysis, time on treatment is derived using patient-level data from VIALE-A and VIALE-C in order to extrapolate future outcomes, as described in Section B.3.3.6. During consultation, clinicians suggested that the proportion of patients remaining on treatment would be lower than what was observed during the trials and as such, sensitivity analyses were explored whereby the expected proportion of patients remaining on treatment with VenAZA and VenLDAC was reduced. In order to achieve this, an exponential distribution was applied to calculate the rate parameter required to achieve 5% and 10% of patients on treatment at two years.

Results of the scenario analysis are presented in Table 82 and Table 83. Compared to the base case, ICERs were much reduced, with some scenarios [redacted] in the 20–30% blasts subgroup. All ICERs remained below the £50,000 per QALY threshold.

Table 82: Results from scenario analyses – impact of alternative time on treatment in the 20–30% VenAZA vs AZA comparison

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
5% of patients receiving VenAZA at 2 years	[redacted]	[redacted]	Dominates
10% of patients receiving VenAZA at 2 years	[redacted]	[redacted]	£927

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax

Table 83: Results from scenario analyses – impact of alternative time on treatment in the >30% blast cell count cohort

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
5% of patients receiving VenAZA at 2 years	[redacted]	[redacted]	£21,587

10% of patients receiving VenAZA at 2 years	[redacted]	[redacted]	£27,643
VenLDAC versus LDAC			
5% of patients receiving VenLDAC at 2 years	[redacted]	[redacted]	£25,694
10% of patients receiving VenLDAC at 2 years	[redacted]	[redacted]	£35,079

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax

Alternative source of utility

In the base case analysis, patients are assumed to receive the utility of the general population. In this scenario, an alternative assumption surrounding the utility of patients whilst in the cure health state is explored whereby patients receive the same utility as is applied to patients in the remission state

The results of the scenario analysis are presented in Table 84 and Table 85. In comparison to the base case, ICERs have reduced marginally, due to the increased health state utility of patients in remission versus the age-adjusted general population. Similar to the base case, all ICERs are considered cost-effective at a willingness-to-pay threshold of £50,000 per QALY.

Table 84: Results from scenario analyses – impact of alternative utility assumption in the 20–30% VenAZA vs AZA comparison

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Patients in cure health state have same utility as patients in remission health state	[redacted]	[redacted]	£37,305

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax

Table 85: Results from scenario analyses – impact of alternative utility assumption in the >30% blast cell count cohort

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
Patients in cure health state have same utility as patients in remission health state	[redacted]	[redacted]	£30,027
VenLDAC versus LDAC			
Patients in cure health state have same utility as patients in remission health state	[redacted]	[redacted]	£24,017

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax

Alternative subsequent treatment

As outlined in Section B.3.5.1, subsequent treatment for patients receiving VenAZA and VenLDAC is comprised of 3% gilteritinib and the remainder of hydroxycarbamide based on clinical expert opinion. Given the uncertainty of the proportion of patients going on to receive subsequent gilteritinib, a scenario analysis has been explored whereby the composition of gilteritinib has been increased to 15% for both VenAZA and VenLDAC, yielding a cyclical subsequent treatment cost of £2,264.33

Results from the scenario analysis are presented in Table 86 and Table 87. Compared to the base case analysis, total costs in the VenAZA and VenLDAC arms are increased which in turn increased the ICERs. However, all ICERs remained below the £50,000 per QALY threshold.

Table 86: Results from scenario analyses – impact of alternative subsequent treatment in the 20-30% VenAZA vs AZA comparison

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
15% of patients receive gilteritinib as a subsequent treatment	[redacted]	[redacted]	£44,942

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax

Table 87: Results from scenario analyses – impact of alternative subsequent treatment in the >30% blast cell count cohort

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
15% of patients receive gilteritinib as a subsequent treatment	[redacted]	[redacted]	£42,434
VenLDAC versus LDAC			
15% of patients receive gilteritinib as a subsequent treatment	[redacted]	[redacted]	£37,946

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax

Alternative time horizon

In the base case analysis, patients are modelled over a lifetime horizon (assumed to be 40 years) in order to account for all future costs and benefits associated with patients with AML. In this scenario, the impact of reducing the time horizon to be 10 years is explored, whereby all patients with long-term survival whilst in the Cure health state is limited. It is noted that this scenario would not be considered plausible and is against recommendations laid out by NICE in the appropriate modelling of patients which state *all* future costs and benefits must be accounted for.

Results from the scenario analysis are presented in Table 88 and Table 89. As expected, all costs, QALYs and life years are reduced in comparison to the base case, resulting in an increase in the ICERs. However, all ICERs remained below the £50,000 per QALY threshold.

Table 88: Results from scenario analyses – impact of alternative time horizon in the 20-30% VenAZA vs AZA comparison

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
10-year model time horizon	[redacted]	[redacted]	£46,239

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax

Table 89: Results from scenario analyses – impact of alternative time horizon in the >30% blast cell count cohort

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
10-year model time horizon	[redacted]	[redacted]	£49,841
VenLDAC versus LDAC			
10-year model time horizon	[redacted]	[redacted]	£40,751

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax

B.3.8.4 Summary of sensitivity analyses results

The impact of uncertainty and alternative inputs/assumptions in the model were explored as part of sensitivity analyses. The results of the cost-effectiveness analysis were seen to be sensitive to changes in parameters related to the cost of treatment, patient age, and model time horizon. The values used in the base case values used for the base case analysis for these parameters are considered to represent the most suitable inputs available.

B.3.9 *Subgroup analysis*

The subgroups of patients with 20–30% blasts and >30% blasts have been considered as distinct populations in the base case cost-effectiveness analysis. No further economic subgroup analyses were conducted as part of this appraisal.

B.3.10 *Validation*

The model methodology was designed to align with NICE's preferred methods. The model was built to align with the NICE reference case, and used an NHS and PSS perspective and discount rates for cost and benefits of 3.5%. The model used a lifetime time horizon in order to capture all costs and QALY gains associated with the interventions.

Economic model verification

Quality-control procedures were undertaken to ensure the programming and physical implementation of the conceptual model was completed correctly. An independent modelling team undertook a cell-by-cell verification process facilitating a check of all input calculations, formulae and Visual Basic code. Any discrepancies were identified, discussed and corrected as required.

Validation of economic model outputs versus clinical trial outcomes

In order to validate the economic model approach, survival curve model inputs and model assumptions, economic model outputs were compared against the observed clinical trial outcomes. This approach ensured that the most appropriate survival curves were used in the economic model and also acted as a check to ensure that the economic model had been implemented correctly.

Predicted model outcomes generally reflected EFS and OS for the 20–30% blast subgroup of VIALE-A (as shown in Figure 120 and Figure 121, respectively). The economic model slightly underpredicted EFS throughout the modelled period. However this underprediction was greater in the VenAZA arm than the AZA arm. OS outcomes were replicated with greater accuracy. Predicted model outcomes accurately reflected EFS and OS for the ≥30% blast subgroup of VIALE-C in the VenLDAC arm, but were slightly overestimated in the LDAC arm (as shown in Figure 122 and Figure 123, respectively). Based on this evidence, modelled outputs are broadly reflective of the observed clinical trial outcomes, with any discrepancies in prediction favouring the control arms (LDAC and AZA). A comparison of clinical outcomes (6-,12- and 24-month survival for EFS and OS) predicted by the model versus the VIALE-A and VIALE-C trials is presented in Appendix J.

Figure 120: Validation of the model output against the Kaplan–Meier of observed EFS for the 20–30% blasts subgroup of the VIALE-A trial

Abbreviations: AZA: azacitidine; EFS: event-free survival; KM: Kaplan–Meier; Ven: venetoclax.

Figure 121: Validation of the model output against the Kaplan–Meier of observed OS for the 20–30% blasts subgroup of the VIALE-A trial

Abbreviations: AZA: azacitidine; KM: Kaplan–Meier; OS: overall survival; Ven: venetoclax.

Figure 122: Validation of the model output against the Kaplan–Meier of observed EFS from the >30% blasts subgroup in the VIALE-C trial

Abbreviations: EFS: event-free survival; LDAC: low dose cytarabine KM: Kaplan–Meier; Ven: venetoclax.

Figure 123: Validation of the model output against the Kaplan–Meier of observed OS from the >30% blasts subgroup in the VIALE-C trial

Abbreviations: LDAC: low dose cytarabine KM: Kaplan–Meier; OS: overall survival; Ven: venetoclax.

Validation of economic model outputs against clinical practice

In order to validate the economic model approach against clinical practice, predicted model outcomes were compared to real-world data from the HMRN. Data for patients treated with AZA in the 20–30% blasts subgroup from the HMRN were compared to predicted model outcomes (as shown in Table 90).[3] Validation against the >30% blasts subgroup was not possible due to a lack of data in the sufficient subgroup from the HMRN. Predicted EFS for AZA in the model was generally consistent with EFS from the HMRN. In terms of OS, the model appears to overestimate OS for AZA for both short-term and long-term predictions compared to the real-world data from the HRMN. Modelled outputs are broadly reflective of outcomes in clinical practice, with any discrepancies in prediction likely favouring the control arms.

Table 90: Validation of the model output against HMRN data for AZA in patients with 20–30% blasts

Outcome	Source	6-month survival, % (95% CI)	12-month survival, % (95% CI)	24-month survival, % (95% CI)
EFS	HMRN	27.0 (14.1–41.8)	5.4 (1.0–15.9)	NA
	Model	[redacted]	[redacted]	[redacted]
OS	HMRN	35.1 (20.4–50.3)	10.8 (3.4–23.1)	4.1 (0.4–15.7)
	Model	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; CI: confidence interval; EFS: event-free survival; HMRN: haematological malignancy research network; NA: not applicable; OS: overall survival.

Validation of economic model outputs against clinical expert opinion

Clinician opinion was used to conceptualise the economic model wherever possible, in order to ensure face validity of model structure, inputs and assumptions. Clinicians were supportive of the possibility of cure in this patient population but highlighted that this was not possible with current therapies. Further, clinicians considered cure to be related to remission, where patients who are in remission for a sustained period are more likely to be considered cured. The economic model was designed in line with this expert opinion, as discussed in Section B.3.3.5. The model predicts [redacted]% of patients receiving VenAZA in the 20–30% blasts cohort to be cured, whilst [redacted]% and [redacted]% of patients receiving VenAZA and VenLDAC, respectively, are predicted to be cured in the >30% blasts cohort. As current non-intensive treatments are not used with curative intent in

clinical practice, it was not deemed clinically plausible to include a cure assumption for patients receiving AZA and LDAC in the model. This is reflected in the model outputs by the very low proportion of patients who would hypothetically transition into the cure health states from the AZA or LDAC treatment arms, if this were permitted ([redacted]% of patients receiving AZA in the 20–30% blasts cohort and [redacted]% of patients receiving LDAC in the >30% blasts cohort).

Comparison of modelled outcomes between 'Non-remission' and 'Remission' states

The economic model reflects clinical expert opinion that outcomes differ greatly between those patients who achieve remission and those who do not achieve remission. As shown in Figure 124 to Figure 126, PD/relapse-free survival (without censoring for death events that occurred prior to PD or relapse) was considerably higher for patients in 'Remission' compared with patients in 'Non-remission'.

Figure 124: Validation of the model output for 'Non-remission' and 'Remission' patients from the 20–30% blasts cohort (VenAZA and AZA)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 125: Validation of the model output for 'Non-remission' and 'Remission' patients from the >30% blasts cohort (VenAZA and AZA [not included in the base case analysis])

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 126: Validation of the model output for 'Non-remission' and 'Remission' patients from the >30% blasts cohort (VenLDAC and LDAC)

Abbreviations: LDAC: low-dose cytarabine; Ven: venetoclax.

B.3.11 *Interpretation and conclusions of economic evidence*

Summary of cost-effectiveness evidence

The cost-effectiveness of VenAZA and VenLDAC for the treatment of [redacted] was evaluated in this submission against the current SoC (AZA or LDAC). In the deterministic base-case analysis, VenAZA demonstrated substantial incremental QALY gains versus both AZA in the 20–30% blast cell count subpopulation, and LDAC in the >30% blast cell count subpopulation. VenLDAC also demonstrated a substantial incremental QALY gains versus LDAC in the >30% blast cell count subpopulation. This demonstrates that venetoclax combinations offer a step change in treatment for patients.

The base-case results in the 20–30% blast cell count subpopulation show that VenAZA is associated with total QALYs of [redacted] compared with [redacted] for patients treated with AZA (an incremental QALY gain of [redacted]), resulting in and ICER of £38,866.. The base case results in the >30% blast cell count subpopulation show that VenAZA is associated with total QALYs of [redacted] compared with [redacted] for patients treated with LDAC (an incremental QALY gain of [redacted], which results in an ICER of £39,449. In the >30% blast cell count subpopulation VenLDAC is associated with total QALYs of [redacted] compared with [redacted] for patients treated with LDAC (an incremental QALY gain of [redacted], which results in an ICER of £31,291. This demonstrates that venetoclax combinations versus all comparators accumulate substantially more QALYs, but higher costs.

The PSA analyses demonstrated that the probability that VenAZA is cost-effective versus AZA in the 20-30% blasts subgroup is estimated to be [redacted]% at a willingness-to-pay threshold of £50,000 per QALY. Similarly, In the >30% blasts subgroup, the probability that VenAZA is cost-effective versus LDAC is estimated to be [redacted]% and for VenLDAC versus LDAC it is estimated to be [redacted]% at a willingness-to-pay threshold of £50,000 per QALY.

The DSA results identified a small number of key influential parameters (treatment costs, patient age, and time horizon) with the model being largely robust to uncertainty in the majority of parameters. Scenario analyses conducted to address sources of uncertainty in the model (extrapolations, cure time point, dose intensity, time-on-treatment, utilities) demonstrated that whilst there was variation in the ICER, the cost-effectiveness conclusions remain the same and

the vast majority of ICERs are considered cost-effective at a willingness-to-pay threshold of £50,000 per QALY.

Overall, the base case ICERs for all comparisons investigated fall below a £50,000 per QALYs willingness-to-pay threshold and VenAZA and VenLDAC can be considered a cost-effective use of NHS resources.

Strengths

The clinical effectiveness evidence presented in this submission has been derived from an SLR of clinical trials investigating the efficacy and safety of a variety of treatment options, including venetoclax combinations, for the treatment of AML in treatment naïve patients who are ineligible for IC. Results from the VIALE-A and VIALE-C trials have demonstrated that VenAZA and VenLDAC were associated with improved EFS, OS and rate of CR +CRi compared with AZA or LDAC, respectively. This translates to an increase in QALYs gained for venetoclax in all comparisons considered. The model was built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizon to capture fully all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5%.

Limitations

A key limitation of the clinical evidence base was the lack of a head-to-head comparison for VenAZA to LDAC, and to address this a propensity score analysis was conducted. In this comparison, VenAZA was found to be associated with significantly longer OS and EFS compared to LDAC. Additionally, VIALE-C did not meet its primary endpoint, with no significant difference observed in OS at the planned primary analysis. However, at the time of the primary analysis, there was greater censoring of patients in the VenLDAC arm than the LDAC arm, because more patients had not yet reached median OS. Results from a subsequent unplanned analysis with an additional 6 months of follow-up (data cut off: 15th August 2019) demonstrated a significant difference in OS between the VenLDAC arm and the LDAC arm.

Finally, due to the restriction of AZA for use in patients with 20–30% blast count, the decision problem necessitated blast-restricted comparisons (VenAZA versus AZA in 20–30% blasts; VenAZA versus LDAC in >30% blasts; VenLDAC versus LDAC in >30% blasts). However, VIALE-A and VIALE-C were not designed to detect differences between the blast restricted subgroups (blast count at baseline was not a stratification factor), and this is therefore an area of uncertainty.

Conclusion

There is an unmet clinical need within clinical practice for an effective and tolerable treatment option for treatment naïve patients with AML who are ineligible for IC, which can offer deep and durable remission and thereby improve long-term outcomes for patients, with the potential for a cure in some patients. It is expected that clinicians will use VenAZA or VenLDAC as an alternative to AZA or LDAC alone. Based on the evidence presented in this submission, the use of VenAZA and VenLDAC can be considered a cost-effective use of NHS resources.

B.4 References

1. National Institute of Health and Care Excellence (NICE). Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia [TA218]. Available at: https://www.nice.org.uk/guidance/ta218 [Last accessed: 18th August 2020].
2. National Institute of Health and Care Excellence (NICE). Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [TA399]. Available at: https://www.nice.org.uk/guidance/ta399 [Last accessed: 18th August 2020].
3. AbbVie. Data on File. Haematological Malignancy Research Network: Clinical Management, Outcome and Resource Utilisation of Acute Myeloid Leukaemia Audit Report v9. 2020. .
4. AbbVie. Data on File. Clinical expert opinion.
5. National Institute of Health and Care Excellence (NICE). [TA10478] Final Scope. Available at. https://www.nice.org.uk/guidance/gid-ta10478/documents/final-scope [Last accessed: 27th November 2020].
6. Plati J, Bucur O, Khosravi-Far R. Apoptotic cell signaling in cancer progression and therapy. Integr Biol (Camb) 2011;3:279-96.
7. Daniel C, Mato AR. BCL-2 as a therapeutic target in chronic lymphocytic leukemia. Clin Adv Hematol Oncol. 2017;15:210-218.
8. Adams JM, Cory S. The Bcl-2 apoptotic switch in cancer development and therapy. Oncogene 2007;26:1324-1337.
9. Fulda S, Gorman AM, Hori O, et al. Cellular Stress Responses: Cell Survival and Cell Death. International Journal of Cell Biology 2010;2010:214074.
10. Venditti A, Del Poeta G, Maurillo L, et al. Combined analysis of bcl-2 and MDR1 proteins in 256 cases of acute myeloid leukemia. Haematologica 2004;89:934-9.
11. Pan R, Hogdal LJ, Benito JM, et al. Selective BCL-2 Inhibition by ABT-199 Causes On-Target Cell Death in Acute Myeloid Leukemia. Cancer Discovery 2014;4:362-375.
12. Leverson JD, Sampath D, Souers AJ, et al. Found in Translation: How Preclinical Research Is Guiding the Clinical Development of the BCL2-Selective Inhibitor Venetoclax. Cancer discovery 2017;7:1376-1393.
13. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013;19:202-8.
14. Bogenberger JM, Delman D, Hansen N, et al. Ex vivo activity of BCL-2 family inhibitors ABT-199 and ABT-737 combined with 5-azacytidine in myeloid malignancies. Leukemia & lymphoma 2015;56:226-229.
15. Nguyen LXT, Troadec E, Kalvala A, et al. The Bcl-2 inhibitor venetoclax inhibits Nrf2 antioxidant pathway activation induced by hypomethylating agents in AML. J Cell Physiol 2019;234:14040-14049.
16. Cojocari D, Jin S, Purkal JJ, et al. 5-Azacytidine Induces NOXA and PUMA Expression to Prime AML Cells for Venetoclax-Mediated Apoptosis. Blood 2018;132:2644-2644.
17. Niu X, Zhao J, Ma J, et al. Binding of Released Bim to Mcl-1 is a Mechanism of Intrinsic Resistance to ABT-199 which can be Overcome by Combination with Daunorubicin or Cytarabine in AML Cells. Clin Cancer Res 2016;22:4440-51.
18. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 2019;133:7-17.
19. Wei AH, Strickland SA, Jr., Hou JZ, et al. Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study. J Clin Oncol 2019;37:1277-1284.
20. Kumar CC. Genetic abnormalities and challenges in the treatment of acute myeloid leukemia. Genes & cancer 2011;2:95-107.
21. De Kouchkovsky I, Abdul-Hay M. 'Acute myeloid leukemia: a comprehensive review and 2016 update'. Blood cancer journal 2016;6:e441-e441.

22. National Cancer Institute. Adult Acute Myeloid Leukemia Treatment. Available at: https://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq [Last accessed: September 2020].
23. Sakata H, Nakao A, Matsuda K, et al. Acute leukemia presenting as bone pain with normal white blood cell count. Acute Med Surg 2014;1:249.
24. Aplastic Anemia & MDS Foundation. Acute Myeloid Leukemia. Available at. https://www.aamds.org/diseases/acute-myeloid-leukemia-aml [Last accessed September 2020].
25. Boucher NA, Johnson KS, LeBlanc TW. Acute Leukemia Patients' Needs: Qualitative Findings and Opportunities for Early Palliative Care. J Pain Symptom Manage 2018;55:433-439.
26. Leunis A, Redekop WK, Uyl-de Groot CA, et al. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. European Journal of Haematology 2014;93:198-206.
27. Lowe JR, Yu Y, Wolf S, et al. A Cohort Study of Patient-Reported Outcomes and Healthcare Utilization in Acute Myeloid Leukemia Patients Receiving Active Cancer Therapy in the Last Six Months of Life. J Palliat Med 2018;21:592-597.
28. Mahmoud D, Skikne BS, Kucmin-Bemelmans I, et al. Overall Economic Burden of Total Treatment Costs in Acute Myeloid Leukemia throughout the Course of the Disease. Blood 2012;120:3614-3614.
29. Heiblig M, Le Jeune C, Elhamri M, et al. Treatment patterns and comparative effectiveness in elderly acute myeloid leukemia patients (age 70 years or older): the Lyon-university hospital experience. Leuk Lymphoma 2017;58:110-117.
30. Daver N, Liu Dumlao T, Ravandi F, et al. Effect of NPM1 and FLT3 mutations on the outcomes of elderly patients with acute myeloid leukemia receiving standard chemotherapy. Clinical lymphoma, myeloma & leukemia 2013;13:435-440.
31. Estey EH. Acute myeloid leukemia: 2019 update on risk-stratification and management. Am J Hematol 2018;93:1267-1291.
32. Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. New England Journal of Medicine 2015;373:1136-1152.
33. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 2012;30:2670-7.
34. Bloomfield CD, Estey E, Pleyer L, et al. Time to repeal and replace response criteria for acute myeloid leukemia? Blood Reviews 2018;32:416-425.
35. Licht JD, Sternberg DW. The molecular pathology of acute myeloid leukemia. Hematology Am Soc Hematol Educ Program 2005:137-42.
36. Cancer Research UK. Acute Myeloid Leukaemia (AML) Statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml [Last accessed: September 2020].
37. National Organization for Rare Disease. Acute Myeloid Leukemia. Available at: https://rarediseases.org/rare-diseases/acute-myeloid-leukemia/. Last accessed: March 2021.
38. Office for National Statistics. Cancer registration statistics, England Statistical bulletins. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/previousReleases [Last accessed: September 2020].
39. Public Health Wales. Cancer incidence in Wales 2001–2017. Available at: http://www.wcisu.wales.nhs.uk/cancer-incidence-in-wales [Last accessed: September 2020].
40. Public Health Scotland. Cancer Statistics. Available at: https://www.isdscotland.org/Health-topics/cancer/cancer-Statistics/ [Last accessed: September 2020].

41. National Cancer Intelligence Network Trends in incidence and outcome for haematological cancers in England: 2001–2010, Public Health England. Available at: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/haematological_cancers/. Last accessed: March 2021.
42. Deschler B, Ihorst G, Platzbecker U, et al. Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. Haematologica 2013;98:208-16.
43. Djunic I, Virijevic M, Novkovic A, et al. Comorbidity as a risk factor for overall survival and decision criteria for intensity of chemotherapy in elderly patients with acute myeloid leukemia. Med Oncol 2012;29:1077-81.
44. Etienne A, Esterni B, Charbonnier A, et al. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. Cancer 2007;109:1376-83.
45. Giles FJ, Borthakur G, Ravandi F, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. Br J Haematol 2007;136:624-7.
46. Klepin HD, Geiger AM, Tooze JA, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood 2013;121:4287-94.
47. Sherman AE, Motyckova G, Fega KR, et al. Geriatric assessment in older patients with acute myeloid leukemia: a retrospective study of associated treatment and outcomes. Leuk Res 2013;37:998-1003.
48. Pettit K, Odenike O. Defining and Treating Older Adults with Acute Myeloid Leukemia Who Are Ineligible for Intensive Therapies. Front Oncol 2015;5:280.
49. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 2010;28:562-9.
50. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015;126:291-299.
51. NHS. Acute Myeloid Leukaemia, Treatment. Available at: https://www.nhs.uk/conditions/acute-myeloid-leukaemia/treatment/ [Last accessed: September 2020].
52. Szende A, Schaefer C, Goss TF, et al. Valuation of transfusion-free living in MDS: results of health utility interviews with patients. Health Qual Life Outcomes 2009;7:81.
53. Abel GA, Efficace F, Buckstein RJ, et al. Prospective international validation of the Quality of Life in Myelodysplasia Scale (QUALMS). Haematologica 2016;101:781-8.
54. Bui CN, Marshall T, Kamalakar R, et al. Transfusion Requirements and Hospitalization during First Line Treatment Among Newly Diagnosed Acute Myeloid Leukemia Patients Who Were Ineligible for Intensive Chemotherapy. Blood 2018;132:4849-4849.
55. Grover S, Rina K, Malhotra P, et al. Correlates of Positive Aspects of Caregiving Among Family Caregivers of Patients with Acute Myeloblastic Leukaemia. Indian J Hematol Blood Transfus 2018;34:612-617.
56. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424-447.
57. Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2020;31:697-712.
58. O'Donnell MR, Tallman MS, Abboud CN, et al. Acute Myeloid Leukemia, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017;15:926-957.

59. Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010;115:453-474.
60. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-2405.
61. Agarwal SK, Mangal N, Menon RM, et al. Response Rates as Predictors of Overall Survival: A Meta-Analysis of Acute Myeloid Leukemia Trials. Journal of Cancer 2017;8:1562-1567.
62. Shallis RM, Pollyea DA, Zeidan AM. Complete, yet partial: the benefits of complete response with partial haematological recovery as an endpoint in acute myeloid leukaemia clinical trials. Lancet Haematol 2020;7:853-856.
63. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood 2018;131:1275-1291.
64. Buccisano F, Dillon R, Freeman SD, et al. Role of Minimal (Measurable) Residual Disease Assessment in Older Patients with Acute Myeloid Leukemia. Cancers 2018;10:215.
65. Ivey A, Hills RK, Simpson MA, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med 2016;374:422-33.
66. Short NJ, Zhou S, Fu C, et al. Association of Measurable Residual Disease With Survival Outcomes in Patients With Acute Myeloid Leukemia: A Systematic Review and Meta-analysis. JAMA Oncol 2020;6:1890-9.
67. Hourigan CS, Gale RP, Gormley NJ, et al. Measurable residual disease testing in acute myeloid leukaemia. Leukemia 2017;31:1482-1490.
68. Grimwade D, Freeman SD. Defining minimal residual disease in acute myeloid leukemia: which platforms are ready for "prime time"? Blood 2014;2014:3345-3355.
69. Dombret H, Gardin C. An update of current treatments for adult acute myeloid leukemia. Blood 2016;127:53-61.
70. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer 2006;106:1090-8.
71. Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol 2005;23:1969-78.
72. Othus M, Garcia-Manero G, Godwin J, et al. Associations between Complete Remissions (CRs) with 7+3 Induction Chemotherapy for Acute Myeloid Leukemia and 2-3 Year Survival ("Potential Cure") over the Past Four Decades: Analysis of SWOG Trial Data. Blood 2017;130:1301-1301.
73. Shimoni A, Labopin M, Savani B, et al. Long-term survival and late events after allogeneic stem cell transplantation from HLA-matched siblings for acute myeloid leukemia with myeloablative compared to reduced-intensity conditioning: a report on behalf of the acute leukemia working party of European group for blood and marrow transplantation. J Hematol Oncol 2016;9:118.
74. Bejanyan N, Weisdorf DJ, Logan BR, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. Biol Blood Marrow Transplant 2015;21:454-9.
75. Craddock C, Versluis J, Labopin M, et al. Distinct factors determine the kinetics of disease relapse in adults transplanted for acute myeloid leukaemia. J Intern Med 2018;283:371-379.
76. National Institute of Health and Care Excellence (NICE). Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [TA642]. Available at: https://www.nice.org.uk/guidance/ta642. [Last accessed: 16th March 2021]. .
77. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-

risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer 2007;109:1114-24.
78. Office for National Statistics (ONS). Overview of UK population: August 2019. Available at. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/august2019 [Last accessed: December.
79. National Institute of Health and Care Excellence (NICE). Decitabine for untreated acute myeloid leukaemia (terminated appraisal) [TA548]. Available at. https://www.nice.org.uk/guidance/ta548 [Last accessed: March 2021].
80. National Institute of Health and Care Excellence (NICE). Glasdegib with chemotherapy for untreated acute myeloid leukaemia (terminated appraisal) [TA646]. Available at. https://www.nice.org.uk/guidance/ta646 [Last accessed: March 2021].
81. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. New England Journal of Medicine 2020;383:617-629.
82. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Blood 2020;135:2137-2145.
83. AbbVie. Data on File. VIALE-A Clinical Study Report.
84. AbbVie. Data on File. VIALE-C Clinical Study Report.
85. Wei AH, Montesinos P, Ivanov V, et al. A phase III study of venetoclax plus low-dose cytarabine in previously untreated older patients with acute myeloid leukemia (VIALE-C): A six-month update. Journal of Clinical Oncology 2020 38:15_suppl, 7511-7511, 2020.
86. DiNardo C, Jonas B, Pullarkat V, et al. A Randomized, Double-Blind, Placebo-Controlled Study Of Venetoclax With Azacitidine Vs Azacitidine In Treatmentnaïve Patients With Acute Myeloid Leukemia Ineligible For Intensive Therapy-VIALE-A. European Hematology Association 2020:LB2601.
87. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. Journal of clinical oncology 2003;21:4642-4649.
88. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination, University of York, 2008. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf [Last accessed: September 2020].
89. Othus M, Estey EH, Garcia-Manero G, et al. Second cycle remission achievement with 7+3 and survival in adults with newly diagnosed acute myeloid leukemia: analysis of recent SWOG trials. Leukemia 2019;33:554-558.
90. National Institute for Health and Care Excellence (NICE). DSU Technical Support Document 1: Introduction to Evidence Synthesis for Decision Making 2011. Available at: http://nicedsu.org.uk/technical-support-documents/evidence-synthesis-tsd-series/ [Last accessed: 9th October 2020].
91. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health 2011;14:417-28.
92. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health 2011;14:429-37.
93. AbbVie. Data on File. Draft SmPC for Venetoclax.
94. National Institute for Healthcare and Excellence (NICE). Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [TA451]. 2017. Available at. https://www.nice.org.uk/guidance/ta451 [Last accessed: January 2021].

95. National Health Service (NHS). National Cost Collection data 2018/19. Available at. https://www.england.nhs.uk/national-cost-collection/ [Last accessed: December 2020].
96. National Health Service (NHS). National Tariff Payment System 2020/21. Available at. https://improvement.nhs.uk/resources/national-tariff-2021-consultation/ [Last accessed: February 2021].
97. Department of Health and Social Care. eMIT national database. Drugs and pharmaceutical market information tool. 2020. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [Last accessed: 16th March 2021].
98. Haymarket Media Group Ltd. Monthly Index of Medical Specialities. 2017. Available from: http://www.mims.co.uk/ [Last accessed 14th June 2017].
99. Tremblay G, Dolph M, Patel S, et al. Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom. Cost Effectiveness and Resource Allocation 2018;16:33.
100. National Institute of Health and Care Excellence (NICE). Liposomal cytarabine–daunorubicin for untreated acute myeloid leukaemia [TA552]. Available at: https://www.nice.org.uk/guidance/ta552 [Last accessed: 18th August 2020].
101. National Institute of Health and Care Excellence (NICE). Midostaurin for untreated acute myeloid leukaemia [TA523]. Available at: https://www.nice.org.uk/guidance/TA523 [Last accessed: 18th August 2020].
102. National Institute of Health and Care Excellence (NICE). Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [TA545]. Available at: https://www.nice.org.uk/guidance/TA545 [Last accessed: 18th August 2020].
103. Office for National Statistics (ONS). National life tables: UK. September 2020. Available at. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables [Last accessed: January 2021].
104. Pollyea DA, Stevens BM, Jones CL, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med 2018;24:1859-1866.
105. National Institute of Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013: The reference case. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case [Last accessed: 9th October 2020].
106. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-108.
107. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15:708-15.
108. National Health Service (NHS). National Tariff Payment System 2016/17. Available at. https://www.england.nhs.uk/pay-syst/national-tariff/tariff-consultation-notice/ [Last accessed: December 2020].
109. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.
110. National Institute of Health and Care Excellence (NICE). DSU Technical Support Document 14: Survival analysis for economic evaluations aloongside clinical trials – extrapolation with patient-level data. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf [Last accessed: 9th October 2020].
111. National Institute for Health and Care Excellence (NICE). DSU Technical Support Document 21: Flexible Methods for Survival Analysis. Available at: http://nicedsu.org.uk/flexible-methods-for-survival-analysis-tsd/ [Last accessed: 16th March 2021].
112. National Institute of Health and Care Excellence (NICE). Process and methods [PMG9], Chapter 5: The Reference Case. Available at https://www.nice.org.uk/process/pmg9/chapter/the-reference-case [Last accessed January 2021].

113. Wehler E, Storm M, Kowal S, et al. A Health State Utility Model Estimating the Impact of Ivosidenib on Quality of Life in Patients with Relapse/Refractory Acute Myeloid Leukemia. 23rd Congress of the European Hematology Association 2018.
114. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13:509-18.
115. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care 2019. 2019. Available at. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/ [Last accessed: December 2020].
116. Jonas, B. A. et al. CYP3A inhibitors and impact of these agents on outcomes in patients with acute myeloid leukemia treated with venetoclax plus azacitidine on the VIALE-A study. Avaliable at: https://ash.confex.com/ash/2020/webprogram/Paper134850.html. last accessed: March 2021.
117. Georghiou T, Bardsley, T. Exploring the cost of care at the end of life. Nuffield Trust, 2014. Available at. https://www.nuffieldtrust.org.uk/files/2017-01/end-of-life-care-web-final.pdf [Last accessed: January 2021].
118. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Med Decis Making 2014;34:343-51.

B.5 Appendices

Appendix C: Summary of Product Characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Additional data from the VIALE-A and VIALE-C trials

Appendix M: Baseline health state occupancy of the overall population in the cost-effectiveness model

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Clarification questions

April 2021

File name	Version	Contains confidential information	Date
ID1564 venetoclax clarification letter to PM	v1.0	Yes	13 April 2021

Section A: Clarification on effectiveness data

Literature searching

A1. Appendix D, pages 6-12. Although the company submission states that the systematic literature review (SLR) was conducted from a global perspective, the results of the MEDLINE, Embase, and CENTRAL searches were restricted to English language only. There are 1,400 non-English results excluded from the SLR, primarily from CENTRAL. Please clarify the reason for excluding non-English publications.

The SLR searches were limited to articles published in the English language because the vast majority of the evidence relevant to this appraisal is expected to have been published in English. In addition, the SLR was conducted in accordance with the NICE methods guide and the decision to limit the SLR to studies published in English is in line with previous appraisals.[1] Whilst it is acknowledged that this approach has the potential to introduce a language bias, the risk of excluding high quality randomised controlled trials for the current network meta-analysis is considered low. Furthermore, according to the Centre for Review and Dissemination (CRD) guidance for SLRs, studies with statistically significant results that have been conducted in non-English speaking countries may be more likely to be published in English language journals than those with non-significant results, and therefore it is considered likely that all studies reporting significant results have been captured by the SLR.[2]

Identification and selection of relevant evidence

A2. Appendix D, Figure 2, page 20. The PRISMA flow diagram of included and excluded studies for the clinical SLR shows a 2-stage process for selection of studies for the network meta-analysis (NMA); first, 83 articles were considered relevant, according to the eligibility criteria (Appendix D, Table 9, pages 17-19). These 83 articles were then further screened for suitability in the NMA, and a total of 21 publications and two CSRs (reporting 9 trials) were finally included. Please clarify the reason for the first stage of the process and the relevance of the eligibility criteria reported in Table 9.

The first stage of the full-text screening was conducted based on the eligibility criteria detailed in Table 9 of Appendix D. This stage of screening included an extensive number of comparators and considered non-randomised clinical trials (e.g., single arm trials; studies with only one arm of interest). This step was conducted in order to identify clinical evidence from a global perspective.

As explained in the footnote of Table 9, the second stage of full-text screening applied additional eligibility criteria to specifically identify evidence for the network meta-analysis (NMA). In this step the treatment of interest was restricted to VenAZA, VenLDAC, Ven + decitabine, AZA, LDAC, decitabine, glasdegib + LDAC, and BSC. In addition, the study design was restricted to randomised clinical trials which contained at least two arms of interest in this step during the second stage of full-text screening.

A3. Appendix D, Table 12, pages 36-40. The company submission states that Table 12 reports 64 studies. However, the table shows only 62 studies. Please clarify this discrepancy.

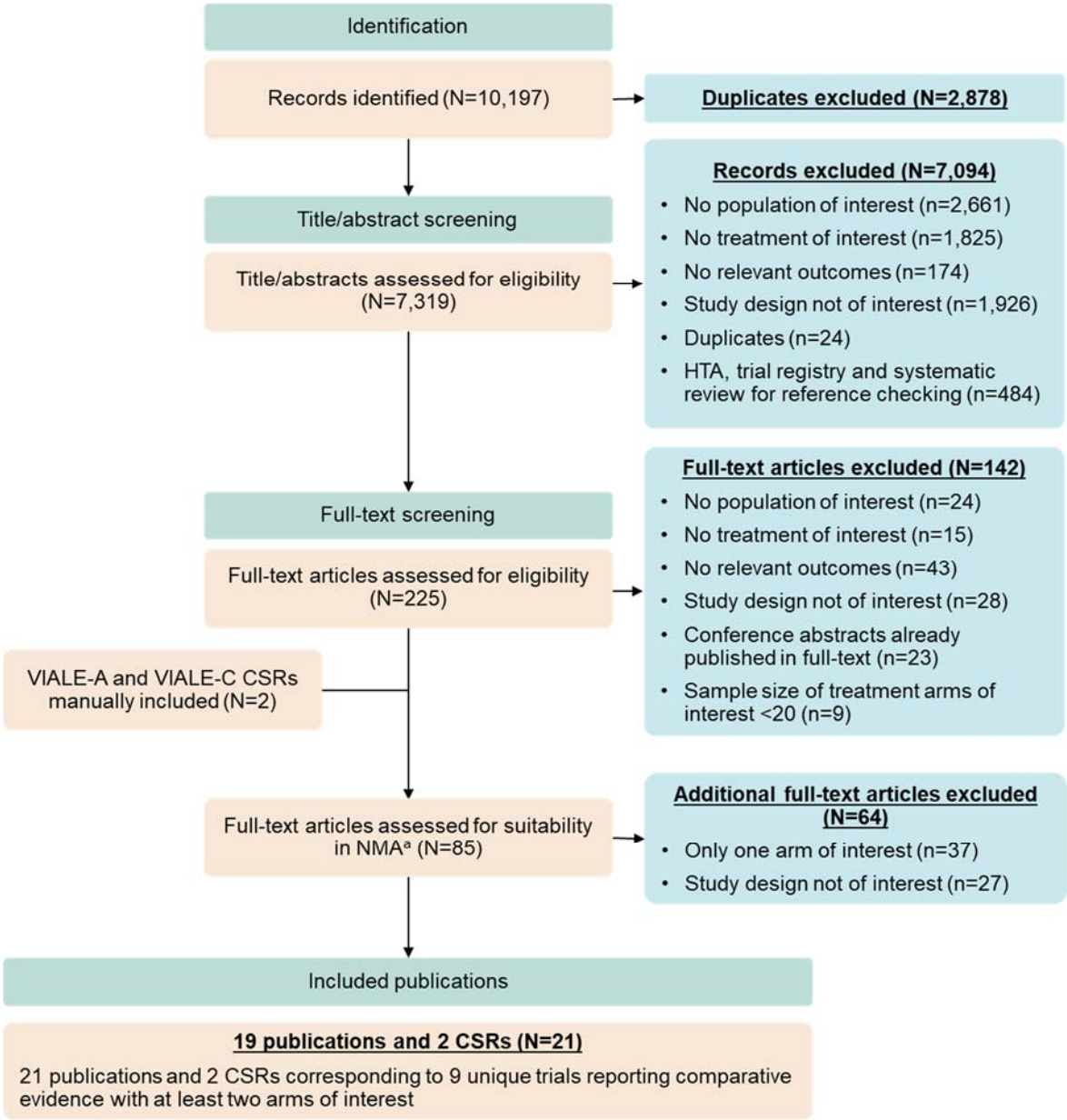
Thank you for spotting this discrepancy. Within Appendix D of the company submission the two studies detailed in Table 1 were mistakenly included in Table 10 rather than Table 12.

In the SLR update which was conducted on 13th October 2020, a total of 10,197 records were identified. After removing 2,878 duplicates, a total of 7,319 records were assessed for eligibility. During the full-text review stage, 225 publications were further assessed for eligibility. At the end of the full-text review stage, the clinical study reports for VIALE-A and VIALE-C were added to the SLR. Thus, 85 records (83 publications out of 225 records and two additional clinical study reports) met the inclusion criteria. Among these records, 27 publications only reported single arm trial evidence and 37 publications reported comparative trial evidence with only one arm of interest. Therefore, the number of articles that were deemed not-suitable for inclusion is 64. For clarity, an updated PRISMA diagram for the clinical SLR is provided in Figure 1.

Table 1: Studies excluded at the second full-text screening stage which were omitted from Table 12 of Appendix D

Author, year	Title	Reason for exclusion
Amadori, 2016[3]	Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial	Only one treatment arm of interest
Burnett, 2013[4]	Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival	Only one treatment arm of interest

Figure 1: PRISMA diagram of included and excluded studies for the clinical SLR



[a] Additional eligibility criteria were applied: Study design of interest, RCTs only. Update treatment of interest: VenAZA, VenLDAC, Ven + decitabine, AZA, LDAC, decitabine, glasdegib + LDAC, and BSC.
Abbreviations: AZA: azacitidine; BSC: best supportive care; CSR: clinical study report; HTA: health technology assessment; LDAC: low-dose cytarabine; N: number of studies; NMA: network meta-analysis; RCT: randomised controlled trial; Ven: venetoclax

Decision problem – outcomes

A4. Document B, Section B.2.2, Table 3, page 31. The outcome 'duration of response' is listed among the 'reported outcomes specified in the decision problem' for VIALE-A and VIALE-C in Table 3. The decision problem table (Document B, Section B.1.1, Table 1, pages 16-18) states "*whilst disease-free survival data were not explicitly collected in the VIALE-A and VIALE-C trials, duration of response data*

were collected, which describe the time spent in a disease-free state". However, the outcome 'duration of response' is not defined in the table of outcome definitions (Document B, Section B.2.3.1, Table 5, page 38). Please clarify the definition of the outcome 'duration of response' and indicate where these data are reported in the company submission.

The duration of response is defined as the number of days from the date of first complete remission or complete remission with incomplete blood count recovery (CR +CRi), as defined by the revised International Working Group (IWG) criteria for patients with acute myeloid leukaemia (AML), to the earliest evidence of minor response (MR), progressed disease (PD), or death due to disease progression.[5, 6]

In VIALE-A (interim analysis 2 [IA2]) the median duration of CR + CRi was 17.5 months in the VenAZA arm and 13.4 months in the AZA arm, demonstrating the improved durability of response with VenAZA.[7] These data are reported on page 52 of Document B of the company submission.

In VIALE-C (6-month follow-up data cut-off) the median duration of CR + CRi was [redacted] months in the VenLDAC arm and [redacted] months in the LDAC arm.[6] These data are reported on page 64 of Document B of the company submission.

Characteristics of VIALE-A and VIALE-C trials

A5. Document B, section B.2.3.2, Table 6, page 40. Please clarify if the range for the variable age is interquartile range or actual range (i.e. minimum and maximum values).

The age range reported for patients in VIALE-A and VIALE-C within Table 6 of Document B of the company submission is an actual range (minimum and maximum), rather than an interquartile range (IQR).[7, 8]

A6. Document B, section B.2.3.2, Table 6, page 40. History of myelodysplastic syndrome or CMML for VIALE-C has been reported as 52 for VenLDAC and 19 for LDAC arm and therapy-related AML has been reported as 6 for VenLDAC and 4 for LDAC arm. Please clarify what these numbers represent (i.e. number of patients in each arm or percentages) as values for VIALE-A are reported as n/N and %.

The values reported in Table 6 of Document B of the company submission relate to the number of patients, rather than a proportion. For clarity, the secondary AML type for patients with secondary AML in VIALE-C is summarised in Table 2.

Table 2: Type of secondary AML for patients with secondary AML in VIALE-C

Secondary AML type, n (%)	VenLDAC (n=58)	LDAC (n=23)

History of myelodysplastic syndrome or chronic myelomonocytic leukaemia	52 (90%)	19 (83%)
Therapy related AML	6 (10%)	4 (17%)

Abbreviations: AML: acute myeloid leukaemia; LDAC: low dose cytarabine; Ven: venetoclax.
Source: Wei *et al.* (2020).[8]

A7. Document B, Section B.2.5.2, Table 16, page 63. Please clarify if the primary endpoint (overall survival analysis using the 15th August 2019 data cut-off) was adjusted for baseline prognostic factors.

The results displayed in Table 16 of Document B of the company submission for the six month follow up data cut-off (15th August 2019) are not adjusted for baseline prognostic factors, but are based on the same method as the primary analysis (cut-off of 15th February 2019), which is stratified log-rank test and stratified HR by AML status (de novo, secondary) and age (18–<75, ≥75 years).

As for the primary analysis (cut-off of 15th February 2019) an additional post hoc stepwise multivariate Cox proportional hazards model was used to determine the independent effect of venetoclax on OS, and identify baseline prognostic factors that may have influenced OS.[8] Similar to the results for the primary analysis, this analysis identified AML status (de novo versus secondary), cytogenetic risk (intermediate versus poor), ECOG performance status (<2 versus ≥2), and age (<75 versus ≥75 years) as significantly correlated with OS (see Table 3). Although not reported in the original company submission, these data are reported on page 173 of the VIALE-C CSR.[6]

Table 3: Multivariate analysis of OS including baseline demographics and disease characteristics as covariates (FAS; 6-month follow up)

Covariate	HR (95% CI)	P-value
Treatment arm (VenLDAC versus LDAC)	[redacted]	[redacted]
Age group (<75 versus ≥75 years)	[redacted]	[redacted]
AML status (de novo versus secondary)	[redacted]	[redacted]
Baseline ECOG (<2 versus ≥2)	[redacted]	[redacted]
Cytogenetic risk (intermediate versus poor)	[redacted]	[redacted]

Abbreviations: AML: acute myeloid leukaemia; EGOG: Eastern Cooperative Oncology Group; FAS: full analysis set; HR: hazard ratio; LDAC: low dose cytarabine; OS: overall survival; Ven: venetoclax.
Source: VIALE-C Clinical Study Report.[6]

A8. Document B, Section B.2.3.2, Table 6 pages 40-41. The table, which shows the baseline characteristics of VIALE-A and VIALE-C trials, appears to report a mixture of data “reported from EDC” and “reported from IVRS/IWRS” (as stated in the

respective CSRs) for “age ≥75 years”, “AML type”, “secondary AML” and “cytogenetic risk category” across the 2 trials.

i. Please clarify the difference between these 2 types of data and the reasons for their inconsistent use in Table 6.

ii. Please provide an amended table using consistent data, both within and across the 2 trials.

Electronic data capture (EDC) and interactive voice/web recording system (IVRS/IWRS) represent two methods used to collect the data in the trials. IVRS/IWRS was used for patient randomisation, which included age (18–<75, ≥75 years) and cytogenetic risk category (intermediate, poor) as stratification factors in VIALE-A, and AML status (de novo, secondary) and age (18–<75, ≥75 years) in VIALE-C. IVRS/IWRS data are only available for these categories, which were used for randomisation and as stratification factors within the primary analysis of each trial, and are not available for any other data category. For this reason, it is not possible to provide an amended table presenting consistent data both within and across VIALE-A and VIALE-C, however, a table of baseline characteristics including both EDC and available IVRS/IWRS data for the previously mentioned stratification factors is presented in Table 4.

Table 4: Baseline characteristics of patients in the VIALE-A and VIALE-C trials

Characteristic	VIALE-A		VIALE-C	
	VenAZA (n=286)	AZA (n=145)	VenLDAC (n=143)	LDAC (n=68)
Age				
Median (range), years	75.6 (49.0–91.0)	75.1 (60.0–90.0)	75.1 (36.0–93.0)	74.3 (41.0–88.0)
≥75 years, n (%) reported from EDC	174 (60.8)	87 (60.0)	[redacted]	[redacted]
≥75 years, n (%) reported from IVRS/IWRS	[redacted]	[redacted]	78 (54.5)	39 (57.4)
Sex, n (%)				
Male/Female	172 (60.1) / 114 (39.9)	87 (60.0) / 58 (40.0)	78 (54.5) / 65 (45.5)	39 (57.4) / 29 (42.6)
AML type, n (%) reported from EDC				
De novo	214 (74.8)	110 (75.9)	[redacted]	[redacted]
Secondary	72 (25.2)	35 (24.1)	[redacted]	[redacted]
AML type, n (%) reported from IVRS/IWRS				
De novo	-	-	92 (64.3)	46 (67.6)
Secondary	-	-	[redacted]	[redacted]
Secondary AML, n/N (%)				
History of myelodysplastic syndrome or CMML	46/72 (63.9)	26/35 (74.3)	52	19
Therapy-related AML	26/72 (36.1)	9/35 (25.7)	6	4
ECOG performance status score, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow blast count, n (%)				
<30%	85 (29.7)	41 (28.3)	[redacted]	[redacted]
≥30 to <50%	61 (21.3)	33 (22.8)	[redacted]	[redacted]
≥50%	140 (49.0)	71 (49.0)	[redacted]	[redacted]
AML with MRC, n (%)	92 (32.2)	49 (33.8)	[redacted]	[redacted]

Antecedent haematologic history of MDS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Cytogenetic risk category, n (%) reported from EDC				
Favourable	-	-	[redacted]	[redacted]
Intermediate	182 (63.6)	89 (61.4)	[redacted]	[redacted]
Poor	104 (36.4)	56 (38.6)	[redacted]	[redacted]
Cytogenetic risk category, n (%) reported from IVRS/IWRS				
Intermediate	[redacted]	[redacted]	-	-
Poor	[redacted]	[redacted]	-	-
Somatic mutations, n/N (%)[a]				
IDH1 or *IDH2*	61/245 (25.7)	28/127 (22.9)	[redacted]	[redacted]
FLT3, ITD or TKD	29/206 (14.1)	22/108 (20.4)	[redacted]	[redacted]
NPM1	27/163 (16.6)	17/86 (19.8)	19 (17.0)	7 (13.5)
TP53	38/163 (23.3)	14/86 (16.3)	22 (19.6)	9 (17.3)
Baseline cytopenia grade ≥3, n (%)[b]				
Anaemia	88 (30.8)	52 (35.9)	[redacted]	[redacted]
Neutropenia	206/286 (72.0)	90/144[c] (62.5)	[redacted]	[redacted]
Thrombocytopaenia	145 (50.7)	73 (50.4)	[redacted]	[redacted]
≥2 Reasons for ineligibility to receive intensive therapy, n (%)	141 (49.3)	65 (44.8)	[redacted]	[redacted]
Prior HMA used (yes), n (%)	NA[f]	NA[f]	[redacted]	[redacted]
RBC or platelet infusion[e] (yes), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RBC transfusion[e] (yes), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Platelet transfusion[e] (yes), n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[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]Cytopenia was graded according to the Common Terminology Criteria for Adverse Events. [c]Data missing for 1 patient due to white blood cell count being too low to perform differential counts and report absolute neutrophil count. [d]Missing data for neutropenia for 12 and 6 patients in the VenLDAC and LDAC arms of VIALE-C, respectively. [e]Within 8 weeks prior to the first dose of study drug (or randomisation for non-treated patients).[f]Prior use with an HMA was part of the exclusion criteria for VIALE-A.

Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; CMML: chronic myelomonocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; EDC: electronic data capture; FLT3: FMS-like tyrosine kinase-3; HMA: hypomethylating agent; IDH: isocitrate dehydrogenase; ITD: internal tandem duplication; IVRS/IWRS: interactive web/voice recording system; LDAC: low-dose cytarabine; MDS: myelodysplastic syndrome; MRC: myelodysplasia related changes; NPM1: nucleophosmin 1; RBC: red blood cell; TKD: tyrosine kinase domain; TP52: tumour protein 53; Ven: venetoclax.
Source: VIALE-A Clinical Study Report,[5] DiNardo et *al.* (2020),[7] VIALE-C Clinical Study Report,[6] Wei *et al.* (2020).[8]

Statistical analyses and clinical effectiveness results

A9. Priority question. Document B, section B.2.8.1, page 82. Please provide a table showing the hazard ratios for overall survival from each of the individual studies included in the NMA.

A summary of the hazard ratios (HR) for overall survival (OS) for trials included in the >30% blast count subgroup NMA is presented in Table 5.

Table 5: Summary of OS for trials included in the NMA (>30% blast count subgroup)

Trial	Treatment Arm	N	OS	
			Hazard Ratio	95% CI
AZA-AML-001[a] (Dombret 2015)[9]	LDAC	158	Reference	
	AZA	154	0.90	[0.70, 1.16]
VIALE-A[7]	AZA	[redacted]	Reference	
	VenAZA	[redacted]	[redacted]	[redacted]
VIALE-C[8]	LDAC	[redacted]	Reference	
	VenLDAC	[redacted]	[redacted]	[redacted]

[a]AZA-AML-001 (Dombret, 2015) included patients with >30% bone marrow blasts. Patients were randomly assigned on the basis of local pathology assessment of baseline bone marrow blast count, which was subsequently reviewed by the central pathologist; in a small number of cases, baseline blast count was <30% upon central review.
Abbreviations: AZA: azacitidine; BSC: best supportive care; CI: confidence interval; LDAC: low-dose cytarabine; NMA: network meta-analysis; OS: overall survival; Ven: venetoclax.

A10. Priority question. Document B, section B.2.8.1, page 83. Please provide a table showing the odds ratios for composite complete remission rate (CR + CRi) from each of the individual studies included in the NMA.

A summary of the odds ratio (OR) for CR + CRi for trials included in the NMA is presented in Table 6.

Table 6: Summary of CR + CRi for trials included in the NMA (>30% blast count subgroup)

Trial	Treatment Arm	N	CR + CRi		Odds ratio (Drug vs Reference arm)
			n	%	
AZA-AML-001[a] (Dombret 2015)[9]	LDAC	158	41	25.95	0.93
	AZA	154	42	27.27	
VIALE-A[7]	AZA	[redacted]	[redacted]	[redacted]	[redacted]
	VenAZA	[redacted]	[redacted]	[redacted]	
VIALE-C[8]	LDAC	[redacted]	[redacted]	[redacted]	[redacted]
	VenLDAC	[redacted]	[redacted]	[redacted]	

[a]AZA-AML-001 (Dombret, 2015) included patients with >30% bone marrow blasts. Patients were randomly assigned on the basis of local pathology assessment of baseline bone marrow blast count, which was subsequently reviewed by the central pathologist; in a small number of cases, baseline blast count was <30% upon central review.
Abbreviations: AZA: azacitidine; BSC: best supportive care; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery: LDAC: low-dose cytarabine; NMA: network meta-analysis; Ven: venetoclax.

A11. Document B. Please provide the NMA results for the 20-30 blast cell count subgroup as these are not reported in the company submission.

As per NICE methods guide, when direct evidence is available, this should supersede indirect evidence via an NMA. Therefore, an NMA in the 20–30% blast cell count subgroup is not relevant to the decision problem.

The only comparison of relevance in the subgroup of patients with 20–30% blast cell count is VenAZA versus AZA, where direct evidence is available from the VIALE-A trial, as described in Table 50 of the company submission (see below).[7] Although LDAC is not restricted by blast cell count, it is only used in patients with blast cell counts of >30% in clinical practice, as AZA is the standard of care for patients with blast cell counts of 20–30%. Thus, an indirect comparison of VenAZA versus LDAC in the 20–30% blast cell count population is not relevant to the decision problem for this appraisal. It should also be noted that an indirect comparison of VenLDAC to AZA is also not relevant to the decision problem for this appraisal (as described in Table 1 of Document B of the company submission).

An NMA was conducted in the subgroup of patients with >30% blasts since this is the relevant population for the comparison of VenAZA versus LDAC. An NMA conducted in the overall population (i.e., not restricted by blast) is presented for reference in Appendix D of the company submission.

Table 7: Summary of intervention comparisons in the model

Intervention	AZA	LDAC
20–30% blast count cohort		
VenAZA	✓	×
>30% blast count cohort		
VenAZA	×	✓
VenLDAC	×	✓

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; Ven: venetoclax

A12. Document B, section B.2.8.1, page 80. Please supply the baseline characteristics of the participants included in the AZA-AML-001 and AZA-001 studies, which are part of the NMA. Please provide this information side by side with the information from the VIALE-A and VIALE-C trials.

Baseline characteristics for studies included in the NMA are presented side by side as requested in Table 8.

Table 8: Baseline characteristics for studies included in the NMA

	VIALE-A		VIALE-C		Dombret, 2015 (AZA-AML-001)				
	VenAZA	AZA	VenLDAC	LDAC	AZA	LDAC	BSC	CCR	IC
	N=286	N=145	N=143	N = 68	N=241	N=158	N=45	N=247	N=44
Demographics									
Age (years)									
Median	76.0	76.0	76.0	76.0	75.0	75.0	78.0	75.0	70.5
Range	49–91	60–90	36–93	41–88	64–91	65–88	67–89	65–89	65–81
Male, n (%)	172 (60.1)	87 (60.0)	78 (54.5)	39 (57.4)	139 (57.7)	94 (59.5)	29 (64.4)	149 (60.3)	26 (59.1)
Female, n (%)	114 (39.9)	58 (40.0)	65 (45.5)	29 (42.6)	102 (42.3)	64 (40.5)	16 (35.6)	98 (39.7)	18 (40.9)
Geographic region, n (%)									
United States	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
North America/Australia	[redacted]	[redacted]	[redacted]	[redacted]	45 (18.7)	NR	NR	47 (19.0)	5 (11.4)
Western Europe/Israel	[redacted]	[redacted]	[redacted]	[redacted]	116 (48.1)	NR	NR	122 (49.4)	22 (50.0)
Eastern Europe					46 (19.1)	NR	NR	44 (17.8)	7 (15.9)
Australia	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Asia	[redacted]	[redacted]	[redacted]	[redacted]	34 (14.1)	NR	NR	34 (13.8)	10 (22.7)
Rest of the world	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Race (%)									
White	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Black	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Other or missing	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Clinical Characteristics									
AML type, n (%)									
Primary	214 (74.8)	110 (75.9)	92 (64.3)	46 (67.6)	NR	NR	NR	NR	NR
Secondary	72 (25.2)	35 (24.1)	51 (35.7)	22 (32.4)	NR	NR	NR	NR	NR
AML Classification									

	VIALE-A		VIALE-C		Dombret, 2015 (AZA-AML-001)				
	VenAZA	AZA	VenLDAC	LDAC	AZA	LDAC	BSC	CCR	IC
	N=286	N=145	N=143	N = 68	N=241	N=158	N=45	N=247	N=44
Not otherwise specified	NR	NR	NR	NR	153 (63.5)	95 (60.1)	22 (48.9)	143 (57.9)	26 (59.1)
With myelodysplasia-related changes	[redacted]	[redacted]	[redacted]	[redacted]	75 (31.1)	50 (31.6)	20 (44.4)	83 (33.6)	13 (29.5)
With therapy-related myeloid neoplasms	26 (36.1) *[for secondary AML only]*	9 (25.7) *[for secondary AML only]*	6 (4.2) *[for secondary AML only]*	4 (5.9) *[for secondary AML only]*	8 (3.3)	9 (5.7)	2 (4.4)	12 (4.9)	1 (2.3)
With recurrent genetic abnormalities	NR	NR	NR	NR	5 (2.1)	4 (2.5)	1 (2.2)	9 (3.6)	4 (9.1)
Prior MDS, n (%)									
Yes	[redacted]	[redacted]	47 (32.9)	17 (25.0)	49 (20.3)	23 (14.6)	11 (24.4)	38 (15.4)	4 (9.1)
No	[redacted]	[redacted]	96 (67.1)	51 (75.0)	192 (79.7)	135 (85.4)	34 (75.6)	209 (84.6)	40 (90.9)
Confirmed prior HMA, n (%)	NR	NR	28 (19.6)	14 (20.6)	NR	NR	NR	NR	NR
BM Blasts (%)									
Median	[redacted]	[redacted]	[redacted]	[redacted]	70	74	76	72	70
Range	[redacted]	[redacted]	[redacted]	[redacted]	2-100	4-100	9-100	2-100	6-100
<30%, n (%)	85 (29.7)	41 (28.3)	[redacted]	[redacted]	NR	NR	NR	NR	NR
30–50%	61 (21.3) *[≥30% to <50%]*	33 (22.8) *[≥30% to <50%]*	[redacted]	[redacted]	NR	NR	NR	NR	NR
>50%, n (%)	140 (49.0) *[≥50%]*	71 (49.0) *[≥50%]*	[redacted]	[redacted]	173 (71.8)	128 (81.0)	36 (80.0)	193 (78.1)	29 (65.9)
Cytogenetic Risk Group, n (%)	NR	NR	n = 138	n = 66	NR	NR	NR	NR	NR
Good	NR	NR	[redacted]	[redacted]	113 (46.9)	65 (41.1)	23 (51.1)	105 (42.5)	17 (38.6)
Intermediate	[redacted] 182 (63.6) *[EDC]*	[redacted] 89 (61.4) *[EDC]*	[redacted]	[redacted]	155 (64.3)	104 (65.8)	29 (64.4)	160 (64.4)	27 (61.4)
Good/intermediate	NR	NR	[redacted]	[redacted]	NR	NR	NR	NR	NR

	VIALE-A		VIALE-C		Dombret, 2015 (AZA-AML-001)				
	VenAZA	AZA	VenLDAC	LDAC	AZA	LDAC	BSC	CCR	IC
	N=286	N=145	N=143	N = 68	N=241	N=158	N=45	N=247	N=44
Poor	[redacted] 104 (36.4) *[EDC]*	[redacted] 56 (38.6) *[EDC]*	[redacted]	[redacted]	85 (35.3)	54 (34.2)	16 (35.6)	85 (34.45)	15 (34.1)
ECOG Performance Status, n (%)									
0-1	[redacted]	[redacted]	[redacted]	[redacted]	186 (77.2)	123 (77.8)	30 (66.7)	189 (76.5)	36 (81.8)
0	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
1	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
2-3	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
2	[redacted]	[redacted]	[redacted]	[redacted]	55 (22.8)	35 (22.2)	15 (33.3)	58 (23.5)	8 (18.2)
3	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
3-4	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Missing	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR

Abbreviations: AZA: azacitidine; CCR: conventional care regimens; BSC: best supportive care; SC: supportive care; DEC: decitabine; BM: bone marrow; HMA: hypomethylating agent; MDS: myelodysplastic syndrome; GLAS: glasdegib; GO: gemtuzumab ozogamicin; ECOG: Eastern Cooperative Oncology Group; WBC: white blood cell; ANC: absolute neutrophil count; Hgb: haemoglobin; LDAC: low-dose cytarabine; AML: acute myeloid leukaemia; MDS: myelodysplastic syndrome; TC: treatment choice; EDC: electronic data capture; IVRS: interactive voice response system; IWRS: interactive web response system; CMML: chronic myelomonocytic leukaemia.

A13. Document B, section B.2.5.1, page 56, last paragraph. The text refers to Table 16. Should this state Table 15 instead?

Thank you for highlighting this. There is a typographical error on page 56 of the company submission, and this should in fact refer to "Table 15".

A14. Document B, section B.2.5.1. Table 14, page 56. The numbers with MRD negativity are higher than the numbers with MRD <0.001 and CR + CRi. Please clarify why some patients with MRD appear not to be classified as CR or CRi.

The vast majority of patients with (minimal residual disease) MRD <0.001 were classified as CR + CRi. It is however possible for patients to be classified as MRD <0.001 but not CR + CRi, due to these patients not recovering their peripheral blood counts to the levels required for CR + CRi (see Table 9). Other reasons could include patients discontinuing the study prior to having a formal disease assessment, and the potential for a low frequency of false MRD negative results.[10] Therefore, given that MRD is most meaningful in patients who have achieved a complete remission (CR or CRi), MRD assessments were evaluated in that group of patients (MRD <0.001 and CR + CRi) – i.e., 67 patients (23.4%) in the VenAZA arm and 11 patients (7.6%) in the AZA arm (see Table 14 in Document B of the company submission).

Table 9: Outcome definitions for CR + CRi and MRD negativity used in VIALE-A and VIALE-C trials

Outcome Measure	Definition
CR + CRi	Proportion of patients who achieve a CR or CRi at any time point during the study as per the modified IWG criteria for AML:[11] • **CR:** ANC ≥ 10^3/μL, platelets ≥ 10^5/μL, RBC transfusion independence, and bone marrow with < 5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease • **CRi:** All criteria as CR except for residual neutropenia ≤ 10^3/μL (1000/μL) or thrombocytopenia ≤ 10^5/μL (100,000/μL). RBC transfusion dependence is also defined as CRi
MRD negativity	MRD negativity was defined as less than one leukaemic cell per 1000 leukocytes (MRD <0.001 or 0.1%) in bone marrow aspirates evaluated via a centralised, validated, multicolour flow cytometry (MFC) assay[10]

Abbreviations: AML: acute myeloid leukaemia; CR: complete remission; CRi: complete remission with incomplete blood count recovery: IWG: International Working Group; MRD: minimal residual disease RBC: red blood cell;
Source: VIALE-A Clinical Study Report,[5] VIALE-C Clinical Study Report.[6]

A15. Document B, section B.2.3.2. Table 6, page 40. This table provides the numbers of patients in VIALE-A with a blast count <30%. These are higher than the numbers in the 20-30% subgroup informing the economic model. Please clarify why this is the case.

Please refer to the response to clarification question B.1 for an explanation of the differences in blast cell count subgroups between the CSR and the post-hoc analysis.

A16. Appendix D, Tables 16 and 17, page 47. For both tables, please clarify the information reported in the treatment arm column. In particular, what do 'combined', 'preselected BSC', 'preselected LDAC' and 'preselected IC' mean?

Table 16 and 17 in Appendix D of the company submission report data from AZA-001 and AZA-AML-001. Before randomisation in these studies, investigators determined which protocol-designated conventional care regime (CCR) out of best supportive care (BSC), LDAC, or intensive chemotherapy (IC) was most appropriate for each patient. The most appropriate CCR was selected on the basis of age, ECOG PS, comorbidities, and regional guidelines and/or institutional practice.[9, 12] A central, stratified, and permuted block randomisation method and IVRS were then used to randomly assign patients 1:1 to receive AZA or CCR. Randomisation was stratified by preselected CCR (BSC, LDAC, or IC), ECOG PS (0–1 or 2), and cytogenetic risk (intermediate or poor). Patients assigned to CCR received their preselected treatment.[9, 12] Tables 16 and 17 in Appendix D of the company submission report baseline characteristics for patients in AZA-001 and AZA-AML-001 by treatment and preselected CCR. The combined group contains patients from all preselected CCR regimens.

Section B: Clarification on cost-effectiveness data

Clinical parameters and variables

B1. Priority question. Document B, sections B.2.6 and B.3.3.2.

i) Please clarify how the baseline distributions of patients in Table 52 were derived and how they relate to Figures 24 and 28.

ii) The numbers in Table 52 appear to differ from the subgroup data presented in Figures 24 and 28. For example, in Figure 24 the number of patients achieving CR+CRi in the <30% subgroup is [redacted] and [redacted] in the AZA and VenAZA groups respectively. However, the corresponding figures in Table 52 are [redacted] and [redacted]. Does the difference relate to the classification of the subgroups (i.e. <30% blast cell count vs 20-30% blast cell count)?

There are two major differences in defining the baseline blast count which results in the different denominators observed between the data presented in Figure 24 and 28 of Document B of the company submission (which have been taken from the VIALE-A and VIALE-C CSRs, respectively) and the data presented in Table 52 of the company submission, which has been generated post-hoc to inform the cost-effectiveness model presented in this appraisal.

- The derivation rule for the CSR data (SAP rule) differs from the rule used for the post-hoc HTA request (non-SAP rule) in how baseline blast count is determined:
    - **CSR derivation rule (SAP rule):** The baseline bone marrow blast count is the last non-missing bone marrow blast count measurement before the first treatment (or the randomisation date if patient is not treated). For this measurement, an aspirate was

preferred to adequate biopsy, however, if an aspirate measurement is missing a biopsy value may be used. Only bone marrow blast data will be considered for the analysis. If multiple assessments have been conducted on the same day then the average value should be taken as the baseline value. For bone marrow samples, the bone marrow blast count was not reported if adequacy information was missing.

- **Derivation rule for post-hoc HTA analysis (Non-SAP rule):** The highest baseline bone marrow or peripheral blood blast prior to or on the date of the randomisation was used. For the derivation, there is no preference of aspirate over biopsy. If more than one from aspirate, biopsy, and peripheral blood blast count are available, the largest value among bone marrow aspirate/biopsy or peripheral blood blast count will be taken. For bone marrow biopsy/aspirate samples, the bone marrow blast count was not reported if adequacy information was missing.

- The cut-off used to define the baseline blast count categories are different between CSR and post-hoc HTA analysis (to align with the NICE recommendation), as detailed below:
  - A different cut-off for baseline blast count was used in the CSR compared with the HTA analysis. In the CSR, patients with <30% blasts were grouped together, whereas in the HTA analysis, this group is instead defined as patients with 20–30% blasts.
  - A different cutoff for baseline blast count was used in the CSR compared with the HTA analysis. In CSR, patients were defined as ≥30% (Including patients with 30–<50% and ≥50% blasts), whereas in the HTA analysis patients were defined as >30% (including patients with >30–50% and >50% blasts).

The tables below summarise the movement of patients, based on the above two reasons, from the baseline distributions to the numbers used in the analyses presented in the submission.

VIALE A

Table 10: Cross tabulation of baseline blast count – CSR analysis versus HTA analysis (FAS Group 2[a]; VenAZA treatment arm)

	HTA analysis (as per NICE recommendation) – Table 6 in CS				
CSR analysis – Table 52 in CS	Baseline blast count	<20% n (%)	20–30% n (%)	>30% n (%)	Missing[b] n (%)
	<30%	[redacted]	[redacted]	[redacted]	[redacted]
	30–<50%	[redacted]	[redacted]	[redacted]	[redacted]
	≥50%	[redacted]	[redacted]	[redacted]	[redacted]

[a] Group 2: Enrolled not under original protocol.
[b] There was one patient with bone marrow or peripheral blood blast missing prior to or on the date of randomisation but available prior to the date of the first dose.
Note: Data included are subject to a cut-off date of 4th January 2020.
Abbreviations: AZA: azacitidine; CS: company submission; CSR: Clinical study report; FAS: full analysis set; HTA: health technology assessment; NICE: The National Institute for Health and Care Excellence; Ven: venetoclax.

Table 11: Cross tabulation of baseline blast count – CSR analysis versus HTA analysis (FAS Group 2[a]; AZA treatment arm)

	HTA method (as per NICE recommendation) – Figure 6 in CS				
CSR analysis –	Baseline blast count	<20% n (%)	20–30% n (%)	>30% n (%)	Missing n (%)

Table 52 in CS	<30%	[redacted]	[redacted]	[redacted]	[redacted]
	30–<50%	[redacted]	[redacted]	[redacted]	[redacted]
	≥50%	[redacted]	[redacted]	[redacted]	[redacted]

[a] Group 2: Enrolled not under original protocol.
Note: Data included are subject to a cut-off date of 4th January 2020.
Abbreviations: AZA: azacitidine; CS: company submission; CSR: Clinical study report; FAS: full analysis set; HTA: health technology assessment; NICE: The National Institute for Health and Care Excellence.

VIALE C

Table 12: Cross tabulation of baseline blast count – CSR analysis vs. HTA analysis (FAS 6-month follow up; VenLDAC treatment arm)

	HTA method (as per NICE recommendation) –Table 6 in CS	
CSR analysis – Table 52 in CS	Baseline blast %	>30%, n (%)
	<30%	[redacted]
	30–<50%	[redacted]
	≥50%	[redacted]

Data included are subject to a cut-off date of 15th August 2019.
Abbreviations: CS: company submission; CSR: Clinical study report; FAS: full analysis set; HTA: health technology assessment; LDAC: low dose cytarabine; NICE: The National Institute for Health and Care Excellence; Ven: venetoclax.

Table 13: Cross tabulation of baseline blast count – CSR analysis vs. HTA analysis (FAS 6-month follow up; LDAC treatment arm)

	HTA method (as per NICE recommendation) – Table 6 in CS	
CSR analysis – Table 52 in CS	Baseline blast %	>30%, n (%)
	<30%	[redacted]
	30–<50%	[redacted]
	≥50%	[redacted]

Data included are subject to a cut-off date of 15th August 2019.
Abbreviations: CS: company submission; CSR: Clinical study report; FAS: full analysis set; HTA: health technology assessment; LDAC: low dose cytarabine; NICE: The National Institute for Health and Care Excellence.

B2. Document B, section B.3.3.4. There appears to be some inconsistency in the selection of extrapolation methods. On a few occasions estimates resulting in 'infinite' durations are dismissed as implausible but are considered reasonable estimates in other situations. This may reflect the challenges in interpreting the individual transitions in isolation (as outlined on page 130 of the submission) and the application of the cure assumption and general population mortality being applied at year 2. To aid interpretation of the extrapolated data, please comment further on the plausibility of the following extrapolations:

i) 20-30% blast count cohort:

- VenAZA – non-remission to progressed disease (PD)/relapse: Mean time to PD/relapse of [redacted]
- VenAZA – remission to death: Mean time to death [redacted]

ii) >30% blast count cohort:

- VenAZA – remission to PD/relapse: Mean time to PD/relapse [redacted]
- VenLDAC – remission to PD/relapse: Mean time to PD/relapse [redacted]

In general, the selection of all extrapolations used in the cost-effectiveness analysis are based on three key criteria, aligned to NICE DSU guidelines:[13]

- Goodness-of-fit statistics (AIC and BIC).
- Visual inspection of fit to Kaplan-Meier data and observed hazard profile.
- Clinician validity and plausibility.

When selecting the most appropriate extrapolative distribution, a careful systematic process was undertaken to ensure these criteria were accurately assessed and that the chosen extrapolations reflected the trial data and clinical practice. Section B.3.10 of the company submission provides detailed validation of the model output, with Figure 120 to Figure 123 presenting the model output compared with the trial data. Each figure shows that the model output accurately reflects what can be seen in the data, providing confidence that the selection of the extrapolative curves reflects the trial data.

During the selection process parametric models were selected based on the observed long-term hazard profile of each distribution in an attempt to only use extrapolations that methodologically fit the data trend best. Particularly in cases where trial Kaplan–Meier data plateaued, the extrapolations were chosen to best reflect this hazard profile. When high mean survival is estimated using parametric functions, the mortality hazard of the general population is applied with the disease-specific curves after the maximum follow-up of the trial (i.e., the extrapolative period), this is reflected in section B.3.3.4 of the company submission. As such, in instances where an infinite mean survival is observed from the parametric function, this is not reflected in the economic model, as patients across all the health states are always subjected to the hazard of the general population mortality and are never deemed ‘risk-free’ of progressive disease, relapse or death.

The clinical plausibility of long-term extrapolation is highly dependent on the underlying population and the transition probabilities between the health states. This assessment of plausibility is based on observed trial evidence, clinical expert opinion and the published literature. As an example, it is useful to consider the hazard associated with disease-related death in the remission and non-remission state. The VIALE-A and VIALE-C trial data present a high initial risk of disease-related death, regardless of attainment of remission. However, patients who achieve remission have a rapidly decreasing risk of disease-related death whilst non-remission patients continue to have a higher risk of disease-related death. This is supported by clinical experts, who note that the risk or relapse or death decreases over time in patients who attain remission.

More specifically, the rationale and plausibility for the requested extrapolations are provided below:

20-30% blast count cohort:

- VenAZA – non-remission to progressed disease (PD)/relapse: Mean time to PD/relapse of [redacted].
    - As noted in the question from the ERG, it is important not to consider these transitions in isolation. Transitions from this health state are informed by a maximum of [redacted] patients, and of these, [redacted] experience a death event and [redacted] experience PD/relapse (as outlined in Section B.3.3.3 of the company submission). Hence, there is a significant risk of death in this state but limited risk of PD/relapse (as reflected in Figure 42 of Document B of the company submission), as patients are dying before PD/relapse. This risk profile is reflected in the relevant extrapolations, which can be considered plausible when considered holistically. In summary, despite the long mean time to PD/relapse, patients do not stay in this health state for a long time, due to the high risk of death.
- VenAZA – remission to death: Mean time to death [redacted].
    - As described in Section B.3.3.3 of the company submission, there are [redacted] patients informing VenAZA for this health state, of whom only [redacted] experience a death event. However, Figure 45 in Document B of the company submission demonstrates that [redacted] of these events occurred after one year of follow up, indicating that there is an [redacted] risk of disease-specific death after this point. This is reflected in several of the extrapolations described in Figure 63 and Figure 64 of Document B of the company submission, where predicted mean survival is either [redacted] or [redacted]. However, as described above, this is aligned with the observed data, clinical expectations, and the published literature. Further, it should be noted that general population mortality is applied as a separate source of mortality risk, so that the modelled population survival never exceeds the general population. Hence, in this scenario, the predicted survival can be considered plausible.

>30% blast count cohort:

- VenAZA – remission to PD/relapse: Mean time to PD/relapse [redacted].
    - As described in Section B.3.3.3 of the company submission (Table 55), there are [redacted] patients informing VenAZA for this health state, of whom [redacted] experience a PD/relapse event. However, Figure 49 in Document B of the company submission demonstrates that [redacted] events occurred after one year of follow up and [redacted] after two years, despite a significant number of patients remaining to inform the analysis, indicating that the hazard is [redacted] based on the observed data. This hazard profile is reflected to a limited extent in the majority of the extrapolations described in Figure 81 and Figure 82 of Document B of the company submission. The generalised gamma function can be considered the exception, somewhat reflecting the decreasing hazards in the tail of the data over time, but even this parametric model fails to adequately capture a decrease in the hazard between year 1 and year 2. Despite this, the decreasing hazard results in the predicted mean extrapolation to approach an [redacted]. However, as described above, this is aligned with the observed data, clinical expectations and the published literature. Hence, in this scenario, the predicted extrapolation can be considered plausible.

- VenLDAC – remission to PD/relapse: Mean time to PD/relapse [redacted].
    - As described in Section B.3.3.3 of the company submission (Table 55), there are [redacted] patients informing VenLDAC for this health state, of whom [redacted] experience a PD/relapse event and [redacted] experience a death event. However, Figure 54 in Document B of the company submission demonstrates that almost all events occur before one year of follow-up, with only [redacted] relapse events occurring after one year of follow up, despite [redacted] patients remaining to inform the analysis, indicating that the hazard is [redacted] based on the observed data. This hazard profile is partially reflected in the majority of the extrapolations described in Figure 93 and Figure 94 of Document B of the company submission. The generalised gamma function can be considered the exception, somewhat reflecting the decreasing hazards in the tail of the data over time, but even this parametric model fails to adequately capture a decrease in the hazard between year 1 and year 2. Despite this, the decreasing hazard results in the predicted mean extrapolation to approach an [redacted]. However, as described above, this is aligned with the observed data, clinical expectations and the published literature. Hence, in this scenario, the predicted extrapolation can be considered plausible.

B3. Document B, section B.3.3.4. It is difficult to draw comparisons between the curves selected for each outcome for each comparator. Please provide plots that show the Kaplan Meier (KM) curve and the selected extrapolation curve for each outcome for each comparator (same graph) in the 2 populations of interest (20-30% blast cell count and >30 % blast cell count).

As described in Section B.3.2.2 of the company submission, the proportion of patients remaining in the 'Remission' or 'Non-remission' heath states, or transitioning to the 'PD/relapse' or 'Death' state at each monthly model cycle are based on time-dependent hazards derived from time-to-event data from the VIALE-A and VIALE-C trials.[5, 6] Furthermore, as described in Section B.3.3.4 of the company submission, the follow-up periods for the VIALE-A and VIALE-C trials were shorter than the model time horizon, which meant that extrapolation from the observed time-to-event data was required. In accordance with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance on survival analyses, a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were explored for extrapolation.[13] A comparison of the time-to-event data from VIALE-A and VIALE-C to the selected parametric extrapolation curves for each transition are shown in Figure 2 to Figure 11. The hazard profiles for these transitions often take a similar shape, wherein there is a higher initial hazard followed by long-term decreasing hazard that approaches zero.

A summary of the selected extrapolations that are presented in each of the figures is shown in Table 14.

Table 14: Summary of health state transition data sources and base-case extrapolation approach

Health state transition	Figure	Extrapolation methods
Non-remission to PD/relapse	**Figure 2**	**VenAZA**: Log-normal **AZA:** Gompertz
Remission to PD/relapse	**Figure 3**	**VenAZA:** Log-normal

		AZA: Weibull
Non-remission to Death	**Figure 4**	**VenAZA:** Log-normal **AZA:** Weibull
Remission to Death	**Figure 5**	**VenAZA:** Generalised gamma **AZA:** Log-normal
PD/relapse to Death	**Figure 6**	**VenAZA:** Log-normal **AZA:** Log-normal
Non-remission to PD/relapse	**Figure 7**	**VenAZA:** Exponential **VenLDAC:** Log-normal **LDAC:** Generalised gamma
Remission to PD/relapse	**Figure 8**	**VenAZA:** Generalised gamma **VenLDAC:** Generalised gamma **LDAC:** Exponential
Non-remission to Death	**Figure 9**	**VenAZA:** Log-normal **VenLDAC:** Log-normal **LDAC:** Log-normal
Remission to Death	**Figure 10**	**VenAZA:** Log-logistic **VenLDAC:** Log-normal **LDAC:** Exponential
PD/relapse to Death	**Figure 11**	**VenAZA:** Log-normal **VenLDAC:** Generalised gamma **LDAC:** Log-normal

[a]As no events occurred in the >30% blast cohort, the curve selected for the overall population was used.
Abbreviations: AZA: azacitidine; EFS: event-free survival; LDAC: low-dose cytarabine; Ven: venetoclax.

Figure 2. Parametric survival extrapolation of time-to-progressive disease for patients in non-remission (20-30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 3. Parametric survival extrapolation of time-to-relapse for patients in remission (20-30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 4. Parametric survival extrapolation of time-to-death for patients in non-remission (20-30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 5. Parametric survival extrapolation of time-to-death for patients in remission (20-30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 6. Parametric survival extrapolation of time-to-death for patients in progressive disease/relapse (20-30% blast cell count cohort)

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Figure 7. Parametric survival extrapolation of time-to-progressive disease for patients in non-remission (>30% blast cell count cohort)

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; Ven: venetoclax.

Figure 8. Parametric survival extrapolation of time-to-relapse disease for patients in remission (>30% blast cell count cohort)

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; Ven: venetoclax.

Figure 9. Parametric survival extrapolation of time-to-death for patients in non-remission (>30% blast cell count cohort)

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; Ven: venetoclax.

Figure 10. Parametric survival extrapolation of time-to-death for patients in remission (>30% blast cell count cohort)

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; Ven: venetoclax.

Figure 11. Parametric survival extrapolation of time-to-death for patients in progressive disease/relapse (>30% blast cell count cohort)

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; Ven: venetoclax.

B4. Document B, section B.3.3.4, Figures 65, 85 and 95. There appear to be some minor labelling errors in Figures 65, 85 and 95. Please confirm that the Figures themselves are correct and if the titles should state ‘time to death for patients in PD/relapse’.

Thank you for highlighting this. The captions of Figure 65, 85, and 95 in Section B.3.3.4 of the company submission contain typographical errors, but the Figures themselves are correct. These captions should read:

- Figure 65: Parametric survival extrapolations of time-to-death for patients in ‘PD/relapse’ – VenAZA (20–30% blast cell count cohort)
- Figure 85: Parametric survival extrapolations of time-to-death for patients in ‘PD/relapse’ – VenAZA (>30% blast cell count cohort)
- Figure 95: Parametric survival extrapolations of time-to-death for patients in ‘PD/relapse’ – VenLDAC (>30% blast cell count cohort)

B5. Document B, section B.3.3.4, page 145. It is stated that the time to death KM data for AZA patients in remission suggests a plateau in the data. Please explain why in the comparator arms of the model transition to cure is not allowed when data suggest a plateau for patients in remission. To explore this further, please provide a sensitivity analysis, which allows patients in the AZA and LDAC arms to transition to the cure health state from remission if alive at 2 years.

As discussed in Section B 1.3 of the company submission, current non-intensive treatments are not used with curative intent in clinical practice. VenAZA, on the other hand, has an innovative mechanism of action which is able to efficiently and selectively target leukaemia stem cells (LSC) by disrupting energy metabolism and thus is able to drive sustained deep remission in combination with these therapies.[14] This is demonstrated by the significantly higher proportion of patients treated with VenAZA achieving sustained deep remissions compared to AZA alone (Section B.2.5 of the company submission). This was aligned with clinical expert opinion at the time of submission.

Since receiving clarification questions, the company has further validated the assumption of ‘no cure for comparators’ with five clinical experts, who agreed that not including a cure function for AZA and LDAC was clinically justified and aligned with what they see in UK clinical practice. The clinical experts explained that achieving a cure with either of these treatments would be exceptionally rare, and patients are counselled on the non-curative intent of these therapies before treatment is initiated. Therefore, it is not clinically plausible to include a cure assumption for patients receiving AZA and LDAC in the model, irrespective of whether these patients are in the ‘Remission’ health state after 2 years.[9, 15] It should be noted that only a small proportion of patients in the AZA (3.5% of patients) and LDAC (0.9% of patients) arms were in the ‘Remission’ health state of the model at 2 years.

Based on the above, it is not appropriate to explore this in a sensitivity analysis.

B6. Priority question. Document B, section B.3.3.5. Clinical advice to the ERG suggests the cure assumptions made in the model are uncertain. In particular, it is considered unlikely that patients considered cured at 2 years would experience general population mortality and QoL. The ERG notes that in NICE technology appraisal (TA) 642, survival for patients considered cured was modelled using general population mortality uplifted using a standardised mortality ratio (SMR) of 2.0. To explore this uncertainty further please provide alternative more conservative scenarios as follows:

i) **Apply general population mortality uplifted with a SMR of 2.0.**

ii) **Assume patients in the cure health state have the same utility as patients in remission health state (see request in question B8 to ensure remission health state utility is not higher than general population values).**

iii) **A scenario that combines the changes in scenarios i) and ii) above.**

Application of general population mortality

As shown in Table 8, the mortality assumption of SMR 2.0 following cure has been used in a previous appraisal in AML (TA642). However, it is not appropriate to apply the same assumption to the current appraisal due to the differences in the population considered in the decision problem, and the population who are deemed eligible for cure.

In TA642, the cure was applied to all patients alive, in contrast to only patients who are in CR + CRi in this appraisal. As described in Section B.3.3.5 of the company submission, clinical experts have explained that patients treated with venetoclax combinations who achieve a sustained remission have the potential to achieve long-term survivorship, whereby their outcomes are in line with those of the general population. To reflect this in the current appraisal, a de novo cost effectiveness model was developed, wherein only patients in the remission health state at two years are deemed to be cured. Hence, the company consider that the current modelling approach has significant advantages over TA642, as it allows the transition probabilities to be estimated separately and separate mortality rates to be applied for CR + CRi patients.[16] It should therefore not be considered appropriate to apply an SMR which represented a patient population with heterogenous outcomes (i.e., all patients alive) and apply the value in a response-stratified population with congruous outcomes (i.e., CR + CRi only).

Whilst aligning to TA642 by applying the same assumptions, i.e., application of cure to all patients alive with an SMR of 2.0, would be favourable to the ICER for both VenAZA and VenLDAC, the company does not believe the assumptions are appropriate to the current appraisal.

Table 8. Comparison of cure assumptions used in TA642 and current appraisal

NICE appraisal	Population appraised	Population cured	SMR

TA642[16]	Relapsed or refractory FLT3-mutation-positive AML	All patients alive	2.0
ID 1564 (current appraisal)	Patients with untreated AML who are ineligible for intensive chemotherapy	Patients alive who achieved CR + CRi	General population mortality

Abbreviations: AML: acute myeloid leukaemia; CR: complete remission; CRi: complete remission with incomplete blood count recovery; SMR: standardised mortality ratio.

Application of remission health state utilities in cure health state

As outlined in response to CQ B8, only small numerical differences exist for utility values describing the remission health state and the cure health state. When applying the remission health state utility to patients in the cure state and ensuring that it does not exceed the utility of the general population, there are only minor changes in inputs. Due to this minor deviation in the utility, in addition to rounding, no changes are made to the cost-effectiveness outcomes and the ICER remains as it does in the base case.

Measurement and valuation of health effects

B7. Document B, section B.3.4.4. It is noted that the VIALE trials were pooled to maximise the sample size of the EQ-5D data. Given there are some differences between the patients included in the VIALE-A and VIALE-C trials, and the population is split by blast count for modelling efficacy, please provide justification for pooling the EQ-5D data across the trials and across the blast count subgroups.

As stated in Section B.3.4.4 of the company submission, health state utilities were pooled across the VIALE-A and VIALE-C trials in order to maximise the sample size and thus reduce any uncertainty that may surround the utility estimates. Whilst there may be small differences in the patient populations across the trials, the differences in health state utilities between the trials presented in Table 15 shows there is not a significant difference in the utility estimates between the trial populations.

Table 15: EQ-5D health state utilities

Health state	Mean	SE	Source
Pooled VIALE-A/C (company base case)			
Remission	[redacted]	[redacted]	Pooled VIALE-A/C data[5, 6]
Non-remission	[redacted]	[redacted]	
PD/relapse	[redacted]	[redacted]	
VIALE-A			
Remission	[redacted]	[redacted]	VIALE-A[5]
Non-remission	[redacted]	[redacted]	
PD/relapse	[redacted]	[redacted]	
VIALE-C			
Remission	[redacted]	[redacted]	VIALE-C[6]

Non-remission	[redacted]	[redacted]	
PD/relapse	[redacted]	[redacted]	

Abbreviations: PD: progressive disease; SE: standard error.

In support of this, scenario analysis have been explored in which non-pooled VIALE-A and VIALE-C data are used in the cost effectiveness analysis. The results of these scenario analyses are presented in Table 16 and Table 17. The use of non-pooled EQ-5D data have a minimal impact on the ICER (increases of ≤ £623), however, all cost-effectiveness conclusions remain unchanged.

Table 16: Results for CQ B7 for 20-30% blasts

Intervention	Total costs (£)	Total LYG[a]	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER inc. (£/QALY)
AZA	£103,749	1.833	1.143	-	-	-	-
VenAZA	[redacted]	[redacted]	[redacted]	[redacted]	2.609	[redacted]	£38,948

[a] Undiscounted.
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; PAS: patient access scheme; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 17: Results for CQ B7 for >30% blasts

Intervention	Total costs (£)	Total LYG[a]	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER inc. (£/QALY)
VenAZA versus LDAC							
LDAC	£33,828	0.839	0.528				
VenAZA	[redacted]	[redacted]	[redacted]	[redacted]	2.926	[redacted]	£39,590
VenLDAC versus LDAC							
LDAC	£33,617	0.832	0.529				
VenLDAC	[redacted]	[redacted]	[redacted]	[redacted]	1.606	[redacted]	£30,808

[a] Undiscounted.
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; LYG, life years gained; QALYs, quality-adjusted life years; Ven: venetoclax.

B8. Priority question. Document B, sections B.3.4.4 and B.3.8.3. Please clarify if utility values in the model are capped such that they do not exceed age-adjusted general population values. Sensitivity analysis provided in section B.3.8.3 shows that applying the remission utility value to cured patients lowers the ICER due to the remission utility value being higher than the age-adjusted general population values. Please provide a revised analysis where the remission health state is capped as described to ensure it does not exceed general population values.

Utility values are not capped by general population values in the company base-case analysis. The company has provided a revised analysis where utility values have been capped and this results in the same cost-effectiveness outcomes as in the company base case (please see Table 71 and Table 72 in the company submission). Given the patients will be aged [redacted] years at the

point of cure, the general population utility of 0.7465 is always less than that of the remission health state utility of [redacted].

When applying the capping of health state utility to patients in the remission health state, there are only four model cycles in which the health state utility of [redacted] exceeds the general population utility of 0.7465. Due to this minor deviation in the utility, in addition to rounding, no changes are made to the cost-effectiveness outcomes and the ICER remains as it does in the base case.

Cost and healthcare resource use identification

B9. Document B, section B.3.5.1 Clinical advice to the ERG suggests a higher proportion of patients than 3% will receive gilteritinib in practice and that this would apply to all patients regardless of first-line treatment. Please provide justification for including this only in the venetoclax arms, and, if appropriate, please provide sensitivity analysis, which assumes 15% of patients in both arms would receive gilteritinib following treatment discontinuation.

The scenario in which 15% of patients received gilteritinib post venetoclax combination treatment was included as a particularly conservative scenario analysis to test potential variations in clinical practice. Following additional clinical consultation, the company have been advised that a smaller proportion of patients that have discontinued AZA or LDAC would be eligible for gilteritinib than those who received VenAZA or VenLDAC. This is because a larger proportion of patients receiving venetoclax combination therapy achieve CR + CRi and would therefore be fitter following treatment and able to receive subsequent treatment with gilteritinib than those receiving AZA or LDAC. Clinical advice also indicated that the scenario of 15% of all patients who discontinue venetoclax combinations is too high to be reflective of patients who are FLT3+ and fit enough for subsequent treatment in this population (ineligible for intensive chemotherapy and of a median age of 75 years). The analysis for 15% gilteritinib applied to all arms is provided for information – although this improves the ICERs in favour of the venetoclax arms, the company does not believe this is reflective of clinical practice for all arms.

Table 18 presents the derivation of the weighted subsequent treatment costs used in the analysis (assuming the same acquisition costs as outlined in Table 65 of Document B of the company submission). The cost of subsequent treatment is applied to patients in the cycle following discontinuation.

Table 18: Subsequent treatment costs assuming 15% gilteritinib use in response to CQ B9

Scenario	Treatment	Proportion receiving subsequent treatment	Total cost per cycle	Weighted cost per cycle	Mean total cost
15% gilteritinib	Gilteritinib	15.0%	£14,315.00	£2,147.25	£2,264.33
	HC/HU	85.0%	£137.74	£117.08	
	HC/HU	95.0%	£137.74	£130.85	

[a]All SEs were assumed to be 20% of the mean value.
Abbreviations: HC/HU: hydroxycarbamide/hydroxyurea.

Results of the analysis are presented in Table 19 and Table 22. When exploring both arms receiving a composition of 15% gilteritinib, versus the base case from the company submission, ICERs are reduced, driven by the increased costs in the comparator arms as a result of a much higher subsequent treatment cost.

Table 19: Results for CQ B9 for 20-30% blasts assuming the subsequent treatment by patients receiving VenAZA and AZA is comprised of 15% gilteritinib

Intervention	Total costs (£)	Total LYG[a]	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER inc. (£/QALY)
AZA	£122,154	1.833	1.139	-	-	-	-
VenAZA	[redacted]	4.442	[redacted]	[redacted]	2.609	[redacted]	£31,736

[a] Undiscounted.
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; PAS: patient access scheme; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 20: Results for CQ B9 for 20-30% blasts assuming the subsequent treatment by patients receiving VenAZA, VenLDAC and LDAC is comprised of 15% gilteritinib

Intervention	Total costs (£)	Total LYG[a]	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER inc. (£/QALY)
VenAZA versus LDAC							
LDAC	£48,500	0.839	0.523				
VenAZA	[redacted]	3.765	[redacted]	[redacted]	2.926	[redacted]	£33,533
VenLDAC versus LDAC							
LDAC	£48,122	0.832	0.518				
VenLDAC	[redacted]	2.438	[redacted]	[redacted]	1.606	[redacted]	£21,841

[a] Undiscounted.
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; PAS: patient access scheme; QALYs, quality-adjusted life years; Ven: venetoclax.

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; LYG, life years gained; QALYs, quality-adjusted life years; Ven: venetoclax.B10. Priority question. Document B, Table 68, page 186. The cost attributed to atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis are all considered to be classed as requiring a day case admission to hospital. Given these are grade 3/4 events, the ERG

believes that it would be more appropriate to apply costs within the non-elective long stay (NEL) HRG code. Please provide:

i) **An update to the "Mean cost per occurrence" column in Table 68 for the above described adverse events, considering them to be non-elective long stay admissions.**

ii) **An adaption to the economic model which incorporates these changes.**

The updated costs using the non-elective long stay (NEL) costs, as opposed to the day case costs used in the company submission, are presented in Table 21.

Table 21. Updated AE costs used in response to CQ B10

AE	Mean cost per occurrence	Currency code	Source
Atrial Fibrillation[a]	£2,152.14	EB07A, EB07B, EB07C, EB07D, EB07E	NHS National Cost Collection 2018–19[17b]
Dyspnoea[a]	£3,080.64	DZ27M, DZ27N, DZ27P, DZ27Q, DZ27R, DZ27S, DZ27T, DZ27U, DZ27V	
Febrile Neutropenia[a]	£2,858.07	SA08G, SA08H, SA08J	
Pyrexia[a]	£2,135.89	WJ07A, WJ07B, WJ07C, WJ07D	
Sepsis[a]	£3,179.66	WJ06A, WJ06B, WJ06C, WJ06D, WJ06E, WJ06F, WJ06G, WJ06H, WJ06J	

[a]Costs derived using a weighted average of non-elective long stay.
[b]All costs from the National Cost Collection 2018/19 inflated from 2019 costs to 2020 costs using an inflation factor of 1.022.

Results from the scenario analyses in which NEL costs are used for AEs are presented in Table 22 and Table 23. As shown, the impact on the ICER is minimal compared with the base case ICERs in the company submission.

Table 22: Results CQ B10 for 20-30% blasts

Intervention	Total costs (£)	Total LYG[a]	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER inc. (£/QALY)
AZA	£104,526	1.833	1.139	-	-	-	-
VenAZA	[redacted]	4.442	[redacted]	[redacted]	2.609	[redacted]	£39,314

[a] Undiscounted.
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; PAS: patient access scheme; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 23: Results for CQ B10 for >30% blasts

Intervention	Total costs (£)	Total LYG[a]	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER inc. (£/QALY)
VenAZA versus LDAC							

LDAC	£34,924	0.839	0.523				
VenAZA	[redacted]	3.765	[redacted]	[redacted]	2.926	[redacted]	£39,633
VenLDAC versus LDAC							
LDAC	£34,714	0.832	0.518				
VenLDAC	[redacted]	2.438	[redacted]	[redacted]	1.606	[redacted]	£31,167

[a] Undiscounted.
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; LYG, life years gained; QALYs, quality-adjusted life years; Ven: venetoclax.

B11. Document B, Table 65, page 183. The dosing schedule and drug acquisition cost of gilteritinib and HC/HU are described. Please clarify the currency code and description within the National Tariff 2020/21 of the cost per administration of gilteritinib and HC/HU (£127).

The administration cost of £127 is sourced from the National Tariff 2020/21 using unbundled chemotherapy delivery (HRG code SB11Z). The HRG description is '*Deliver exclusively oral chemotherapy*'.[18]

B12. Document B, page 178. The text refers to the following assumption: "...ventoclax is an oral therapy, it was assumed that there were no administration costs associated with venetoclax treatment." As gilteritinib and HC/HU are also oral therapies, please explain why an administration cost has been assumed.

VenAZA is a combination medication which consists of an infusion or subcutaneous injection (AZA) and an oral chemotherapy (venetoclax), therefore, the cost of £159.00 for the delivery of simple parenteral chemotherapy at first attendance (National Tariff 2020/21, unbundled chemotherapy delivery, HRG code SB12Z) is assumed to cover the cost of dispensing any tablet-based chemotherapies from the pharmacy.[18] No additional costs are assumed for dispensing of venetoclax.

In contrast, gilteritinib is an exclusively oral chemotherapy; therefore, the administration cost of £127 is deemed necessary to cover the cost of dispensing tablets from the pharmacy.[18] When calculating the cost of subsequent treatments (Table 65 and Table 66 of the company submission), separate administration costs for gilteritinib and HC/HU are used as both treatments are assessed individually rather than in combination with another therapy, as is the case with VenAZA.

B13. Document B, Table 63, page 179. Please clarify the currency code and description within the National Tariff 2020/21 for the cost per administration (£159) applied to azacitidine (AZA) therapy and low dose cytarabine (LDAC).

The administration cost of £159 is sourced from the National Tariff 2020/21 using unbundled chemotherapy delivery (HRG code SB12Z). The HRG description is '*Deliver simple parenteral chemotherapy at first attendance'*.[18]

B14. Economic model. Please provide a brief commentary summarising the implementation of the cost-effectiveness model, the purpose of the independent

sheets and VB code, and where user inputs may be toggled in order to produce the scenario analyses described in Document B, section B.3.8.3, page 202 onwards.

Please see separate document entitled ‘Venetoclax AML CEM User-Guide’.

Section C: Textual clarification and additional points

Reference package

C1. Please provide the clinical expert meeting notes (reference 4 of Document B, AbbVie, ‘Data on File: Clinical expert opinion’), as this is not included in the reference package we have received.

Further documentation for discussion with clinical experts is not available. All clinical expert opinion received by the company which is of relevance to this appraisal has been presented within the company submission.

References

1. National Institute of Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013: The reference case. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case [Last accessed: 9th October 2020].
2. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination, University of York, 2008. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf [Last accessed: September 2020].
3. Amadori S, Suciu S, Selleslag D, et al. Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial. J Clin Oncol 2016;34:972-9.
4. Burnett AK, Russell NH, Hunter AE, et al. Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival. Blood 2013;122:1384-94.
5. AbbVie. Data on File. VIALE-A Clinical Study Report.
6. AbbVie. Data on File. VIALE-C Clinical Study Report.
7. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. New England Journal of Medicine 2020;383:617-629.
8. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Blood 2020;135:2137-2145.
9. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015;126:291-299.
10. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood 2018;131:1275-1291.
11. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. Journal of clinical oncology 2003;21:4642-4649.
12. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 2010;28:562-9.
13. National Institute of Health and Care Excellence (NICE). DSU Technical Support Document 14: Survival analysis for economic evaluations aloongside clinical trials – extrapolation with patient-level data. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf [Last accessed: 9th October 2020].
14. Pollyea DA, Stevens BM, Jones CL, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med 2018;24:1859-1866.
15. AbbVie. Data on File. Haematological Malignancy Research Network: Clinical Management, Outcome and Resource Utilisation of Acute Myeloid Leukaemia Audit Report v9. 2020. .
16. National Institute of Health and Care Excellence (NICE). Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [TA642]. Available at: https://www.nice.org.uk/guidance/ta642. [Last accessed: 16th March 2021]. .
17. National Health Service (NHS). National Cost Collection data 2018/19. Available at. https://www.england.nhs.uk/national-cost-collection/ [Last accessed: December 2020].
18. National Health Service (NHS). National Tariff Payment System 2020/21. Available at. https://improvement.nhs.uk/resources/national-tariff-2021-consultation/ [Last accessed: February 2021].

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

May 2021

ERG additional clarification question: Document B, section B.3.8.3, Tables 84 and 85 and clarification response question B6.

It would be helpful if you could provide some further explanation for some inconsistencies in the scenario analysis results presented showing the impact of patients in the cure health state having the same utility as the patients in the remission health state. Please could you clarify the following, providing corrected analyses if necessary:

i) In table 85, why are the incremental costs different from the base case analysis when only the utility values have been changed?

The company wishes to apologise for the error in the results provided in Table 85 in the company submission and has provided the corrected results in

Table *2*. When compared to the base case (Table 1), incremental costs are the same (as expected when only changing utility values) and ICERs are slightly reduced.

Table 1: Base-case results for >30% blasts at Ven PAS price (deterministic)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
VenAZA versus LDAC							
LDAC	£33,828	0.839	0.523				
VenAZA	[redacted]	3.765	[redacted]	[redacted]	2.926	[redacted]	£39,449
VenLDAC versus LDAC							
LDAC	£33,617	0.832	0.518				
VenLDAC	[redacted]	2.438	[redacted]	[redacted]	1.606	[redacted]	£31,291

Abbreviations: AZA: azacytidine; ICER: incremental cost-effectiveness ratio; inc.: incremental; LDAC: low dose cytarabine; LYG: life years gained; QALYs: quality-adjusted life years; Ven: venetoclax.

Table 2: Results from scenario analyses - impact of alternative utility assumption in the >30% blast cell count cohort

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
Patients in cure health state have same utility as patients in remission health state	[redacted]	[redacted]	£38,008

VenLDAC versus LDAC			
Patients in cure health state have same utility as patients in remission health state	[redacted]	[redacted]	£30,027

Abbreviations: AZA: azacytidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine; QALYs: quality-adjusted life years; Ven: venetoclax.

ii) Why is there such a large fall in the QALY gain for the VenAZA vs LDAC analysis (from [redacted] to [redacted]) when the change in the QALY gain for the other comparisons is relatively small?

As stated in Question i), the corrected results have been provided in

Table ***2***. When comparing the differences in the incremental QALYs versus the base case, small changes are now observed (from [redacted] to [redacted]).

iii) It is noted that this analysis results in a fall in the ICERs, which is explained in the CS as 'due to the increased health state utility of patients in remission versus the age-adjusted general population.' This seems counterintuitive when it is stated that the cure health state utility is 0.79 vs 0.74 for the remission health state (see page 178 of the CS). In addition, in response to clarification question B6 ii) it is stated that '....only small numerical differences exist for utility values describing the remission health state and the cure health state....and the ICER remains as it does in the base case.' Please clarify why these two analyses produce different results.

As stated in Question i), the corrected results have been provided in Table 2 and those utilities are not capped in any health state by the utility of the general population. When capping the health state utilities for this scenario to be less than or equal to the general population, the results will be equivalent to the base case results provided in Table 1 where general population utility is applied to cure health state only.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Leukaemia Care is a national blood cancer charity, first registered with the Charity Commission in 1969. We work to ensure that everybody affected by blood cancer has access to the right information, advice and support. Key services fall into 4 categories; • Patient services: such as a freephone helpline, nurse advisors, conferences and information booklets • Advocacy: individual advocacy, health technology appraisals, information and patient surveys • Campaigns: our biggest campaign is Spot Leukaemia, aiming to raise awareness of the signs and symptoms of leukaemia • Services for healthcare professionals, including conferences and online learning platforms. In 2016/17 and 2017/18, over 80% of our funding came from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, which in total represent approximately 15% of our annual income. Any funds received from the pharmaceutical industry are in accordance with the ABPI Code of Practice and the Leukaemia Care Code of Practice, our voluntary commitment that governs how we work with, and accept funding from, the pharmaceutical industry: www.leukaemiacare.org.uk/resources/code-of-practice.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	n/a

5. How did you gather information about the experiences of patients and carers to include in your submission?	Information primarily gathered through Leukaemia Care patient experience survey – 'Living with Leukaemia' (www.leukaemiacare.org.uk/living-with-leukaemia). The latest survey, run in 2017, had 2884 responses (including 443 AML patients). We also spoke to patients who have had venetoclax treatment for their AML to gather qualitative and in depth information on their experiences. Additionally, we have gathered information through our online forums, helpline, support groups, communication with our membership and one to one discussion with patients. We also work closely with other patient groups and share expertise.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Acute myeloid leukaemia (AML) accounts for around a third of cases of leukaemia in adults. 2662 people were newly diagnosed with AML in England in 2016. Approximately two thirds of patients are diagnosed aged 65 and over; older age is associated with poorer prognosis. Due to the rapidly progressing nature of AML, 54% of patients in our survey said they had experienced symptoms for less than a month before visiting their GP. The most common symptoms encountered by AML patients since their diagnosis are fatigue (73%), feeling weak or breathless (51%), memory loss or loss of concentration (38%), bleeding and bruising (37%), itchy skin (35%), nausea or vomiting (35%), sleeping problems (34%), infections (32%), bone or joint pain (31%), weight loss (28%) and muscle pain (23%). The NCIN 'Routes to Diagnosis' report shows that 53% of AML patients are diagnosed via emergency presentation, compared to a cancer average of 22%, and emergency diagnosis is correlated with poor prognosis. Patients with acute leukaemia often get ill suddenly and must start treatment quickly; 55% of AML patients surveyed started treatment within a week of diagnosis. AML patients experience a considerable emotional impact as a results of their emergency diagnosis. AML can have a huge emotional impact, prompting patients and their families to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. Our survey reports 51% of AML patients have felt depressed or anxious more often since their diagnosis. AML also has a wider practical impact, with 52% of patients experiencing pain as a direct result of their condition (31% occasionally, 17% regularly and 4% constantly). Additionally, 51% of patients have

	difficulty moving around (sometimes 27%, often 15% and always 9%) and 69% of AML patients have difficulty performing some of their daily routines, such as cooking or cleaning. Another 38% reported that they have problems taking care of themselves. Of those in work or education before their diagnosis, 77% have been impacted (32% reduced hours, 45% no longer able to work or continue education). Consequently, 53% of AML patients reported a negative financial impact as a result of having cancer (increased costs or reduced income). This financial impact can be particularly devastating when in those with a reduced income already, such for those who are retired. The emotional impact does not affect the patient in isolation and is often also felt by carers and family members. This can place huge emotional strain on families and friends, many of whom may be affected by the diagnosis. According to an international survey run by the Acute Leukaemia Advocates Network in 2019, 35% of patients reported their AML definitely had an emotional impact on their family, friends or carers. As such, improvements in a patients treatment and prognosis will also have a wider impact on the lives of their family and friends. “My dad of 81 years old has been diagnosed with AML and given 6 months to live…. It’s just really sad and upsetting. We lost mum 2 years ago to cancer - can anyone give me any more info on my dads condition or anything else I should be prepared for?” – patient’s relative, online forum “My ex-partner [was] diagnosed with AML. I feel as though I’m in a fog but been with him throughout.” – patients relative, online forum In addition to the emotional impact on family and friends, if patients are unable to care for themselves, these family and friends can then become carers. Many patients (41% of those surveyed) feel their AML has had an impact, to some extent, on the social activities of their family, friends or carers, this is likely due to increased responsibilities. This can be a huge change in dynamics in the relationship between the patients and their relative/friend, with emotional effects. Additionally, caring is physically exhausting and may be done in addition to paid work. Alternatively, family may have to give up work to care for the patients, leaving the family in even more financial difficulty.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatment for those who cannot tolerate intensive chemotherapy is restricted to azacitidine (if patient has 20-30% blasts and multilineage dysplasia), low dose cytarabine and daunorubicin (LDAC) or best supportive care. These have limited efficacy, with low response rates and most patients experiencing relapse quickly. Treatment for AML was much the same for 20 years, up until the last couple of years, which have seen a breakthrough in treatment options. These include treatments targeting specific genetic mutations (e.g. FLT3-ITD inhibitors) and improved formulations of chemotherapy. However, these are all intensive treatments, only suitable for those who can tolerate such intensive options. Chemotherapy based treatments are associated with severe side effects as reported by patients. [“I was given standard chemotherapy. I suffered various side effects from rashes, high fevers of 41.7, sepsis, erythema nodosum, lung fungal infections and the usual vomiting and diarrhoea. I also suffered an excruciating inflammation of the small intestine”].
8. Is there an unmet need for patients with this condition?	Those who are ineligible for intensive chemotherapy are usually people who are older, although age should not be the only factor in this decision. However, these is a misconception that all older patients do not want to be treated, and this has led to some inequalities in treatment options presented to patients (“I wasn’t born yesterday” report, Leukaemia Care).There are limited non-intensive chemotherapy options for these patients that are effective and prevent patients from relapsing. Older patients are still wanting effective treatments, and they deserve to have these treatments made available to them. AML patients would like a choice of treatment options, 69% of patients feel like there are not enough treatments available on the NHS in the UK. Given the age and acute nature of their condition, additional targeted and effective treatment options with tolerable side effects profile are needed.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	This treatment benefits patients that cannot tolerate the current intensive therapy options. In the phase 3 VIALE trial, this new treatment combination is being compared to the currently available option for this set of patients, which is azacitidine. The novel treatment is showing improved medial overall survival (OS) rates of 14.7 months compared to 9.6 months and a higher complete remission rates of 36.7% compared to 17.9%. The most popular feature of a new treatment for patients is improved or longer survival (indicated as preferable by 80% of AML patients surveyed). It offers an important alternative in older patients, who currently have very few effective options available to them, with manageable side effects profile. The treatment is delivered orally, which is a positive as oral medication is the most popular route of delivery among respondent to our survey. Oral medications also reduces burden on hospitals, as treatments can be delivered at home. A patient on venetoclax reports positive feedback, in terms of being able to carry out normal day-to-day activities and the impact on quality of life as a result: “Admitted for one week as an inpatient for monitoring and to check for signs of Tumour Lysis which did not affect me at all. Even during this week, I was able to leave the hospital and go out and pick-up meals and see friends and not spend long bouts in isolation as I had done before” “My MRD was negative within the first cycle and remain negative” [“There are many benefits of this drug. I was able to continue to be a mother to my young children and carry out all my usual duties, driving, housework, cooking, and looking after myself. I could spend time on the weekends doing normal family activities like walking and cycling. I was able to meet friends, go to the gym regularly, and even go on holidays enjoy a quality of life that was not possible as an inpatient in hospital. My hair started to grow back which made me feel more normal and less sick, and I did not have any nasty rashes or other side effects when on the Venetoclax”]

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Venetoclax can lead to tumour lysis syndrome in some patients. However, this is managed by dose modification and patients are aware of this. A patient has reported side effects of low dose cytarabine, this includes nausea and vomiting, however this is managed by treatments. "During the Cytarbine part of the cycle, I did feel fairly queasy, a bit like having a really bad hangover and about 6 month into treatment I began to suffer increasingly worse nausea and vomiting from the cytarabine only which did slow me down a little. As soon as I stopped the injections I felt better and resumed normal activities. This was helped with different anti-nausea drugs and I did need GCSF at times to boost my neutrophils".
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It will benefit all patients unable to tolerate intensive chemotherapy.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- AML is a rapidly progressing life-threatening disease, largely affecting those over the age of 65.
- Patients unable to tolerate an intensive chemotherapy option, largely those who are elderly but no exclusively, have very limited effective treatment options. Some patients choose not to have the intensive options available to avoid side effects and the less intensive options are not as effective.
- Venetoclax offers a life extending option; it has an improved overall survival (OS) rate of 14.7 months compared to 9.6 months with current standard treatment options for older patients.
- Patients report a positive feedback with venetoclax, including the oral tablet aspect and improvement in their symptom burden, which impacts positively on their quality of life.
- There is a clear unmet need of effective treatment options with tolerable side effects profile, for patients unable to tolerate intensive chemotherapy, which this new targeted treatment offers.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Professional organisation submission

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology specialities.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The main aim of this treatment is to prolong life and improve quality of life in patients with AML in whom intensive treatment is unsuitable.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improved overall survival. A significant reduction transfusion requirement. Significant improvement in event free survival
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a major unmet clinical need for new therapies for AML in this group of patients. Treatment options for this group are very limited with the only active treatment option for patients with >30% blasts being low dose cytarabine (LD AraC). This has been the case since the 1970s and outcomes for this group remain dismal. Response rates for LD AraC as a single agent are also poor ranging from 10-20% in published studies and OS <6 months. Outcome are particularly poor in patients with secondary AML and those with complex karyotype or p53 mutation who do not benefit from LDAraC. The agents outlined in this technology appraisal, Venetoclax/Azacitidine and Venetoclax/LD AraC are well tolerated given mainly on an outpatient basis. This is a major advance in therapy for patients with AML and for the clinicians taking care of them.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients are assessed for fitness for intensive chemotherapy at diagnosis. This is based on age, co-morbidities (particularly cardiac), and performance status. Those who are not fit enough to receive intensive chemotherapy are treated with one of four options below. 1. Patients with 20-30% blasts are eligible for treatment with azacitidine (TA218).

	2. Low dose Ara-C given subcutaneously 3. Supportive care (blood products, antibiotics) 4. Investigational agents on a clinical trial Fit patients are treated where possible on national clinical trials (AML18 and AML19) or with chemotherapy - daunorubucin and Ara-C with or without myelotarg or midostaurin depending on diagnostic features (TA545 and TA523 respectively), or Vyxeos (TA552). At the current time there is interim NICE guidance in place due to COVID-19 that gives the option to use venetoclax with either low-dose AraC or azacitidine (as described in this TA) instead of standard induction chemotherapy for newly diagnosed acute myeloid leukaemia, to reduce the need for prolonged in-patient admission and reduce risk of neutropenia.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are currently no national guidelines for the treatment of AML in the UK (although some are currently in preparation). However, there are a number of regional guidelines, such as the pan London Haemato-Oncology clinical guideline. https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-AML-Guidelines-Jan-2020.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined. The main varibility in care for this patient group is likely to arise in relation to an individual clinicians assessment of whether a patient is "fit" for intensive chemotherapy, particularly if there is any delay in initial diagnostic testing which can assist in predicting outcome for older patients who receive intensive chemotherapy[1]. The patient's geographical location may also impact care since intensive chemotherapy is only delivered in centres providing level 2b or level 3 care. Therefore some patients may not wish to travel to these locations and elect supportive care closer to home.
• What impact would the technology have on the current pathway of care?	The technology would increase the options of care for those unfit for chemotherapy who currently have extremely limited options. It is possible that some patients may be recommended to receive this technology where in the past they might have been considered fit enough for intensive chemotherapy by some

	clinicians (see comments above). This may be driven by the ability for this technology to be delivered in Level 2a centres and predominantly as an outpatient.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. As a result of COVID-19 interim guidelines we now have 9 months of experience using this technology. There are differences in the level of monitoring and in-patient stays compared to the comparator arms (LD Ara -C, Aza or best supportive care (BSC)) with the technology requiring a modest increase in regular blood tests.
• How does healthcare resource use differ between the technology and current care?	The technology is designed to be given in the outpatient setting. Single agent Azacitidine and LD-Ara C are routine options given to this patient group (the former only available in a subset of patients) and venetoclax is an oral agent. However due to concern over side effects of the combination treatment and the known issues in other haematological malignancies of tumor lysis, current practice (from local experience and in common with clinicians I have discussed with around the country) is to admit patients for the first 10-14 days of therapy of the first cycle of treatment. As our confidence and experience of the technology improves we are increasingly commencing treatment in the outpatient setting and expect eventually to only admit selected patients in whom there is risk of tumor lysis (patients with high white cell counts). The incidence of tumor lysis in the Viale-A and Viale-C studies was only 1% and 6% respectively. We have seen one case of TLS in the patients treated at our centre (out of 30) who had other major risk factors for this (very high presenting white cell count) which is in keeping with published data.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be administered in specialist haematology units but is likely to be accessible to centres delivering level 2a care as well as 2b and 3.
• What investment is needed to introduce the	No new facilities or equipment are required to deliver this technology.

technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The technology has clear clinical benefits over the current standard of care and is a major step change in the management of patients with AML in those unsuitable for intensive chemotherapy.
• Do you expect the technology to increase length of life more than current care?	Yes. The main body of evidence is derived from the recently published randomised placebo controlled VIALE-A study[2]. This study randomised patients to Ven/Aza vs Placebo/Aza that showed a highly significant improvement in OS (14.7 months compared to 9.6 months p<0.001) as well as significance across a range of secondary endpoints favouring Ven/Aza . The data for LD AraC/Ven is phase 1b/II [3] and the Phase 3 randomised placebo control VIALE-C study[4]. Notably VIALE-C included patients who had received therapy with azacidtine (or other hypomethylating agent- HMA, presumably for MDS) in 20% of patients. Subgroup analysis of OS in patients who had not received an HMA showed greater effect of Ven/LD-AraC (OS 8.8 vs 3.7 months). From this published evidence patients also respond favourably to this combination but the survival benefit is most prominent in those patients who have not received prior hypomethylating agents. Additional factors to point note are that many AML patients would not be eligible to receive azacitidine single agent (the control arm in VIALE-A) and therefore the appropriate comparator arm for this appraisal is against LD AraC alone (as in Viale-C) or BSC. Although a direct comparison is not possible between studies, and a small proportion of patients can currently receive aza monotherapy under TA218, the median survival in VIALE-A Ven/Aza arm was 14.7 months compared to the LD-AraC control arm at 3.7 months. This comparison is closer appropriation to what we would expect in the majority of AML patients treated in the UK in this patient group.

• Do you expect the technology to increase health-related quality of life more than current care?	Non-statistically significant quality of life improvements were observed in the Viale-C but not the Viale-A study.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are clearly some groups of patients who do extremely well with the Ven/Aza combination (e.g. patients with IDH2, NPM1 or p53 mutations) however the data support that all subgroups benefit from this combination. In the Ven/LD AraC study, similarly IDH and NPM1 mutated patients fared extremely well (median OS not reached at the time of last analysis in the publication for the NPM1 group) but again I feel the benefit is across all patients.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Overall the technology delivery is not more difficult to use the single agent Aza or LD-AraC but does increase the incidence of neutropenia. Admissions with febrile neutropenia were greater with the technology combinations, however there was no overall difference in adverse events compared to control arm in the Phase III studies. Because of concern regarding neutropenia we routinely monitor full blood counts on patients on a weekly basis. Patients on supportive care or single agent Aza are more likely to monitored in an ad hoc manner depending on symptoms and transfusion needs.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The treatment will be stopped if the patient shows progression of disease. This will usually require a bone marrow biopsy.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, a greater number of patients will become transfusion independent receiving the technology. In Viale-A this was 68.5% for platelet independence (vs 49.7% aza alone) and 59.8% for red cell independence (vs 35.2% aza alone). In Viale-C a composite figure for both red cell and platelet independence of 37% for LD-AraC/Ven vs 16% LD AraC alone is given. Patients receiving best supportive care would not be expected to have any improvements, and again only a small number of patients with AML in the UK would be eligible to receive single agent Aza therefore the comparators are not the same as given in the study so the benefit of the TA may be under represented. Transfusion independence significantly reduces the amount of time they will spend attending hospital due to the need for pre transfusion bloods (and COVID swab currently) and the actual duration of the transfusion itself (usually several hours)

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Venetoclax is a first in class agent for its use in AML and is innovative in both mechanism and synergy with existing agents. Both phase 1b/II and Phase 3 published trial data support that this technology is a major step change in how we manage AML. Importantly the administration of these agents can be given largely on an outpatient basis (with the exception of the induction phase) thereby minimizing hospitalisation days and overall toxicity profiles are favourable permitting delivery to this group of patients who otherwise have extremely limited options and a dismal outlook.
• Is the technology a 'step-change' in the management of the condition?	Yes. The mechanism of action and the toxicity profile are very different to our currently available therapies. This therefore permits administration to life-prolonging treatments to patients who would otherwise have very limited options. The response profile also includes subgroups of patients whose disease would generally respond poorly to LD-AraC or intensive chemotherapies.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. The active treatment option for most of these patients is so limited in its efficacy that BSC is often the only thing appropriate to offer these patients. This is particularly true of high risk disease with complex karyotype or p53 mutations who do not respond to single agent LD AraC. Therefore there has long been a significant unmet need for active therapies suitable for this patient group which this TA delivers.
17. How do any side effects or adverse effects of the technology affect the	The main difference in side effects of the TA is the increased incidence of febrile neutropenia. Treatment of febrile neutropenia requires admission to hospital for management. As our experience with the technology increases we expect to more aggressively and pre-emptively manage neutropenia. Nonetheless, such

management of the condition and the patient's quality of life?	events are offset by a reduction in the number of hospital visits for transfusions which are both labour and time intensive for patients.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Viale-A uses Aza+placebo as the control arm for the Ven/Aza combination. Azacitidine for AML with more than 30% blasts is not approved for use in the UK (TA399). Therefore only those patients with AML whose disease subtype was treated in the initial MDS studies with 20-30% blasts (at that time referred to as MDS - refractory anaemia with excess blasts in transformation) are eligible for Aza. Therefore the Azacitidine comparator is not the standard of care available to UK clinicians for most AML patients
• If not, how could the results be extrapolated to the UK setting?	In the Viale-C study the comparator (LD-AraC+placebo) is reasonable to compare with the TA (with either Ven+LD AraC or Ven+Aza) since many of this group of AML patients will receive LD-Ara. For patients with low blast counts (20-30%) the subgroup analysis of the MDS-Aza 001 study may provide useful information about responses to Aza alone in this group, however there is no subgroup analysis using only these patients in VIALE studies with which to compared the combination TA with the single agent Aza to obtain a meaningful comparison[5]. Azacitidine monotherapy has also been assessed in AML patients in a phase III open label study with blast counts over 30% in the AML-AZA-001 study. This resulted in the licencing but not NICE approval of Aza for this indication. The comparator arm in this study was a composite group of 3 treatment arms assigned by the patient's clinician. This was made up of LD-AraC (64%), intensive chemotherapy (17.8%) and best

	supportive care (18.2%). This comparator, while it does include some patients receiving intensive chemotherapy, represents an alternative reasonable reflection of current UK practise for AML patients that would be eligible for this TA. The OS of patients on this composite comparator arm was 6.5 months.[6]
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival is the most important outcome which was measured in both VIALE studies. This was measured in both trials with VIALE-A (Ven/Aza) meeting its primary endpoint. VIALE-C (Ven/LD AraC) did not meet its primary endpoint at the planned analysis point (at a median follow-up of 12 months - OS 7.2 vs 4.1 months) however following a further 6 months of follow-up this reached statistical significance (OS 8.4 vs 4.1 months). Important secondary endpoints are response rate and reduction in transfusions. Both studies showed significantly in favour of the TA in this regard. Outcomes for Ven/LD AraC are not as striking as for Ven/Aza. However, the Ven/LD AraC combination benefits from the capability for patients to be managed almost exclusively at home since LD AraC does not have the stability and administration issues that Azacitidine does which requires daily OP attendances at the majority of institutions. Furthermore, certain subsets do very well with this combination.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	

21. How do data on real-world experience compare with the trial data?	Real-world experience differs due to the widespread use of prophylactic azoles for prevention of fungal infection in patients receiving the technology. These are strong CYP3A inhibitors and lead to a reduction in the dosing of venetoclax. In addition we have found that the incidence of neutropenia is high and to offset this 10-14 days of venetoclax is usually sufficient. Limited real-world outcome data has been published (33 patients) and compared to historical controls suggesting promising but slightly inferior outcomes [7]. Data collated from our UCLH cohort since April 2020 following departmental and subsequently NICE approval to use the TA combination in the COVID-19 pandemic, consists of 30 patients with a median age of 72 years. Response rates to the TA were 82%. Data on OS are not mature due to the short time we have been able to use this therapy but response rates are very promising.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	NA

Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Venetoclax plus azacitidine or low dose AraC is the greatest advance in treatment for patients with AML not suitable for intensive chemotherapy in over 30 years and represents a step change in therapy for this disease.
- The ventoclax/Azacitidine combination results in significant prolongation of life
- Venetoclax/Azacitidine and Venetoclax/LD AraC are well tolerated and given mainly as outpatient based therapies
- Venetoclax/Azacitidine and Venetoclax/LD AraC reduce transfusion requirements in AML patients
- Venetoclax/Azacitidine and Venetoclax/LD AraC are effective in all risk groups but strikingly effective in certain subsets of patients. Some of these best improvements are seen in patients with the highest risk disease.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

References

1. Wheatley K, Brookes CL, Howman AJ, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. *Br J Haematol*. 2009;145(5):598-605.

2. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med*. 2020;383(7):617-629.
3. Wei AH, Strickland SA, Jr., Hou JZ, et al. Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study. *J Clin Oncol*. 2019;37(15):1277-1284.
4. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135(24):2137-2145.
5. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol*. 2010;28(4):562-569.
6. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126(3):291-299.
7. Winters AC, Gutman JA, Purev E, et al. Real-world experience of venetoclax with azacitidine for untreated patients with acute myeloid leukemia. *Blood Adv*. 2019;3(20):2911-2919.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**RCP-ACP-NCRI**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCR**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Acute Myeloid Leukaemia is the most aggressive common blood cancer. It is fatal usually within 2-4 months without disease modifying treatment. Fatality and poor quality of life arises as the AML dramatically reduces the body's ability to make new blood cells. The human body needs to make new blood cells daily to prevent life-threatening infection, bleeding and anaemia. The aim of treatment is to prolong life and improve quality of life by reducing AML cell infiltration of the bone marrow (blood factory) and allow restoration of daily blood cell production. ~70% of AML patients are over the age of 65 years old. Most of these patients cannot be treated curatively with intensive chemotherapy

or prevent progression or disability.)	(with or without allogeneic stem cell transplant) due to excessive toxicity of this approach. The majority of less biologically fit AML patients are considered for less intensive therapies to prolong survival and improve quality of life. This is achieved if treatment produces a clinical response (remission) that results in a sufficient blood production to prevent infection, bleeding and anaemia. This then allows a patient to be at home, to not have to be repeatedly admitted to hospital for intravenous antimicrobials and blood component transfusions.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Increased overall survival (OS) with improved quality of life. Significant responses are therefore those where complete remission (CR) or complete remission with incomplete count recovery (CRi) (but sufficient to reduce infection and bleeding) is achieved which usually translates into increased survival and fewer disease related complications (disease related symptoms, infections, transfusions and hospital admissions) and improved quality of life. The current standard of care treatment, low dose Ara-C (for patients with greater than 30% blasts) and azacitidine (for patients with less than 30% blasts) achieve complete remission rates of 10-17% with a median survival for patients of only 7-9 months. Patients who achieve complete remission have a better overall survival that those who do not. So new treatments that improve OS and CR/CRi are clinically significant. Of course, the longer the increase in OS and the greater the CR/CRi rate over current standard of care the better. From a patient perspective, any gain in OS and CR/CRi must be balanced with any increased toxicity of treatment. Thus, the overall time the patient has functioning independently and away from hospital is also crucial.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Absolutely- AML is predominantly a disease of older patients many of whom cannot receive conventional intensive/curative approaches. Current therapies are inadequate and patients are poorly served by them. From a health care utilisation point of view, patients who fail to achieve CR/CRi to current therapies (80-90%) have high demand of in-patient care (from infection) and blood products delivered through day units and as in-patients.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	When intensive therapy is unsuitable the UK standards of care are low dose ara-C (LDAC) and the hypomethylating agent azacitidine (AZA) in addition to best supportive care (including hydroxycarbamide, antimicrobials and blood products). In recognition of the poor outcomes with standard therapy many patients have entered clinical trials to evaluate novel approaches in this setting. During the COVID19 pandemic Venetoclax based combination therapy (with LDAC and AZA) has been made available for older patients considered fit for intensive therapy- to reduce hospitalisation and intensity of therapy. The published evidence of such combination therapy is overwhelming for the older unfit AML population so may have been used in this patient population too.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no relevant UK-based guidelines (currently in development). The ELN (European Leukaemia Net) Guidelines published in 2017 stating 'Treatment of unfit and most older patients with AML is currently unsatisfactory. We strongly recommend enrolling these patients in clinical trials'. All regional cancer networks have their own agreed guidelines of which there are many examples https://gmcancerorguk.files.wordpress.com/2019/04/guidelines-for-the-management-of-acute-myeloid-leukaemia-2019.pdf All the published guidelines predate publication of the most recent VIALE-A/C studies.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Treatment pathways/networks are well established in all regions for managing AML.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	In the early development of Venetoclax there were concerns about the development of tumour lysis syndrome and therefore treatment is always initiated as an inpatient to provide appropriate supportive measures. Currently the standard therapies are usually administered in the ambulatory/day care setting. Therefore, short duration inpatient admissions would be required. On the flip side, venetoclax-AZA and venetoclax-LDAC achieve CR/CRi in a higher percentage of patients and after a median of 1-2 cycles, as opposed to the lower CR/CRi rates with AZA and LDAC that take more cycles to achieve. This will reduce in-patient stay. Furthermore, it would be anticipated that venetoclax-AZA and venetoclax–LDAC may be considered more appropriate for some AML patients, who on the cusp of are being considered fit, who have historically had intensive therapy (with prolonged hospital admissions). The net effect on inpatient bed utilisation likely to be insignificant.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes- Some UK sites participated in the licensing study (VIALE-A) and since the COVID19 guidance most if not all UK Haematology unites now have experience of using Venetoclax combined with either LDAC or AZA.
• How does healthcare resource use differ between the technology and current care?	Largely unaltered
• In what clinical setting should the technology be	Outpatient/day-case units of specialist Haematology units (secondary/tertiary care)

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None beyond current standard of care
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes The FDA approval was based upon Venetoclax studied in two open-label non-randomized trials in patients with newly-diagnosed AML who were ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, or Crcl <45 mL/min or other comorbidity. Efficacy was established based on the rate of complete remission (CR) and the duration of CR. 145 patients were treated in combination with hypomethylating agents (AZA and Decitabine) with a 67% response rate (CR/CRi) and median OS of 17.5 months. 82 patients were treated in combination with LDAC with a response rate of 54% (CR/CRi) and median OS of 10.1months. Very high rates of response were observed in the NPM1 and IDH1/2 mutated subgroups. The results of the completed randomised phase 3 studies VIALE-C (LDAC+/- VEN) (Wei AH, Strickland SA Jr, Hou JZ, et al. Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study. J Clin Oncol. 2019;37(15):1277-1284.) and VIALE-A (AZA +/- VEN) (DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383(7):617-629) have both been published last year. VIALE-C confirmed the high response rates with the addition of Venetoclax but did not meet the predetermined primary endpoint in terms of improved overall survival. VIALE-A demonstrated at a median follow-up of 20.5 months, the median overall survival was 14.7 months in the azacitidine–

	venetoclax group and 9.6 months in the control group (hazard ratio for death, 0.66; 95% confidence interval, 0.52 to 0.85; P<0.001).a composite complete remission (complete remission or complete remission with incomplete hematologic recovery) (66.4% vs. 28.3%; P<0.001) NEJM 2020. The results have been widely accepted as VEN-AZA being the new standard of care for this patient group.
• Do you expect the technology to increase length of life more than current care?	Yes (Median 5.1 months in VIALE-A)
• Do you expect the technology to increase health-related quality of life more than current care?	Yes VIALE-A QOL data currently only presented in abstract form from the 2020ASH meeting https://ash.confex.com/ash/2020/webprogram/Paper133912.html
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	All sub populations of older AML appear to benefit compared to standard of care. Molecular sub-groups (% incidence in older AML patients) of IDH1(7%), IDH2 (15%) and NPM1(20%) have higher CR and OS compared to the population as a whole.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare	Very similar, with all sites experienced in Venetoclax combinations during this last year.

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Concomitant use of azole antifungal therapy (Posaconazole, Voriconazole….) is common (these are strong cytochrome P450 3A (CYP3A) inhibitors, as Venetoclax is a CYP3A substrate elevated levels are experienced and so substantial dose reductions of Venetoclax are required. The major toxicity is haematological- predominantly neutropenia which clinical teams are experienced in the management of.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Regular blood and bone marrow monitoring will be undertaken- largely in line with the current standard of care. No additional testing is anticipated.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	No

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes This is the first combined non-intensive therapy which has improved OS for older AML patients. Many agents have been evaluated without success. We finally have a new standard of care.
• Is the technology a 'step-change' in the management of the condition?	Yes As the new standard of care all subsequent evaluations/clinical trials will be evaluated against Venetocax-AZA. AML Studies in development are building on this platform.
• Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the	Broadly the side effects are very similar to the standard of care (LDAC or AZA)- one area of significant difference is in grade 3 or higher haematological toxicity especially neutropenia (42% with VEN vs. 28%)

technology affect the management of the condition and the patient's quality of life?	and associated febrile neutropenia (42% vs 19%). The majority of patients require dose reductions or delays. Although the 30-day mortality is very low for this population (6-7%) indicating effective prophylactic and supportive strategies.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes There were 3 UK sites for VIALE-A and 7 sites in the comparable VIALE-C study. Contemporaneously there were several similar studies active in the UK.
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	•overall survival • event-free survival • disease-free survival • response rates, including remission • adverse effects of treatment • health-related quality of life. Yes- all measured in the P3 studies

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Largely as defined in Q7 in terms of survival and response- which is comparable to findings in the placebo arm of VIALE-A
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	NA
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to	

be required for every appraisal.]	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Venetoclax combined with LDAC or AZA improves response rates
- Venetoclax with AZA improves overall survival
- Venetoclax with LDAC may be the optimal combination for NPM1 mutated AML patients
- The combinations are well tolerated with low treatment related toxicity and manageable side effects
- Venetoclax with AZA is the new standard of care for all AML when intensive chemotherapy is unsuitable

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia unsuitable for intensive chemotherapy [ID1564]

Produced by Aberdeen HTA Group

Authors

Moira Cruickshank[1]
Charlotte Kennedy[2]
Lorna Aucott[1]
Corinne Booth[3]
Mari Imamura[1]
Thenmalar Vadiveloo[1]
Paul Manson[1]
Gavin Preston[4]
Graham Scotland[1,2]
Miriam Brazzelli[1]

1 Health Services Research Unit, University of Aberdeen, UK
2 Health Economics Research Unit, University of Aberdeen, UK
3 Health Economist, Independent Consultant
4 NHS Grampian, Aberdeen, UK

Correspondence to Miriam Brazzelli
Health Services Research Unit, University of Aberdeen
3rd Floor, Health Sciences Building, Foresterhill
Aberdeen, AB25 2ZD
m.brazzelli@abdn.ac.uk

Date completed **28 May 2021**

Contains [redacted]

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number **133147**

Declared competing interests of the authors

No competing interests to disclose.

Acknowledgements

The authors are grateful to

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows*: Cruickshank M, Kennedy C, Aucott L, Booth C, Imamura M, Vadiveloo T, Manson P, Preston G, Scotland G, Brazzelli M. Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia unsuitable for intensive chemotherapy [ID1564]. Aberdeen HTA Group, 2021*.

Contribution of authors

Moira Cruickshank and Mari Imamura summarised and critiqued the clinical effectiveness evidence; Lorna Aucott and Thenmalar Vadiveloo checked and critiqued the statistical analyses presented in the company submission; Graham Scotland was the health economics lead for the appraisal; Charlotte Kennedy and Corinne Booth reviewed and critiqued the cost-effectiveness evidence and model; Paul Manson checked and critiqued the company's search strategies; Gavin Preston provided clinical guidance and comments on the draft report. Miriam Brazzelli was the clinical effectiveness lead for the appraisal and coordinated it. All authors contributed to the writing of this report and approved its final version.

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse event
AIC	Akaike information criteria
AML	Acute myeloid leukaemia
AZA	Azacitidine
BCL-2	B-cell lymphoma 2
BIC	Bayesian information criteria
BM	Bone marrow
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for M
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CR	Complete remission
CRD	Centre for Reviews and Dissemination
CRh	Complete remission with or without partial haematological recovery
CrI	Credible interval
CRi	Complete remission with incomplete blood count recovery
CRp	Complete remission with incomplete platelet recovery
CS	Company submission
CSR	Clinical study report
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EFS	Event free survival
ELN	European Leukaemia Net
EORTC	European Organisation Research and Treatment of Cancer
EPAR	European Public Assessment Report
ERG	Evidence review group
ESMO	European Society of Medical Oncology
FAS	Full analysis set

GHS	Global health status
HMA	Hypomethylating agent
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
IA1/2	Interim analysis 1/2
IC	Intensive chemotherapy
ICER	Incremental cost-effectiveness ratio
IVRS/IWRS	Interactive voice response system/ interactive response system
KM	Kaplan Meier
LDAC	Low-dose cytarabine
LY	Life year
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicine and Healthcare Products Regulatory Agency
MID	Minimum important difference
MRC	Myelodysplasia-related changes
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NHS	(UK) National Health Service
NMA	Network meta-analysis
OR	Odds ratio
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PSA	Probabilistic sensitivity analysis
PSA	Propensity score analysis
PSS	Personal social services
PSW	Propensity score weighting
QALY	Quality adjusted life year
RCT	Randomised controlled trial

SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
TEAE	Treatment emergent adverse event
Ven	Venetoclax
WHO	World Health Organisation

1. Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of submitted evidence and ERG's key issues

The company submission focuses on venetoclax [redacted].

The clinical effectiveness evidence is provided by two ongoing, phase III randomised, double-blind, placebo controlled, international studies: VIALE-A (comparing venetoclax plus AZA [VenAZA] with AZA) and VIALE-C (comparing venetoclax plus LDAC [VenLDAC] with LDAC). The clinical outcomes used in the economic model are overall survival (OS), complete remission (CR) + CR with incomplete haematological recovery (CRi), event -free survival (EFS), adverse effects, and health-related quality of life (HRQoL). In VIALE-A, the company submission reports the results of CR + CRi from an initial interim analysis (IA1) with a 6-month follow-up (cut-off date 1st October 2018). Results from IA2 with a median follow-up of 20.5 months (cut-off date 4th January 2020) are presented for all outcomes. For VIALE-C, the company presents results for OS from a primary IA (cut-off date 15th February 2019). Results from a subsequent, unplanned analysis with an additional 6 months of follow-up (cut-off date 15th August 2019) are presented for all outcomes. Meta-analysis was not performed.

In VIALE-A, treatment with VenAZA was associated with a statistically significant prolonged OS compared with the AZA group. The composite complete remission rate (CR + CRi) was achieved by a statistically significant higher proportion of participants treated with VenAZA then those treated with AZA. In VIALE-C, no significant difference was observed in OS between the VenLDAC and LDAC groups at the primary analysis. However, treatment with VenLDAC was associated with prolonged OS in the VenLDAC group compared with the LDAC group in the subsequent unplanned analysis with an additional 6 months of follow-up. The composite complete remission rate was achieved by a statistically significantly higher proportion of the VenLDAC group than the LDAC group.

There was no direct head-to-head evidence to compare the relative efficacy of VenAZA with LDAC. The company chose two indirect approaches; using IPD data from both VIALE-A and VIALE-C matched with propensity scoring and the standard anchored network meta-analyses which included the AZA-AML-001 study as well as VIALE-A and VIALE-C. The propensity score approach could use all the samples (matched) but only from the two VIALE studies. The company split these and reported mainly on those with >30% bone marrow blasts. This was to be comparable with the NMA results which could only be conducted on a common sub-group of >30% blasts hence, with reduced sample size albeit with the advantage of the additional included trial. The propensity scoring approach and NMAs all showed that treatment with VenAZA was associated with a lower risk of mortality than treatment with LDAC, and the difference was statistically significant. In addition, those receiving VenAZA were statistically significantly more likely to achieve composite complete remission than those receiving LDAC.

With respect the company's economic case, the ERG mains concern relates to uncertainty regarding the plausibility of a cure assumption being applied in the economic model for patient who remain in remission at two years in the venetoclax arms. Further issues regarding the company's modelling assumptions are outlined in Table 1, with more details provided in section 1.5.

Table 1 Summary of key issues

ID1564	Summary of issue	Report sections
1	Cure assumptions applied to those on VenAZA and VenLDAC who are in remission at 2 years	4.2.6
2	Uncertainty regarding the justification for using general population mortality to adjust the curves used to estimate transition probabilities to progressive disease health state	4.2.6
3.	Inconsistent assumptions related to modelling of time on treatment and subsequent treatment	4.2.6
4.	Impact of adverse events on quality of life	4.2.7
5.	Potential for wastage of venetoclax	4.2.8
6.	The distribution of subsequent treatments by treatment arm	4.2.8

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are the removal of the cure assumption for those in the venetoclax arms who remain in remission at two years.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients who achieve remission
- Delaying or preventing progression of disease or relapse from remission
- Increasing survival

Overall, the technology is modelled to affect costs by:

- Its higher unit price compared to current treatments.
- Influencing the time patients spend in different health states

The modelling assumptions that have the greatest effect on the ICER are:

- Whether or not a cure assumption is applied to those in remission at 2 years in the venetoclax arms
- The curve selections for time to relapse (from remission) and time to death from progressive disease

1.3 The decision problem: summary of the ERG's key issues

The ERG considers that the decision problem addressed by the company was in line with the final scope issued by NICE. The population and interventions included in the evidence submitted by the company are consistent with the expected marketing authorisation. The ERG's clinical expert is of the opinion that the study participants are reflective of patients with untreated acute AML and ineligible for intensive chemotherapy in clinical practice in the UK and he is not concerned with the difference between the dose of venetoclax used in the trials (400mg in VIALE-A; 600mg in VIALE-C) and the dose usually used in UK clinical practice (100mg).

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG considers the company's methods used to conduct the systematic review of clinical effectiveness evidence to be acceptable and in line with current methodological standards. A limitation of the clinical effectiveness evidence submitted by the company relates to the splitting of the VIALE trials data into the 20-30% blasts sub-population and the >30% blasts sub-population. Although it is recognised by the company that the VIALE trials were not powered to identify a clinical benefit in these sub-populations, positive outcomes were still observed for participants treated with venetoclax. However, the further splitting of data to inform transition probabilities in the economic model, results in some further uncertainty with respect to model extrapolations.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The ERG's key issues that relate to the cost-effectiveness evidence are detailed below (Issues 1-6).

Issue 1 Cure assumption

Report section	4.2.6 (Treatment effectiveness and extrapolation)
Description of issue and why the ERG has identified it as important	The ERG does not believe the "cure" assumption to be fully justified based on the available data. Historically, non-intensive treatments have never been curative in this generally [redacted].These patients [redacted] that is used with curative intent in the broader AML population. There is currently a lack of long-term follow-up data to validate a cure assumption for venetoclax. The maximum follow up of the VIALE-A and VIALE-C trials (2.56 and [redacted] years respectively) are not sufficiently long to determine whether patients who are in remission at two years can achieve the same outcomes as the general population and no longer be at risk of relapse. Furthermore, the argument that the Kaplan-Meier EFS and OS curves for venetoclax in each population appear to plateau is dependent upon a small amount of data. The ERG clinical expert finds the assertion that AML patients in this indication could experience the same outcomes as the general population after achieving remission for two years uncertain. The "cure" assumption has a significant impact upon the ICER and therefore affects the determination of the cost-effectiveness of venetoclax.
What alternative approach has the ERG suggested?	Due to the lack of data to validate the "cure" assumption, the ERG suggest some alternative scenarios that remove it.
What is the expected effect on the cost-effectiveness estimates?	The removal of the cure assumption substantially increases the ICER in the company base case. QALYs decrease as patients would continue to be at risk of relapse and higher risk of death. Costs increase as patients would continue to receive active treatment in remission and the progressive disease state caries a higher cost over the remission and cure states.
What additional evidence or analyses might help to resolve this key issue?	As there is insufficient evidence from the VIALE trials to support the "cure" assumption. Further engagement and clinical consultation, and ideally longer-term data, would be beneficial to further determine whether the notion of a cure is plausible for this population.

Issue 2 General population mortality adjustment for transitions to non-death health states

Report section	4.2.6 (Treatment effectiveness and extrapolation)
Description of issue and why the ERG has identified it as important	The company has applied a applied a general population mortality adjustment to all the parametric survival curves used to inform the transition probabilities in the model - from maximum follow-up of the VIALE trials. The ERG is uncertain of the justification for application of the adjustment to the time-to-relapse/progressive disease curves. This effectively seems to use the general population mortality risk to increase the risk of transitioning to progressive disease conditional on survival. The adjustment in the time-to-death curves is more intuitive, and particularly from the remission state where the hazard of mortality falls below that of the general population in the long-term extrapolation of the curves.
What alternative approach has the ERG suggested?	Removal of the general population mortality adjustment to non-death state transitions in the model, unless a clear justification for the approach can be provided.
What is the expected effect on the cost-effectiveness estimates?	The ERG is uncertain of the effect the proposed approach would have upon the cost-effectiveness of venetoclax as it has not been able to implement it. It is anticipated that the costs would decrease and QALYs increase as patients would progress in the model at a slower rate. However, the impact is uncertain in the context of fairly complex model.
What additional evidence or analyses might help to resolve this key issue?	1. Removal of general population mortality adjustment from transitions to non-death states. 2. Scenarios which explore the removal of the adjustment by selecting time-to-death extrapolations which do not surpass general population survival.

Issue 3 Modelling of treatment and subsequent treatment

Report section	4.2.6 (Treatment effectiveness and extrapolation)
Description of issue and why the ERG has identified it as important	Time-to-treatment discontinuation is modelled independently of the health states in the model. The modelling of patients who receive 1st line and subsequent treatment seems to implicitly infer some counterintuitive and unjustified assumptions. Upon implementation of the "cure" state at two years, the number of patients receiving subsequent treatment in the venetoclax arms of the model falls by the number of patients who had achieved remission by two years. Therefore, the model seems to imply that from two years, the majority of patients with progressed disease who were previously on subsequent treatment are then assumed to be receiving venetoclax, whilst those considered cured are assumed to be receiving no treatment. The ERG finds the implied assumptions counterintuitive and implausible. The ERG clinical expert does not think it plausible that patients in remission at two years would cease treatment and the draft SmPC for venetoclax suggest treatment should continue until disease progression or unacceptable toxicity is observed. The company provides little commentary on the assumptions.
What alternative approach has the ERG suggested?	In the context of a cure assumption, the ERG believes that it would be more plausible to assume that those patients still on treatment beyond two years represent those in the cure state and non-remission state, and that the number on subsequent treatment should broadly follow progressive disease state occupancy.
What is the expected effect on the cost-effectiveness estimates?	The above approach leads to a modest increase in the ICER. The removal of the "cure" assumption, as per issue 1 above, also resolves the above inconsistency around subsequent treatment.
What additional evidence or analyses might help to resolve this key issue?	Further analysis conducted by the company to revise their approach in line with the SmPC and clinical opinion.

Issue 4: Impact of adverse events on quality of life

Report section	4.2.7 (Health-related quality of life)
Description of issue and why the ERG has identified it as important	The EQ-5D data from the VIALE trials were adjusted to account for adverse events and provide treatment-independent utility values for use in the model. Adverse event disutilities were then applied using a separate data source in a different patient group of relapse/refractory AML patients and furthermore it was not possible to verify a number of the values used in the model. The ERG is concerned there could be differences in quality of life between the treatment arms based on the EQ-5D data that have not been explored and also has concerns about how the alternative disutility values are applied in the model.
What alternative approach has the ERG suggested?	Instead of adjusting the EQ-5D data from the trials to remove the impact of adverse events, the ERG would prefer to see the observed data from the trials used in the model to estimate adverse event disutilities.
What is the expected effect on the cost-effectiveness estimates?	Adverse events are not key drivers of the model and therefore any impact is likely to be small, unless the EQ-5D data show a significant difference between the treatment arms.
What additional evidence or analyses might help to resolve this key issue?	The ERG would welcome further justification and evidence to support the use of applying treatment-independent utility values combined with a separate data source for disutilities, instead of using the EQ-5D data directly from the trials to capture adverse events. Furthermore, a sensitivity analysis using the EQ-5D data by treatment arm would allow this issue to be explored.

Issue 5: The cost of venetoclax may be underestimated

Report section	4.2.8 (Resources and costs)
Description of issue and why the ERG has identified it as important	The model may not appropriately account for drug wastage associated with venetoclax tablets that are prescribed but not used due to patients dying or discontinuing treatment during a cycle (in the context of the dose intensity adjustment applied). This may result in a modest underestimation of the cost of venetoclax.
What alternative approach has the ERG suggested?	The ERG believes that some wastage is likely upon discontinuation of venetoclax, and has considered the inclusion of 7 days and 14 days worth of wastage in scenarios. This is consistent with the adjustment applied in TA642.
What is the expected effect on the cost-effectiveness estimates?	Increasing the cost of venetoclax due to the inclusion of wastage results in a small increase in the ICER.
What additional evidence or analyses might help to resolve this key issue?	There is uncertainty associated with the amount of wastage that should be included in the model. The ERG would welcome additional expert input on the inclusion and quantity of wastage for venetoclax in the model.

Issue 6: The distribution of subsequent treatments by treatment arm

Report section	4.2.8 (Resources and costs)
Description of issue and why the ERG has identified it as important	The company base case assumes 3% of patients receive gilteritinib as a subsequent treatment following VenAZA and VenLDAC, with the remainder receiving hydroxycarbamide. The ERG's clinical advice was that a similar and higher proportion would be expected to receive gilteritinib as subsequent treatment in both arms.
What alternative approach has the ERG suggested?	The ERG suggested a scenario whereby 15% was assumed in both arms. The company provided this at the clarification stage, but noted clinical advice suggesting that 15% was too high to be reflective of patients that are FLT3+ and fit enough for subsequent treatment in this population. They also noted clinical advice suggesting that a smaller proportion of patients that have discontinued AZA or LDAC would be eligible for gilteritinib than those who received VenAZA or VenLDAC.
What is the expected effect on the cost-effectiveness estimates?	Assuming equal use of gilteritinib as subsequent treatment improves the ICERs for VenAZA and VenLDAC.
What additional evidence or analyses might help to resolve this key issue?	Additional clinical expert opinion on the expected distribution of subsequent therapies following VenAZA, VenLDAC, AZA and LDAC would be beneficial.

1.6 Summary of ERG's preferred assumptions and resulting ICER

Reflecting on the evidence base, the ERG acknowledges the potential for patients in remission at two years on venetoclax to achieve long-term survivorship. However, it does not believe that the current data conclusively supports the application of a cure assumption in the model. Given the uncertainty surrounding the validity of a cure assumption, the ERG offers an alternative base case that removes it whilst retaining the company's preferred parametric curves for time to relapse from remission.

The removal of the cure assumption also resolves the inconsistencies around proportions on treatment and subsequent treatment in the venetoclax arms of the model. The ERG also prefers to apply the adverse event costs which assume atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis require inpatient admission as per the company scenarios provided in the response to clarification queries. The results of this alternative base case are provided in Table 2 below.

Table 2 Summary of the ERG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
VenAZA versus AZA (20-30% blasts)			
Company's base case	[redacted]	[redacted]	£38,866
Adverse event costs to account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries.	[redacted]	[redacted]	£39,314
Removal of cure assumption (see issues 1 and 3)	[redacted]	[redacted]	£96,408
ERG's preferred base case	[redacted]	[redacted]	£97,184
VenAZA versus LDAC (>30% blasts)			
Company's base case	[redacted]	[redacted]	£39,449
Adverse event costs to account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries.	[redacted]	[redacted]	£39,633
Removal of cure assumption (see issues 1 and 3)	[redacted]	[redacted]	£109,417
ERG's preferred base case	[redacted]	[redacted]	£109,708
VenLDAC versus LDAC (>30% blasts)			
Company's base case	[redacted]	[redacted]	£31,291
Adverse event costs to account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries.	[redacted]	[redacted]	£31,167
Removal of cure assumption (see issues 1 and 3)	[redacted]	[redacted]	£112,650
ERG's preferred base case	[redacted]	[redacted]	£112,356

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for this submission is untreated acute myeloid leukaemia unsuitable for intensive chemotherapy. The company's description of this health condition in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is venetoclax (Venclyxto®, AbbVie) in combination with a hypomethylating agent or low-dose cytarabine.

2.2 Background

Acute myeloid leukaemia (AML) is an aggressive clonal haematopoietic malignancy of myeloid precursor cells.[1, 2] AML is caused by genetic alterations in haematopoietic stem cells, characterised by accumulation of abnormal immature cells in the bone marrow, known as blasts. Normal haematopoietic function is then hampered and the blast cells can leak into the blood and invade the lungs and central nervous system.[1, 3, 4] AML is clinically heterogenous, involving large chromosomal translocations and genetic mutations.[1, 5] Disease can be stratified according to cytogenetic profile, with prognosis differing markedly among the categories.[4, 5] If left untreated, AML is likely to be fatal within months of clinical presentation.[1, 3]

AML is the most common acute leukaemia in adults.[6] In the UK, there are an estimated 3200 new AML cases every year. Of these, around 1400 are in females and around 1800 in males.[7] Hospital Episode Statistics for England for the year 2019-2020 reported a total of 1699 finished consultant episodes (consisting of 950 males and 749 females) and 1592 admissions with a mean length of stay of 19.3 days for "AML with multilineage dysplasia" (Code C92.8).[8] Mean age of patients was 68 years. Despite accounting for <1% of all new cancer cases in the UK in 2017, AML contributed 2% of deaths to the total deaths from cancer during the period 2016-2018.[7]

Typically, patients present with symptoms of anaemia.[4] Other early signs of AML include fever, weakness, fatigue, weight loss, loss of appetite and aches and pains in joints or bones.[1] More than half of AML diagnoses are in people aged 65 years or over.[9] Diagnostic criteria for AML published by the WHO in 2016 specify: ≥20% blasts in bone marrow or blood. The

WHO criteria classify AML into four categories: AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related myeloid neoplasms and AML, not otherwise specified.[10, 11]

In general, treatment of AML has remained largely unchanged for some years. Treatment guidelines in the UK are based on those of the European LeukemiaNet (ELN),[11] European Society of Medical Oncology (ESMO)[12] and the National Comprehensive Cancer Network (NCCN).[13]

In summary, the focus of initial assessment is eligibility for standard induction and consolidation chemotherapy.[11, 12] Eligibility for IC is largely based on assessment of age and fitness by experienced haematologists. Factors which may make a patient ineligible for IC include age > 75 years; pre-existing disease of the heart, lung, kidney or liver; active infection; mental illness; or ECOG performance status ≥3 not related to leukaemia.[14] The aim of IC is achieving complete remission, defined as bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 x 10^9/L (1000/μL); platelet count ≥100 x 10^9/L (100 000/μL).[11, 15] The mainstay of standard regimens of chemotherapy for treating AML is cytarabine plus an anthracycline, commonly daunorubicin.[13] Recommendations for treating adults with AML who are not eligible for IC include azacitidine, low-dose cytarabine, decitabine and best supportive care.[11, 12] In addition, the guidelines published by the ESMO in 2020 report that venetoclax in combination with a hypomethylating agent or LDAC is a promising alternative treatment that awaits a recommendation based on RCT evidence.[12]

Venetoclax (Venclyxto®, AbbVie) is a potent, specific, oral B-cell lymphoma-2 (BCL-2) inhibitor. BCL-2 prevents apoptosis by binding to, and taking possession of, pro-apoptotic proteins, on which AML blasts and stem cells depend for survival.[2, 16-19] Venetoclax in combination with a hypomethylating agent or LDAC can induce malignant cell death and outcomes compare favourably with clinical trials of the individual agents in comparable patient populations.[17, 18, 20, 21]

Venetoclax has three licensed indications. According to the summary of product characteristics (SmPC), Veneclyxto:

- In combination with Obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)

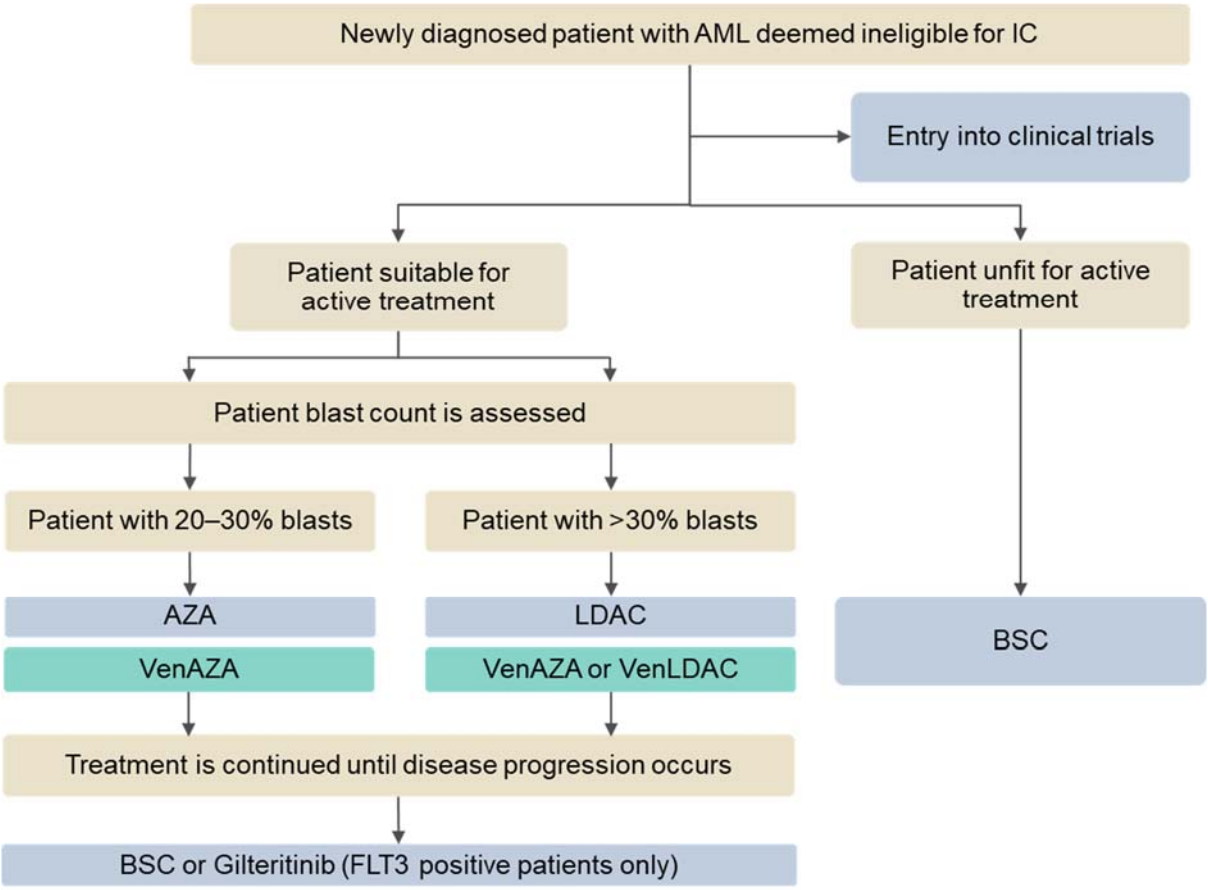
- In combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy
- Monotherapy is indicated for the treatment of CLL:
    - in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed 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.

Further information regarding venetoclax is presented in the company submission (Document B, Section B.1.2, Table 2).

The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 22 April 2021 for the following new indication: "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". The updated SmPC and EPAR had not been published at the time of submitting the ERG report.[22]

The company's proposed positioning for venetoclax in the clinical care pathway is presented in Figure 1. The ERG clinical expert considers the company's positioning of venetoclax to be reasonable and in line with current clinical practice.

Figure 1 Current treatment pathway for patients with newly diagnosed AML and proposed positioning of venetoclax in combination with AZA or LDAC [reproduced from Document B, Section B.1.3.3, Figure 2 of the company submission]



Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; BSC: best supportive care; FLT3: FMS-like tyrosine kinase 3; IC: intensive chemotherapy; LDAC: low-dose cytarabine; Ven: venetoclax.
Source: Döhner *et al.* (2017),[11] NICE TA218,[23] NICE TA399,[24] Clinical expert opinion.[25]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 4.

Table 3 Summary of the company's decision problem and ERG's comments

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with untreated AML for whom IC is unsuitable	Adult patients with newly diagnosed AML who are ineligible for IC. This patient population is in line with the full anticipated marketing authorisation for VenAZA and VenLDAC in AML	In line with the final NICE scope.	The population described in the company submission matches that described in the NICE final scope. The study populations in the VIALE-A and VIALE-C trials (the main sources of evidence in the company submission) comprise patients with a confirmed diagnosis of AML, previously untreated and ineligible for standard IC due to age or comorbidities. The ERG clinical expert notes that people with de novo AML will likely have better outcomes than those with secondary disease. The distribution of the study populations was skewed towards de novo type AML, representing 75.2% and 65.4% in VIALE-A and VIALE-C, respectively. The evidence presented in the company submission may be more relevant for de novo type AML. In addition, greater proportions of participants in VIALE-C than VIALE-A had a red blood cell or platelet transfusion or infusion prior to starting on study drug, indicating more severe disease. Overall though, the ERG clinical expert considers that the clinical evidence submitted by the company reflects the characteristics of the patient population who would be eligible for this treatment in the UK and has no concerns about differences at baseline between participants in the two trials.
Intervention	Venetoclax in combination with an HMA or LDAC	Venetoclax in combination with an HMA or LDAC. The decision problem addresses this by providing separate clinical	In line with the final NICE scope. Azacitidine (AZA) is the HMA used in UK clinical practice and hence would be the HMA used in combination	The intervention described in the company submission matches the intervention described in the final scope. Venetoclax (Venclyxto®) [in combination with AZA or LDAC] did not have a marketing authorisation for the relevant indication from the European Medicines Agency (EMA) at the time of the CS. An application was submitted in [redacted] and approval was expected in

		and cost-effectiveness evidence for: • Venetoclax with azacitidine (VenAZA) • Venetoclax with LDAC (VenLDAC)	with venetoclax in the UK upon a positive recommendation for this appraisal. Use of AZA as the HMA is in line with the VIALE-A trial	[redacted]. The anticipated EU marketing authorisation in the relevant indication for the company submission was [redacted]. The CHMP adopted the following new indication on 22 April 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". The updated SmPC and EPAR were not published at the time of submission of the ERG report. The company submission states that: *The expected licensed dose of venetoclax in combination with an HMA or LDAC is:* • *Venetoclax orally (400 mg per day [QD]) in combination with AZA (75 mg/m^2 on days 1–7 of each 28-day cycle). Patients should receive a three-day dose ramp-up to reach the target 400 mg dose (D1: 100 mg, D2: 200 mg, D3 onwards: 400 mg).* • *Venetoclax orally (600 mg QD) in combination with LDAC (20 mg/m^2 on days 1–10 of each 28-day cycle). Patients should receive a four-day dose ramp-up increase to reach the target 600 mg dose (D1: 100 mg, D2: 200 mg, D3: 400, D4 onwards: 600 mg).* The ERG clinical expert is of the opinion that the dosages of venetoclax used in the VIALE-A and VIALE-C trials are standard in trials. However, in UK clinical practice, the dosage is usually 100mg, as it is administered alongside an antifungal (Posaconazole) which increases

				the drug exposure and is, in effect, equivalent to the doses reported in the two trials.
Comparator(s)	Established clinical management without venetoclax, for example: • LDAC • AZA for adults who are not eligible for haematopoietic stem cell transplantation (HSCT) and have AML with 20–30% blasts and multilineage dysplasia • BSC	The decision problem is split into distinct populations: • VenAZA comparators: o Blast cell count 20-30%: AZA o Blast cell count >30%: LDAC • VenLDAC comparators: o Blast cell count >30%: LDAC	Given that the use of AZA is only recommended by NICE for patients with a blast cell count of 20–30%, comparisons have been split into two populations: AML with 20–30% blasts and AML with >30% blasts. LDAC is not restricted by blast cell count but, in clinical practice, it is used in patients with blast cell counts of >30%, as AZA is used in patients with blast cell counts of 20–30%. Therefore, in this appraisal VenLDAC is compared only with LDAC in patients with >30% blasts. This approach has been validated by UK clinicians experienced in the treatment of AML. BSC is not considered a relevant comparator for this appraisal. Patients who receive BSC alone are not considered fit for treatment with AZA or LDAC due to being frail or elderly, or refusing treatment. This is evidenced by data from	The ERG clinical expert agrees that LDAC and azacitidine are standard components of established clinical management in this context. The company submission did not consider BSC as a relevant comparator, contrary to the NICE final scope. The ERG clinical expert is of the opinion that its exclusion is reasonable and agrees with the company's explanation for doing so. The ERG clinical expert also agrees that splitting the population into those with blast cell count 20-30% and those with blast cell count > 30% is reasonable.

			real-world clinical practice in the UK, which demonstrate that those who receive BSC comprise a different population to those who would receive VenAZA or VenLDAC (e.g. when considering age and performance status), and has been validated by UK clinicians	
Outcomes	The outcome measures to be considered include: • Overall survival • Event-free survival • Disease-free survival • Response rates, including remission • Blood transfusion dependence • Adverse effects of treatment • Health-related quality of life	The outcome measures considered include: • Overall survival • Event-free survival • **Duration of response** • Response rates, including remission • Blood transfusion dependence • Adverse effects of treatment • Health-related quality of life • **Minimal residual disease (MRD)**	Whilst disease-free survival data were not explicitly collected in the VIALE-A and VIALE-C trials, duration of response data were collected, which describe the time spent in a disease-free state. Whilst not specified in the NICE scope, MRD negativity has been included in the submission as it serves as a marker of the depth of response to treatment, and has been shown to be correlated with long-term disease free survival	The outcomes in the company submission broadly match the outcomes described in the final scope. Disease-free survival was not assessed by the company; instead, duration of response was assessed. The ERG considers the company's explanation that duration of response describes the time spent in a disease-free state to be reasonable. In addition to the outcomes specified in the final scope, the company submission assessed MRD. The ERG clinical expert agrees with the company's rationale for its inclusion that MRD negativity is a marker of depth of response to treatment. In addition, MRD has been accepted by the FDA as a surrogate outcome in clinical practice.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be	As per final scope and NICE reference case	In line with the NICE final scope	The company's economic analysis is in line with the reference case.

	expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.			
Subgroups	No subgroup analyses were specified in the NICE scope	The decision problem will be split into two distinct populations according to blast cell count, since the relevant comparators differ in these subpopulations: • Blast cell count: 20–30% • Blast cell count: >30%	Economic subgroup analyses were conducted for VenAZA and VenLDAC for subgroups based on blast cell count, using patient level data from the VIALE-A and VIALE-C trials, respectively. These subgroup analyses informed the base case cost-effectiveness analysis for comparisons versus AZA (in patients with	The ERG agrees with the splitting of the decision problem into two distinct populations from the clinical effectiveness perspective. The ERG agrees with the data selections used to inform the economic modelling for the two populations of interest.

			blast cell count 20–30%) and LDAC (in patients with blast cell count >30%). It should be noted that these subgroup analyses were conducted to account for the current NICE restrictions on the use of AZA only in patients with a blast count of 20–30%, and the VIALE trials were not designed to split patients by blast count.	
Special considerations including issues related to equity or equality	No special considerations were specified	Not specified	Not applicable	The ERG agrees with the company that there are no anticipated equality issues related to venetoclax

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG appraisal of the company's systematic review methods is presented in Table 4.

Table 4 ERG appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details are provided in Appendix D.1 of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research; DARE and CDSR were searched for evidence syntheses. Relevant conference proceedings and trial registers were also searched. Full details are provided in Appendix D.1.1 of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	The company's eligibility criteria (Appendix D, Table 9) included a range of interventions/ comparators, over and above those specified in the decision problem. The company's submission stated the SLR was conducted "from a global perspective" (Appendix D, page 6) but restricted inclusion to articles published in English language (Appendix D, Table 9)
Was study selection conducted by two or more reviewers independently?	Yes	Appendix D, Figure 1
Was data extraction conducted by two or more reviewers independently?	No	Appendix D, Page 19: Data were extracted by one reviewer "with a second individual independently verifying the extracted information and checking that no relevant information had been missed"
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	The University of York CRD checklist for RCTs was used
Was risk of bias assessment conducted by two or more reviewers independently?	Unclear	Not reported in the CS

Was identified evidence synthesised using appropriate methods?	Yes	NMA was used for the HR and OR variables

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence (main included studies) using the Centre for Reviews and Dissemination (CRD) criteria (see Table 5).

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence (VIALE-A and VIALE-C)

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company identified two ongoing, phase III randomised, double-blind, placebo controlled, international trials providing evidence for the efficacy and safety of venetoclax [redacted] VIALE-A and VIALE-C. Trial methods are summarised in Table 3, Section B.2.2 of the CS and reproduced as Table 6 below.

Table 6 Clinical effectiveness evidence [reproduced from Table 3, Section B.2.2 of the CS]

Study	VIALE-A (NCT02993523)	VIALE-C (NCT03069352)
Study design	Phase III, international, randomised, double-blind, placebo-controlled trial	
Population	Newly diagnosed adult patients with AML who are treatment naïve and ineligible for standard Intensive chemotherapy (IC) due to age or comorbidities[a]	
Interventions	Venetoclax (400 mg QD[b]) + AZA (75 mg/m^2 on days 1–7 of each 28-day cycle)	Venetoclax (600 mg QD[c]) + LDAC (20 mg/m^2 on days 1–10 of each 28-day cycle)
Comparator	Placebo + AZA (75 mg/m^2 on days 1–7 of each 28-day cycle)	Placebo + LDAC (20 mg/m^2 on days 1–10 of each 28-day cycle)
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	Yes	Yes
Rationale for use/non-use in the model	Both VIALE-A and VIALE-C were included in the economic model as they provide the primary source of evidence for the clinical efficacy and safety of VenAZA and VenLDAC, respectively, are relevant to the decision problem and informed the marketing authorisation application.	
Reported outcomes specified in the decision problem[d]	• **OS** • **CR + CR with incomplete haematological recovery (CRi)** • **EFS** • Duration of response • Blood transfusion dependence • **Adverse effects of treatment** • **HRQoL outcomes**	
All other reported outcomes	AML is a heterogenous disease which lacks a simple, uniform signature to identify malignant cells capable of causing relapse. MRD is the persistence of leukaemic cells following treatment and serves as an independent, post-diagnosis, prognostic indicator in AML MRD negativity, defined by the ELN guidelines as levels below 1 leukaemic cell per 1,000 leukocytes (<0.001; <0.1%), has been shown to be prognostic for OS and risk of relapse in patients who have received IC.	

[a]Presence of AML was confirmed using the WHO definition. [b]In cycle 1 patients received a three-day dose ramp-up of venetoclax to reach the target 400 mg dose (100, 200, 400). [c]In cycle 1 patients received a four-day dose ramp up of venetoclax to reach the target 600 mg dose (100, 200, 400, 600). [d]Outcomes in bold indicate those used in the cost effectiveness analysis.

Abbreviations: AML: acute myeloid leukaemia; AZA: azacitidine; CR: complete remission; CRi: complete remission with incomplete haematological recovery; EFS: event-free survival; ELN: European Leukaemia Net; HRQoL: health-related quality of life; IC: intensive chemotherapy; LDAC: low-dose cytarabine; MRD: minimal residual disease; OS: overall survival; QD: once daily; Ven: venetoclax.

Details of VIALE-A and VIALE-C are reported in Sections B.2.2 and B.2.3 of the CS. Participant flows of the two studies are presented in the CS (Appendix D, Section D.2, Figures 9 and 10). High numbers of participants discontinued the study treatment and study itself in both trials, the majority of which were due to mortality. Participants who discontinued the study treatment were followed up for survival, but those who discontinued the study itself were not followed up. Table 7 summarises the numbers of discontinuations in VIALE-A and VIALE-C. The ERG's clinical expert considers these numbers in line with those expected in clinical practice and has no concerns.

Table 7 Numbers of participants discontinuing study treatment and study in VIALE-A and VIALE-C

Study name and groups	Discontinued study treatment, n (%)	Discontinued study, n (%)
VIALE-A		
VenAZA	209/286 (73.1%)	173/286 (60.5%)[a]
AZA	127/145 (87.6%)	112/145 (77.2%)[b]
VIALE-C		
VenLDAC	117/143 (85.3%)	103/143 (72.0%)[c]
LDAC	63/68 (92.1%)	56/68 (72.1%)[d]

Notes. Deaths: [a]161/173 (93.1%), [b]109/112 (97.3%), [c]97/103 (94.2%), [d]53/56 (94.6%). Ven: venetoclax; AZA: azacitidine; LDAC: low-dose cytarabine

VIALE-A was funded by AbbVie and Genentech; VIALE-C was funded by AbbVie. VIALE-A was conducted in 134 sites in 27 countries (not including the UK) and VIALE-C was conducted in 76 sites in 21 countries (including the UK, where a total of [redacted] participants were randomised, [redacted] to VenLDAC and [redacted] to placebo). The methods used in the two trials were similar, with the exception of the interventions and comparators. In both trials, participants were randomised 2:1 to either the intervention or control group. VIALE-A and VIALE C were identically designed studies in which participants were randomised in a 2:1 ratio to the intervention (venetoclax plus azacitidine [VenAZA] or venetoclax plus low dose cytarabine [VenLDAC], respectively) or the control group (azacitidine [AZA] or low dose cytarabine [LDAC], respectively). A total of 433 participants were randomised in VIALE-A (431 were included in the ITT analysis) and 211 were randomised in

VIALE-C. The study population in both VIALE-A and VIALE-C was adults aged 18 years or older, newly diagnosed with AML considered ineligible for IC. Treatment was continued in both studies until disease progression, unacceptable side effects, withdrawal of consent or any protocol-defined criteria were met.

Participants were hospitalised on or before the first day of cycle 1 and remained in hospital during the venetoclax/placebo ramp-up period (days 1-3 in VIALE-A; days 1-4 in VIALE-C) for tumour lysis syndrome evaluation and prophylaxis, including uric acid-reducing agent and oral and/or intravenous hydration. The ERG clinical expert considers this to be an appropriate strategy. The ERG clinical expert is of the opinion that the dosages of venetoclax used in the VIALE-A and VIALE-C trials are standard in trials. However, in UK clinical practice, the dosage is usually 100mg, as it is administered alongside an antifungal (posaconazole) which increases the drug exposure and is, in effect, equivalent to the doses reported in the two trials.

There were some differences between the trials. For example, VIALE-A had co-primary endpoints of OS and CR + CRi, whilst the primary endpoint in VIALE-C was OS. The exclusion criteria in VIALE-A specified "favourable risk cytogenetics according to the AML NCCN (National Comprehensive Cancer Network) guidelines". In addition, patients with prior therapy with a hypomethylating agent (HMA), venetoclax and/or chemo-therapeutic agents for myelodysplastic agents were excluded from VIALE-A but not VIALE-C.

The company assessed the risk of bias of VIALE-A and VIALE-C using the seven criteria of the Centre for Reviews and Dissemination checklist for RCTs (Table 21, Appendix D.1.6 of the CS) and concluded that both trials were of high quality and at low risk of bias.[26] In general, the ERG agrees with the company's assessments.

The CS presents details of baseline characteristics of participants in VIALE-A and VIALE-C (CS, Document B, Section B.2.3.2, Table 6). The ERG noted some inconsistencies between the reporting of the baseline characteristics between the studies, in terms of the sources of the items "≥75 years", "AML type", "cytogenetic risk category" specified in the respective CSRs: either "reported from EDC" [electronic data capture] or "reported from IVRS/IWRS". At clarification, the

company explained "*Electronic data capture (EDC) and interactive voice/web recording system (IVRS/IWRS) represent two methods used to collect the data in the trials. IVRS/IWRS was used for patient randomisation, which included age (18–<75, ≥75 years) and cytogenetic risk category (intermediate, poor) as stratification factors in VIALE-A, and AML status (de novo, secondary) and age (18–<75, ≥75 years) in VIALE-C. IVRS/IWRS data are only available for these categories, which were used for randomisation and as stratification factors within the primary analysis of each trial, and are not available for any other data category.*" The company provided an updated version of the table of baseline characteristics of participants in VIALE-A and VIALE-C, including variables reported as IVRS/IWRS and EDC, which is reproduced as Table 8 below.

Table 8 Baseline characteristics of participants in VIALE-A and VIALE-C [reproduced from Table 4 of the company's clarification response]

Characteristic	VIALE-A		VIALE-C	
	VenAZA (n=286)	AZA (n=145)	VenLDAC (n=143)	LDAC (n=68)
Age				
Mean (range) SD, years	75.6 (49.0–91.0) 6.1	75.1 (60.0–90.0) 5.7	75.1 (36.0–93.0) 8.1	74.3 (41.0–88.0) 8.6
≥75 years, n (%) reported from EDC	174 (60.8)	87 (60.0)	[redacted]	[redacted]
≥75 years, n (%) reported from IVRS/IWRS	[redacted]	[redacted]	78 (54.5)	39 (57.4)
Sex, n (%)				
Male/Female	172 (60.1) / 114 (39.9)	87 (60.0) / 58 (40.0)	78 (54.5) / 65 (45.5)	39 (57.4) / 29 (42.6)
AML type, n (%) reported from EDC				
De novo	214 (74.8)	110 (75.9)	[redacted]	[redacted]
Secondary	72 (25.2)	35 (24.1)	[redacted]	[redacted]
AML type, n (%) reported from IVRS/IWRS				
De novo	-	-	92 (64.3)	46 (67.6)
Secondary	-	-	[redacted]	[redacted]
Secondary AML, n/N (%)				
History of myelodysplastic syndrome or CMML	46/72 (63.9)	26/35 (74.3)	[redacted]	[redacted]
Therapy-related AML	26/72 (36.1)	9/35 (25.7)	[redacted]	[redacted]
ECOG performance status score, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow blast count, n (%)				
<30%	85 (29.7)	41 (28.3)	[redacted]	[redacted]
≥30 to <50%	61 (21.3)	33 (22.8)	[redacted]	[redacted]
≥50%	140 (49.0)	71 (49.0)	[redacted]	[redacted]
AML with MRC, n (%)	92 (32.2)	49 (33.8)	[redacted]	[redacted]
Antecedent haematologic history of MDS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Cytogenetic risk category, n (%) reported from EDC				
Favourable	-	-	[redacted]	[redacted]
Intermediate	182 (63.6)	89 (61.4)	[redacted]	[redacted]
Poor	104 (36.4)	56 (38.6)	[redacted]	[redacted]
Cytogenetic risk category, n (%) reported from IVRS/IWRS				
Intermediate	[redacted]	[redacted]	-	-
Poor	[redacted]	[redacted]	-	-
Somatic mutations, n/N (%)[a]				
IDH1 or *IDH2*	61/245 (25.7)	28/127 (22.9)	[redacted]	[redacted]
FLT3, ITD or TKD	29/206 (14.1)	22/108 (20.4)	[redacted]	[redacted]
NPM1	27/163 (16.6)	17/86 (19.8)	19 (17.0)	7 (13.5)
TP53	38/163 (23.3)	14/86 (16.3)	22 (19.6)	9 (17.3)
Baseline cytopenia grade ≥3, n (%)[b]				
Anaemia	88 (30.8)	52 (35.9)	[redacted]	[redacted]
Neutropenia	206/286 (72.0)	90/144[c] (62.5)	[redacted]	[redacted]
Thrombocytopaenia	145 (50.7)	73 (50.4)	[redacted]	[redacted]
≥2 Reasons for ineligibility to receive intensive therapy, n (%)	141 (49.3)	65 (44.8)	[redacted]	[redacted]
Prior HMA used (yes), n (%)	NA[f]	NA[f]	[redacted]	[redacted]
RBC or platelet infusion[e] (yes), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RBC transfusion[e] (yes), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Platelet transfusion[e] (yes), n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[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]Cytopenia was graded according to the Common Terminology Criteria for Adverse Events. [c]Data missing for 1 patient due to white blood cell count being too low to perform differential counts and report absolute neutrophil count. [d]Missing data for neutropenia for 12 and 6 patients in the VenLDAC and LDAC arms of VIALE-C, respectively. [e]Within 8 weeks prior to the first dose of study drug (or randomisation for non-treated patients).[f]Prior use with an HMA was part of the exclusion criteria for VIALE-A. **Abbreviations:** AML: acute myeloid leukaemia; AZA: azacitidine; CMML: chronic myelomonocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; EDC: electronic data capture; FLT3: FMS-like tyrosine kinase-3; HMA: hypomethylating agent; IDH: isocitrate dehydrogenase; ITD: internal tandem duplication; IVRS/IWRS: interactive web/voice recording system; LDAC: low-dose cytarabine; MDS: myelodysplastic syndrome; MRC: myelodysplasia related changes; NPM1: nucleophosmin 1; RBC: red blood cell; TKD: tyrosine kinase domain; TP52: tumour protein 53; Ven: venetoclax. **Source:** VIALE-A Clinical Study Report, DiNardo et *al.* (2020)[20], VIALE-C Clinical Study Report, Wei *et al.* (2020)[21]. Table adapted by ERG as original table incorrectly stated median (range) age was reported instead of mean. SD added by ERG for completeness. Table updated by ERG for secondary AML categories using data from Table 2 of the company clarification response

In general, baseline characteristics were balanced within and across VIALE-A and VIALE-C. Mean age was 75.4 years in VIALE-A and 74.8 years in VIALE-C. Median age was 76 years in both trials. The proportion of participants aged at least 75 years was similar in the two trials (VIALE-A: [redacted]; VIALE-C: 55.5%) [reported from IVRS/IWRS]. There was a higher proportion of males than females in both trials (VIALE-A: 60.1%; VIALE-C: 55.5%). The proportion of participants with *de novo* AML was similar between the arms of each study but numerically higher in VIALE-A (75.2%) than VIALE-C [redacted], reported from EDC. The ERG clinical expert is of the opinion that participants with *de novo* AML are likely to have better outcomes than those diagnosed with secondary disease. The ERG clinical expert also considers that people in the favourable cytogenetic risk category are likely to have better outcomes; however, these patients were excluded from VIALE-A and accounted for only [redacted] of participants in VIALE-C. The greatest proportion of participants were in the bone marrow blast count category of ≥50% on both VIALE-A (49%) and VIALE-C ([redacted]), as compared to those with <30% blasts (VIALE-A: 29.2%; VIALE-C: [redacted]) and ≥30% to <50% (VIALE-A: 21.8%; VIALE-C: [redacted]). The proportions of participants in VIALE-C for RBC or platelet infusion ([redacted] in VenLDAC arm, [redacted] in LDAC arm), RBC transfusion ([redacted] respectively) and platelet transfusion ([redacted] respectively) were higher than those in VIALE-A (RBC or platelet infusion: [redacted] in VenAZA arm, [redacted] in AZA arm; RBC transfusion: [redacted] respectively; platelet transfusion: [redacted] respectively). The ERG clinical expert considers that these three variables are markers of more severe disease and, therefore, the participants in VIALE-C had more severe disease than those in VIALE-A. However, this is not of concern to the ERG clinical expert. Overall, the baseline characteristics of participants in VIALE-A and VIALE-C are reflective of patients with newly diagnosed AML unsuitable for IC in UK clinical practice. The ERG clinical expert is not concerned with any differences between baseline characteristics of participants in the two trials.

The company presented details of concomitant medications used by ≥20% of patients in each of the two trials (Document B, Section B.2.3.3, Tables 7 and 8). Although there were differences between trial arms in proportions of some medication, the ERG clinical expert had no concerns.

At the time of the data cut-off for interim analysis 2 of VIALE-A (4th January 2020), median duration of follow-up for overall survival was 20.5 months. At the time of the pre-planned primary analysis in VIALE-C, median follow-up was 12 months.

3.2.2 Primary and secondary efficacy endpoints

The outcome measures to be considered, as specified in the NICE final scope were: overall survival (OS); event-free survival (EFS); disease-free survival (reported as 'duration of response' in the CS; at clarification, the company defined duration of response as '*the number of days from the date of first complete remission or complete remission with incomplete blood count recovery (CR +CRi), as defined by the revised International Working Group (IWG) criteria for patients with acute myeloid leukaemia (AML), to the earliest evidence of minor response (MR), progressed disease (PD), or death due to disease progression'*); response and remission rate; blood transfusion dependence; adverse effects of treatment; and health-related quality of life (HRQoL). In addition, minimal residual disease (MRD) negativity was included in the submission.

The definitions of the efficacy outcomes used in VIALE-A and VIALE-C are presented in Document B, Table 5, Section B.2.3.1 of the CS, reproduced as Table 9 below.

Table 9 Outcome definitions used in VIALE-A and VIALE-C trials [reproduced from Table 5, Section B.2.3.1, Document B]

Outcome Measure	Definition
OS	Number of days from the date of randomisation to the date of death or last known alive date
CR + CRi	Proportion of patients who achieve a CR or CRi at any time point during the study as per the modified IWG criteria for AML **CR:** ANC ≥ 10^3/μL, platelets ≥ 10^5/μL, RBC transfusion independence, and bone marrow with < 5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease **CRi:** All criteria as CR except for residual neutropenia ≤ 10^3/μL (1000/μL) or thrombocytopenia ≤ 10^5/μL (100,000/μL). RBC transfusion dependence is also defined as CRi
CR + CRi by the Initiation of Cycle 2	Proportion of patients who achieved a CR or CRi by the initiation of Cycle 2 per the modified IWG criteria for AML
Event-free survival (EFS)	Number of days from randomisation to the date of progressive disease (PD), confirmed MR from CR or CRi, treatment failure defined as failure to achieve CR, CRi, or morphologic leukaemia-free state (MLFS) after at least 6 cycles of study treatment or death from any cause
Transfusion Independence Rate	The rate is defined as the proportion of patients who achieved transfusion independence post baseline. Transfusion Independence is defined as a period of at least 56-days with no RBC and platelet transfusion-while on study therapy (patients who did not receive study drug were considered transfusion dependent during the study)
MRD negativity	MRD negativity was defined as less than one leukaemic cell per 1000 leukocytes (MRD <0.001 or 0.1%) in bone marrow aspirates evaluated via a centralised, validated, multicolour flow cytometry (MFC) assay
PROMIS Cancer Fatigue SF 7a	A seven-item questionnaire that assesses the impact and experience of fatigue over the prior 7 days
EORTC QLQ-C30	A 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). Patients rate items on a four-point scale, with 1 as "not at all" and 4 as "very much"

Abbreviations: AML: acute myeloid leukaemia; ANC: absolute neutrophil count; CR: complete remission; CRi: complete remission with incomplete blood count recovery: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core; ELN: European Leukemia Net; IWG: International Working Group; MLFS: morphologic leukaemia-free state; MR: morphologic relapse; MRD: minimal residual disease; OS: overall survival; PD: progressive disease; PROMIS SF-7a: Patient Reported Outcomes Measurement Information System Short Form 7a; RBC: red blood cell;

In VIALE-A, the data presented in the CS for CR + CRi rate are from an initial interim analysis (IA1) for the first [redacted] randomised participants (VenAZA: n= [redacted]; AZA: n = [redacted]) with a 6-month follow-up, representing a cut-off date of 1st October

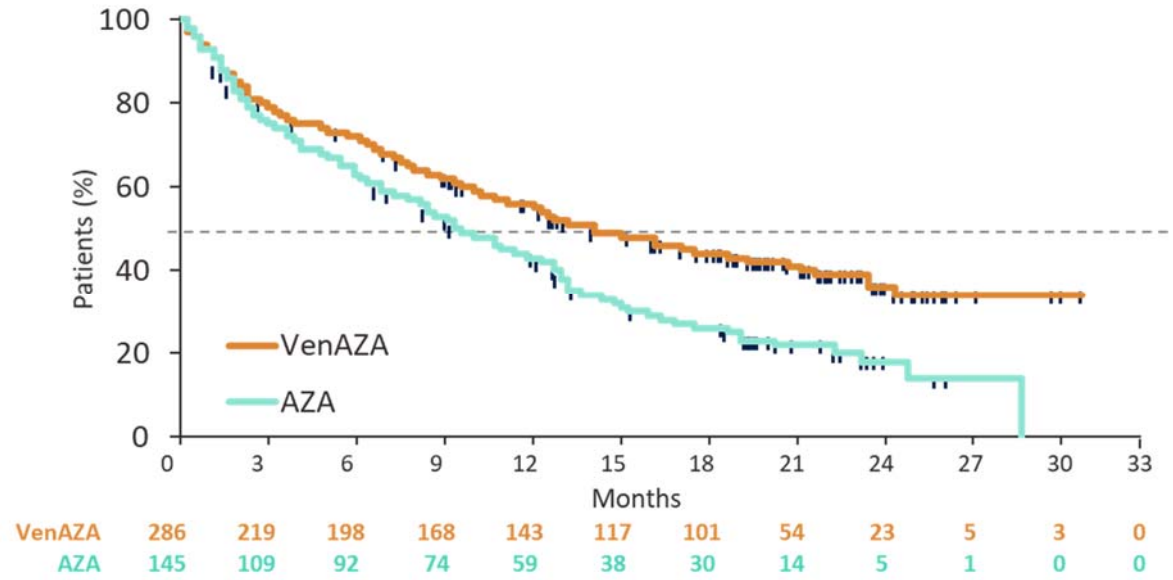
2018. Results from a second interim analysis (IA2) are presented for all outcomes (including CR + CRi) in VIALE-A for 431 randomised patients (VenAZA: n = 286; AZA: n = 145) with a median follow-up of 20.5 months, representing a cut-off date of 4th January 2020.

In VIALE-C, the data presented for OS are from a primary interim analysis for 211 participants (VenLDAC: n = 143; LDAC: n = 68), representing a cut-off date of 15th February 2019. Results from a subsequent unplanned analysis with an additional 6 month of follow-up are presented for all outcomes (including OS) in VIALE-C with a median follow-up of [redacted] months, corresponding to a cut-off date of 15th August 2019.

VIALE-A: venetoclax plus azacitidine (VenAZA) versus placebo plus azacitidine (AZA)

The dual primary efficacy endpoints of VIALE-A were OS and composite complete remission rate (complete remission or complete remission with incomplete hematologic recovery, or CR + CRi):

- **OS (IA2)**. Based on a median 20.5 months of follow-up, treatment with VenAZA was associated with prolonged OS (hazard ratio [HR] 0.66, 95% confidence interval [CI]) 0.52, 0.85, $p < 0.001$) with a corresponding improvement in median OS at 14.7 months in the VenAZA group compared with 9.6 months in the AZA group. The Kaplan-Meier plots (Figure 5, Section B.2.5.1, page 51 of the CS, reproduced as Figure 2) showed that the survival rate at 24 months was [redacted] and [redacted] in the VenAZA and AZA groups, respectively.



Abbreviations: AZA: azacitidine; FAS: full analysis set; IA2: Interim Analysis 2; OS: overall survival; Ven: venetoclax.

Figure 2 Kaplan–Meier plot of OS in VIALE-A (FAS, IA2) [reproduced from Figure 5, Section 2.5.1, Document B]

- **Composite complete remission rate (CR + CRi) (IA1).** The IA1 analysis showed that CR + CRi was achieved by a higher proportion of participants treated with VenAZA ([redacted] than those treated with AZA ([redacted] participants; [redacted] and the difference was statistically significant (p<0.001). The CR + CRi rates from the sensitivity analysis based on the IA2 data cut were consistent with those observed at IA1 (66.4% versus 28.3%, p < 0.001). At IA2, the median duration of CR + CRi was longer in the Ven AZA group (17.5 months) than in the AZA group (13.4 months).

Secondary efficacy endpoints and patient-reported outcomes of VIALE-A reported in the CS, all based on the IA2 data cut, were the following.

- **Acquisition of CR + CRi before initiation of Cycle 2:** The proportion of participants who achieved CR + CRi within the first cycle of treatment was higher in the VenAZA group compared with the AZA group (43.4% versus 7.6%, p<0.001).
- **Event-free survival (EFS):** Based on a median 20.5 months of follow-up, the HR estimates for EFS were statistically significant in favour of VenAZA (HR

0.63, 95% CI 0.50, 0.80, p <0.001), with a longer median EFS in the VenAZA group (9.8 months) compared with the AZA group (7.0 months). The Kaplan-Meier plots (Figure 9, Section B.2.5.1, page 54, Document B) showed that the proportion of participants who were event-free at 12 months was [redacted] and [redacted] in the VenAZA and AZA groups, respectively. At 24 months, [redacted] of participants in the VenAZA group remained event-free.

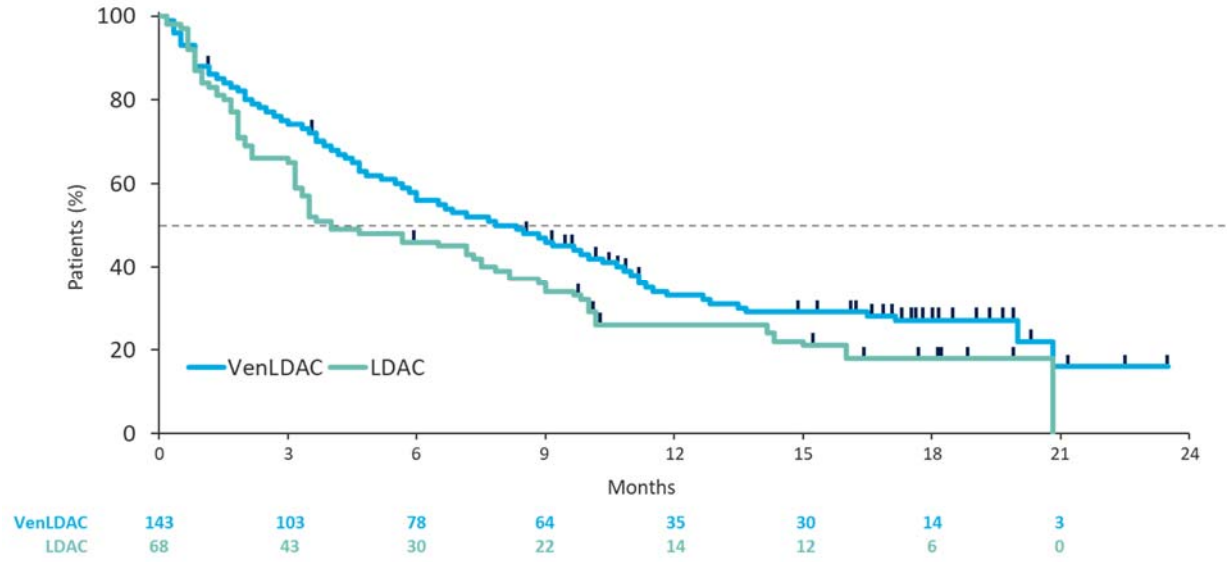
- **Transfusion independence:** Red blood cell (RBC) and platelet transfusion independence occurred in [redacted] of the participants in the VenAZA group and [redacted] of those in the AZA group. Rates of conversion from baseline RBC and platelet transfusion dependence to independence during the course of treatment was significantly higher in those treated with VenAZA compared with those treated with AZA ([redacted] versus [redacted]).
- **Minimal residual disease (MRD):** MRD negativity (MRD value of <0.001) was observed in [redacted] participants ([redacted]) in the VenAZA group and [redacted] participants ([redacted]) in the AZA group. The VenAZA group achieved a statistically significantly higher rate of a combined MRD < 0.001 and CR + CRi (defined as 'deep remission') compared with the AZA group (n = [redacted], 23.4% for VenAZA and n = [redacted], 7.6% for AZA, [redacted]). The Kaplan-Meier plots in Figure 12 of the CS (page 57) show that, in both treatment groups, OS was longer among participants achieving CR + CRi with MRD negativity compared with those who achieved CR + CRi alone. In participants achieving CR + CRi and MRD negativity, median OS was [redacted] in the VenAZA group (n = [redacted]) but was [redacted] months in the AZA group (n = [redacted]). In participants achieving CR + CRi alone, median OS was [redacted] months and [redacted] months in the VenAZA (n = [redacted]) and AZA (n = [redacted]) groups, respectively.
- **Patient-reported outcomes – fatigue:** Participants in both groups experienced [redacted] from baseline, as determined by the PROMIS Cancer Fatigue SF7a, and the difference across the two groups was [redacted] considered [redacted].
- **Patient-reported outcomes – HRQoL:** Participants in both groups experienced an improvement in Global Health Status/Quality of Life (GHS/QoL) score, as determined by the EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30). In general, a [redacted] was

observed in the VenAZA group compared with the AZA group on Day 1 of all cycles, although the difference across the two groups was considered [redacted].

VIALE-C: venetoclax plus LDAC (VenLDAC) versus placebo plus LDAC (LDAC)

The primary efficacy endpoint of VIALE-C was OS.

- **OS (FAS, primary analysis)**. At the planned primary analysis, no significant difference was observed in OS between the VenLDAC and LDAC groups and, therefore, the primary endpoint was not achieved (HR 0.75, 95% CI 0.52, 1.07, p = 0.11). In a subsequent unplanned analysis with an additional 6 months of follow-up, treatment with VenLDAC was associated with prolonged OS (HR 0.70, 95% CI 0.50, 0.99, p = 0.041) with median OS at 8.4 months in the VenLDAC group compared with 4.1 months in the LDAC group. The Kaplan-Meier plots (Figure 16, Section B.2.5.2 of the CS, reproduced as Figure 3) showed that the survival rate at 12 months was [redacted] and [redacted] in the VenLDAC and LDAC groups, respectively.



Abbreviations: FAS: full analysis set; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax

Figure 3 Kaplan-Meier plot of OS in VIALE-C (FAS 6-month follow-up) [reproduced from Figure 16, Section B.2.5.2, Document B]

Secondary efficacy endpoints and patient-reported outcomes of VIALE-C reported in the CS, all based on additional 6-month follow-up data cut-off, were the following.

- **Composite complete remission rate (CR + CRi):** The incidence of CR + CRi was statistically significantly higher with VenLDAC compared with LDAC ([redacted] versus [redacted], [redacted]). The median duration of CR + CRi was longer in the VenLDAC group ([redacted] months) than in the LDAC group ([redacted] months). The proportion of participants who achieved CR + CRi by the initiation of Cycle 2 was also higher in the VenLDAC group than in the LDAC group ([redacted] versus [redacted] [redacted]).
- **Event-free survival (EFS):** Based on a median [redacted] months of follow-up, the HR estimates for EFS were statistically significant in favour of VenLDAC (HR [redacted], 95% CI [redacted], [redacted]), with a longer median EFS in the VenLDAC group ([redacted] months) compared with the LDAC group ([redacted] months). The Kaplan-Meier plots (Figure 18, Section B.2.5.2, page 66 of the CS) showed that the proportion of participants who were event-free at 18 months was [redacted] and [redacted] in the VenLDAC and LDAC groups, respectively.

- **Transfusion independence:** RBC and platelet transfusion independence occurred in [redacted] of participants in the VenLDAC group and [redacted] of those in the LDAC group (p = [redacted]). Rates of conversion from baseline RBC and platelet transfusion dependence to independence during the course of treatment were higher in those treated with VenLDAC compared with those treated with LDAC ([redacted] versus [redacted]).
- **Minimal residual disease (MRD).** MRD negativity (MRD value of <0.001) was observed in [redacted] participants ([redacted]) in the VenLDAC group and [redacted] participants ([redacted]) in the LDAC group. In addition, a combined MRD < 0.001 and CR + CRi (defined as 'deep remission') was achieved by [redacted] and [redacted] of participants treated with VenLDAC and LDAC, respectively ([redacted]).
- **Patient-reported outcomes – fatigue:** Participants treated with VenLDAC experienced a greater reduction in fatigue from baseline (measured by PROMIS Cancer Fatigue SF7a), compared with those treated with LDAC. However, the threshold for the minimum important difference (MID) of 3 points was only met early on at Cycles 3 and 5.
- **Patient-reported outcomes – HRQoL:** Participants treated with VenLDAC also experienced an improvement in GHS/QoL from baseline, as determined by EORTC QLQ-C30, compared with those treated with LDAC. The threshold for the MID of 5 points was only met at [redacted] (CSR, section 11.1.1.2.6, page 143).[28]

Summaries of primary and secondary endpoints from the 4th January 2020 data cut (IA2) of the VIALE-A trial and the 15h August 2019 data cut (with additional 6-month follow-up) from the VIALE-C trial are presented in Table 10 and Table 11 below.

Table 10 Summary of survival outcomes in the VIALE-A and VIALE-C trials [adapted from Table 31, Section B.2.5, Document B]

Outcome	VIALE-A				VIALE-C			
	Overall Population (Error! Reference source not found.)		**20–30% blast count** (Error! Reference source not found.)		**Overall Population** (Error! Reference source not found.)		**>30% blast count** (Error! Reference source not found.)	
	VenAZA (N=286)	**AZA (N=145)**	**VenAZA (N=78)**	**AZA (N=36)**	**VenLDAC (N=143)**	**LDAC (N=68)**	**VenLDAC (N=108)**	**LDAC (N=52)**
Overall Survival								
Events, n (%)	161 (56.3)	109 (75.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	14.7 (11.9–18.7)	9.6 (7.4–12.7)	[redacted]	[redacted]	8.4 (5.9–10.1)	4.1 (3.1–8.1)	[redacted]	[redacted]
HR (95% CI), *P*	0.66 (0.52–0.85), *P* < 0.001[a]		[redacted]		0.70 (0.50–0.99), *P* = 0.041[b,c]		[redacted]	
Event-free Survival								
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median EFS, months (95% CI)	9.8 (8.4–11.8)	7.0 (5.6–9.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI), *P*	0.63 (0.50–0.80), *P* < 0.001[a]		[redacted]		[redacted][b, c]		[redacted]	

[a] Stratified by age (17–<75, ≥75 years) and cytogenetics (immediate risk, poor risk).
[b] Stratified by age (18–<75, ≥75 years) and AML status (de novo, secondary).
[c] P value descriptive in nature only.

Abbreviations: AZA: azacitidine; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete haematological recovery; EFS: event-free survival; HR: hazard ratio; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax

Table 11 Summary of other efficacy outcomes in the VIALE-A and VIALE-C trials [adapted from Figures 7, 8, 10 and Table 14, Section B.2.5.1; Figures 17, 19 and Table 18, Section B.2.5.2, Document B of CS; VIALE-A CSR,[29] Table 17, VIALE-C CSR[28]

	VIALE-A (FAS, IA2)			VIALE-C (FAS 6-month follow-up)		
	VenAZA (N=286)	AZA (N=145)	p-value	VenLDAC (N=143)	LDAC (N=68)	p-value
Composite complete remission rate - % (95% CI)[d]						
CR	[redacted]	[redacted]		[redacted]	[redacted]	
CRi	[redacted]	[redacted]		[redacted]	[redacted]	
CR + CRi (as best response)	66.4 (60.6, 71.9)	28.3 (21.1, 36.3)	<0.001[a]	[redacted]	[redacted]	[redacted][b,c]
CR + CRi before initiation of Cycle 2	43.4 (37.9, 49.3)	7.6 (3.8, 13.2)	<0.001[a]	[redacted]	[redacted]	[redacted][b,c]
Median duration of CR + CRi – months, (95% CI)	17.5 (13.6, -)	13.4 (5.8, 15.5)		[redacted]	[redacted]	
Post-baseline transfusion independence - % (95% CI)[d]						
Red blood cell (RBC)	59.8 (53.9, 65.5)	35.2 (27.4, 43.5)	<0.001[a]	[redacted]	[redacted]	[redacted][b,c]
Platelets	68.5 (62.8, 73.9)	49.7 (41.3, 58.1)	<0.001[a]	[redacted]	[redacted]	[redacted][b,c]
RBC and platelet	58.0 (52.1, 63.8)	33.8 (26.2, 42.1)	<0.001[a]	[redacted]	[redacted]	[redacted][b,c]
Minimal residual disease (MRD)						
Patients with MRD negativity (<0.001), n (%)	[redacted]	[redacted]		[redacted]	[redacted]	
Patients with MRD <0.001 and CR + CRi ('deep remission'), % (95% CI)[d]	23.4 (18.6, 28.8)	7.6 (3.8, 13.2)	[redacted][a]	[redacted]	[redacted]	[redacted][b]

A P-value is from Cochran-Mantel-Haenszel test stratified by age (18 to <75, ≥75) and cytogenetics (intermediate risk, poor risk). b P value is from Cochran-Mantel-Haenszel test stratified by age (18 to <75, ≥75 years) and AML status (*de novo*, secondary). c P value is descriptive in nature only. d 95% CI is from the exact binomial distribution.

Abbreviations: AZA: azacitidine; CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete haematological recovery; FAS: full analysis set; IA2: interim analysis 2; LDAC: low-dose cytarabine; MRD: minimal residual disease; Ven: venetoclax

3.2.3 Subgroup analyses

Subgroups for consideration were not specified in the NICE final scope. The CS reports the following pre-planned subgroups for the outcomes of OS and CR + CRi in Figures 23 and 24, Section B.2.6.1 (VIALE-A), and Figures 27 and 28, Section B.2.6.2 (VIALE-C), Document B of the CS:

- Gender
- Age group
- Region
- Baseline ECOG score
- Type of AML
- Cytogenetic risk group at diagnosis
- Molecular mutational status at diagnosis
- Antecedent hematologic history of myelodysplastic syndrome (MDS)
- AML with myelodysplasia-related changes (AML-MRC).

In both trials, venetoclax combined with either AZA or LDAC had a beneficial effect for both outcomes across the majority of subgroups evaluated. Subgroup analyses for CR, CR + CRi by initiation of Cycle 2, and CR + CRh and CR + CRh by initiation of Cycle 2 (VIALE-C only) are presented in Appendix L of the CS.

With regard to the post-hoc subgroup analyses of participants in VIALE-A with 20-30% blasts at diagnosis, as well as patients in VIALE-C with a blast count of >30%, the CS presents OS and EFS in Figures 25 and 26, Section B.2.6.1 (VIALE-A), and Figures 29 and 30, Section B.2.6.2 (VIALE-C), Document B of the CS. These analyses were to address the specific issue in the context of this submission that AZA is considered a relevant comparator for the treatment of patients with a blast count of 20-30%, while LDAC is relevant only for the treatment of patients with a blast count of >30% in clinical practice. Although it is stated by the company that the VIALE trials were not powered to identify a clinical benefit in these sub-populations, positive outcomes were still observed for participants treated with venetoclax. A broad summary of the post-hoc subgroup analyses is presented in Table 11 above.

3.2.4 Adverse events

The safety population of the VIALE trials included all participants who received at least one dose of venetoclax/placebo and AZA or LDAC (N = 427 for VIALE-A and N = 210 for VIALE-C). The methods used to assess safety are reported in Sections B.2.3.5 and B.2.9, Document B of the CS and are considered appropriate by the ERG. In general, the safety profile for venetoclax is as expected for patients with this clinical condition.

Table 34 (Section B.2.9.1, page 101) and Table 41 (Section B.2.9.2, page 105) of the CS, Document B, reproduced as Table 12 below, summarise the frequency of adverse events (AE) for VIALE-A and VIALE-C. [redacted] participants in VIALE-A, and [redacted] participants in VIALE-C ([redacted] and [redacted] for VenLDAC and LDAC, respectively) reported at least one AE. AEs of Grade 3 or higher were reported in [redacted] participants in both treatment groups across both trials ([redacted] and [redacted] in the VenAZA and AZA groups, respectively, for VIALE-A; [redacted] and [redacted] in the VenLDAC and LDAC groups, respectively, for VIALE-C). The rate of AE leading to discontinuation of study drugs was similar between treatment groups across both trials.

In VIALE-A, the system organ class (SOC) with a higher incidence of treatment-emergent AEs (TEAEs) of Grade ≥3 in the VenAZA group compared with the AZA group included blood and lymphatic system disorders (82.3% and 68.1%, respectively), infections and infestations (63.6% and 51.4%), investigations ([redacted] vs [redacted]), respiratory, thoracic and mediastinal disorders ([redacted] and [redacted]) and gastrointestinal disorders ([redacted] and [redacted]) (VIALE-A CSR, Section 12.1.2.2, page 217).[29] The most common Grade ≥ 3 TEAEs (occurring in ≥ 10% of participants) that were reported in a higher percentage (by ≥2%) of participants in the VenAZA group compared with the AZA groups included thrombocytopenia (44.5% and 38.2%, respectively), neutropenia (42.0% and 28.5%), febrile neutropenia (41.7% and 18.8%), anaemia (26.1% and 20.1%) and leukopenia (20.5% and 11.8%). There was a higher proportion of deaths in the AZA group ([redacted]) compared with the VenAZA group ([redacted]). This reflected a higher proportion of deaths attributed to disease progression in the AZA group compared with the VenAZA group.

Table 12 Overview of patients with adverse events in VIALE-A and VIALE-C [reproduced from Table 34, Section B.2.9.1, and Table 41, Section B.2.9.2, of Document B]

Type of AE, n (%)	VIALE-A		VIALE-C	
	VenAZA (N=283)	AZA (N=144)	VenLDAC (N=142)	LDAC (N=68)
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Any AE with NCI-CTCAE toxicity Grade ≥ 3	[redacted]	[redacted]	[redacted]	[redacted]
Any reasonable possibility venetoclax/placebo-related AE[a]	[redacted]	[redacted]	[redacted]	[redacted]
Any reasonable possibility azacitidine-related AE[a]	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to venetoclax/ placebo discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to azacitidine/ LDAC discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Fatal AE (AE leading to death)	[redacted]	[redacted]	[redacted]	[redacted]

[a]As assessed by investigator.
Abbreviations: AE: adverse event; AZA: azacitidine; LDAC; low-dose cytarabine; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; Ven: venetoclax.

In VIALE-C, the SOCs with a higher incidence of Grade ≥3 TEAEs in the VenLDAC group compared with the LDAC group were blood and lymphatic disorders ([redacted] and [redacted], respectively), investigation ([redacted] vs [redacted]), and gastrointestinal disorders ([redacted] vs [redacted]) (CSR, Section Section 12.1.2.2, page 236).[28] The most common SOC of Grade ≥3 TEAEs reported in a lower percentage of participants in the VenLDAC group compared with the LDAC group included infections and infestations ([redacted] versus [redacted]), and metabolism and nutrition disorders ([redacted] versus [redacted]). The most common GRADE ≥ 3 TEAE (occurring in ≥ 10% of participants) that were reported in a higher percentage (by ≥2%) of participants in the VenLDAC group included neutropenia ([redacted] versus [redacted]), thrombocytopenia ([redacted] versus [redacted]), febrile neutropenia ([redacted] versus. [redacted]) and anaemia ([redacted] versus [redacted]). There was a higher proportion of deaths in the LDAC group ([redacted]) compared with the VenLDAC group ([redacted]). This reflected a higher proportion of deaths attributed to disease progression in the LDAC group compared with the VenLDAC group. Table 13 and Table 14 below provides a summary of GRADE ≥ 3 TEAEs occurring in ≥ 5% of participants in either treatment group of VIALE-A and VIALE-C.

Table 13 TEAEs Grade ≥3 reported for ≥5% of patients in either arm of VIALE-A [adapted from Table 35, Section B.2.9.1, Document B]

AE, n (%)	VenAZA (N=283)	AZA (N=144)
Haematologic adverse events	233 (82.3)	98 (68.1)
Thrombocytopenia	126 (44.5)	55 (38.2)
Neutropenia	119 (42.0)	41 (28.5)
Febrile neutropenia	118 (41.7)	27 (18.8)
Anaemia	74 (26.1)	29 (20.1)
Leukopenia	58 (20.5)	17 (11.8)
Non- Haematologic adverse events		
Atrial fibrillation	[redacted]	[redacted]
Hypokalaemia	30 (10.6)	15 (10.4)
Hypophosphatemia	[redacted]	[redacted]
Infections and infestations	180 (63.6)	74 (51.4)
Pneumonia	56 (19.8)	36 (25.0)
Sepsis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]

Abbreviations: TEAE: Treatment-emergent adverse event; AZA: azaciticine; Ven: venetoclax

Table 14 TEAEs Grade ≥3 reported for ≥5% of patients in either arm of VIALE-C [adapted from Table 42, Section B.2.9.2, Document B]

AE, n (%)	VenLDAC (N=142)	LDAC (N=68)
Haematologic adverse events	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Leukocytosis	[redacted]	[redacted]
Non-haematologic adverse events		
Hypertension	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]

Abbreviations: TEAE: treatment-emergent adverse event; LDAC: low dose cytarabine; Ven: venetoclax.

3.2.5 Meta-analyses

As the VIALE-A and VIALE-C trials investigated different venetoclax combinations for patients with AML, a meta-analysis was not performed by the company.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company identified no direct head-to-head evidence comparing VenAZA with LDAC. The company reported two types of indirect comparison, based on VIALE-A and VIALE-C: network meta-analysis (NMA) comparing the VenAZA arm of VIALE-A to the LDAC arm of VIALE-C via a connected network; and propensity score analysis (PSA) using individual patient data (IPD) to compare the same two arms.

PSA is a method that reweights participants from different studies according to covariates that might predict treatment allocation, as an attempt to reduce any treatment assignment bias. This allows to a degree for different treatments in different studies (normally cohorts) may be compared.

VIALE-A versus VIALE-C: The company had access to IPD for both VIALE-A and C and were thus able to 'match' the VIALE-A participants to those in the VIALE-C study. The chosen covariates were a list of baseline characteristics (age, race, gender, geographic region, AML status, MRC status, history of MDS status, ECOG score, cytogenetic risk category, bone marrow blasts, and prior systemic therapy use).

VIALE-A versus HMRN: The company also had access to the real-world evidence for comparators from the Haematological Malignancy Research Network (HMRN) database and were likewise able to match VIALE-A patients to similarly treated participants in HMRN database.

The ERG accepts the propensity score analysis as a legitimate approach to 'match' for treatment comparisons from both data sources above.

The CS also further report participant sub-groups: 20-30% bone cancer blasts and >30% blasts. OS and EFS for these two different database combinations, were estimated for:

a. VenAZA vs AZA treatments for the 20-30% subgroup
b. VenAZA vs LDAC treatments for the >30% subgroup
c. VenLDAC vs LDAC treatments for the >30% subgroup

The CS also report above treatment comparisons for the full population (both data sources) in Appendix D.

Network meta-analysis

The company's SLR identified two international, multi-centre, randomised, open-label, phase III trials for inclusion in the NMAs:

- AZA-AML-001:[30] comparing azacitidine (n=241) with conventional care regimens (namely, Best Supportive Care (BSC) [n=45], LDAC [n=158] or IC [n=44]) in patients aged 65 years or over with newly diagnosed AML with >30% bone marrow blast counts. Included by the company in the NMA of the >30% blast count and in the NMA of the overall population.
- AZA-001:[31] comparing azacitidine (n=55) with conventional care regimens (namely BSC [n=27], LDAC [n=20] or IC [n=11]) in patients aged 18 years or over with AML with ≥20% bone marrow blast counts. The median BM count for all groups was <30%. Only 2/113 participants had BM counts >30% (one in the AZA group with BM blast count 34%, the other in the intensive chemotherapy group with BM blast count 68.9%). Included by the company in the NMA of the overall population only. Given that only two participants had a BM blast count of >30%, the ERG agrees with this approach.

The CS reports summaries of study characteristics (Appendix D, Table 14), key reported outcomes (Appendix D, Table 15) and baseline characteristics (Appendix D, Table 16, Table 17) of AZA-AML-001 and AZA-001 alongside VIALE-A and VIALE-C. The company compared study characteristics and outcomes reported by the four studies and concluded that it was feasible to include VIALE-A, VIALE-C and AZA-AML-001 in a NMA for OS and CR+CRi. The company considered the remaining trial (AZA-001) unsuitable for the NMA due to its inclusion criterion of participants with 20-30% blasts

for those treated with LDAC. The ERG agrees with this approach, given that normally LDAC is not considered suitable for those with <30% blast count, as is the criteria for VIALE-A, VIALE-C and AZA-AML-001.

At clarification, the company provided a table of baseline characteristics of VIALE-A and VIALE-C alongside those of AZA-AML-001. The table is reproduced as Table 15 below. Demographic characteristics were generally similar across the three studies. The AZA-AML-001 study did not report the type of AML in participants. The median proportion of bone marrow blasts was higher in AZA-AML-001 (ranging from 70%-76%) than in VIALE-A ([redacted]) and VIALE-C ([redacted]). This difference is because although the inclusion criteria for AZA-AML-001 was blast count of > 30 %, the actual participants in the study according to the baseline characteristics was > 50% BM blasts whilst the VIALE-A and C trials used the >30% criteria. The ERG's clinical advisor pointed out that while this may indicate severity it does not imply these participants will respond better or worse than the VIALE trial patients. Thus, the ERG considers the AZA-AML-001 sufficiently comparable to the VIALE-A and C trials making it suitable for inclusion in the NMA models. Proportions of participants with poor cytogenetic risk were similar across all arms of the three trials, ranging from [redacted] (VIALE-C, LDAC arm) to 38.6% (VIALE-A, AZA arm, source EDC).

Table 15 Baseline characteristics for studies included in the NMA [reproduced from Table 8 of the company's clarification response]

	VIALE-A		VIALE-C		Dombret, 2015 (AZA-AML-001)				
	Ven AZA	**AZA**	**Ven LDAC**	**LDAC**	**AZA**	**LDAC**	**BSC**	**CCR**	**IC**
	N=286	N=145	N=143	N = 68	N=241	N=158	N=45	N=247	N=44
Demographics									
Age (years)									
Median	76.0	76.0	76.0	76.0	75.0	75.0	78.0	75.0	70.5
Range	49–91	60–90	36–93	41–88	64–91	65–88	67–89	65–89	65–81
Male, n (%)	172 (60.1)	87 (60.0)	78 (54.5)	39 (57.4)	139 (57.7)	94 (59.5)	29 (64.4)	149 (60.3)	26 (59.1)
Female, n (%)	114 (39.9)	58 (40.0)	65 (45.5)	29 (42.6)	102 (42.3)	64 (40.5)	16 (35.6)	98 (39.7)	18 (40.9)
Geographic region, n (%)									
United States	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
North America/ Australia	[redacted]	[redacted]	[redacted]	[redacted]	45 (18.7)	NR	NR	47 (19.0)	5 (11.4)
Western Europe/ Israel	[redacted]	[redacted]	[redacted]	[redacted]	116 (48.1)	NR	NR	122 (49.4)	22 (50.0)
Eastern Europe					46 (19.1)	NR	NR	44 (17.8)	7 (15.9)
Australia	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Asia	[redacted]	[redacted]	[redacted]	[redacted]	34 (14.1)	NR	NR	34 (13.8)	10 (22.7)
Rest of the world	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Race (%)									
White	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Black	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Other or missing	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR

	VIALE-A		VIALE-C		Dombret, 2015 (AZA-AML-001)				
	Ven AZA	**AZA**	**Ven LDAC**	**LDAC**	**AZA**	**LDAC**	**BSC**	**CCR**	**IC**
	N=286	N=145	N=143	N = 68	N=241	N=158	N=45	N=247	N=44
Clinical Characteristics									
AML type, n (%)									
Primary	214 (74.8)	110 (75.9)	92 (64.3)	46 (67.6)	NR	NR	NR	NR	NR
Secondary	72 (25.2)	35 (24.1)	51 (35.7)	22 (32.4)	NR	NR	NR	NR	NR
AML Classification									
Not otherwise specified	NR	NR	NR	NR	153 (63.5)	95 (60.1)	22 (48.9)	143 (57.9)	26 (59.1)
With myelodysplasia-related changes	[redacted]	[redacted]	[redacted]	[redacted]	75 (31.1)	50 (31.6)	20 (44.4)	83 (33.6)	13 (29.5)
With therapy-related myeloid neoplasms	26 (36.1) *[for secondary AML only]*	9 (25.7) *[for secondary AML only]*	6 (4.2) *[for secondary AML only]*	4 (5.9) *[for secondary AML only]*	8 (3.3)	9 (5.7)	2 (4.4)	12 (4.9)	1 (2.3)
With recurrent genetic abnormalities	NR	NR	NR	NR	5 (2.1)	4 (2.5)	1 (2.2)	9 (3.6)	4 (9.1)
Prior MDS, n (%)									
Yes	[redacted]	[redacted]	47 (32.9)	17 (25.0)	49 (20.3)	23 (14.6)	11 (24.4)	38 (15.4)	4 (9.1)
No	[redacted]	[redacted]	96 (67.1)	51 (75.0)	192 (79.7)	135 (85.4)	34 (75.6)	209 (84.6)	40 (90.9)
Confirmed prior HMA, n (%)	NR	NR	28 (19.6)	14 (20.6)	NR	NR	NR	NR	NR
BM Blasts (%)									

	VIALE-A		VIALE-C		Dombret, 2015 (AZA-AML-001)				
	Ven AZA	**AZA**	**Ven LDAC**	**LDAC**	**AZA**	**LDAC**	**BSC**	**CCR**	**IC**
	N=286	N=145	N=143	N = 68	N=241	N=158	N=45	N=247	N=44
Median	[redacted]	[redacted]	[redacted]	[redacted]	70	74	76	72	70
Range	[redacted]	[redacted]	[redacted]	[redacted]	2-100	4-100	9-100	2-100	6-100
<30%, n (%)	85 (29.7)	41 (28.3)	[redacted]	[redacted]	NR	NR	NR	NR	NR
30–50%	61 (21.3) *[≥30% to <50%]*	33 (22.8) *[≥30% to <50%]*	[redacted]	[redacted]	NR	NR	NR	NR	NR
>50%, n (%)	140 (49.0) *[≥50%]*	71 (49.0) *[≥50%]*	[redacted]	[redacted]	173 (71.8)	128 (81.0)	36 (80.0)	193 (78.1)	29 (65.9)
Cytogenetic Risk Group, n (%)	NR	NR	n = 138	n = 66	NR	NR	NR	NR	NR
Good	NR	NR	[redacted]	[redacted]	113 (46.9)	65 (41.1)	23 (51.1)	105 (42.5)	17 (38.6)
Intermediate	[redacted] 182 (63.6) *[EDC]*	[redacted] 89 (61.4) *[EDC]*	[redacted]	[redacted]	155 (64.3)	104 (65.8)	29 (64.4)	160 (64.4)	27 (61.4)
Good/intermediate	NR	NR	[redacted]	[redacted]	NR	NR	NR	NR	NR
Poor	[redacted] 104 (36.4) *[EDC]*	[redacted] 56 (38.6) *[EDC]*	[redacted]	[redacted]	85 (35.3)	54 (34.2)	16 (35.6)	85 (34.4)	15 (34.1)
ECOG Performance Status, n (%)									
0-1	[redacted]	[redacted]	[redacted]	[redacted]	186 (77.2)	123 (77.8)	30 (66.7)	189 (76.5)	36 (81.8)
0	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR

	VIALE-A		VIALE-C		Dombret, 2015 (AZA-AML-001)				
	Ven AZA	**AZA**	**Ven LDAC**	**LDAC**	**AZA**	**LDAC**	**BSC**	**CCR**	**IC**
	N=286	N=145	N=143	N = 68	N=241	N=158	N=45	N=247	N=44
1	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
2-3	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
2	[redacted]	[redacted]	[redacted]	[redacted]	55 (22.8)	35 (22.2)	15 (33.3)	58 (23.5)	8 (18.2)
3	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
3-4	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR
Missing	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR

Abbreviations: AZA: azacitidine; CCR: conventional care regimens; BSC: best supportive care; SC: supportive care; DEC: decitabine; BM: bone marrow; HMA: hypomethylating agent; MDS: myelodysplastic syndrome; GLAS: glasdegib; GO: gemtuzumab ozogamicin; ECOG: Eastern Cooperative Oncology Group; WBC: white blood cell; ANC: absolute neutrophil count; Hgb: haemoglobin; LDAC: low-dose cytarabine; AML: acute myeloid leukaemia; MDS: myelodysplastic syndrome; TC: treatment choice; EDC: electronic data capture; IVRS: interactive voice response system; IWRS: interactive web response system; CMML: chronic myelomonocytic leukaemia.

The company conducted risk of bias assessments of AZA-AML-001 and AZA-001 using the CRD guidance (Appendix D.1.6, Table 21 of the CS). In general, the ERG agrees with the company's assessments. Both trials were open-label and, therefore, at high risk of the associated biases.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Table 16 below presents the CS results for the unadjusted PSA weighted results for OS and EFS based on just the VIALE-A and VIALE-C trials in the >30% blast sub-group. Table 16 also includes the NMA OR and CR+CRi estimates, although these are based on VIALE_A and C and AZA-AML-001. OS and EFS are measures of survival with EFS possibly reflecting improved quality of life being event free. While all the PSA estimates are statistically significant in favour of venetoclax in addition to either azacitidine or to low dose cytarabine, the EFS estimates are less impacted, perhaps suggesting some event progression in both arms. These results are similar to the PSA analyses if conducted on the original unweighted data (given in the original submission Document B, page 94). Not presented here are the similar PSA estimates of treatment comparisons from VIALE-A and VIALE-C with appropriate treatment arms from the HMRN database (Document B, Table 30 – this table usefully shows more of the treatment combinations rather than just VenAZA versus LDAC, and includes 20-30% blasts as well as >30% blasts) where the impact of venetoclax seems greater, which may be a reflection of real world or because (as acknowledged by the company and the ERG agrees) the effective sample sizes from the HMRN database were small (all reported in Document B.2.8.3).

Table 16 Indirect treatment comparison estimates for OS, EFS and CR+CRi [adapted from Tables 46, 27, 23 and 24 of Document B]

			PSA After weighting	NMA
		BC blasts	**Estimate**	**Estimate**
VenAZA vs LDAC (>30% blasts)	OS	(>30%)	HR= [redacted] [a]	OR= [redacted] [b]
	EFS	(>30%)	HR= [redacted] [a]	-
	CR + CRi	(>30%)	OR= 1 [redacted] [c]	OR= [redacted] [b]

[a] HR and 95% Confidence Intervals (95% CI) after PAS weights to compare studies VIALE-A and VIALE-C
[b] OR and 95% Credible Intervals (95% CrI) estimated using NMA model using VIALE-A, VIALE-C and AZA-AML-001
[c] OR and 95% Confidence interval (95% CI) estimated using PSA weights to compare studies VIALE-A and VIALE-C
Abbreviations: AZA: azacitidine; EFS: event-free survival; HR: hazard ratio; LDAC: low-dose cytarabine; OS: overall survival; Ven: venetoclax.

The NMA results for the comparison of VenAZA with LDAC are reported in full in the CS (Document B, Section B.2.8.1, Table 23, Figure 32, Table 24, Figure 33). However, the main VenAZA versus LDAC comparison is also in Table 16 above, showing the NMA treatment comparative estimates for OS and CR+CRi (presented as ORs). The OS may be contrasted with the PSA OS and EFS estimates. These NMA results are slightly more conservative than the PSA estimates (although not directly comparable being ORs rather than HRs). However, they too indicate that the addition of venetoclax has beneficial effects (improves OS and increases the chance of recovery). The original CS (Document B, Table 23) also gives all other NMA pairwise comparisons and one of interest shows VenAZA to be superior (but non-significantly) compared with VenLDAC in the >30% blasts sub-group [redacted].

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG did not have access to the IPD data and so were not able to verify these results for any of the PSA estimates.

Using HRs provided by the company, the ERG obtained similar results for the NMA OS estimates (see Table 17)

Table 17 Pairwise treatment comparisons for OS (>30% blasts)

	ERG Median (2.5% 97.5%)	Company's estimates[a]
VenAZA vs VenLDAC	0.86 (0.51, 1.46)	[redacted]
VenAZA vs AZA	0.60 (0.46, 0.79)	[redacted]
VenAZA vs LDAC	0.55 (0.38, 0.80)	[redacted]
VenLDAC vs VenAZA	1.16 (0.69, 1.97)	[redacted]
VenLDAC vs AZA	0.71 (0.46, 1.09)	[redacted]
VenLDAC vs LDAC	0.64 (0.44, 0.94)	[redacted]
AZA vs VenAZA	1.67 (1.27, 2.18)	[redacted]
AZA vs VenLDAC	1.42 (0.92, 2.18)	[redacted]
AZA vs LDAC	0.91 (0.705, 1.16)	[redacted]
LDAC vs VenAZA	1.83 (1.26, 2.63)	[redacted]
LDAC vs VenLDAC	1.57 (1.07, 2.28)	[redacted]
LDAC vs AZA	1.01 (0.86, 1.42)	[redacted]

a Extracted from the CS Document B, Table 23, page 82.

For the CR+CRi treatment comparison NMA estimates using the OR's provided by the company and the literature, the ERG has verified the CS results are plausible, although the standard models failed to run. Instead the ERG ran pairwise comparisons using Bucher estimates see Table 18 below, illustrating them to be comparable to the CS point estimates.

Table 18 Pairwise treatment comparisons for CR+CRi (>30% blasts)

	Odds ratio (95% CI) (Bucher)	Company's estimates[a]
VenAZA vs VenLDAC	0.97 (0.60, 1.57)	[redacted]
VenAZA vs AZA	5.79 (3.39, 9.89)	[redacted]
VenAZA vs LDAC	6.20 (4.71, 8.16)	[redacted]
VenLDAC vs VenAZA	1.03 (0.63, 1.66)	[redacted]
VenLDAC vs AZA	5.95 (3.36, 10.53)	[redacted]
VenLDAC vs LDAC	6.37 (2.51, 16.16)	[redacted]
AZA vs VenAZA	0.17 (0.10, 0.29)	[redacted]
AZA vs VenLDAC	0.16 (0.09, 0.30)	[redacted]
AZA vs LDAC	1.07 (0.65, 1.77)	[redacted]
LDAC vs VenAZA	0.16 (0.12, 0.21)	[redacted]
LDAC vs VenLDAC	0.16 (0.06, 0.40)	[redacted]
LDAC vs AZA	0.93 (0.57, 1.54)	[redacted]

a Extracted from the CS, Document B, Table 24 page 83.

3.6 Conclusions of the clinical effectiveness section

The company mostly kept to the original brief. The ERG and their clinical advisor consider the slight deviations sensible and acceptable. The company presented two of its relevant studies: VIALE-A comparing VenAZA with AZA alone and VIALE-C comparing VenLDAC with LDAC alone. Independently, each study indicated strong evidence that the addition of venetoclax was beneficial for OS, EFS and CR+CRi. However, there is some suggestions that for VenAZA this may be mainly beneficial for participants able to achieve deep remission (it is not clear the direction of the cause and effect – the company indicating this to be because of VenAZA). In VIALE-A, participants with lower MRD levels, indicating improved prognosis, had better response to VenAZA compared to the same sub-group on AZA alone. There was little difference between the treatment arms for the higher MRD subgroup.

Being separate Phase III RCTs, VIALE-A and VIALE-C treatment arms were not directly comparable. NICE restricts the use of AZA to bone marrow blast count of 20-30%, whilst clinical practice means that LDAC is normally only given to patients >30% blasts resulting in both study results being divided into two sub-groups: 20-30% blast count and >30% blast count.

The indirect comparison methods considered were NMA and PSA, both considered by the ERG to be viable approaches. PSA requires IPD and was conducted on i) the two VIALE trials and then ii) on the two VIALE trials plus the inclusion of the data from the HMRN database. The CS restricted their results to the VenAZA versus LDAC treatment groups only for >30% blasts for the first scenario, whilst both blast sub-groups were considered for the second along with some other treatment combinations. This second scenario may have limitations since the comparable treatments meant small sample sizes. The overall conclusion from the first PSA scenario is that the VenAZA >30% blast count sub-group showed significantly better results in terms of OS [HR=[redacted] EFS [HR=[redacted]] and CR+CRi [OR= 1[redacted]] than LDAC. Given the ERG had no access to the IPD, these results could not be replicated.

The NMA results included another independent study AZA-AML-001. The blasts for this latter study however was >50%. The ERG was assured by their clinical advisor that this was compatible with the >30% blast sub-group from the two VIALE trials. Summary effect estimates were used for the NMA. The main CS reported for the >30% blast sub-group (the whole population results were available in Appendix D- which were similar but not truly reflective). The CS presents all pairwise treatment combinations but focusses on the VenAZA versus LDAC treatment groups again for >30% blasts. For the common outcomes the addition of venetoclax proved to be beneficial; for OS [OR=[redacted]] and CR+CRi [OR=[redacted]]. The ERG was able to verify the methods and most results.

All the results indicate benefit of the addition of venetoclax to either azacitidine or low-dose cytarabine for patients ineligible for IC and from the individual VIALE studies seems to be rapid and durable. Both VenAZA and VenLDAC had acceptable safety profiles. In both studies the data are relatively mature, although for VIALE-C the primary endpoint still had not been met with more in the VenLDAC treatment arm being censored (i.e. were surviving) - a further analysis of an unplanned 6 month follow-up did, however, demonstrate a positive difference of VenLDAC compared to LDAC. The main limitation, fully recognised by the company, is the use of bone marrow blasts sub-groups to fit with clinical practice - the VIALE studies were not designed to detect such sub-group differences. The propensity score approach has the advantage of adjusting for variation between the studies' characteristics but requires full individual data and so was restricted to the VIALE studies and data from HMRN. The NMA analyses were able to include other studies but were restricted to the groups in common, namely the >30% blasts sub-group, thus relied on smaller sample sizes and not all treatment group groups could be compared, making these results to be view with some caution, as the CS indicates.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify publications conducted in adult patients with newly diagnosed AML receiving established first-line treatment. Searches were conducted in three broad categories: economic evaluation, resource use and utilities. The SLR identified studies to 4th August 2020 where full details of the review and searches can be found in appendix G of the CS. The company also included the NICE appraisal of gilteritinib (TA642) retrospectively as it was published after the original SLR was conducted.[32]

The eligibility criteria were sufficiently broad to capture economic evaluations and resource use of any intervention within this population. Evaluations were not limited to cost-effectiveness studies but also, cost-utility, cost-benefit and cost-minimisation analyses. Inclusion of economic evaluations and resource use publications were restricted to UK studies which are published in English. Eligibility criteria for the utility publications included a wider patient population of any adult with AML for any intervention and inclusion was not conditional upon being a UK study. Searches were performed in a range of databases and included a search of HTA websites and conference abstracts for the period 2017-2020.

The company selected 5 out of 12 publications initially identified as meeting the inclusion in the review to inform the structure of their model. Upon inclusion of TA642 post-hoc, 6 publications in total were used to inform the model structure and inputs for the economic analysis. This includes one journal article and 5 previous TAs: 1) A UK cost-effectiveness analysis of midostaurin versus standard of care in adult patients (aged 18-59) with newly diagnosed AML;[33] 2) NICE appraisal (TA552) of liposomal cytarabine-daunorubicin (CPX-351) versus standard cytarabine and daunorubicin chemotherapy in patients with untreated AML aged ≥60 years;[34] 3) NICE appraisal (TA523) of midostaurin for adult patients (18-60 years) with untreated AML;[35] 4) NICE appraisal (TA545) of gemtuzumab ozogamicin in patients aged ≥15 years with untreated AML;[36] 5) NICE appraisal (TA399) of azacitidine in adult patients (≥65years) with AML, not eligible for haematopoietic stem cell

transplant and ≥30% bone marrow blasts;[24] and 6) NICE appraisal (TA642) of gilteritinib in patients with relapsed or refractory FLT3 mutation positive AML.[32] Details of the chosen studies can be found in Table 47, page 117 of the CS. The company notes that a prior appraisal of azacitidine (TA218) was not included as no subgroup analyses were performed upon the population of interest in this submission.

The company was not able to identify any economic evaluations or TAs which addressed the population of interest in this submission and, therefore, did not draw any conclusions regarding the cost effectiveness of the identified technologies. However, the company advises that these publications informed the structure and inputs of the economic model.

The ERG is satisfied with the companies review of cost-effectiveness studies. The search strategies and eligibility criteria are comprehensive, and an appropriate selection of databases were included. Of the six studies considered, four used some form of partitioned survival model approach. The remaining studies, TA545 and TA399, used a cohort state transition model and a semi-markov model respectively.[24, 36] These are most structurally relevant to the model used for this submission. The states utilised in TA399 are broadly similar to the model used for this submission aside from the addition of the "cure" state. The company in TA399 was criticised by the ERG as the model's simplicity did not allow for active subsequent treatment.[37] The model used for this submission allows for this with respect to cost, but does not allow for changes to subsequent treatment to effect post-progression survival. A discussion of how the models of the identified studies informed the company's own model structure and inputs would help to justify and cross validate its de-novo structure and assumptions.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 19 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Aligns with reference case.
Perspective on costs	NHS and PSS	Aligns with reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligns with reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with reference case.
Synthesis of evidence on health effects	Based on systematic review	A systematic review was conducted, but all clinical effectiveness evidence is sourced from the VIALE-A and VIALE-C trials.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Aligns with reference case. Pooled EQ-5D data from both VIALE trials was used for both populations (20-30%, >30% blast cell count). The ERG has some concerns about comparability of EQ-5D values across the trials and between the blast count subgroups, but is generally satisfied the pooled utilities are appropriate for both populations (4.2.7)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligns with reference case.
Source of preference data for valuation of	Representative sample of the UK population	Aligns with reference case.

changes in health-related quality of life		
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligns with reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Aligns with reference case. Although, a full breakdown of the components of the health state costs are not provided.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with reference case.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a five-state, cohort-level Markov model to compare:

- VenAZA with AZA and LDAC, and;
- VenLDAC with LDAC

for the treatment of [redacted]

The model consists of five health states: Remission, non-remission, cure, progressive disease/relapse and death (Company submission, Document B, figure 41). Patients enter the model in either the remission or non-remission health state which is based upon the rate of CR + CRi observed for patients in the VIALE-A and VIALE-C trials. The baseline distribution of patients in either health state can be found in Document B, Table 52, page 125 of the company submission. Upon entering the model, all patients are at risk of progressive disease/relapse or death. In the company base case, all patients remaining in the remission state at 2 years in the VenAZA or VenLDAC arms transition to the cure state where they experience the same outcomes as the general population in terms of mortality risk and health related quality of life. No cure assumption is applied to those on AZA or LDAC.

Transitions to progressive disease/relapse, death, and treatment discontinuation are determined by parametric survival functions derived from time-to-event data from the VIALE-A and VIALE-C trials. Time to treatment discontinuation is modelled independently of the health state transitions, where all patients receive active treatment (VenAZA, VenLDAC, AZA or LDAC) in the first cycle of the model. The model has functionality so that the total population receiving treatment does not surpass overall survival minus those considered to be cured. Subsequent treatment costs in the model are applied to all patients who are alive, not on active treatment and not cured. A downward adjustment for general population mortality risk is also applied to all state transition and time to treatment discontinuation survival functions. This is discussed in more detail in section 4.2.6.

The ERG believes that structurally, the company's models is generally appropriate for addressing the decision problem. The company's preference for a Markov model is understandable given their contention that those who achieve a sustained remission on VenAZA or VenLDAC may be considered cured from two years. However, the ERG does have some concerns regarding parameterisation of the model given the small numbers of patients and events available to inform some of the transitions (see 4.2.6 below). Further structural concerns relate to the validity of the cure assumption in the absence of longer-term data, the use of general population mortality to adjust all the time to event curves, and the independent modelling and assumptions around treatment discontinuation and subsequent treatment. These issues are addressed in sections 4.2.6 below.

4.2.3 Population

The population is adult patients with newly diagnosed AML who are ineligible for IC with a bone marrow blast cell count of ≥20%. A patient's eligibility for IC is determined by clinician assessed risk of treatment-related mortality and patient preference. The economic evaluation considers venetoclax in combination with AZA or LDAC compared with AZA or LDAC alone in two populations:

1. Patients with a bone marrow blast cell count of 20-30%
2. Patients with a bone marrow blast cell count of >30%

The two populations are considered separately since treatment with AZA alone is restricted by NICE for patients with a blast cell count of 20-30% and treatment with LDAC alone is predominantly used for patients with a blast cell count of >30% in UK clinical practice.

The ERG agrees that it is appropriate to consider the two populations separately based on NICE guidance and their own clinical expert advice.

4.2.4 Interventions and comparators

Interventions

Venetoclax is combined with either AZA or LDAC depending on bone marrow blast cell count. According to the draft summary of product characteristics, treatment with venetoclax should be continued until disease progression or unacceptable toxicity is observed.[38] Dose reductions of venetoclax may be necessary for patients with neutropenia, infections or for the management of cytopenia. These treatment interruptions and reductions are accounted for by applying a relative dose intensity to each component of treatment in the model (CS, Document B, page 181, Table 64).

Patients with a bone marrow blast count of 20-30%

VenAZA consists of venetoclax orally (400 mg per day) in combination with AZA (75mg/m^2 of body surface area) on days 1-7 of each 28-day cycle. In order to reach the 400mg daily dose, a dose ramp-up of 100mg and then 200mg is administered on days 1 and 2, respectively, followed by 400mg from day 3 onwards. This is in line with the dosing schedule of the VenAZA arm of the VIALE-A trial and the draft SmPC for venetoclax.[38]

Patients with a bone marrow blast count of >30%

Patients can receive either VenAZA or VenLDAC in this population. The dosing schedule for VenAZA is the same for both populations. VenLDAC consists of a 600mg dose of venetoclax daily in combination with 20mg/m^2 of LDAC on days 1-10 of each 28-day cycle. A dose ramp-up of 100mg, 200mg and 400mg per day of occurs for venetoclax on days 1 to 3, respectively, with 600mg per day from day 4 onwards. This is in line with the dosing schedule of the VenLDAC arm of the VIALE-C trial and the draft SmPC of venetoclax.[38]

Comparators

The comparators are AZA and LDAC alone which is in line with the NICE scope and the comparators in the VIALE-A and VIALE-C trials respectively. Treatments are administered using the same regimen as used when in combination with venetoclax. The use of AZA alone is not recommended by NICE in the population with >30% blast cell count. Therefore, the comparators are different for each population: AZA alone in those with a blast cell count of 20-30%; and LDAC alone in those with a blast cell count is >30%. A summary of the intervention comparisons used in the model can be found in the company submission, Document B, page 124, Table 50.

Following active treatment discontinuation, patients in the intervention arms receive either gilteritinib (3%) or hydroxycarbamide (97%). Patients in the comparator arms all go onto receive hydroxycarbamide (100%). The company qualifies this as clinical opinion advised that as higher CR+CRi rates were observed for venetoclax, patients would be expected to be fitter upon discontinuation and more able to tolerate gilteritinib.

The ERG clinical expert did not concur with subsequent treatment distribution, and was of the opinion that a similar proportion of patients in the comparator arms would also receive gilteritinib. The ERG's clinical expert further considered the 3% treatment share for gilteritinib to be conservative, and suggested a scenario whereby 15% is assumed in all arms of the model. The company provided the scenario in response to the clarification letter, which favoured the venetoclax combinations, but noted further clinical opinion suggesting that 15% is too high to to be reflective of patients who are FLT3+ and fit enough for subsequent treatment in this population, and that a smaller proportion of patients that discontinued AZA or LDAC would be fit enough for gilteritinib than those who received VenAZA or VenLDAC.

4.2.5 Perspective, time horizon and discounting

The model utilises a 28-day cycle length and a lifetime horizon of 40 years. A discount rate of 3.5% is applied to costs and QALYs as per NICE guidance. The age of patients at model entry is [redacted] which is based on the pooled baseline

characteristics of the VIALE-A and VIALE-C trials. Therefore, by 40 years, any remaining survivors in the model would be [redacted] years old. However, as Table 20 shows, less than 1% of the cohort remains alive well before this time point in all arms of the model

Table 20 Year by which <1% survivorship is realised in the company model by treatment arm and population.

Treatment arm	20-30% blast cell count	>30% blast cell count
VenAZA	[redacted]	[redacted]
VenLDAC	N/A	[redacted]
AZA	11.42	N/A
LDAC	N/A	6.75

4.2.6 Treatment effectiveness and extrapolation

Informing model transition probabilities

The company's model uses rates of CR + CRi by treatment arm to distribute patients between the remission and non-remission states to commence the model. A set of parametric survival curves is used to determine time dependent, treatment specific transition probabilities for each of the state transitions allowed in the model. Separate independently fitted curves are used for each relevant alternative in the two populations of interest (blast count 20-30%, blast count >30%).

For the cohort of patients with 20-30% blast count, data from the relevant subgroup of the VIALE-A trial are used to inform the curves for VenAZA and AZA alone. For the cohort with >30% blast count, data from the relevant subgroup of VIALE-C are used to inform the VenLDAC and LDAC curves, and unadjusted data from the relevant subgroup of VIALE-A are used to inform the curves for VenAZA. The latter decision was justified on grounds that the baseline covariates and hazard ratios from the indirect comparison between the VenAZA arm of VIALE-A and the LDAC arm of VIALE-C were similar before and after weighting for propensity scores (see Tables 25 and 26 of the company submission, Document B). The NMA results were not used to inform the comparison between VenAZA and LDAC because it was argued that the

AZA-AML-001 trial (included in the network) was less generalisable to the UK population compared to the VIALE trials.

The ERG is generally satisfied with the company's approach to the selection of data to inform comparisons in the model. Whist some questions may be raised over the choice of using unweighted rather than propensity score weighted data, the ERG acknowledges that the differences in comparative OS, EFS and response are very small between the two approaches.

To inform the transition probabilities the company conducted time to event analysis for each event arising from each state (progression or death), whereby patients were censored if they experience the competing event (See Table 53 of the CS for a summary of the assumptions). For example, the analyses of time to relapse (from remission) and time to progressive disease from non-remission were censored for death. Similarly, analyses of time to death were censored for progression. See section B.3.3.3. of the CS for details. Time to death from PD, is modelled using the time of confirmed progression as the index time.

The ERG follows the logic of the company's approach for the purpose of informing the transitions in the Markov model, but suggest it is associated with some general uncertainties:

1. *The model is already based on post-hoc subgroup data from the VIALE-A and VIALE C trials, and so splitting the data further by response status (remission/ non-remission) and disease progression, and censoring for competing events, results in small numbers of patients and events informing some of the survival analyses. It could be argued that there are insufficient data in some cases to inform meaningful parametric time to event analysis (See Tables 54 and 55 of the CS for details on numbers of events and censors in the time to event data used to inform the transitions in the model).*
2. *The validation of selected individual time to event curves in isolation is challenging given the small amount of observed data on which to base the selections and the censoring for competing risks. Whilst the overall model output provides a good fit to the observed trial data, the extrapolations remain uncertain based on the selected curves and assumptions applied.*

Adjustment for general population mortality

In addition to basing transition probabilities on the selected curves, the company make the case that it is appropriate to incorporate general population mortality to account for the risk of death from other causes. This seems to imply that data from the trial captures disease specific mortality and not all-cause mortality. Whilst this is not the strictly true, the tails of some of the Kaplan Meier curves, particularly those from the remission state, do not appear to be capturing the ongoing risk of death from other causes. Therefore, to account for this, the company multiply all the selected time to event curves by the cycle specific probability of age/sex matched general population survival from the end of the trial observation periods onwards in the model.

The ERG can see the argument for adjusting for general population mortality in the selected time to death curves. However, the ERG is less clear on the need to apply such an adjustment to the time to relapse/progressive disease curves. This appears to use the general population mortality risk to increase the risk of transitioning to progressive disease conditional on survival. This would benefit from further justification.

Cure assumption

In the VenAZA and VenLDAC treatment arms of the model, the company apply an assumption that any patients still in remission at two years are considered cured and therefore transition to the "Cure" state. From this point onwards, these patients have zero chance of progression and are assigned age/sex matched general population mortality risk and health related quality of life. The company argue that the application of a cure assumption for the AZA or LDAC would be inappropriate based on expert clinical opinion and what they see in clinical practice. The company's argument is that venetoclax in combination with AZA, on the other hand, "*has an innovative mechanism of action which is able to efficiently and selectively target leukaemia stem cells (LSC) by disrupting energy metabolism and thus is able to drive sustained deep remission".*

The ERG's clinical advisor agrees with the company that current non-intensive treatments are not used with curative intent, and that no cure assumption should be applied to patients on these treatments. However, the ERG's clinical advisor is of the

opinion that the cure assumption applied to VenAZA and VenLDAC is also highly uncertain given the limited follow-up data currently available.

The company refer to clinical expert advice suggesting that patients treated with venetoclax who "*achieve a sustained deep remission have the potential to achieve long-term survivorship, whereby their outcomes are in line with the general population*." The company also refer to data which demonstrates that "VenAZA provides deep and durable complete remission rates (CR/CRi with/without MRD) that have historically only been associated with IC" and highlight that "depth and duration of remission has been positively correlated with length of survival in patients who receive IC". The company also note that the rate of relapse after two years is low based on experience in intensive chemotherapy and provide clinical expert opinion that "the proportion of patients in CR/CRi for whom cure is assumed at year 2 will be enriched with those with no/low MRD". The company argue that this is corroborated by a plateau in the Kaplan-Meier EFS and OS curves for those on VenAZA in the 20-30% blast count and >30% blast count populations. However, the numbers at risk in the tails of these distributions are low, and there is insufficient follow-up beyond two years to validate the assumption.

Whilst the ERG does not rule out the potential for patients in remission at two years to achieve long-term survivorship, it does not believe that the current data conclusively supports the application of a cure assumption in the model. It is the ERG's clinical expert's view that the cure assumption is uncertain and that modelling should also consider scenarios that reflect an ongoing risk of relapse over the time horizon of the model. Whilst a cure assumption was accepted as plausible in the NICE appraisal of gilteritinib (TA642), the population in this appraisal was adults with relapsed or refractory FLT3-mutation-positive acute myeloid leukaemia (AML), which would include [redacted] *in which gilteritinib could act as a bridge to stem cell transplant.*[32] *However, cure assumptions reflected all patients alive at two years, regardless of transplant status. It cannot be assumed that a cure assumption is equally valid in the current appraisal. Historically, non-intensive treatments have never been curative in this generally* [redacted]. *These patients* [redacted] *that is used with curative intent in the broader AML population. There is currently a lack of long-term follow-up data to validate a cure*

assumption for venetoclax. The company have not explored the impact of removing the cure assumption but have provided scenarios which extend the timepoint from which it is applied, out to maximum of 3 years.

A further concern of the ERG relates to the fact that even if a cure assumption is accepted (zero risk of progressive disease for those in remission beyond 2 years), survival of those in the "Cure" state is assumed to match that of the general population. The ERG noted the previous appraisal of gilteritinib for relapsed or refractory acute myeloid leukaemia (TA642), in which a cure assumption was accepted as plausible, but an uplifted general population mortality risk (standardised mortality ratio of 2.0) was applied to long-term survivors.[32] The ERG requested a scenario that applied a similar assumption to mortality in the cure state of the company's model, but the company declined to provide this. They argued that "it is not appropriate to apply the same assumption to the current appraisal due to the differences in the population considered in the decision problem, and the population who are deemed eligible for cure". They note that the population which the SMR of 2 was applied in TA642 was all patients alive at 2 years in the context of a partitioned survival model. They argue that it would be inappropriate to apply an SMR of 2 to the stratified population achieving a sustained remission (CR + CRi at two years) in the current Markov model. The ERG acknowledges the company's point that application of a SMR of 2 for those in the cure state would not align with the assumption in TA642. However, it is still questionable, even if a cure assumption is accepted, whether those surviving in the cure state would have equivalent survival to the age/sex matched general population. The population for the current appraisal [redacted] *. Therefore, the background mortality due to other causes would be expected to be higher in all states of the model. The ERG believes this to be an area of uncertainty which would benefit from sensitivity analysis.*

Observations on individual curve fitting and selections

As indicated above, the company have informed the transition probabilities in their model with time to event curves for each transition that can arise from the individual health states of the model – censoring for competing events. This results in five

Kaplan Meier curves being estimated for each treatment option in each of the populations modelled. Parametric survival analysis methods were used by the company to fit parametric curves to each of these for extrapolation of the transition probabilities.

Observations on curve fitting

Related to the uncertainty raised by the small number of events to inform individual transitions in the model, there is the uncertainty associated with choice of curve for each transition. The company have provided an extensive set of scenario analyses to assess the impact of selecting each different curve for each transition in the model. This shows the results to be fairly robust to individual changes. However, given the uncertainties related to the cure assumption, the ERG believes that the impact of changing curve selections for remission to relapse, for VenAZA and VenLDAC, should also be assessed in combination with scenarios that remove the cure assumption. Therefore, the ERG has explored scenarios that assess the impact of this, using plausible alternative curve selections for each treatment in the relevant population:

- VenAZA (20-30% blast count) – the generalised gamma was selected as an alternative to the company's preferred log normal base case (see Figures 61 and 62 of the company submission). Whilst the Weibull provided the lowest AIC/BIC, there was little to choose between the curves in terms of statistical fit. Therefore, the ERG assessed the generalised gamma as having a potentially better visual fit compared to the Weibull and offering a middle ground in terms of projected mean time to relapse. It was further noted in the CS, that clinical experts expressed a preference for the log logistic distribution for VenAZA in this population. Therefore, the ERG has also explored this option.
- VenAZA (>30% blast count) – the lognormal distribution, having the second best statistical fit and offering a middle ground in terms of mean projected time to relapse, was selected as an alternative to the company's preferred generalised gamma (see Figures 81 and 82 of the company submission).
- VenLDAC (>30% blast count) – the lognormal distribution, having the second best statistical fit and offering a middle ground in terms of mean projected

time to relapse, was selected as an alternative to the company's preferred generalised gamma (see Figures 91 and 92 of the company submission). It was further noted in the CS, that clinical experts expressed a preference for the exponential distribution for VenLDAC in this population. Therefore, the ERG has also explored this option.

A further uncertainty of the ERG, related to curve fitting, is that the preferred curves for VenAZA suggest a small post-progression survival advantage compared to AZA and LDAC (see figure 6 and figure 11 in the company's response to the clarification letter). The ERG is uncertain if this represents a true effect of treatment or is down to chance given the small patient numbers. Thus, the ERG has explored scenarios that equalise the time to death curves from the progressive disease state.

Treatment discontinuation and subsequent treatment extrapolation

Time to treatment discontinuation

Time to treatment discontinuation is modelled independently of the health state transition probabilities in the model. Patients are assumed to be at risk of treatment discontinuation from model entry, where the risk of discontinuation is determined by time-to-event analysis of data from the VIALE-A and VIALE-C trials. Similar to the health state transition probabilities, the company produced 6 different parametric survival curves. A curve was chosen for each population on the grounds of the plausibility of projected mean time on treatment, visual inspection, and lowest AIC/BIC statistics. There is functionality in the model to ensure that the population on treatment is never higher than the number of patients who are alive and not "cured". A general population mortality adjustment has been applied to the time to treatment discontinuation survival curve, in line with all other survival curves in the model, post maximum follow-up of the VIALE-A and VIALE-C trials.

Subsequent treatment

The proportion of patients receiving subsequent treatment is determined by parametric extrapolation of the time-to-treatment discontinuation curve, overall survival and the number of patients assumed "cured" in the model. Therefore, subsequent treatment is independent of the relative occupancy of the progressive disease health state. Instead,

subsequent treatment consists of those who are not on treatment (as determined by the time to treatment discontinuation curve), not dead and not cured.

The company's approach to modelling time on treatment and subsequent treatment implies several assumptions which the ERG does not believe have been well justified by the company. These are listed and explored further below:

1. *Patients on venetoclax who are in remission at two years (considered "cured") no longer receive active treatment.*
2. *1. (above) then implies that the number remaining on treatment beyond two years consists of patients in the non-remission or progressive disease states.*
3. *The application of 1 and 2 in the model leads to a sudden drop in the number of patients in the venetoclax arms assumed to be on subsequent treatment from 2 years onwards (Table 21). This also seems to infer that a proportion of those considered cured at 2 years had been on subsequent treatment prior to 2 years, which is not plausible.*

Table 21 Health state occupancy of progressive disease and death health states compared to those on treatment at alternate time points – VenAZA 20-30% (no half cycle correction)

Months	Progressive disease	Death	Treatment	Subsequent treatment
0	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]

The ERG believes that the company's approach underestimates subsequent treatment in the venetoclax arms. Since the draft SmPC states that venetoclax in combination with HMA or LDAC should be continued until disease progression or unacceptable toxicity, the assumption that those still in remission at two years would stop their

treatment has not been justified. The VIALE-A and VIALE-C trials did not have a long enough follow-up to justify the assumption that patients in remission would stop receiving treatment after 2 years, and the preferred curve fits show a slowing in the rate of treatment discontinuation for VenAZA and VenLDAC. The ERG clinical expert was also of the opinion that first-line treatment would not currently be stopped routinely for patients who are in remission at 2 years. Accordingly, it would be expected that those on treatment beyond two years would be made up of those in remission ("cured" or within the cure disease state) and non-remission (not yet progressed or non-remission disease state), and we should expect subsequent treatment to broadly follow the occupancy of the progressive disease state.

Table 20 above shows that subsequent treatment is somewhat higher than progressive disease state occupancy up to 12 months in the company base case (VenAZA arm (20-30% blast count population)), but that it drops substantially below it from 24 months when the cure assumption is applied. A similar pattern is observed for the venetoclax arms in the >30% blast count population.

The ERG believes that if a cure assumption is applied, it is more plausible to assume that those still on first line treatment beyond two years, according to the selected TTD curve, should be assumed to be those in remission ("cured" or cure disease state) and non-remission, and all those with progressive disease should be assumed to be on subsequent treatment. However, this does require an adjustment in the model to the number on subsequent treatment, to ensure that the combined number on treatment and subsequent treatment never exceeds the number of patients surviving. An alternative approach would be to let treatment/subsequent treatment follow the state occupancy rather than applying the TTD curves independently. However, this would assume that all those in remission or non-remission stay on treatment, and doesn't allow for the possibility of discontinuation for reasons other than progression. Finally, if the cure assumption is removed, and an ongoing risk of progression is applied beyond two years to those in remission, then the company assumptions may no longer be problematic. They simply infer that the number on subsequent treatment equates with the number surviving minus the number still on first line treatment (as is assumed in the AZA and LDAC arms of the model).

The ERG also notes what it assumes to be a reporting error on page 170 of the company submission (Document B), whereby the company reports that the log-normal parametric extrapolation was chosen for time on treatment for AZA in the 20-30% blast count cohort, on grounds that it provided the lowest AIC/BIC, whilst also providing a reasonable fit to the data. In fact, the exponential curve provides the lowest AIC/BIC for AZA in this cohort, and it is the exponential that has been applied in the company base case.

The ERG is also uncertain about the justification for adjusting the time on treatment curves for general population mortality, although it may be appropriate if death was treated as a discontinuation event in the analysis of time on treatment, and the VIALE trials fail to adequately capture the risk of death from other causes.

4.2.7 Health related quality of life

Health-related quality of life data were collected in the VIALE-A and VIALE-C trials using the EQ-5D-5L and the QLQ-C30 (see section 3.2.2), with the EQ-5D-5L data used to inform utility values in the model. In order to increase sample size for use in the model and reduce uncertainty, the data from the trials were pooled. In line with the NICE reference case, the data were cross-walked to EQ-5D-3L utility scores using the van Hout et al (2012) algorithm.[39] The resulting values are then used to estimate health-state dependent utility values for the remission, non-remission, and PD/relapse health states in the model. For patients in the cure health state it is assumed, based on clinical opinion, that their quality of life is the same as the age-matched general population. Utility decrements due to adverse events were taken from a separate published study.[40]

EQ-5D-5L data collected in the VIALE trials

In the VIALE trials, EQ-5D data were collected on day 1 of cycle 1, then day 1 of alternate cycles and on the patient's final visit, which was defined as the last visit on or after the date of disease progression, relapse from CR + CRi, or treatment failure. The number of patients who provided EQ-5D scores at each cycle is presented in Table 60 on page 175 of the CS. The EQ-5D data were stratified according to the model health states and remission status as follows:

- EFS without CR/CRi – any EQ-5D measurements for patients in the EFS health state without remission, defined as any assessment before the date of CR+CRi
- EFS with remission – any EQ-5D measurements for patients in the EFS health state with remission, defined as any assessment on or after the date of CR+CRi
- PD/relapse – any EQ-5D measurements for patients in the PD or relapsed disease health state, defined as any assessment on or after the date of disease progression, relapse from CR+ CRi, or treatment failure.

Descriptive statistics for the pooled EQ-5D data by health state are presented in Table 22 below.

Table 22 Descriptive statistics for EQ-5D health state utility data pooled across VIALE-A and VIALE-C trials [reproduced from Table 61, section 3.4.4 of Document B]

Health state	Number of patients	Number of assessments	Mean (SD)
Before treatment	[redacted]	[redacted]	[redacted]
EFS without CR/CRi (non-remission)	[redacted]	[redacted]	[redacted]
EFS with CR/CRi (Remission)		[redacted]	[redacted]
PD/relapse	[redacted]	[redacted]	[redacted]

Abbreviations: EFS = event-free survival, CR = complete remission, CRi = complete remission with incomplete blood count recovery, PD = progressive disease, SD = standard deviation

To account for the longitudinal nature of the data the company used a linear mixed-effects regression model to estimate utility values for each health state with the EQ-5D score as the dependent variable and the health states used as the independent variables. As the utility values applied in the model were treatment independent and adverse events were included separately as one-off utility decrements, the EQ-5D data were adjusted to account for the impact of adverse events on the utility values. Grade 3 or 4 adverse events occurring in ≥5% of patients were included as covariates, which resulted in the following adverse events being included: neutropenia, thrombocytopenia, anaemia, leukopenia, hypokalaemia, pneumonia, and hypertension. The company also stated that as the majority of patients receiving AZA and LDAC died during the trial period ([redacted] and [redacted] respectively), the decreasing quality of life of patients as they approach death is already captured in the trial EQ-5D

data. The ERG notes that the corresponding figures for the VenAZA and VenLDAC patients are lower ([redacted] and [redacted] respectively).

The utility values applied in the model based on the regression analysis are summarised in Table 23.

Table 23 EQ-5D health state utilities derived from pooled VIALE trial data [reproduced from Table 62, section 3.4.4 of Document B].

Health State	Mean	SE
Remission	[redacted]	[redacted]
Non-remission	[redacted]	[redacted]
PD/relapse	[redacted]	[redacted]

Abbreviations: PD = progressed disease, SE = standard error

The use of EQ-5D data collected in the VIALE trials to derive utility estimates is appropriate and consistent with the NICE reference case. However, the ERG has some concerns with the way the utility values are derived and used in the economic model. Although the pooling of the EQ-5D data allows for increased sample size and thus would reduce uncertainty, there are some differences between the patients included in the VIALE-A and VIALE-C trials (e.g. patients in VIALE-C had more severe disease). In addition it is noted that the populations are split by blast count for modelling efficacy but not for estimating utility values. Further justification was requested to support the assumption that the pooling of the quality of life data is appropriate and can generalise across the blast subgroups. In response, the company presented the EQ-5D data from the VIALE-A and VIALE-C trials separately (see response to clarification question B7, Table 15) which showed the utility values to be similar across the trials. An additional sensitivity analysis was presented using the trial EQ-5D data separately which had minimal impact on the results. It is not clear to the ERG, however, how the un-pooled data were applied. It may be reasonable to assume the VIALE-A data were used for the VenAZA vs AZA comparison and the VIALE-C trial for the VenLDAC vs LDAC comparison, but it is not clear which trial data were used for the VenAZA vs LDAC comparison. Furthermore, the impact of blast count on quality of life was not discussed. The ERG identified a published systematic literature review of health-related quality of life in AML patients not eligible for intensive chemotherapy which shows there is some evidence to support the hypothesis that blast count may be related to quality of life, although this was not observed across all studies in the review.[41] The impact of applying different utility values split by blast count on the cost-effectiveness estimates is unknown. Clinical advice to the ERG suggests a number of factors influence quality of life and while

blast count may be a factor, response to treatment is likely the main driver. The ERG concludes the pooling of the EQ-5D data is reasonable and supports the company's base case approach in this regard.

One potential remaining issue was noted by the ERG in relation to the adjustment of the EQ-5D data to account for adverse events. No justification was provided for applying treatment-independent utility values in the model. The ERG notes that there could be some differences in quality of life between the treatment arms due to adverse events but the EQ-5D data have not been presented separately by treatment arm to explore this further. The ERG would welcome further consideration of this point by the company.

Cure assumption

As described previously, patients who are alive in the remission health state at 2 years are considered cured and experience the same quality of life as the age-adjusted general population utilities. This assumption is based on clinical opinion and appears to suggest a higher utility value for patients who are cured compared to those in remission (0.79 versus [redacted]). This is justified by the company on the basis that only patients in the remission health state following VenAZA or VenLDAC can be cured in the model.

The assumption that patients in the cure health state would have the same quality of life as the general population is uncertain. However, the ERG notes that at the timepoint it starts to be applied in the model (2 years), it is very similar to the observed remission health state utility estimate. This helps to validate its application.

Adverse events

To capture the impact of adverse events on quality of life, one-off utility decrements from a separate published study (Wehler et al, 2018) were applied during cycle 1. This study estimated the impact of another treatment (ivosidenib) on quality of life in patients with relapse/refractory AML. The utility decrements are summarised in Table 59 of the CS based on grade 3 or 4 adverse events occurring in ≥5% of patients in the VIALE trials.

No justification was given for applying disutilities separately in the model instead of using the EQ-5D data from the trials. The data source used is in a different patient group of relapsed/refractory AML patients and the ERG was unable to source a number of the disutilities listed in Table 59 of the CS from the source paper. The company justified the selected data source as being from a similar population of interest but the disutility values summarised in the Wehler et al study are derived from a number of different data sources from the broader oncology literature, not specifically AML patients.[40] Although the disutility values are not key drivers of the results, the ERG would welcome further reassurance that the company's approach does not underestimate the quality of life impact of adverse events in the model.

4.2.8 Resources and costs

The company conducted a systematic review to find relevant cost and resource use data for naïve patients with AML, which identified 7 studies. Costs in the model include drug acquisition, subsequent treatments, monitoring and disease management, palliative care and adverse event costs. In accordance with the NICE reference case, only direct medical costs incurred by the NHS and PSS are included.

Drug and administration costs

Within the model, the lifetime acquisition cost is estimated based on the unit cost per pack, the planned treatment schedule, the relative dose intensity and the time on treatment observed in the VIALE trials extrapolated over the model time horizon. In the context of the relative dose intensity adjustment, the model does not appear to fully account for wastage associated with prescribed venetoclax tablets not used by patients who discontinue treatment prior to using their prescribed supply. Wastage is included for AZA and LDAC.

The expected licensed dose of venetoclax is 400mg daily when used in combination with AZA and 600mg daily when used in combination with LDAC. A confidential simple patient access scheme is included for venetoclax offering a discount of [redacted] off the list price. Venetoclax is an oral treatment and no administration costs are included on the basis that venetoclax is given in combination with an infusion or subcutaneous injection. Thus, any cost of dispensing the treatment is captured in the administration costs applied to the non-oral treatments. Clinical advice to the ERG indicates that

there will be a small additional pharmacy dispensing cost for venetoclax that has not been included in the model.

For AZA and LDAC, administration costs were £159 per administration taken from NHS National Tariff cost SB12Z: deliver simple parenteral chemotherapy at first attendance.[42] The ERG notes that comparator PASs are available for AZA and LDAC; the impact of these PASs on the cost-effectiveness of venetoclax is presented in a confidential appendix to this ERG report. Treatment and administration costs for venetoclax, AZA and LDAC are summarised in Table 24.

Table 24 Treatment acquisition and administration costs [reproduced from Table 63, section 3.5.1 of Document B]

Treatment arm	Dosing schedule[a]	Acquisition cost per treatment cycle[b,c]		Cost per admin	Admins per cycle	Total admin cost per treatment cycle
		List price	PAS price[g]			
VenAZA						
Ven [Cycle 1: treatment initiation]	Orally, QD, three-day dose ramp-up: D1: 100 mg, D2: 200 mg, D3: 400 mg	£299.34	[redacted]	£0.00	3	£0.00
Ven [Cycle 1: post treatment initiation]	400 mg, orally, QD	£4,276.29	[redacted]		25	£0.00
Ven [Subsequent cycles]	400 mg, orally, QD	£4,789.44	[redacted]		28	£0.00
AZA	(All cycles) 75 mg per m^2 BSA on days 1–7 of each cycle	£ 3,080.00[c,d]		£159.00[e]	7	£1,113.00
VenLDAC						
Ven [Cycle 1: treatment initiation]	Orally, QD, four-day dose ramp-up: D1: 100 mg, D2: 200 mg, D3: 400 mg, D4: 600 mg	£555.88	[redacted]	£0.00	4	£0.00
Ven [Cycle 1: post treatment initiation]	600 mg, orally, QD	£6,157.85	[redacted]		24	£0.00
Ven [Subsequent cycles]	600 mg, orally, QD	£7,184.16	[redacted]		28	£0.00
LDAC	(All cycles) 20 mg per m^2 BSA on days 1–10 of each cycle	£26.40[c,f]		£159.00[e]	10	£1,590.00
Comparators						
AZA	(All cycles) 75 mg per m^2 BSA on days 1–7 of each cycle	£3,080.00 [c,d]		£159.00[e]	7	£1,113.00
LDAC	(All cycles) 20 mg per m^2 BSA on days 1–10 of each cycle	£26.40[c,f]		£159.00[e]	10	£1,590.00

[a]Each treatment cycle was 28 days. [b]List prices for Ven and AZA were sourced from the MIMS,[43] the list price for LDAC was sourced from the eMIT database.[44] [c]List prices were used for AZA and LDAC as it was not possible to determine PAS prices. [d]Per cycle acquisition costs based on 138.57 mg of AZA per day on days 1–7 (assuming a BSA of 1.85 m^2 and wastage of the remainder of the vial) [e]National Tariff 2020/21; SB12Z; deliver simple parenteral chemotherapy at first attendance.[42] [f]Per cycle acquisition costs based on 36.02 mg of LDAC per day on days 1–10 (assuming a BSA of 1.80m^2 and wastage of the remainder of the vial).[g]Any diversion from table 63 of the CS represent minor typographical errors which have been corrected in this table.

Abbreviations: AZA: azacitidine; BSA: body surface area; D: day; LDAC: low-dose cytarabine; eMIT: Drugs and Pharmaceutical Electronic Market Information Tool; MIMS: Monthly Index of Medical Supplies; PAS: patient access scheme; QD: once daily; Ven: venetoclax

The ERG notes that the model may slightly underestimate the cost of venetoclax as it does not include any wastage associated with venetoclax tablets that are prescribed but not used due to patients dying or discontinuing treatment during a cycle. This issue was discussed in TA642 where it was considered appropriate to include 7 days wastage for patients who die prior to the cure point in the model. The ERG considers a similar adjustment should be made to account for venetoclax wastage.

Dose intensity

Dose intensity estimates were included in the model based on a combination of the VIALE trials and clinical expert opinion. The company highlighted that AML patients often receive antimicrobial prophylaxis treatment (CYP3A inhibitors) as neutropenia and infections are common, however no costs of concomitant medications were included presumably as they would apply equally in both treatment arms. In addition, responders to VenAZA can experience cytopenia which may result in delays between cycles or within-cycle dose reductions. For the VenLDAC, AZA and LDAC arms of the model the dose intensity estimates from the post-hoc analyses of the VIALE trials were used. However, for the Ven component of the VenAZA arm the dose intensity estimate was adjusted using expert opinion from [redacted] observed in VIALE-A to 50% on the basis that the dose intensity was higher than would be expected in clinical practice. The ERG clinical advisor agreed with the adjustment applied by the company and confirmed that lower doses of venetoclax are used in practice without compromising efficacy. The dose intensity estimates applied in the model are summarised in Table 64, section B.3.5.1 of the CS.

Subsequent treatments

Following treatment discontinuation, subsequent treatments are included in the model based on expert opinion. Patients treated with VenAZA and VenLDAC are assumed to receive gilteritinib (3%) or hydroxycarbamide (97%) as subsequent treatments and all patients receiving AZA and LDAC receive hydroxycarbamide. A PAS is also available for gilteritinib; the impact of this PAS on the cost-effectiveness of venetoclax is presented in a confidential appendix to this report.

Clinical expert advice to the ERG is that a higher proportion of patients would go on to receive gilteritinib in practice regardless of their initial treatment. Sensitivity analysis is provided where the proportion receiving gilteritinib is increased to 15% but is only applied following VenAZA and VenLDAC. An additional analysis provided at clarification stage assumes 15% of all patients receive gilteritinib following treatment discontinuation, which resulted in a reduction to the ICERs. The company stated they did not believe this analysis to be representative of clinical practice as it is likely the proportion of patients fit enough to receive gilteritinib as a subsequent treatment would be smaller following AZA and LDAC due to the lower proportion experiencing CR + CRi. Clinical advice to the ERG indicates the proportion receiving gilteritinib would be the same regardless of initial treatment and as such the preferred base case analysis assumes 15% of all patients would receive gilteritinib as a subsequent treatment. However, this remains an area of uncertainty that would benefit from further consultation with clinical experts, and if possible data to inform the proportions eligible.

Health-state unit cost and resource use

Resource use associated with remission, non-remission and PD/relapse health states was included in the model and assumed to be the same as used in TA642.[32] As the health states included in the model are different from those in TA642 some assumptions were made to apply the costs to the health states in the venetoclax model. Resource use included outpatient and emergency department visits, hospitalisations, blood transfusions, diagnostic procedures and tests. The unit costs and resource frequencies for each health state were not provided separately. An assumption was made that patients in the cure health state require the same resources as remission patients. A one-off cost of death was included to capture end of life care costs. The health state costs are summarised in Table 25.

Table 25 Mean total health state costs [adapted from Table 67 of the CS]

Health state	Mean total costs per cycle (SE)[a]	Source
Non-remission[b]	£2,432.86 (484.77)	TA642[d,f,45]
Remission[b]	£163.55 (32.71)	
PD/relapse[b]	£2,638.21 (527.64)	
Cure[b]	£163.55 (32.71)	Assumption
Death[c]	£2,603.40 (520.68)	Georghio & Bardsley (2014)[46e,f,]

[a]All SEs were assumed to be 20% of the mean value.[b] Per cycle cost. [c] One-off cost. [d] Costs from TA642 were inflated from 2018 to 2019 costs using an inflation factor of 1.023. [e]Costs from Georghiou and Bardsley were adjusted to a 28-day cost be multiplying by a ratio of 28/90. Costs were inflated from 2011 costs to 2020 costs using an inflation factor of 1.148. [f] All inflation factors were calculated using data from the PSSRU Unit Costs of Health and Social Care (2019).[47]
Abbreviations: NA: not applicable; SE: standard error

No breakdown of the component costs included in the health state costs per cycle were provided in the submission to allow a further critique of the unit costs and resource use frequencies. It is also noted that despite costs being inflated to 2019 prices the per cycle costs are marginally higher in TA642.[32] From TA642 some information is provided which describes the frequencies of different resource use based on information collected in a retrospective chart review study of relapsed or refractory FLT3 mutation positive AML patients in Europe, including the UK. The ERG notes there are some differences between the patient populations of the VIALE trials and those relevant to TA642 that may affect resource use, such as patients eligible for venetoclax being generally older and less fit than those receiving gilteritinib. Despite this, the ERG considers it is appropriate to use the health state costs from TA642 in the model as clinical advice indicates they will provide a reasonable proxy for the resource use of venetoclax treated patients in clinical practice.[32]

Adverse event unit costs and resource use

As noted previously, grade 3 or 4 adverse events occurring in >5% of patients in the VIALE trials are included in the model. Adverse event management costs are included as one-off costs applied in cycle 1. See Table 68 of the CS for details of the mean cost per occurrence. The ERG notes that while the costs included are similar to

the adverse event costs used in TA642, there was concern that the costs of treating some adverse events had been underestimated. Specifically, expert advice indicated treatment for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis would not be conducted as day-cases but would require admission to hospital. At clarification stage the company provided updated analysis using non-elective long stay (NEL) costs for these adverse events, which had minimal impact on the ICERs.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's base case results are presented separately for the two populations. The deterministic results are presented in Table 71 and Table 72 of the company submission (Document B), for the 20-30% blast count and the >30% blast count cohort, respectively. These are reproduced as Tables 26 and 27 below. For the >30% blast count cohort, pairwise comparisons were made between VenAZA and LDAC, and VenLDAC and LDAC. A full incremental analysis was not provided. However, there is a slight discrepancy in the costs and QALYs between the LDAC arms in the respective comparisons (Table 72). This is due a difference in the year from which the general population mortality adjustment is applied for these comparisons (2.56 and [redacted] years, respectively), making it impossible to make a consistent comparison between VenAZA and VenLDAC without altering the company base case assumption for one on the intervention arms. However, it is clear from the analysis that VenAZA is associated with greater cost (assuming list price for AZA) and greater benefit than VenLDAC.

Results incorporating available PAS prices on AZA and gilteritinib will be provided in a confidential appendix to this report.

Table 26 Base-case results for 20–30% blasts at Ven PAS price (deterministic) [reproduced from Table 71, Document B]

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER inc. (£/QALY)
AZA	£103,749	1.833	1.139	-	-	-	-
VenAZA	[redacted]	4.442	[redacted]	[redacted]	2.609	[redacted]	£38,866

[a] Undiscounted.
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; PAS: patient access scheme; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 27 Base-case results for >30% blasts at Ven PAS price (deterministic) [reproduced from Table 72, Document B]

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
VenAZA versus LDAC							
LDAC	£33,828	0.839	0.523				
VenAZA	[redacted]	3.765	[redacted]	[redacted]	2.926	[redacted]	£39,449
VenLDAC versus LDAC							
LDAC	£33,617	0.832	0.518				
VenLDAC	[redacted]	2.438	[redacted]	[redacted]	1.606	[redacted]	£31,291

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; LYG, life years gained; QALYs, quality-adjusted life years; Ven: venetoclax.

In the 20-30% blast count subgroup, the QALY gains for VenAZA versus AZA are driven primarily by increased time spent in the remission and cure states of the model, but also a slightly longer time spent in the progressive disease state – owing a slightly higher risk of death being applied to patients who progress on AZA alone than those who progress on VenAZA. The cost increment is driven primary by the higher first line treatment costs.

In the >30% blast count subgroup, the QALY gains for VenAZA and VenLDAC versus LDAC are driven by longer time spent in the remission and cure states of the model. The cost increment is driven primary by the higher first line treatment costs.

5.2 Company's sensitivity analyses

The company also provided a probabilistic analysis for their preferred based case, which produced mean ICERs that were similar to the deterministic point estimates (See Company submission, document B, section B.3.8.1).

With respect to one-way sensitivity analysis, individual parameters were varied by +/- 20%. The results showed baseline age and treatment costs to consistently have the greatest impact on the ICER for VenAZA versus AZA (20-30% blast count cohort), and VenAZA and VenLDAC versus LDAC (>30% cohort).

The company presented a full range of scenarios around the curve selections informing each transition probability and time on treatment in the model (Tables 75 to 77 of the CS, document B). They also provided some scenarios around the cure assumptions for VenAZA and VenLDAC. However, this only considered an extension to time from which the cure assumption was applied. No scenarios considered the impact of its removal.

5.3 Model validation and face validity check

Section B.3.10 of Document B (page 214) summarises the validation checks of the model carried out by the company. This includes:

- Quality control checks of the cost-effectiveness model undertaken by an independent modelling team.
- Comparison of the model outputs for EFS and OS to observed clinical trial outcomes, clinical practice and clinical expert opinion.
- Comparison of modelled outcomes between 'Non-remission' and 'Remission' states

Comparison of model outputs to trial data

Document B of the CS, figures 120-123, page 215-216 compare the model output of observed EFS and OS for VenAZA vs. AZA (20-30% blasts) and VenLDAC vs. LDAC (>30% blasts). Appendix J of the CS, Table 46, summarises the model predictions for EFS and OS for VenAZA, VenLDAC, AZA and LDAC arms of the model against clinical trial data from VIALE-A and VIALE-C in the 20-30% blasts subgroup. There is no validation output presented in the CS for VenAZA vs. LDAC in the >30% blast subgroup.

The company note that EFS is underpredicted compared to the trial data throughout the trial follow-up period for VenAZA vs. AZA (20-30% blasts). Conversely, EFS and OS outcomes were slightly overestimated for the LDAC arm in the >30% blast subgroup. Inspection of Table 46, appendix J shows that model outputs of OS at 24-months is underestimated for AZA and slightly overestimated for VenAZA in the 20-30% blasts subgroup. The table does not clearly identify which trial and model outcomes for VenLDAC and LDAC arms are presented. Overall, upon visual inspection, the model output closely follows the Kaplan-Meier curves for EFS and OS for the trial follow-up period for VenAZA vs. AZA and VenLDAC vs. LDAC.

Comparison of model outputs against clinical data

Document B, page 216, Table 90 compares the model output for AZA in the 20-30% blast subgroup against data from the HMRN. The company notes that there is insufficient data in the HMRN to compare against the >30% blast subgroup. The model overestimates OS at every timepoint reported (6,12 and 24 months). The greatest discrepancy is at 6 months where the HMRN reports 35.1% (95% CI: 20.4 – 50.3) against model output [redacted] for AZA (20-30% blasts). Given the paucity of HMRN data for the >30% blast subgroup, it is not possible to ascertain whether the model output overpredicts OS for all comparators.

Comparison of model outputs against clinical expert opinion

The company reports clinical expert opinion on a subset of the survival curve extrapolations used in the economic model throughout document B, section B.3.3.4, page 137 to 168. The ERG notes that the company did not use any of the curves suggested by the clinicians where clinical opinion was reported. The ERG also notes that the company's reporting of clinical opinion is not consistent across comparators. For example, clinical opinion is reported in the discussion of curve choice for "PD/relapse to death" state for LDAC (document B, page 163) but not for the comparator VenLDAC (Document B, page 157).

The company clinical experts support the assumption that that those who achieve sustained remission under venetoclax treatment have the potential to be cured. While the ERG do not rule out the possibility for a cure, the plausibility of the cure assumption is uncertain with regard to the patient population in this indication, and

given the lack of long-term follow-up data. For further discussion of the ERG's critique of the cure assumption see section 4.2.6.

Comparison of modelled outcomes between 'Non-remission' and 'Remission' states
Document B, page 217, figures 124-125 show that patients who achieve remission have a higher progression free survival than those in non-remission for venetoclax. This is not true for AZA in the 20-30% blasts cohort, where progression free survival for those in remission crosses those in non-remission. This suggests that, from 18 months, patients receiving AZA who are in remission are at a higher risk of progressive disease than those in non-remission. The company's clinical experts advise that outcomes differ greatly between these two groups, where those in non-remission should experience a greater risk of progressive disease over those in remission.

Black-box verification checks
The ERG conducted quality checks upon the model by recreating the company's deterministic analysis. In addition, black box checks of the model as suggested by Tappenden and Chilcott were carried out.[48] The results of this are reported in Table 28, no issues were found.

Table 28 Results of black-box verification checks carried out by the ERG

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	None
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	None
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	None
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	None
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced	None
	Increase intervention cost	ICER is increased	None
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	Sample tested. No issues found.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	None.
	Amend value of each individual model parameter	ICER is changed	None. Parameters behave as expected under the model structure.
	Switch all treatment-specific parameter values	QALYs and costs for each option should be switched	None

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG carried out further scenario analyses to explore the identified uncertainties in the modelling assumptions and inputs. A description of each scenario is listed with the results presented in Tables 28-30 for VenAZA versus AZA (20-30% blasts), VenAZA versus LDAC (>30% blasts) and VenLDAC versus LDAC (>30%) respectively.

1. Active treatment and subsequent treatment are determined by the state occupancy of the remission/non-remission and progressed disease/relapse state respectively.
2. Active treatment is determined by the independent parametric extrapolation of time-to-progressive disease curve and subsequent treatment is determined by the occupancy of the progressed disease/relapse state. An adjustment is made to ensure that the total in the model receiving any treatment does not surpass OS.
3. Removal of the cure assumption. Patients do not enter the cure state from the remission state and continue to be at risk of progression or death for the modelled time horizon.
4. Removal of general mortality adjustment to time-to-treatment discontinuation curve.
5. Standardised mortality ratio of 1.5 applied to general population mortality.
6. Standardised mortality ratio of 2 applied to general population mortality.
7. 7-day tablet wastage of venetoclax assumed for all patients who progress.
8. 14-day tablet wastage of venetoclax assumed for all patients who progress.
9. Equalisation of progressive disease/relapse to death curves to venetoclax.
10. Equalisation of progressive disease/relapse to death curves to comparator.
11. Scenario 1 + 3.

Further scenarios (12 onwards) combine alternate time-to-relapse parametric curve extrapolations with the removal of the "cure" assumption (scenario 3).

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The impact of each scenario described in section 6.1 can be seen in Tables 29-31 below. The ERG explored alternate assumptions regarding the treatment/subsequent treatment modelling approach are found in scenarios 1 and 2. Scenario 1 results in a lower ICER in all populations, this is to be expected as the total on 1st line treatment consists of those in the

non-remission and remission health states. Therefore, at the two-year time point, the total number of patients receiving venetoclax reduces by those in the remission state. It should be noted that this scenario results in higher subsequent treatment costs yet, as it is comparatively inexpensive, it has little impact upon the ICER. Scenario 2, results in a modest increase in the ICER as conditioning subsequent treatment upon the progressed disease state results in a greater number of modelled patients receiving subsequent treatment. The removal of the "cure" assumption (scenario 3) has the greatest impact, resulting in ICERs of £96,408, £109,417 and £112,650 for VenAZA(20-30%), VenAZA(>30%) and VenLDAC(>30%) respectively. This is as expected as, patients in the remission state continue to receive treatment and be at risk of progression from 2 years onwards. Further, the use of subsequent treatment is no longer adjusted downward for the cure assumption at two years in this scenario. The adjustment of the chosen parametric survival curve for the non-remission to relapse state and removal of the "cure" assumption, found in scenarios 12 and 13, results in a further increase in the ICER from scenario 3 alone as more patients are modelled to progress.

Table 29 ERG scenario analyses results VenAZA vs. AZA (20-30%)

Scenario	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Company base case	[redacted]	[redacted]	£38,866
1. Active treatment and subsequent treatment determined by state occupancy	[redacted]	[redacted]	£17,934
2. Subsequent treatment determined by PD/relapse state with OS adjustment	[redacted]	[redacted]	£42,094
3. Removal of "cure" assumption	[redacted]	[redacted]	£96,408
4. General population adjustment removed from TTD curve	[redacted]	[redacted]	£40,713

5. Standardised Mortality Ratio applied to general population mortality (SMR=1.5)	[redacted]	[redacted]	£42,066
6. Standardised Mortality Ratio applied to general population mortality (SMR=2)	[redacted]	[redacted]	£44,702
7. 7-day tablet wastage assumed for treatment discontinuation of venetoclax	[redacted]	[redacted]	£39,344
8. 14-day tablet wastage assumed for treatment discontinuation of venetoclax	[redacted]	[redacted]	£39,823
9. Equalisation of PD/relapse curves to intervention arm	[redacted]	[redacted]	£33,923
10. Equalisation of PD/relapse curves to comparator arm	[redacted]	[redacted]	£18,852
11. Scenario 1 + 3	[redacted]	[redacted]	£87,985
12. Scenario 3 + log-logistic extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£97,536

13. Scenario 3 + generalised gamma extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£108,323

Table 30 ERG scenario analyses results VenAZA vs. LDAC (>30%)

Scenario	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Company base case	[redacted]	[redacted]	£39,449
1. Active treatment and subsequent treatment determined by state occupancy	[redacted]	[redacted]	£33,470
2. Subsequent treatment determined by PD/relapse state with OS adjustment	[redacted]	[redacted]	£40,124
3. Removal of "cure" assumption	[redacted]	[redacted]	£109,417
4. General population adjustment removed from TTD curve	[redacted]	[redacted]	£39,447
5. Standardised Mortality Ratio applied to general population mortality (SMR=1.5)	[redacted]	[redacted]	£44,712
6. Standardised Mortality Ratio applied to general population mortality (SMR=2)	[redacted]	[redacted]	£49,248

7. 7-day tablet wastage assumed for treatment discontinuation of venetoclax	[redacted]	[redacted]	£39,861
8. 14-day tablet wastage assumed for treatment discontinuation of venetoclax	[redacted]	[redacted]	£40,273
9. Equalisation of PD/relapse curves to intervention arm	[redacted]	[redacted]	£39,425
10. Equalisation of PD/relapse curves to comparator arm	[redacted]	[redacted]	£40,964
11. Scenario 1 + 3	[redacted]	[redacted]	£108,321
12. Scenario 3 + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(>30%)	[redacted]	[redacted]	£133,869

Table 31 ERG scenario analyses results VenLDAC vs. LDAC (>30%)

Scenario	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Company base case	[redacted]	[redacted]	£31,291
1. Active treatment and subsequent treatment determined by state occupancy	[redacted]	[redacted]	£27,559
2. Subsequent treatment determined by PD/relapse state with OS adjustment	[redacted]	[redacted]	£31,682
3. Removal of "cure" assumption	[redacted]	[redacted]	£112,650

4. General population adjustment removed from TTD curve	[redacted]	[redacted]	£31,319
5. Standardised Mortality Ratio applied to general population mortality (SMR=1.5)	[redacted]	[redacted]	£36,749
6. Standardised Mortality Ratio applied to general population mortality (SMR=2)	[redacted]	[redacted]	£41,797
7. 7-day tablet wastage assumed for treatment discontinuation of venetoclax	[redacted]	[redacted]	£32,438
8. 14-day tablet wastage assumed for treatment discontinuation of venetoclax	[redacted]	[redacted]	£33,585
9. Equalisation of PD/relapse curves to intervention arm	[redacted]	[redacted]	£32,968
10. Equalisation of PD/relapse curves to comparator arm	[redacted]	[redacted]	£37,422
11. Scenario 1 + 3	[redacted]	[redacted]	£116,670
12. Scenario 3 + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenLDAC(>30%)	[redacted]	[redacted]	£135,963
13. Scenario 3 + exponential extrapolation of time-to-relapse for patients in	[redacted]	[redacted]	£148,210

'Remission' - VenLDAC(>30%)			

6.3 ERG's preferred assumptions

Reflecting on the evidence base, the ERG acknowledges the potential for patients in remission at two years on venetoclax to achieve long-term survivorship. However, it does not believe that the current data conclusively supports the application of a cure assumption in the model. Given the uncertainty surrounding the validity of a cure assumption, the ERG offers an alternative base case that removes the cure assumptions whilst retaining the company's preferred parametric curves for time to relapse from remission. The removal of the cure assumption also resolves the inconsistencies around proportions on treatment and subsequent treatment in the venetoclax arms of the model. The ERG also prefers to apply the adverse event costs which assume atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis require inpatient admission as per the company scenarios provided in the response to clarification queries. The results of this alternative base case are provided in Tables 32-34 below.

Table 32 ERG's preferred model assumptions - VenAZA versus AZA (20-30% blasts)

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company's base case		£38,866
Adverse event costs to account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries.	*4.2.8*	£39,314
Removal of cure assumption (see issues 1 and 3)	*4.2.6*	£96,408
ERG's base case		£97,184

Table 33 ERG's preferred model assumptions - VenAZA versus LDAC (>30% blasts)

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company's base case		£39,449
Adverse event costs to account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries.	*4.2.8*	£39,633
Removal of cure assumption (see issues 1 and 3)	*4.2.6*	£109,417
ERG's base case		£109,708

Table 34 ERG's preferred model assumptions - VenLDAC versus LDAC (>30% blasts)

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company's base case		**£31,291**
Adverse event costs to account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries.	*4.2.8*	£31,167
Removal of cure assumption (see issues 1 and 3)	*4.2.6*	£112,650
ERG's base case		**£112,356**

6.4 Conclusions of the cost effectiveness section

The company has provided a comprehensive submission to support decision making, if a cure assumption is accepted as plausible in the proposed positioning based on the evidence available. However, the ERG is of the opinion that application of a cure assumption remains uncertain given a lack of long-term data currently available to validate it, and believe that it is also relevant to consider scenarios in which no cure is assumed. Removal of the cure assumptions results in substantial upward uncertainty in the ICERs for the venetoclax combinations versus the relevant comparators.

Several further uncertainties remain, including the appropriate distribution of subsequent treatments to apply in the intervention and comparator arms of the model, the potential impact of drug wastage, the preferred curve fits for time to relapse from remission in the event that a cure assumption is not accepted, and the appropriateness of adjusting the time to progressive disease/relapse and time on treatment curves for general population mortality. These issues would benefit from further consideration during technical engagement.

7 END OF LIFE

Table 34 below summarises the evidence presented in the CS which supports the company's argument that venetoclax meets NICE's end of life criteria.

Table 35 Summary of evidence proposed in the CS that supports the consideration of venetoclax as meeting NICE's end of life criteria [reproduced from Table 46 of the CS]

End of life criterion	Evidence presented
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• Median OS from the VIALE trials of [redacted] months and [redacted] months for AZA(20-30% blasts and LDAC(>30% blasts) respectively. • Mean undiscounted life years of 1.833 and 0.832-0.839 for AZA(20-30% blasts and LDAC(>30% blasts) respectively.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.	VenAZA versus AZA (20-30% blasts) • Difference in median OS of [redacted] months • 2.61 incremental life years in economic model VenAZA versus LDAC (>30% blasts) • Difference in median OS of [redacted] months • 2.93 incremental life years in economic model VenLDAC versus LDAC (>30% blasts) • Difference in median OS of [redacted] months • 1.61 incremental life years in economic model

The ERG considers the mean life years provided by the economic model a more appropriate measure of expected survival, all modelled scenarios conducted by the company and the ERG meet the criterion life expectancy less than two years for the comparator arms in both populations. The removal of the "cure" assumption on the company base case has the greatest impact upon the undiscounted incremental life years modelled, where the incremental life years of venetoclax becomes 1.48,1.68 and 0.56 for VenAZA vs. AZA (20-30% blasts), VenAZA vs. LDAC (>30% blasts) and VenLDAC vs. LDAC (>30% blasts) respectively. Therefore, the ERG is confident that venetoclax is likely to meet the NICE end of life criteria.

8 References

1. Kumar CC. Genetic abnormalities and challenges in the treatment of acute myeloid leukemia. *Genes Cancer* 2011; 2(2), 95-107.

2. Saxena K, Konopleva M. New treatment options for older patients with acute myeloid leukemia. *Curr Treat Options Oncol* 2021; 22(5), 39.

3. Shipley JL, Butera JN. Acute myelogenous leukemia. *Exp Hematol* 2009; 37(6), 649-58.

4. Estey EH. Acute myeloid leukemia: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol* 2012; 87(1), 89-99.

5. De Kouchkovsky I, Abdul-Hay M. Acute myeloid leukemia: a comprehensive review and 2016 update. *Blood Cancer J* 2016; 6(7), e441.

6. Yamamoto JF, Goodman MT. Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997-2002. *Cancer Causes Control* 2008; 19(4), 379-90.

7. Cancer Research UK. *Acute myeloid leukaemia (AML) statistics* [Online] Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml. [Accessed: April 2021]

8. NHS Digital. 2020. *Hospital Admitted Patient Care Activity 2019-20* [Online] Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20. [Accessed: 26 April 2021]

9. National Organisation for Rare Disorders. 2017. *Rare diseases database: Acute Myeloid Leukemia* [Online] Available from: https://rarediseases.org/rare-diseases/acute-myeloid-leukemia/. [Accessed: May 2021]

10. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127(20), 2391-405.

11. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017; 129(4), 424-47.

12. Heuser M, Ofran Y, Boissel N, 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.

13. O'Donnell MR, Tallman MS, Abboud CN, et al. Acute Myeloid Leukemia, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; 15(7), 926-57.

14. Ferrara F, Barosi G, Venditti A, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia* 2013; 27(5), 997-9.

15. Kantarjian H, Ravandi F, O'Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood* 2010; 116(22), 4422-9.

16. Chao DT, Korsmeyer SJ. BCL-2 family: regulators of cell death. *Annu Rev Immunol* 1998; 16(395-419.

17. Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. *Leukemia* 2019; 33(12), 2795-804.

18. Pollyea DA, Amaya M, Strati P, et al. Venetoclax for AML: changing the treatment paradigm. *Blood Adv* 2019; 3(24), 4326-35.

19. Kantarjian H, Kadia T, DiNardo C, et al. Acute myeloid leukemia: current progress and future directions. *Blood Cancer J* 2021; 11(2), 41.

20. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med* 2020; 383(7), 617-29.

21. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood* 2020; 135(24), 2137-45.

22. European Medicines Agency. 2021. *Venclyxto* [Online] Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/venclyxto-1. [Accessed: May 2021]

23. National Institute for Health and Care Excellence. 2011. *Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia [TA218]* [Online] Available from: https://www.nice.org.uk/guidance/ta218. [Accessed: April 2021]

24. National Institute for Health and Care Excellence. 2016. *Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [TA399]* [Online] Available from: https://www.nice.org.uk/guidance/ta399. [Accessed: April 2021]

25. AbbVie. *Haematological Malignancy Research Network: Clinical Management, Outcome and Resource Utilisation of Acute Myeloid Leukaemia Audit Report v9 [Data on file]*. North Chicago, IL: 2020.

26. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking systematic reviews in health care*. University of York: Centre for Reviews and Dissemination. 2009. Available from: URL:

http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm [Accessed 4 March 2020]

27. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood* 2018; 131(12), 1275-91.

28. AbbVie. *VIALE-C Clinical Study Report [data on file]*. North Chicago, IL: AbbVie. 2021.

29. AbbVie. *VIALE-A Clinical Study Report [data on file]*. North Chicago, IL: AbbVie. 2021.

30. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood* 2015; 126(3), 291-9.

31. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol* 2010; 28(4), 562-9.

32. National Institute for Health and Care Excellence. 2020. *Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [TA642]* [Online] Available from: https://www.nice.org.uk/guidance/ta642. [Accessed: April 2021]

33. Tremblay G, Dolph M, Patel S, et al. Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom. *Cost Eff Resour Alloc* 2018; 16(33).

34. National Institute for Health and Care Excellence. 2018. *Liposomal cytarabine–daunorubicin for untreated acute myeloid leukaemia [TA552]* [Online] Available from: https://www.nice.org.uk/guidance/ta552. [Accessed: April 2021]

35. National Institute for Health and Care Excellence. 2018. *Midostaurin for untreated acute myeloid leukaemia[TA523]* [Online] Available from: https://www.nice.org.uk/guidance/ta523. [Accessed: April 2021]

36. National Institute for Health and Care Excellence. 2018. *Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [TA545]* [Online] Available from: https://www.nice.org.uk/guidance/ta545. [Accessed: April 2021]

37. Mujica Mota R, Varley-Campbell J, Tikhonova I, et al. *Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts*. Exeter: 2016. Available from: https://www.nice.org.uk/guidance/ta399/documents/committee-papers. [Accessed: April 2021]

38. AbbVie Deutschland GmbH. *Summary of product characteristics [data on file]*. Ludwigshafen, Germany: AbbVie Deutschland GmbH.

39. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; 15(5), 708-15.

40. Wehler E, Storm M, Kowal S, et al. A health state utility model estimating the impact of ivosidenib on quality of life in patients with relapse/refractory acute myeloid leukemia. *23rd Congress of the European Hematology Association, Stockholm, 14-17 June,* Stockholm. 2018

41. Forsythe A, Kwon CS, Bell T, et al. Health-related quality of life in acute myeloid leukemia patients not eligible for intensive chemotherapy: results of a systematic literature review. *Clinicoecon Outcomes Res* 2019; 11(87-98.

42. NHS England. *National tariff payment system* [Online] Available from: https://www.england.nhs.uk/pay-syst/national-tariff/national-tariff-payment-system/. [Accessed: April 2021]

43. Haymarket Media Group Ltd. 2021. *Monthly Index of Medical Specialities* [Online] Available from: http://www.mims.co.uk/. [Accessed: April 2021]

44. Department of Health and Social Care. 2021. *Drugs and pharmaceutical electronic market information tool (eMIT)* [Online] Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. [Accessed: April 2021]

45. National Institute of Health and Care Excellence (NICE). Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [TA642]. Available at: https://www.nice.org.uk/guidance/ta642. [Last accessed: 16th March 2021]. .

46. Georghiou T, Bardsley T. *Exploring the cost of care at the end of life*. London: Trus N. 2014. Available from: https://www.nuffieldtrust.org.uk/files/2017-01/end-of-life-care-web-final.pdf [Accessed: April 2020]

47. Curtis L, Burns A. 2019. *Unit Costs of Health and Social Care 2019* [Online] Personal Social Services Research Unit, University of Kent, Canterbury. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/. [Accessed: April 2021]

48. Tappenden P, Chilcott JB. Avoiding and identifying errors and other threats to the credibility of health economic models. *Pharmacoeconomics* 2014; 32(10), 967-79.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Thursday 10th June** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Section 1: Major comments

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page XIV states "*In VIALE-C, no significant difference was observed in OS between the VenLDAC and LDAC groups at the primary analysis".* Page 25 states *"At the planned primary analysis, no significant difference was observed in OS between the VenLDAC and LDAC groups and, therefore, the primary endpoint was not achieved (*HR 0.75, 95% CI 0.52, 1.07, p = 0.11*)".*	On page XIV please consider amending this wording to: "In VIALE-C, no significant difference was observed in OS between the VenLDAC and LDAC groups at the primary analysis. **However, at the time of the primary analysis in VIALE-C, there was greater censoring of patients in the VenLDAC arm than the LDAC arm, as more patients receiving VenLDAC had not yet reached median OS.**" On page 25 please consider amending this wording to: "At the planned primary analysis, no significant difference was observed in OS between the VenLDAC and LDAC groups and, therefore, the primary endpoint was not achieved (HR 0.75, 95% CI 0.52, 1.07, p = 0.11). **However, at the time of the primary analysis in VIALE-C, there was greater censoring of patients in the VenLDAC arm than the LDAC arm, as more patients receiving VenLDAC had not yet reached median OS**".	As described on page 45 of the company submission and page 68 of the ERG report, there was greater censoring of patients in the VenLDAC arm of VIALE-C compared with the LDAC arm at the time of the planned primary analysis, as more patients in the VenLDAC arm had not reached median OS. It is important to provide this context to avoid misinterpretation.	Not a factual error. The ERG's statement indicates that there was no significant difference in OS at primary analysis.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page XIV states "*The company*	Please consider amending this wording to the	The justification for presenting the	Not a factual error. The ERG's

split these and reported mainly on those with >30% bone marrow blasts. This was to be comparable with the NMA results which could only be conducted on a common sub-group of >30% blasts".	following: "The company split these and reported mainly on those with >30% bone marrow blasts. This was ~~to be comparable with the NMA results which could only be conducted on a common sub-group of >30% blasts~~ **because although LDAC is not restricted by blast cell count but, in clinical practice, it is used in patients with blast cell counts of >30%, and therefore the VenAZA versus LDAC comparison is only relevant for this subpopulation of patients**".	NMA for the subgroup of patients with >30% blasts is provided on page 80 of the company submission. This NMA is presented as this is the most relevant comparison for VenAZA versus LDAC based on the use of LDAC in UK clinical practice (see page 80 of the CS). An NMA for the overall population was also conducted as part of this submission and is presented in Appendix D 1.7. In this NMA the data for patients in the 20–30% blast count subgroup is provided by the AZA-001 study.	statement simply indicates that the NMA was conducted on a subgroup of patients with >30% blasts, which is correct.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page XVII states "*Historically, non-intensive treatments have never been curative in this generally* [redacted]" This should be amended to reflect that the patient population are unable to receive potentially curative therapies due to age or comorbidities. This patient population are not inherently different to the broader AML population, except for an inability	Please consider amending the text on page XVII to: "Historically, ~~non intensive treatments have never been curative in~~ this generally [redacted] **that is curative in the broader AML population**" Please consider amending the text on page 56 to align with the proposed changes on page XVII	This should be amended to reflect that the patient population are unable to receive potentially curative therapies due to age or comorbidities. IC is the preferred route for the treatment of AML as these treatments are used with curative intent and are able to drive deep and lasting remission. However, IC is also associated with significant toxicity. Therefore, many patients	We do not believe this to be a factual inaccuracy but have added the clarification that these patients cannot tolerate IC which is used with curative intent in the broader AML population. "*Historically, non-intensive treatments available have never been curative in this generally* [redacted]. ***These patients are unable to***

to tolerate the more intensive therapies Page 56 states *"Historically, non-intensive treatments have never been curative in this [redacted]".*		with AML are ineligible for IC due to older age or other comorbidities leading to a high risk of TRM. In the absence of a tolerable but efficacious therapy, patients have been unable to achieve cure. However, there is no rationale to anticipate that patients in this population who achieve CR would need have similar benefits to the broader AML population.	***tolerate IC that is used with curative intent in the broader AML population**."*

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 2 states "*Criteria for definition of unfitness for IC include age > 75 years; pre-existing disease of the heart, lung, kidney or liver; active infection; mental illness; or ECOG performance status ≥3 not related to leukaemia*".	Please consider amending this wording to "~~Criteria for definition of unfitness~~ **Eligibility for IC is largely based on assessment of age and fitness by experienced haematologists. Factors which may make a patients ineligible** for IC include age > 75 years; pre-existing disease of the heart, lung, kidney or liver; active infection; mental illness; or ECOG performance status ≥3 not related to leukaemia".	As mentioned on page 25 of the company submission, there are currently no consensus guidelines for objectively determining patient eligibility for IC, and decisions are largely based on assessment of age and fitness by experienced haematologists with particular reference to previous levels of physical activity and exercise tolerance in conjunction with careful evaluation of the presence of comorbidities. This important context should be included when discussing eligibility for IC. The factors presented here do represent important predictors for	The sentence has been amended as described.

		treatment related mortality and do often form the basis for determining ineligibility. The reference which is provided in the ERG report for this wording (Ferrara et al. 2013) has been conducted from an Italian perspective and therefore may not fully represent UK clinical practice.	

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 15 states "*The study population in both VIALE-A and VIALE-C was adults aged 60 years or older*".	Please amend this to: "The study population in both VIALE-A an VIALE-C was adults aged ~~60~~ **18** years or older".	It is not accurate that VIALE-A and VIALE-C only included patients aged 60 and older. As mentioned on page 34 of the company submission the key eligibility criteria for VIALE-A and VIALE-C was patients aged 18 years or older with a confirmed diagnosis of AML by WHO criteria, previously untreated and be ineligible for treatment with standard IC due to age or comorbidities. Although a generally older population in both VIALE trials, it is important to reflect the total study population where the age ranged between age 49–91 in VIALE-A and age 36–93 in VIALE-C.	The sentence has been amended as described.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 36 states: "*This difference is largely due to the participants in the AZA-AML-001 study restricting their patients to those with >50% BM blasts whilst the VIALE-A and C trials used the >30% criteria*." Page 45 states: "*The NMA results included another independent study AZA-AML-001. The blasts for this latter study however was >50%."*	Please consider removing wording which implies that AZA-AML-AML-001 only included patients with >50% blasts.	As discussed on page 80 of the company submission AZA-AML-001 included patients with a blast count of >30% The eligibility criteria for AZA-AML-001 (as described in Dombret et al. 2015 is: "Eligible patients were age ≥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, with intermediate- or poor-risk cytogenetics (NCCN 2009 criteria), Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤2, and white blood cell count ≤15 × 10^9/L".	Although the inclusion criteria for AZA-AML-001 was blast count of > 30 %, the actual participants in the study according to the baseline characteristics was > 50%. We have amended the text to reflect this.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 56 states: "The company refer to clinical expert advice suggesting that patients treated with venetoclax who "achieve a sustained deep remission have the potential to achieve long-term survivorship, whereby their	Please consider amending this to "The company refer to clinical expert advice suggesting that patients treated with venetoclax who "achieve a sustained deep remission have the potential to achieve long-term survivorship, whereby their outcomes are in line with the general population." **The company also refer**	Please provide the full rationale for the cure assumption used in the company base case, as described on page 167 of the company submission.	This is not a factual inaccuracy; however, we accept the proposed amendment.

outcomes are in line with the general population." They also note that the rate of relapse after two years is low based on experience in intensive chemotherapy. The company argue that this is corroborated by a plateau in the Kaplan-Meier EFS and OS curves for those on VenAZA in the 20-30% blast count and >30% blast count populations. However, the numbers at risk in the tails of these distributions are low, and there is insufficient follow-up beyond two years to validate the assumption."	**to data which demonstrates that "VenAZA provides deep and durable complete remission rates (CR/CRi with/without MRD) that have historically only been associated with IC" and highlight that "depth and duration of remission has been positively correlated with length of survival in patients who receive IC".** **The company** ~~They~~ also note that the rate of relapse after two years is low based on experience in intensive chemotherapy **and provide clinical expert opinion that "the proportion of patients in CR/CRi for whom cure is assumed at year 2 will be enriched with those with no/low MRD".** The company argue that this is corroborated by a plateau in the Kaplan-Meier EFS and OS curves for those on VenAZA in the 20-30% blast count and >30% blast count populations. However, the numbers at risk in the tails of these distributions are low, and there is insufficient follow-up beyond two years to validate the assumption."		

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 56 states *"the population in this appraisal was adults with relapsed or refractory FLT3-mutation-positive acute myeloid leukaemia (AML), which would include* [redacted] *in which*	Please consider amending this wording to: "The population in this appraisal was adults with relapsed or refractory FLT3-mutation-positive acute myeloid leukaemia (AML), which would include [redacted] in which gilteritinib could act as a bridge to stem cell transplant.[32] **However, cure**	This text is currently misleading and suggests that the cure assumption was dependent on the patients who are [redacted] in which gilteritinib could act as a bridge to stem cell transplant. The suggested	We accept the proposed amendment.

gilteritinib could act as a bridge to stem cell transplant".	**assumptions reflected all patients alive at two years, regardless of transplant status.**"	amendment clarifies the cure assumption. It is also inaccurate to refer to these younger patients as "[redacted]" than patients eligible to receive venetoclax, considering that they are patients with relapsed or refractory AML.	

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 60 states "*Accordingly, it would be expected that those on treatment beyond two years would be made up those still in remission ("cured") or non-remission (not yet progressed), and we should expect subsequent treatment to broadly follow the occupancy of the progressive disease state"* Page 61 states: '*The ERG believes that if a cure assumption is applied, it is more plausible to assume that those still on first line treatment beyond two years, according to the selected TTD curve, should be assumed to be those in remission ("cured") or non-remission, and all those with progressive disease should be assumed to be on subsequent*	These sentences are mis-leading and provide confusions over the health states included in the model. The health states for remission and cure are separate health state in the model On Page 60 please amend to: "Accordingly, it would be expected that those on treatment beyond two years would be made up those still in remission ~~("cured")~~ or non-remission (not yet progressed), and we should expect subsequent treatment to broadly follow the occupancy of the progressive disease state". On page 61 please amend to: "The ERG believes that if a cure assumption is applied, it is more plausible to assume that those still on first line treatment beyond two years, according to the selected TTD curve, should be assumed to be those in remission ~~("cured")~~ or non-remission, and all those with progressive disease should be assumed to be on subsequent treatment."	The ERG suggest that patients can remain on treatment whilst in the *cure* health state, which is not in line with clinical practice. The company suggests that the sentence be reworded to include only patients who are in the *remission* and *non-remission* health states as being eligible for treatment.	The ERG accepts that the description of the cure health state could be clearer in this context and have made editions to the text to reflect our position. Page 60 amended to: "*Accordingly, it would be expected that those on treatment beyond two years would be made up those still in remission ("cured" **or within the cure disease state**) **and** non-remission (not yet progressed or **non-remission disease state**), and we should expect subsequent treatment to broadly follow the occupancy of the progressive disease state".* Page 61 amended to: "*The*

treatment.'			*ERG believes that if a cure assumption is applied, it is more plausible to assume that those still on first line treatment beyond two years, according to the selected TTD curve, should be assumed to be those in remission ("cured" or* ***cure disease state****)* ***and*** *non-remission, and all those with progressive disease should be assumed to be on subsequent treatment."* As described on page 60, the ERG does not agree with the company position that treatment would be discontinued after achieving remission for 2 years in the VenAZA or VenLDAC treatment arms. The ERG cites their reasons as: (1) the ERG clinical expert is of the opinion that "*first-line treatment would not currently be stopped routinely for patients who are in remission at 2 years".* (2)The smpc for venetoclax states that treatment should be continued until disease progression. (3) The VIALE-A and VIALE-C trials did not have a treatment stopping rule for patients in remission at 2 years. Therefore, the assertion by the

			company that the discontinuation of treatment after 2 years of remission is clinical practice is a factual inaccuracy, so no further changes were made

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 73 states: *This is due a difference in the year from which the general population mortality adjustment is applied for these comparisons ([redacted] years and 2.56 years, respectively)*	The company apologies for this mistake in the CEM. Within the model the general population mortality adjustment has been applied to treatment arms after the maximum follow-up period from the VIALE trials. The maximum follow up for VIALE-C (used to inform the VenLDAC and LDAC treatment arms in the CEM) at the time of the six month follow up analysis was [redacted] years. The value of [redacted] years presented on the ERG report corresponds to the maximum length of follow up in the VIALE-C primary analysis (without six month follow up). The company intends to supply an updated model in which this issue is corrected as part of technical engagement.	To align the model with the most recent clinical trial data.	We accept the proposed amendment.

Section 2: Minor comments

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page XIII states "*The clinical effectiveness evidence is provided by two ongoing, phase III randomised, double-blind, placebo controlled, international studies: VIALE-A (comparing venetoclax plus AZA [VenAZA] with AZA) and VIALE-C (comparing venetoclax plus LDAC [VenLDAC])".*	Please amend this wording to: The clinical effectiveness evidence is provided by two ongoing, phase III randomised, double-blind, placebo controlled, international studies: VIALE-A (comparing venetoclax plus AZA [VenAZA] with AZA) and VIALE-C (comparing venetoclax plus LDAC [VenLDAC] **with LDAC**)".	As described on page 33 of the company submission, VIALE-C compared patients receiving VenLDAC to patients receiving LDAC.	The sentence has been amended as described.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page XVII states "The maximum follow up of the VIALE-A and VIALE-C trials ([redacted] and [redacted] respectively)".	Please amend this wording to: "The maximum follow up of the VIALE-A and VIALE-C trials (2.56 and [redacted] **years**, respectively)".	In Table 4 of the company submission the maximum follow up of VIALE-A and VIALE-C were 30.7 and [redacted] months, respectively. This corresponds to 2.56 years for VIALE-A and [redacted] years for VIALE-C. The value of [redacted] years presented on the ERG report corresponds to the maximum length of follow up in the VIALE-C primary analysis (without six month follow up).	We accept the proposed amendment. Similar adjustment also made to page 73.

		It should also be specified that these values are presented in years in the ERG report, to avoid any ambiguity. Additionally, the maximum follow-up for VIALE-A does not need to be marked as AIC, as this information is published in Di Nardo 2020.	

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page XVII states *"patients who are in remission at two yeas can achieve the same outcomes as the general population and no longer be at risk of relapse".*	Please amend to: "patients who are in remission at two year**s** can achieve the same outcomes as the general population and no longer be at risk of relapse".	Minor typographical error.	We accept the proposed amendment.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page XXI states *"The company provided this at the clarification stage, but noted clinical advice suggesting that 15% was too high be reflective of patients that are FLT3+ and fit enough for subsequent treatment in this population".*	Please amend to: "The company provided this at the clarification stage, but noted clinical advice suggesting that 15% was too high **to** be reflective of patients that are FLT3+ and fit enough for subsequent treatment in this population".	Minor typographical error.	We accept the proposed amendment.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 6 states "*The anticipated EU marketing authorisation in the relevant indication for the company submission was* [redacted]	Please amend this wording to: "The anticipated EU marketing authorisation in the relevant indication for the company submission was [redacted]	The abbreviation for intensive chemotherapy used within the company submission is "IC".	The sentence has been amended as described.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Table 7 contains the following information regarding study discontinuation in VIALE-C: **VIALE-C** | **Discontinued treatment, n(%)** | **Discontinued study, n (%)** VenLDAC | 105/143 (73.4%) | 91/143 (63.6%)[c] LDAC | 61/68 (89.7%) | 49/68 (72.1%)[d] Deaths: [c]85/91 (93.4%), [d]46/49 (93.9%).	Please amend the values in this table to: **VIALE-C** | **Discontinued treatment, n(%)** | **Discontinued study, n (%)** VenLDAC | ~~105/143 (73.4%)~~ [redacted] | ~~91/143 (63.6%)~~[e] [redacted] LDAC | ~~61/68 (89.7%)~~ [redacted] | ~~49/68 (72.1%)~~[d] [redacted] Deaths: [c]~~85/91 (93.4%)~~ [redacted] [d]~~46/49 (93.9%)~~ [redacted]	The data presented for VIALE-C on page 70 of the company submission appendix mistakenly reports patient disposition data for the primary analysis (15th February 2019) rather than the six month follow up (15th August 2019). The correct data for the six month follow up data cut-off should be included. This is presented on page 98–99 of the VIALE-C CSR.	The table has been amended as described.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 19 states "*The ERG clinical*	Please amend this to: "The ERG clinical expert	As presented on page 110 of the	The sentence has been

expert also considers that people in the favourable cytogenetic risk category are likely to have better outcomes; however, these patients were excluded from VIALE-A and accounted for only [redacted] of participants in VIALE-C".	also considers that people in the favourable cytogenetic risk category are likely to have better outcomes; however, these patients were excluded from VIALE-A and accounted for only [redacted] of participants in VIALE-C".	VIALE-C CSR, a total of 4 (2.0%) of patients had a favourable cytogenic risk.	amended as described.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 19 states "*The proportions of participants in VIALE-C for RBC or platelet infusion ([redacted] in VenLDAC arm, [redacted] in LDAC arm), RBC transfusion ([redacted] respectively) and platelet transfusion ([redacted] respectively)".*	Please amend this to: "The proportions of participants in VIALE-C for RBC or platelet infusion ([redacted] in VenLDAC arm, [redacted] in LDAC arm), RBC transfusion ([redacted] respectively) and platelet transfusion ([redacted], respectively)	As presented in Table 4 of the company clarification question responses, and Table 8 of the ERG report, the proportion of patients receiving a platelet transfusion within eight weeks prior to baseline was [redacted]% in the LDAC arm of VIALE-C.	The sentence has been amended as described.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The caption for Table 10 currently reads *"Summary of survival outcomes in the VIALE-A and VIALE-C trials [adapted from Table 1, Section B.2.5, Document B]".*	Please amend this to: "Summary of survival outcomes in the VIALE-A and VIALE-C trials [adapted from Table 1**1**, Section B.2.5, Document B]".	Minor typographical error.	The table caption has been amended as described.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 32 states "*The most common SOC of Grade ≥3 TEAEs reported in a lower percentage of participants in the VenLDAC group compared with the LDAC group included infections and infestations ([redacted] versus [redacted]), and metabolism and nutrition disorders ([redacted] versus [redacted])".*	Please amend this to: "The most common SOC of Grade ≥3 TEAEs reported in a lower percentage of participants in the VenLDAC group compared with the LDAC group included infections and infestations ([redacted] versus [redacted]), and metabolism and nutrition disorders ([redacted] versus [redacted]).	Minor typographical error; Correct data are presented on page 237 of the VIALE-C CSR.	The sentence has been amended as described.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 36 states "*The median proportion of bone marrow blasts was higher in AZA-AML-001 (ranging from 70%-76%) than in VIALE-A ([redacted] in both groups) and VIALE-C (ranging from [redacted])*".	Please amend this to "The median proportion of bone marrow blasts was higher in AZA-AML-001 (ranging from 70%-76%) than in VIALE-A ([redacted] in both groups) and VIALE-C (ranging from [redacted])".	Minor typographical error; Correct data are presented in table 8 of the company clarification question responses, and in Table 15 of the ERG report.	The sentence has been amended as described.

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
In Table 15 the figure reported for patients in the CCR arm of AZA-AML-001 who were classified as being in the Poor cytogenic risk	Please amend this to "85 (34.4~~5~~)" (i.e. remove struck through 5).	Minor typographical error in company clarification question responses which has been copied	The table has been amended as described.

group was "*85 (34.~~45~~)".*		across into the ERG report.	

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 42 states "*The OS may be contrasted with the PSA OS and ERS estimates".*	Please amend this to "The OS may be contrasted with the PSA OS and ~~ERS~~ **EFS** estimates".	Minor typographical error.	The sentence has been amended as described.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 45 states "*For the common outcomes the addition of venetoclax to be proved to be beneficial".*	Please amend this to "For the common outcomes the addition of venetoclax ~~to be~~ proved to be beneficial".	Minor typographical error.	The sentence has been amended as described.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 45 states "*The propensity score approach has the advantage of adjusting for variation between the studies' characteristics but requires full individual data and so was restricted to the VIALE studies".*	Please amend this to "The propensity score approach has the advantage of adjusting for variation between the studies' characteristics but requires full individual data and so was restricted to the VIALE studies **and data from HMRN**".	As described on page 34 of the ERG report and Section 2.8.3 of the company submission, the company also had access to the real-world evidence for comparators from the Haematological Malignancy Research Network (HMRN) database and were likewise able to match VIALE-A patients to similarly treated participants in HMRN	The sentence has been amended as described.

		database.	

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 53 states "*Separate independently fitted curves are used for each relevant alternative in the two populations of interest (blast count 20-30%, blast count ≥30%).*"	Please amend to "Separate independently fitted curves are used for each relevant alternative in the two populations of interest (blast count 20-30%, blast count ≧>30%)."	Minor typographical error.	We accept the proposed amendment.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 55 states *"The company's argument is that venetoclax, on the other hand, 'has an innovative mechanism of action which is able to efficiently and selectively target leukaemia stem cells (LSC) by disrupting energy metabolism and thus is able to drive sustained deep remission in combination with these therapies [AZA or LDAC]'".*	Please amend to "The company's argument is that venetoclax **in combination with AZA**, on the other hand, has an has an innovative mechanism of action which is able to target leukaemic stem cells LSC) by disrupting energy metabolism and thus is able to drive sustained deep remission ~~in combination with these therapies [AZA or LDAC]~~'". .	This point was incorrectly described in the company clarification question responses, please adjust this wording.	We accept the proposed amendment.

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Table 24 states the PAS price of venetoclax for subsequent cycles, as part of VenAZA, is priced at [redacted]. Table 24 states the PAS price of venetoclax for cycle 1 during treatment initiation, as part of VenLDAC, is priced at [redacted]. Table 24 states the PAS price of venetoclax for subsequent cycles, as part of VenLDAC, is priced at [redacted].	The company apologises for making the typographical error in Document B of the company submission. The PAS price of venetoclax for subsequent cycles, as part of VenAZA, should be amended to [redacted]. The PAS price of venetoclax for cycle 1 during treatment initiation, as part of VenLDAC, should be amended to [redacted]. The PAS price of PAS price of venetoclax for subsequent cycles, as part of VenLDAC, should be amended to [redacted].	The discounted price is an important feature of the product profile and economic analysis. The error has unfortunately been carried forward into some of the scenario analyses provided by the ERG, however due to rounding, there are no changes needed to be made	We accept the proposed amendment A footnote has also been added to the table describing that: "*Any diversion from table 63 of the CS represent minor typographical errors which have been corrected in this table*."

Issue 29

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 75 states *"Document B of the CS, figures 120-123, page 216-216 compare the model output of observed EFS and OS for VenAZA vs. AZA (20-30% blasts) and VenLDAC vs. LDAC (>30% blasts)."*	Please amend to "Document B of the CS, figures 120-123, page 216~~5~~-216 compare the model output of observed EFS and OS for VenAZA vs. AZA (20-30% blasts) and VenLDAC vs. LDAC (>30% blasts)."	Minor typographical error.	We accept the proposed amendment.

Section 3: Cost effectiveness results issues

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG's response</th></tr>
<tr>
<td>Page 70; Table 25 – ERG scenario analyses results VenAZA vs. AZA (20-30%)

The ERG states that when applying a standardised mortality ratio of 1.5 to general population mortality it resulted in incremental costs of [redacted], incremental QALYs of [redacted] and an ICER of £41,024.</td>
<td>The results should be amended as there is an error in the calculations by the ERG in the cost-effectiveness model. The results should be as such:
<table><tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr><tr><td>[redacted]</td><td>[redacted]</td><td>£42,066</td></tr></table></td>
<td>In the calculations, there is a small error with the parentheses, meaning the standardised mortality ratio is only applied to male patients. This error leads to incorrect results. The company also wishes to highlight that the standardised mortality ratio has incorrectly been applied even after adjustment by the company, as it is suggesting that a mortality ratio is applied on top of the extrapolated survival curves in the remission, non-remission and progressive disease/relapse health states. During clarification stage, the ERG suggested that a standardised mortality ratio would be applied for patients in the cure health state, however, when they have made the adjustment themselves, it has now been applied to all survival curves, irrespective of health state.</td>
<td>We accept the proposed correction to ERG calculation error.

The standardised mortality ratio after the correction to the parentheses is as the ERG intended. We have clarified the justification for this scenario on page 57 of the ERG report; the characteristics of the model population suggests a higher background mortality rate may be appropriate irrespective of model state.

However, the ERG does suggest exploring removal of the background mortality adjustment from curves of time to progression as described in issue 2 of the ERG report.</td>
</tr>
<tr>
<td>Page 82; Table 29 – ERG scenario analyses results VenAZA vs. AZA (20-30%)

The ERG states that when</td>
<td>The results should be amended as there is an error in the calculations by the ERG in the cost-effectiveness model. The results should be as such:
<table><tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr></table></td>
<td>In the calculations, there is a small error with the parentheses, meaning the standardised mortality ratio is only applied to male patients. This error leads to incorrect results. The company</td>
<td>We accept the proposed correction to ERG calculation error.

The standardised mortality ratio after the correction to the parentheses is as the</td>
</tr>
</table>

<table>
<tr>
<td>applying a standardised mortality ratio of 2 to general population mortality it resulted in incremental costs of [redacted], incremental QALYs of [redacted] and an ICER of £42,918.</td>
<td>
<table>
<tr><td>[redacted]</td><td>[redacted]</td><td>£44,702</td></tr>
</table>
</td>
<td>also wishes to highlight that the standardised mortality ratio has incorrectly been applied even after adjustment by the company, as it is suggesting that a mortality ratio is applied on top of the extrapolated survival curves in the remission, non-remission and progressive disease/relapse health states. During clarification stage, the ERG suggested that a standardised mortality ratio would be applied for patients in the cure health state, however, when they have made the adjustment themselves, it has now been applied to all survival curves, irrespective of health state.</td>
<td>ERG intended. We have clarified the justification for this scenario on page 57 of the ERG report; the characteristics of the model population suggests a higher background mortality rate may be appropriate irrespective of model state.

However, the ERG does suggest exploring removal of the background mortality adjustment from curves of time to progression as described in issue 2 of the ERG report.</td>
</tr>
<tr>
<td>Page 82; Table 29 – ERG scenario analyses results VenAZA vs. AZA (20-30%)

The ERG states that when applying a 7-day wastage for treatment discontinuation of venetoclax it resulted in incremental costs of [redacted] and an ICER of £39,344.</td>
<td>The results should be amended as there is an error in the PAS price used by the ERG in the cost-effectiveness model. The results should be as such:
<table>
<tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>£39,344</td></tr>
</table>
</td>
<td>As noted in Issue 27, there is a minor reporting error in the cost for venetoclax after a PAS has been applied.

Note the results of this comparison have not been impacted and therefore do not require updating</td>
<td>We accept the proposed amendment.</td>
</tr>
<tr>
<td>Page 82; Table 29 – ERG scenario analyses results VenAZA vs. AZA (20-30%)</td>
<td>The results should be amended as there is an error in the calculations by the ERG in the cost-effectiveness model. The results should be as such:</td>
<td>In the calculations, there is an error with the PAS price of venetoclax, which means that scenario results are presented</td>
<td>We accept the proposed amendment.</td>
</tr>
</table>

<table>
<tr>
<td>The ERG states that when assuming a 14-day tablet wastage for venetoclax resulted in incremental costs of [redacted] and an ICER of £40,271.</td>
<td><table>
<tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>£39,823</td></tr>
</table></td>
<td>incorrectly.</td>
<td></td>
</tr>
<tr>
<td>Page 83; Table 30 – ERG scenario analyses results VenAZA vs. LDAC (>30%)

The ERG states that when applying a standardised mortality ratio of 1.5 to general population mortality it resulted in incremental costs of [redacted], incremental QALYs of [redacted] and an ICER of £42,983.</td>
<td>The results should be amended as there is an error in the calculations by the ERG in the cost-effectiveness model. The results should be as such:
<table>
<tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>£44,712</td></tr>
</table></td>
<td>In the calculations, there is a small error with the parentheses, meaning the standardised mortality ratio is only applied to male patients. This error leads to incorrect results. The company also wishes to highlight that the standardised mortality ratio has incorrectly been applied even after adjustment by the company, as it is suggesting that a mortality ratio is applied on top of the extrapolated survival curves in the remission, non-remission and progressive disease/relapse health states. During clarification stage, the ERG suggested that a standardised mortality ratio would be applied for patients in the cure health state, however, when they have made the adjustment themselves, it has now been applied to all survival curves, irrespective of health state.</td>
<td>We accept the proposed correction to the ERG calculation error.

The standardised mortality ratio after the correction to the parentheses is as the ERG intended. We have clarified the justification for this scenario on page 57 of the ERG report; the characteristics of the model population suggests a higher background mortality rate may be appropriate irrespective of model state.

However, the ERG does suggest exploring removal of the background mortality adjustment from curves of time to progression as described in issue 2 of the ERG report.</td>
</tr>
<tr>
<td>Page 83; Table 30 – ERG</td>
<td>The results should be amended as there is an error in</td>
<td>In the calculations, there is a</td>
<td>We accept the proposed</td>
</tr>
</table>

<table>
<tr>
<td>scenario analyses results VenAZA vs. LDAC (>30%)

The ERG states that when applying a standardised mortality ratio of 2 to general population mortality it resulted in incremental costs of [redacted], incremental QALYs of [redacted] and an ICER of £46,181.</td>
<td>the calculations by the ERG in the cost-effectiveness model. The results should be as such:
<table><tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr><tr><td>[redacted]</td><td>[redacted]</td><td>£49,248</td></tr></table></td>
<td>small error with the parentheses, meaning the standardised mortality ratio is only applied to male patients. This error leads to incorrect results. The company also wishes to highlight that the standardised mortality ratio has incorrectly been applied even after adjustment by the company, as it is suggesting that a mortality ratio is applied on top of the extrapolated survival curves in the remission, non-remission and progressive disease/relapse health states. During clarification stage, the ERG suggested that a standardised mortality ratio would be applied for patients in the cure health state, however, when they have made the adjustment themselves, it has now been applied to all survival curves, irrespective of health state.</td>
<td>correction to the ERG calculation error.

The standardised mortality ratio after the correction to the parentheses is as the ERG intended. We have clarified the justification for this scenario on page 57 of the ERG report; the characteristics of the model population suggests a higher background mortality rate may be appropriate irrespective of model state.

However, the ERG does suggest exploring removal of the background mortality adjustment from curves of time to progression as described in issue 2 of the ERG report.</td>
</tr>
<tr>
<td>Page 83; Table 30 – ERG scenario analyses results VenAZA vs. AZA (20-30%)

The ERG states that when assuming a 14-day tablet wastage for venetoclax resulted in incremental costs of [redacted] and an ICER of £40,458.</td>
<td>The results should be amended as there is an error in the calculations by the ERG in the cost-effectiveness model. The results should be as such:
<table><tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr><tr><td>[redacted]</td><td>[redacted]</td><td>£40,273</td></tr></table></td>
<td>In the calculations, there is an error with the PAS price of venetoclax, which means that scenario results are presented incorrectly.</td>
<td>We accept the proposed amendment to Table 30 – ERG scenario analyses results VenAZA vs. LDAC (>30%).</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Page 85; Table 31 – ERG scenario analyses results VenLDAC vs. LDAC (>30%)

The ERG states that when applying a standardised mortality ratio of 1.5 to general population mortality it resulted in incremental costs of [redacted] and an ICER of £34,922.</td><td>The results should be amended as there is an error in the calculations by the ERG in the cost-effectiveness model. The results should be as such:
<table><tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr><tr><td>[redacted]</td><td>[redacted]</td><td>£36,749</td></tr></table></td><td>In the calculations, there is a small error with the parentheses, meaning the standardised mortality ratio is only applied to male patients. This error leads to incorrect results. The company also wishes to highlight that the standardised mortality ratio has incorrectly been applied even after adjustment by the company, as it is suggesting that a mortality ratio is applied on top of the extrapolated survival curves in the remission, non-remission and progressive disease/relapse health states. During clarification stage, the ERG suggested that a standardised mortality ratio would be applied for patients in the cure health state, however, when they have made the adjustment themselves, it has now been applied to all survival curves, irrespective of health state.</td><td>We accept the correction to the ERG calculation error.

The standardised mortality ratio after the correction to the parentheses is as the ERG intended. We have clarified the justification for this scenario on page 57 of the ERG report; the characteristics of the model population suggests a higher background mortality rate may be appropriate irrespective of model state.

However, the ERG does suggest exploring removal of the background mortality adjustment from curves of time to progression as described in issue 2 of the ERG report.</td></tr>
<tr><td>Page 85; Table 31 – ERG scenario analyses results VenLDAC vs. LDAC (>30%)

The ERG states that when applying a standardised mortality ratio of 2 to general</td><td>The results should be amended as there is an error in the calculations by the ERG in the cost-effectiveness model. The results should be as such:
<table><tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr><tr><td>[redacted]</td><td>[redacted]</td><td>£41,797</td></tr></table></td><td>In the calculations, there is a small error with the parentheses, meaning the standardised mortality ratio is only applied to male patients. This error leads to incorrect results. The company also wishes to highlight that the standardised mortality ratio has</td><td>We accept the correction to the ERG calculation error.

The standardised mortality ratio after the correction to the parentheses is as the ERG intended. We have clarified the justification for this scenario on page 57 of</td></tr>
</table>

<table>
<tr>
<td>population mortality it resulted in incremental costs of [redacted] and an ICER of £38,371.</td>
<td></td>
<td>incorrectly been applied even after adjustment by the company, as it is suggesting that a mortality ratio is applied on top of the extrapolated survival curves in the remission, non-remission and progressive disease/relapse health states. During clarification stage, the ERG suggested that a standardised mortality ratio would be applied for patients in the cure health state, however, when they have made the adjustment themselves, it has now been applied to all survival curves, irrespective of health state.</td>
<td>the ERG report; the characteristics of the model population suggests a higher background mortality rate may be appropriate irrespective of model state.

However, the ERG does suggest exploring removal of the background mortality adjustment from the survival curves of time to progression as described in issue 2 of the ERG report.</td>
</tr>
<tr>
<td>Page 85; Table 31 – ERG scenario analyses results VenLDAC vs. LDAC (>30%)

The ERG states that when assuming a 7-day tablet wastage for venetoclax resulted in incremental costs of [redacted] and an ICER of £32,463.</td>
<td>The results should be amended as there is an error in the calculations by the ERG in the cost-effectiveness model. The results should be as such:

<table>
<tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (cost/QALY)</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>£32,438</td></tr>
</table>
</td>
<td>In the calculations, there is an error with the PAS price of venetoclax, which means that scenario results are presented incorrectly.</td>
<td>We accept the proposed amendment.</td>
</tr>
<tr>
<td>Page 85; Table 31 – ERG scenario analyses results VenLDAC vs. LDAC (>30%)

The ERG states that when</td>
<td>The results should be amended as there is an error in the calculations by the ERG in the cost-effectiveness model. The results should be as such:

<table>
<tr><th>Incremental</th><th>Incremental</th><th>ICER</th></tr>
</table>
</td>
<td>In the calculations, there is an error with the PAS price of venetoclax, which means that scenario results are presented incorrectly.</td>
<td>We accept the proposed amendment.</td>
</tr>
</table>

assuming a 14-day tablet wastage for venetoclax resulted in incremental costs of [redacted] and an ICER of £33,510.	**costs** / **QALYs** / **(cost/QALY)** [redacted] / [redacted] / £33,585		

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 21 July 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text:: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	AbbVie
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Correction to the company base case	N/A	AbbVie would like to thank NICE for the opportunity to respond to the key issues raised by the ERG. Ahead of addressing the key technical engagement issues raised by the ERG, a correction has been made to the original company base case in response to errors identified in Key Issue 3 of the ERG report, and Issue 10 of the ERG report factual accuracy check. Within the original company base case analysis, time-on-treatment was applied using a time-on-treatment curve, which allowed patients to continue first-line treatment irrespective of the progression status. The company accept the ERG feedback (Key issue 3) that the way in which time-on-treatment was modelled in the original company base case was inconsistent with the anticipated use of venetoclax in clinical practice, and not aligned with the summary of product characteristics (SmPC) for venetoclax, which states that patients receiving venetoclax should continue treatment until disease progression or unacceptable toxicity is observed.[1] In order to align the economic model with the licenced use of venetoclax, the formulae in the economic model were amended to ensure patients cannot receive VenAZA or VenLDAC post-progression. Additionally, a small amendment has been made to the maximum follow-up of the VIALE-C trial (FAC Issue 10). As part of the economic modelling, a general population mortality adjustment was used to cap survival from the point of maximum trial follow-up, which for patients receiving VenLDAC or LDAC was informed by the maximum follow up from VIALE-C. In the original company base case, a value of [redacted] years was

used, however, this value related to the primary analysis of VIALE-C rather than the six-month follow up analysis which is presented in the company submission. To correct this issue, the correct value of [redacted] years is now used in the model at the timepoint after which patients in the VenLDAC or LDAC treatment arms receive a general population mortality adjustment.

All of the survival analyses which are already included as part of the company submission account for this additional six months of follow-up. Therefore, the original company base case analysis has been amended to align with the trial data from VIALE-C.

The corrected company base case results are presented in Table 1 and Table 2. It should be noted that these corrections are applied in all further analyses presented below as part of the company responses to the key issues for engagement.

Table 1: Corrected company base case results for patients with 20–30% blasts

Intervention	Total costs (£)	Total LYG[a]	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER (£/QALY)
AZA	£94,430	1.833	1.139	-	-	-	-
VenAZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,638

[a] Undiscounted.
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 2: Corrected company base case results for patients with >30% blasts

Intervention	Total costs (£)	Total LYG[a]	Total QALYs	Inc. costs (£)	Inc. LYG[a]	Inc. QALYs	ICER (£/QALY)
VenAZA versus LDAC							
LDAC	£33,828	0.839	0.523	-	-	-	-
VenAZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,858

		VenLDAC versus LDAC LDAC £33,718 0.835 0.521 - - - - VenLDAC [redacted] £27,182 [a] Undiscounted. **Abbreviations:** AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; LYG, life years gained; QALYs, quality-adjusted life years; Ven: venetoclax.
Key issue 1: Cure assumptions applied to those on VenAZA and VenLDAC who are in remission at 2 years	Yes	Venetoclax represents a novel therapy with an innovative mechanism of action, and provides a step-change in the treatment of patients with AML who are ineligible for intensive chemotherapy (IC). Venetoclax combinations are different from historical non-intensive treatments, due to the observed ability to provide rapid, deep, and durable remissions, which are closer to the achievements historically seen for IC treatments in younger/fitter patients. In VIALE-A, treatment with VenAZA resulted in [redacted]% of patients achieving complete remission (CR + CRi), which is comparable to the rate of 40–60% that has previously been observed in older patients (>60 years) receiving treatment with intensive 7+3 regimens.[2, 3] Furthermore, in patients eligible for treatment with IC, minimal residual disease (MRD) negativity has been shown to be a strong prognostic indicator for overall survival (OS) and risk of relapse, and as such achieving MRD negativity can be indicative of a potential curative response.[4] In VIALE-A, a significantly greater proportion of patients treated with VenAZA achieved sustained deep remission (defined as MRD <0.001 and CR + CRi) compared with AZA alone ([redacted]% vs. [redacted]%; *P* < 0.001).[3] Evidence from VIALE-A has also demonstrated a similar trend in improved OS for patients achieving MRD negativity to that observed for patients treated with IC.[5] In VIALE-A, those patients that achieved MRD <0.001 and CR + CRi had longer duration of response (DoR), event free survival (EFS), and OS, regardless of when MRD negativity was achieved.[5] Therefore, based on this evidence it is reasonable to assume that VenAZA may offer IC ineligible patients clinical outcomes which are more aligned to their IC eligible counterparts, including a possible cure for some patients.

		The ability of venetoclax combinations to provide deep and durable remissions in patients with AML is further supported by the current NHS England interim treatment policy (NG161), which has provided access to venetoclax combinations in those patients who would normally be eligible to receive IC, in order to prevent prolonged hospitalisation during the COVID-19 pandemic.[6] This guidance states that venetoclax can achieve remission rates (CR + CRi) which parallel those achieved with IC in older patients, and it is therefore reasonable to draw parallels with IC for the long term outcomes that can be achieved with venetoclax combinations.[6] Furthermore, recent preliminary data from 254 patients who have received venetoclax combinations via this policy was presented, response data was available in [redacted] patients and this demonstrated a CR + CRi of 60%.[7] The company acknowledges that there is a degree of uncertainty relating to the lack of long-term follow-up data beyond VIALE-A ([redacted] months) and VIALE-C ([redacted] months). However, published evidence has demonstrated that for patients who receive IC (without stem-cell transplant) the rate of relapse after two years is low and the majority who subsequently relapse do so primarily in the first year post-treatment.[8-12] Furthermore, clinical experts have confirmed that given the currently available data regarding the ability of venetoclax combinations to drive a deep and durable remission, and MRD negativity, a cure assumption is plausible. Therefore, it is reasonable to apply the cure assumption to the proportion of patients treated with venetoclax combinations who remain in the 'remission' health state after two years. This assumption is further corroborated by the plateau in the Kaplan–Meier curves which is observed in VIALE-A at ~24 months of treatment. As stated in Section B.3.3.5 of the company submission, consulted clinical experts explained that IC ineligible patients treated with venetoclax combinations who achieve a sustained deep remission have the potential to achieve long-term survivorship, whereby their outcomes are in line with those of the general population. However, in response to the ERG, it has been acknowledged that there may be uncertainty as to whether patients who do achieve a sustained deep remission are able to achieve

survival that is fully aligned to the survivorship of the general population. Additional clinical expert opinion suggested that an increase in mortality of ~20% compared with the general population is reasonable for patients with AML who have achieved long-term remission. Therefore, a scenario analysis exploring the impact of applying an increased mortality rate for patients in the 'cure' health state has been explored.

A standardised mortality ratio (SMR) describes whether a specific population (e.g. AML patients) are more or less likely to die than the general population. For example, an SMR of 1.2 would equate to patients with AML being 1.2 times more likely to die than the general population. A scenario analysis has been conducted in which an SMR of 1.2 is applied to patients in the 'cure' health state.

The results of this scenario analysis are presented in Table 3 and Table 4. A modest increase in the incremental costs combined with a minor reduction in incremental QALYs leads to a higher ICER versus the base case. However, all ICERs remain below the £50,000 per QALY threshold.

Table 3: Scenario analysis to assess the impact of including an SMR of 1.2 for patients in the 'cure' health state (20–30% blasts)

Comparison	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
VenAZA Vs. AZA	[redacted]	[redacted]	£17,554

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 4: Scenario analysis to assess the impact of including an SMR of 1.2 for patients in the 'cure' health state (>30% blasts)

Comparison	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
VenAZA Vs. LDAC	[redacted]	[redacted]	£35,723
VenLDAC Vs. LDAC	[redacted]	[redacted]	£28,825

		Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; QALYs, quality-adjusted life years; Ven: venetoclax.

<table>
<tr>
<td>Key issue 2: Uncertainty regarding the justification for using general population mortality to adjust the curves used to estimate transition probabilities to progressive disease health state</td>
<td>Yes</td>
<td>
The company accept the ERG's concerns and have explored a scenario analysis in which the general population mortality adjustment to non-death state transitions has been removed from the model.

The company has assessed the impact of removing general population mortality from non-time-to-death curves and the results are presented in Table 5 and Table 6. As can be seen, the ICERs are slightly increased versus the company base case. This is primarily driven by the increased time-on-treatment, which in turn increases the total costs per patient in the VenAZA and VenLDAC arms.

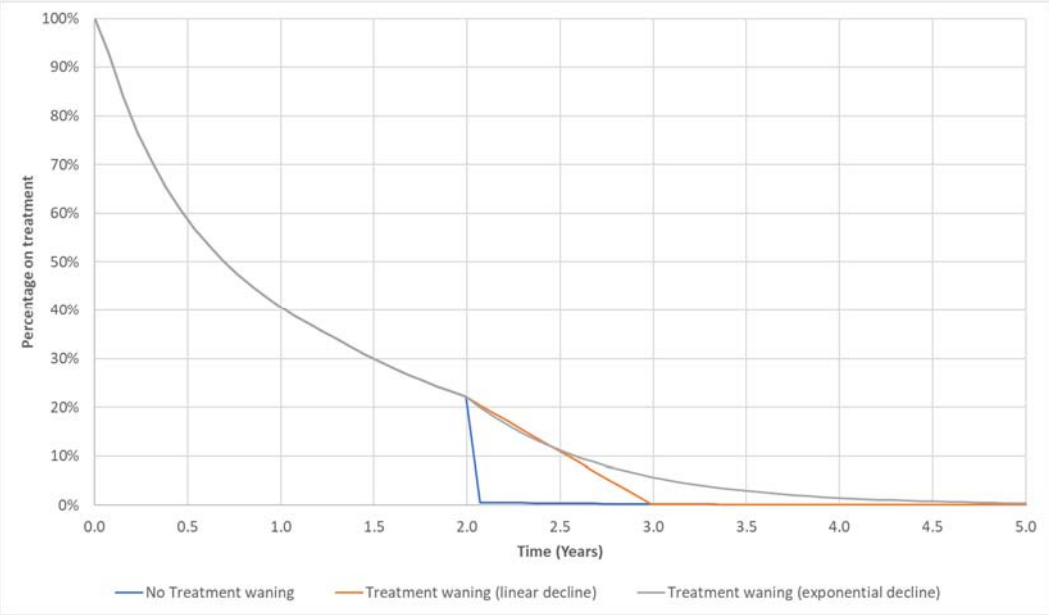
Table 5: Scenario analysis to assess the impact of removing general population mortality from non-time-to-death survival curves (20–30% blasts)
<table>
<tr><th>Comparison</th><th>Inc. costs (£)</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>VenAZA Vs. AZA</td><td>[redacted]</td><td>[redacted]</td><td>£16,613</td></tr>
</table>
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 6: Scenario analysis to assess the impact of removing general population mortality from non-time-to-death survival curves (>30% blasts)
<table>
<tr><th>Comparison</th><th>Inc. costs (£)</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>VenAZA Vs. LDAC</td><td>[redacted]</td><td>[redacted]</td><td>£33,880</td></tr>
<tr><td>VenLDAC Vs. LDAC</td><td>[redacted]</td><td>[redacted]</td><td>£27,120</td></tr>
</table>
Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; QALYs, quality-adjusted life years; Ven: venetoclax.
</td>
</tr>
</table>

Key issue 3: Inconsistent assumptions related to modelling of time on treatment and subsequent treatment	Yes	The company accept that the way in which time-on-treatment was modelled in the original company base case was inconsistent with the anticipated use of venetoclax in clinical practice, and not aligned with the SmPC for venetoclax, which states that patients receiving venetoclax should continue treatment until disease progression or unacceptable toxicity is observed.[1] As explained above, the company have now corrected the base case to align with the licensing of venetoclax and ensure treatment is only administered until progression. During additional clinical consultation with five consultants, clinical experts stated that patients would be extremely unlikely to remain on treatment with venetoclax beyond three years. However, as 'cure' is linked to patients achieving a sustained deep clinical remission, and not the time which a patient has spent on treatment, a proportion of CR/CRi patients may remain on treatment within the 'cure' health state, whilst still experiencing the clinical benefits of achieving a deep remission. Clinical experts stated that they would expect some variation in the time that patients remain on treatment after achieving remission, due to a combination of patient- and clinician-dependent factors, particularly toxicities, but consistently estimated that patients would remain on treatment between 12 and 24 months after achievement of CR/CRi. Therefore, a scenario analysis has been explored where patients in CR/CRi at two years are moved to the 'cure' state but can continue to receive VenAZA and VenLDAC for up to one year whilst in the 'cure' state. The proportion of patients receiving treatment in the 'cure' state wanes across this one-year period. This is reflective of clinical practice where there may be clinician- and patient-dependent differences in when treatment is discontinued following CR/CRi, as confirmed during the additional clinical consultation. Two options have been explored for this waning effect, one using a linear decline and one using an exponential decline, as shown in Figure 1. With a linear decline in the proportion of patients receiving treatment, it is assumed that an equal decrement in the number of CR/CRi patients in the cure state is subtracted in each cycle across the whole year, until no patients are on treatment at the end of year three.

With the exponential approach, an arbitrary proportion of 5% of patients on treatment at three years is pre-determined and a rate parameter is generated to inform the exponential curve. Whilst both approaches are associated with uncertainty, the exponential approach was considered to be more plausible, since it reflects a small proportion of patients who may be tolerating treatment well and who may therefore continue treatment beyond 3 years.

Figure 1: Illustrative representation of patients waning on treatment from two years



The results of the analyses are presented in Table 7 and Table 8. In comparison to the base case, ICERs are slightly increased due to the increase in treatment costs during year three. However, all ICERs remain below the £50,000 per QALY threshold.

Table 7: Scenario analysis to assess the impact of waning time on treatment for patients in the cure health state (20–30% blasts)

Comparison	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Linear waning			
VenAZA Vs. AZA	[redacted]	[redacted]	£21,146
Exponential waning			
VenAZA Vs. AZA	[redacted]	[redacted]	£23,388

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 8: Scenario analysis to assess the impact of waning time on treatment for patients in the cure health state (>30% blasts)

Comparison	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Linear waning			
VenAZA Vs. LDAC	[redacted]	[redacted]	£37,939
VenLDAC Vs. LDAC	[redacted]	[redacted]	£31,157
Exponential waning			
VenAZA Vs. LDAC	[redacted]	[redacted]	£39,687
VenLDAC Vs. LDAC	[redacted]	[redacted]	£35,435

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; QALYs, quality-adjusted life years; Ven: venetoclax.

Key issue 4: Impact of adverse events on quality of life	Yes	In the cost-effectiveness analysis the EuroQoL 5-dimensions (EQ-5D) data pooled from the VIALE-A and VIALE-C trials were used to derive health state utility values. Since utilities estimated were treatment-independent, the impact of adverse events (AEs) on utility estimates were considered and were adjusted for in the model. Grade 3 or 4 AEs that occurred in ≥5% in the VIALE-A and VIALE-C trials were included as covariates. Specifically, selected AEs included neutropenia (including neutropenia, neutrophil count decreased and febrile neutropenia), thrombocytopenia (including thrombocytopenia, and platelet count decreased), anaemia, leukopenia (including

leukopenia and white blood cell count decreased), hypokalaemia (including hypokalaemia, hyponatraemia and hypophosphatemia), pneumonia, and hypertension. The linear mixed-effects (LMM) regression analysis was conducted using the SAS PROC GLIMMIX procedure with an identity link function and normal error term distribution. To account for the effect of AEs, utility decrements sourced from Wehler *et al.* (2018) were applied as a one off decrement during Cycle 1.

The ERG scenario is presented in Table 9. It shows the treatment-dependent health state utility estimates derived using the same methodology that is outlined in Section B.3.4.4 of the company submission. There are no statistically significant differences in the adverse events found between the treatment arms, with all P-values greater than 0.05.

As well as the non-significant differences observed between the treatment arms, the plausibility of some of the treatment-dependent utilities are uncertain. For example, the utility value for patients in remission within the VenLDAC arm ([redacted]) [redacted] that of the general population. Stratifying analyses by treatment arm leads to lower patient numbers and more spurious results. Increasing patient numbers in the analyses reduces the variance and uncertainty in the utility values obtained from the pooled analysis.

Therefore, the approach taken in the company base case represents a reasonable, conservative approach, as pooling of data maximises overall sample sizes, thereby reducing the uncertainty in the utility estimates.

Table 9: Treatment dependent EQ-5D health state utilities

Health state	Arm	Mean (95% CI)	p-value	Source
Pooled VIALE-A/VIALE-C (original company base case)				
Remission	VenAZA	[redacted]	-	Pooled VIALE-A/VIALE-C
	AZA			
Non-remission	VenAZA	[redacted]	-	

			AZA			
		PD/relapse	VenAZA	[redacted]	-	
			AZA			
		VIALE-A				
		Remission	VenAZA	[redacted]	0.857	VIALE-A
			AZA	[redacted]		
		Non-remission	VenAZA	[redacted]	0.741	
			AZA	[redacted]		
		PD/relapse	VenAZA	[redacted]	0.198	
			AZA	[redacted]		
		VIALE-C				
		Remission	VenLDAC	[redacted]	0.954	VIALE-C
			LDAC	[redacted]		
		Non-remission	VenLDAC	[redacted]	0.324	
			LDAC	[redacted]		
		PD/relapse	VenLDAC	[redacted]	0.067	
			LDAC	[redacted]		

Abbreviations: AZA: azacitidine; CI: confidence interval; EQ-5D: EuroQoL 5-dimensions; LDAC: low dose cytarabine; PD: progressed disease; Ven: venetoclax.

Key issue 5: Potential for wastage of venetoclax	Yes	The company agrees with the ERG that there is the potential for drug wastage associated with venetoclax tablets that are prescribed to patients but not used due to patients discontinuing treatment or dying midway through a treatment cycle. The company have reviewed the gilteritinib NICE appraisal (TA642) which also references the sorafenib NICE appraisal (TA474).[14, 15] These appraisals conclude that NHS trusts issue patients with a one month supply of medication at a time, and that prescriptions are aligned with patient's monthly follow-up visits. Patients tablet supplies are generally managed by splitting packs where necessary to reduce wastage. This

aligns with clinical expert opinion received by the company that venetoclax would be managed in the same way and only be prescribed at a maximum of one-months' supply at a time. In both the referenced previous appraisals (TA642 and TA474), a decision was made to include wastage of up to seven days of treatment, and therefore it is appropriate to take the same approach for venetoclax.

The results of the scenario analyses are provided in Table 10 and Table 11. Accounting for wastage resulted in a small increase in the ICER for all comparisons, however none of the scenarios resulted in ICERs which exceeded the £50,000 per QALY threshold.

Table 10: Scenario analysis to assess the impact of wastage for venetoclax for 20–30% blasts

Comparison	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
VenAZA Vs. AZA	[redacted]	[redacted]	£17,127

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 11: Scenario analysis to assess the impact of wastage for venetoclax for >30% blasts

Comparison	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
VenAZA Vs. LDAC	[redacted]	[redacted]	£34,272
VenLDAC Vs. LDAC	[redacted]	[redacted]	£28,303

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; QALYs, quality-adjusted life years; Ven: venetoclax.

Key issue 6: The distribution of subsequent treatments by treatment arm	Yes	In the original company base case, the distribution of subsequent treatments was based on clinical expert opinion, which stated that 3% of patients would receive subsequent gilteritinib after receiving VenAZA and VenLDAC with the remaining patients receiving hydroxycarbamide. Patients receiving AZA and LDAC would be ineligible to receive gilteritinib and therefore all receive hydroxycarbamide. During a further round of clinical consultation, it was acknowledged that some patients receiving AZA and LDAC would in fact be eligible to receive subsequent treatment with gilteritinib. It was also highlighted that a scenario in which 15% of all patients who discontinue venetoclax combinations subsequently receiving gilteritinib is too high to be reflective of the proportion patients who are FLT3+ and fit enough for subsequent treatment in this population (ineligible for intensive chemotherapy and of a median age of 75 years). Clinical advice also indicated that a smaller proportion of patients that have discontinued AZA or LDAC would be eligible for gilteritinib than those who received VenAZA or VenLDAC. This is because a larger proportion of patients receiving venetoclax combination therapy achieve CR + CRi and would therefore be fitter following treatment and able to receive subsequent treatment with gilteritinib than those receiving AZA or LDAC. Clinical advice to the company suggests that a proportion of 5% of VenAZA/VenLDAC treated patients, and 3% of AZA/LDAC treated patients is most reflective of clinical practice (scenario 1). However, to address the ERG's concerns, a scenario analysis has been conducted in which 15% of patients receiving VenAZA or VenLDAC, and 10% of patients receiving AZA or LDAC, go on to subsequently receive treatment with gilteritinib (scenario 2). The subsequent treatment costs were derived using the same acquisition and administration costs as presented in Table 65 of the company submission and are presented in Table 12.

Table 12: Subsequent treatment cost derivation

Scenario	Treatment	Proportion	Total cost per cycle	Weighted cost per cycle	Mean total cost
VenAZA and VenLDAC					
Scenario 1	Gilteritinib	5.0%	£14,315.00	£715.75	£846.60
	HC/HU	95.0%	£137.74	£130.85	
Scenario 2	Gilteritinib	15.0%	£14,315.00	£2,147.25	£2,264.33
	HC/HU	85.0%	£137.74	£117.08	
AZA and LDAC					
Scenario 1	Gilteritinib	3.0%	£14,315.00	£429.45	£536.06
	HC/HU	97.0%	£137.74	£133.61	
Scenario 2	Gilteritinib	10.0%	£14,315.00	£1,431.50	£1,555.47
	HC/HU	90.0%	£137.74	£123.97	

Abbreviations: AZA: azacitidine; HC/HU: hydroxycarbamide/hydroxyurea; LDAC: low dose cytarabine; Ven: venetoclax.

The results of the scenario analyses are provided in Table 13 and Table 14. As expected, the impact of applying a higher proportion of patients receiving gilteritinib resulted in a higher ICER driven by larger incremental costs. However, all ICERs remained below the £50,000 per QALY threshold.

Table 13: Impact of alternative subsequent treatment derivation for 20–30% blasts

Comparison	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Scenario 1			
VenAZA Vs. AZA	[redacted]	[redacted]	£16,234
Scenario 2			
VenAZA Vs. AZA	[redacted]	[redacted]	£21,905

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; QALYs, quality-adjusted life years; Ven: venetoclax.

Table 14: Impact of alternative subsequent treatment derivation for >30% blasts

Comparison	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Scenario 1			
VenAZA Vs. LDAC	[redacted]	[redacted]	£33,023
VenLDAC Vs. LDAC	[redacted]	[redacted]	£25,534
Scenario 2			
VenAZA Vs. LDAC	[redacted]	[redacted]	£32,920
VenLDAC Vs. LDAC	[redacted]	[redacted]	£24,521

Abbreviations: AZA: azacitidine; ICER, incremental cost-effectiveness ratio; inc., incremental; LDAC: low dose cytarabine; QALYs, quality-adjusted life years; Ven: venetoclax.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

In response to errors identified in Key Issue 3 of the ERG report and Issue 10 of the ERG report factual accuracy check, AbbVie have corrected the company base case. In response to the Key Issues raised, AbbVie have presented scenario analyses as well as a revised economic base case which addresses the ERG's concerns regarding:

- The cure assumption
- General population mortality adjustment for transition probabilities to 'progressive disease' health state
- Time-on-treatment assumptions
- Wastage of venetoclax
- The distribution of subsequent treatments by treatment arm

This revised base case is associated with incremental cost-effectiveness ratios (ICER) of between £24,824 and £41,481 across all blast count subgroups, demonstrating venetoclax combinations represent a cost-effective use of NHS resources.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Original company base case	**Incremental QALYs:** 20–30% blasts: VenAZA Vs. AZA: [redacted] >30% blasts: VenAZA Vs. LDAC: [redacted]	**Incremental costs:** 20–30% blasts: VenAZA Vs. AZA: [redacted] >30% blasts: VenAZA Vs. LDAC: [redacted]	**ICER:** 20–30% blasts: VenAZA Vs. AZA: £38,866 >30% blasts: VenAZA Vs. LDAC: £39,449

	VenLDAC Vs. LDAC: [redacted]	VenLDAC Vs. LDAC: [redacted]	VenLDAC Vs. LDAC: £31,291
Corrected original company base case	**Incremental QALYs:** 20–30% blasts: VenAZA Vs. AZA: [redacted] >30% blasts: VenAZA Vs. LDAC: [redacted] VenLDAC Vs. LDAC: [redacted]	**Incremental costs:** 20–30% blasts: VenAZA Vs. AZA: [redacted] >30% blasts: VenAZA Vs. LDAC: [redacted] VenLDAC Vs. LDAC: [redacted]	**ICER:** 20–30% blasts: VenAZA Vs. AZA: £16,638 >30% blasts: VenAZA Vs. LDAC: £33,858 VenLDAC Vs. LDAC: £27,182
Key Issue 1: cure assumption	The company base case did not include any SMR for patients in the cure health state.	The company applied an SMR of 1.2 to account for an increase in the risk of death for patients who are deemed cured.	20–30% blasts: VenAZA Vs. AZA: £17,554 >30% blasts: VenAZA Vs. LDAC: £35,723 VenLDAC Vs. LDAC: £28,825
Key Issue 2: general population mortality	The company base case included general population mortality for time to remission, time to progressive disease and time on treatment survival curves.	The company has removed general population mortality from time to remission, time to progressive disease and time on treatment survival curves.	20–30% blasts: VenAZA Vs. AZA: £16,613 >30% blasts: VenAZA Vs. LDAC: £33,880

			VenLDAC Vs. LDAC: £27,120
Key Issue 3: time on treatment	The company base case ensured all patients who moved to the cure health state immediately discontinued treatment.	The revised company base case has allowed some patients to continue treatment whilst in the cure health state, with a waning of time on treatment occurring using an exponential curve.	20–30% blasts: VenAZA Vs. AZA: £23,388 >30% blasts: VenAZA Vs. LDAC: £39,687 VenLDAC Vs. LDAC: £35,435
Key Issue 5: wastage of venetoclax	The company base case did not account for the potential of wastage with venetoclax.	The revised company base case accounts for the potential of the wastage with venetoclax by including an additional 7-days of costs for venetoclax for patients who discontinue.	20–30% blasts: VenAZA Vs. AZA: £17,127 >30% blasts: VenAZA Vs. LDAC: £34,272 VenLDAC Vs. LDAC: £28,303
Key Issue 6: distribution of subsequent treatment	The company base case assumed that 3% of patients receiving VenAZA and VenLDAC would receive subsequent gilteritinib and no patients receiving AZA and LDAC would be eligible for subsequent gilteritinib.	The revised company base case assumes that 5% of patients receiving VenAZA and VenLDAC and 3% of patients receiving AZA and LDAC will receive subsequent gilteritinib.	20–30% blasts: VenAZA Vs. AZA: £16,234 >30% blasts: VenAZA Vs. LDAC: £33,023 VenLDAC Vs. LDAC: £25,534

Company's preferred base case following technical engagement (Preferred base case incorporating all changes made to the company base case in response to Key Issues 1, 2, 3, 5, and 6)	**Incremental QALYs:** 20-30% blasts: VenAZA Vs. AZA: [redacted] >30% blasts: VenAZA Vs. LDAC: [redacted] VenLDAC Vs. LDAC: [redacted]	**Incremental costs:** 20-30% blasts: VenAZA Vs. AZA: £[redacted] >30% blasts: VenAZA Vs. LDAC: £[redacted] VenLDAC Vs. LDAC: £[redacted]	**ICER:** 20–30% blasts: VenAZA Vs. AZA: £24,824 >30% blasts: VenAZA Vs. LDAC: £41,481 VenLDAC Vs. LDAC: £36,995

References

1. Electronic Medicines Compendium (EMC) Venclyxto 10 mg film-coated tablets. SmPC. Available at: https://www.medicines.org.uk/emc/product/2267/smpc#gref [Last accessed: June 2021].
2. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424-447.
3. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. New England Journal of Medicine 2020;383:617-629.
4. Ivey A, Hills RK, Simpson MA, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med 2016;374:422-33.
5. Pratz K, Jonas BA, Pullarkat V, et al. Measurable residual disease response in acute myeloid leukemia treated with venetoclax and azacitidine. Journal of Clinical Oncology 2021;39:7018-7018.
6. Cure Leukaemia. Recommendations for the management of patients with AML during the COVID19 outbreak: a statement from the NCRI AML Working Party. Available at: http://www.cureleukaemia.co.uk/media/upload/files/aml-covid-v4.0%281%29.pdf. [Last accessed: July 2021].
7. Dillon, R. Different treatments for AML during the COVID19 pandemic: British Society for Haematology Annual Meeting 2021.
8. Othus M, Garcia-Manero G, Godwin J, et al. Associations between Complete Remissions (CRs) with 7+3 Induction Chemotherapy for Acute Myeloid Leukemia and 2-3 Year Survival ("Potential Cure") over the Past Four Decades: Analysis of SWOG Trial Data. Blood 2017;130:1301-1301.
9. Shimoni A, Labopin M, Savani B, et al. Long-term survival and late events after allogeneic stem cell transplantation from HLA-matched siblings for acute myeloid leukemia with myeloablative compared to reduced-intensity conditioning: a report on behalf of the acute leukemia working party of European group for blood and marrow transplantation. J Hematol Oncol 2016;9:118.
10. Bejanyan N, Weisdorf DJ, Logan BR, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. Biol Blood Marrow Transplant 2015;21:454-9.
11. Bloomfield CD, Estey E, Pleyer L, et al. Time to repeal and replace response criteria for acute myeloid leukemia? Blood Reviews 2018;32:416-425.
12. Craddock C, Versluis J, Labopin M, et al. Distinct factors determine the kinetics of disease relapse in adults transplanted for acute myeloid leukaemia. J Intern Med 2018;283:371-379.
13. Wehler E, Storm M, Kowal S, et al. A Health State Utility Model Estimating the Impact of Ivosidenib on Quality of Life in Patients with Relapse/Refractory Acute Myeloid Leukemia. 23rd Congress of the European Hematology Association 2018.
14. National Institute for Health and Care Excellence (NICE). Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [TA642]. Available at: https://www.nice.org.uk/guidance/ta642. [Last accessed: March 2021]. .
15. National Institute for Health and Care Excellence (NICE). Sorafenib for treating advanced hepatocellular carcinoma [TA474]. Available at: https://www.nice.org.uk/guidance/ta474. [Last accessed: July 2021].

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Wednesday 21 July 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with acute myeloid leukaemia and current treatment options	
About you	
1. Your name	**Elspeth Payne**
2. Name of organisation	**Royal College of Pathologists**
3. Job title or position	**Associate Clinical Professor of Haematology**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with acute myeloid leukaemia? ☒ a specialist in the clinical evidence base for acute myeloid leukaemia or venetoclax? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ **As per initial submission**
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for acute myeloid leukaemia when intensive chemotherapy is unsuitable	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in acute myeloid leukaemia when intensive chemotherapy is unsuitable?	
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	

• What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful	

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Cure assumptions applied to those	There are 2 lines of evidence that support the cure assumption. 1. Stem cell Transplantation:

on VenAZA and VenLDAC who are in remission at 2 years	The majority of individuals eligible for the therapy in this TA are unlikely to be transplant candidates since they are deemed to be unfit for intensive chemotherapy. However, in the published Ven/Aza studies with longest follow-up around 20% of individuals did go on to receive a stem cell transplant (Pollyea et al, American Journals of Hematology, Sept 2020, DOI: 10.1002/ajh.26039), with good outcomes (75% still alive at time of publication) but with notably short follow-up. This situation my arise due to the fact that a subset of patients are unfit at presentation, but following therapy recover and are deemed to be fit enough for transplant. Indeed, the absence of intensive induction chemotherapy may well facilitate maintaining a good performance status in these individuals. This is in keeping with real world experiences of patients who received azacitidine as initial first line therapy (with 20-30% blasts) who may subsequently be suitable for either more intense therapy or transplantation. The number of potentially transplant eligible patients is similar to the numbers who underwent transplantation in the ADMIRAL study (25%) using gilteritinib (where a cure assumption was accepted) and will include patients with lower risk disease than the flt3 + patients treated with gilteritinib (therefore potentially with a lower relapse risk) although a higher risk population (due to presumed prior poor performance status since not given intensive chemo). While this is a plausible assumption the cost models do not include transplantation as an option. 2. Evidence of prolonged remissions/cure in patients off therapy Evidence for prolonged remission off therapy was recently presented at the European society for haematology. https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/325183/chong.chyn.chua.treatment.free.remission.28tfr29.after.ceasing.venetoclax-based.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dvenetoclax The data presented is small numbers but a significant duration (median follow-up was 55 months) of follow-up that gives confidence in the durability of the findings. 25 patients were included and 13 stopped therapy (reasons for stopping were patient or clinician choice). Median treatment free remission was 45 months in the study. The number of patients who remained off therapy in the subgroup with NPM1 or IDH1 mutations was 7/8.

	The proportion of patients who relapsed was higher in those who were on therapy than those that were off therapy, therefore continuing therapy did not appear in this small study to provide additional protection against relapse. Although these are small numbers these provide support that long term survival off therapy (and thus the cure assumption) is plausible, however this needs to be assessed in a prospective study.
Key issue 2: Uncertainty regarding the justification for using general population mortality to adjust the curves used to estimate transition probabilities to progressive disease health state	Patients who are deemed "cured" are likely to be comprised of those both post-transplant cure and patients who become MRD negative on treatment and cease all therapy. Therefore, I would suggest the former group are likely to have some residual morbidity post-transplant above that of the general population, the latter are likely to have similar mortality to the general population if they are truly cured.
Key issue 3: Inconsistent assumptions related to modelling of time on treatment and subsequent treatment	This issue is complicated by the possibility that some patients may be cured and some not. Patients may relapse whether or not they remain on venetoclax after 2 years. But some may still be cured. Subsequent treatments are likely to be supportive/hydroxycarbamide in most cases, but it is plausible some patients who have had longer remissions would be reinduced with ven/aza (if off therapy post 2 years) or ven/ldac or an intensive regime or gilteritinib if flt3+. Longer follow-up and detail on the subsequent therapies that patients actually received who participated in the VIALE studies if available may be helpful here.

Key issue 4: Impact of adverse events on quality of life	It seems reasonable to remove impact of adverse events from EQ-5D data since there was no clear difference in adverse events between groups, but similarly I don't therefore understand why not leave this in (since it should have no overall effect) . Impact of SAEs may be significant on HRQoL given hospitalisation and recovery times.
Key issue 5: Potential for wastage of venetoclax	Patients will occasionally be advised to stop venetoclax during a cycle due to toxicity. There is no reason that these venetoclax packs cannot be carried forward to subsequent cycles. Some wastage may occur at the end of therapy however due to progressive disease. See other comments below regarding dosage. Most patients would not be in receipt of a dosage more than 100mg daily with our current practice. 7 days of waste of 100mg tablets at progression would seem a reasonable estimate.
Key issue 6: The distribution of subsequent treatments by treatment arm	A large series of mostly intensively treated patients with AML (pre TKI era) indicates that about 15% acquire an ITD at relapse (and therefore be eligible for gilteritinib). Comorbidities within the group of patients addressed in this TA are likely to be higher than average such that this treatment is not always appropriate at relapse. From our own local data (total 51 patients treated with Ven/LDAC or Ven/Aza - notably a slightly different population as per the interim NICE guidance) 3/10 patients (30%) who relapsed acquired a flt3 itd at relapse. This hints that the rate of flt3 positive patients post relapse is a bit higher after ven based regimens but the numbers are too small to reliably inform this TA. As stated above a small subset of patients may be fit enough to receive transplant which is not accounted for. Similarly a small number of patients may be fit enough at this stage for an intensive induction chemotherapy cycle. Nonetheless the majority would receive supportive care or hydroxycarbamide as suggested.
Are there any important issues that have been missed in ERG report?	Yes The current interim guidance and the current practise in the UK is to use azole based prophylaxis for prevention of fungal infection (with Posaconazole or itraconazole) in AML patients. This is standard practise in all patients with AML regardless of therapy. Azoles are strong CYP3A inhibitors and therefore as per the dose reduction recommendations in the VIALE trials the dose of venetoclax prescribed in the

	vast majority of uk patients treated to date is 100mg. Pharmocokinetic studies have been undertaken to confirm this dose reduction is required to maintain the steady state of venetoclax at that expected without azole. In fact the SmPC data indicates even lower dosages of venetoclax when receiving such concomitant drugs (recommended 70mg) . In line with this is also common practise to reduce the duration of venetoclax to 21, 14 or even 7 days to minimise toxicity once the patients enter remission. All of the costings appear to have been based on the 400mg dosing (Ven/Aza) or 600mg (Ven/LDAC) for 4 weeks adjusted only to 0.5 for the venetoclax dose. Significant cost reductions are likely/inevitable therefore compared to that shown by the company in this TA for the venetoclax component. It is unlikely there were no patients on the study that received these therapies and therefore the lower dose of venetoclax. It would be helpful if the company to clarify this (and provide any relevant data - is this where the 0.5 adjustment has been derived from?) . It is critical that the review consider this quite marked potential price differential compared to what is shown.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Combination venetoclax based therapies for AML are the biggest forward change in therapies for patients ineligible for intensive chemotherapy in decades
- The ventoclax/Azacitidine combination results in significant prolongation of life
- Venetoclax/Azacitidine and Venetoclax/LD AraC are well tolerated and given mainly as outpatient based therapies
- A cure assumption is plausible but the data to support this remains immature

- Cost of therapy is likely to be significantly overestimated by the models provided due to the concomitant antifungal therapies used in the UK and associated appropriate necessary dose reductions in venetoclax

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Wednesday 21 July.**

Completing this form
Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with acute myeloid leukaemia and current treatment options	
About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with acute myeloid leukaemia? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with acute myeloid leukaemia? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Leukaemia Care
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with acute myeloid leukaemia? If you are a carer (for someone with acute myeloid leukaemia) please share your experience of caring for them.	In March 2019 I was diagnosed with AML. I was [redacted]. I had been fit and healthy and had come down with a bad case of flu that I could not shake, and I also noticed swollen glands and some lumps and bruises on my legs. After 3 visits to the GP and requesting a blood test, I received a phone call telling me to go to the local hospital immediately. The next morning, I went into St Bart's Hospital to start treatment. The shock and upheaval was enormous and very disorientating. I have two young boys, my [redacted] runs [redacted] own business and I am a [redacted]. We had to make immediate arrangements to cover childcare and work appointments and then look at how to sustain this for the coming months. The impact of a disease like this ripples through your immediate family and into your network of friends and colleagues. I was to start 3 rounds of intensive chemotherapy as an inpatient for 3 months with short breaks at home in between. The side effects were brutal, and on top of the expected vomiting and relentless diarrhoea, my body threw up many infections to fight with sepsis, high fevers of 41.7, a lung fungus infection, excruciating body pain,

	angry rashes, and bruising to name a few. I lost all my hair and the use of my legs for a couple of weeks due to the pain of erythema nodosum. I had 3 separate PICC lines inserted into my arms, as they had become infected, one through my jugular and one large central line across my chest. During the last round I had an agonising inflammation of the small intestine and was fed through an NG tube. I was often too ill to see my children and spent most of my hospital stays in isolation. The hospital is about [redacted] miles from our [redacted] home which also made it complicated for my [redacted] to visit between [redacted] work and looking after our children. After the second month of chemotherapy, I was told that I was in the high risk of relapse category and would need a stem cell transplant following the 3rd month of treatment. I have [redacted] who were all tested as potential donors and my [redacted] was flown over from [redacted] being the closest match, leaving [redacted] 3 children for a month. Two weeks before the transplant was due, antibody levels in my blood flared up making us incompatible. A trial plasma exchange to reduce the antibodies at Guys Hospital was unsuccessful and the transplant was suddenly called off. The devastation at this point was inconceivable, it felt like a very cruel joke and there really are no words for the bleakness I often felt at this time. I began suffering daily panic attacks and felt emotions I had never experienced on top of fear, complete disorientation and disbelief. Despite a generous donor drive from family, friends, colleagues and acquaintances, I was told that due to my rare tissue type it would be unlikely that a close enough match would be found anywhere in the world. During the time that we were hoping an alternative donor would be found, my medical team offered me Venetoclax in combination with low dose cytarabine. Having been so ill from the last round of Flag-ida, they wanted to offer me something which would be less toxic and leave me in better condition overall. We were also hoping that I would become MRD negative. I took this option as I did not want to spend more long

	weeks in hospital away from my children or be as ill as I had previously been. I was terrified at the thought of going through another round of chemotherapy in hospital. I was admitted for one week whilst they escalated the dose of Venetoclax and monitored me for TLS. I was shown how to administer the cytarabine injections myself so that I did not have to visit a hospital more than I needed to. I would also be closely monitored by my local hospital having local blood tests every week. I was MRD negative after only a few weeks on this treatment and over all apart from taking the injections It did not feel like the chemotherapy I had experienced previously. Throughout the time I was taking the Venetoclax I was well in myself, and able to carry out normal everyday activities like housework, cooking, the school run and meeting friends. I went to the gym regularly and attended Pilates classes. We went on short holidays and my hair started to grow back and my children often forget that I was still on treatment. We would often go off road biking, on long walks and I was able to drive with confidence. Being able to do all of these activities gave me a sense of independence and control over my life. I knew I couldn't control the disease, I left that to the Venetoclax, but I did feel that I could at least enjoy myself and spend time with people who were important to me and needed me for as long as I could. Because I was able to continue most normal daily activities, then mentally and emotionally it also made me feel a stronger sense of hope and maintain a more positive outlook which I think has helped me overall to deal with the shock of the diagnosis and the trauma I had been through. Anxiety is a usual companion for cancer patients, but I was now able to focus on living and not feel like I might be dying. It was also extremely important for my children to have me at home to look after them and for my [redacted] to continue to work. The impact of my disease on my family and the disruption it caused whilst I was in and out of hospital is also something to consider for patients. If you can maintain a sense of routine for patients it also helps those around you and everyone can function in a more predictable way, I decided

	not to return to work whilst on treatment as I was often neutropenic and felt that [redacted] might not be the best place for my low immune system. I was generally a bit tired at times but able to pace myself. The weeks where I injected cytarabine did make me feel quite woozy and as the months progressed the nausea did increase only whilst on the cytarabine. However, I was able to plan around this and ensure that I had the right medication to combat the nausea and any vomiting. I did not suffer any other noticeable side effects and the only other medication I took was GCSF to boost my neutrophils when the levels dropped. I was aware of being neutropenic at times and took precautions at home and when around other people. The original plan for the Venetoclax was to monitor the pattern of response and continue for up to 12 months if I was continuing to respond positively. The [redacted] Trust were funding the treatment however it was rejected by both the Trust and the Individual Funding Review at 8 months. I was given the choice to stop treatment or self fund. I decided to self fund for the last 4 cycles. I finished my treatment in July 2020. My antibodies were retested but sadly they had not reduced significantly for me to be compatible with my [redacted] again and no other donor has been found. We hope that I will not need any further treatment as I have been MRD negative for nearly 2 years now. I have 3 monthly bone marrow check-ups at [redacted] and regular blood tests to keep an eye on my blood levels.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for acute myeloid leukaemia on the NHS when intensive chemotherapy is unsuitable?	7**a.** I have not had personal experience of this, and my understanding is that people who cannot undergo intensive chemotherapy are given less intensive chemotherapy which is often not as effective however is the only current option. I am not personally in this group however I am a patient who had experienced such adverse side effects to the intensive chemotherapy I had that my medical team did not want me to have another round of such intensive treatment. Therefore, I was also facing limited options as people in this group also face. I think currently there needs to be more treatments which can help people who present with complicated disease presentations or other health conditions to prolong their lives. If the current treatment is too harsh for people to be effective then there most certainly needs to be alternatives, which are both effective and safe and help patients maintain a better quality of life.
7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7b.I do not know anyone who has had less intensive chemotherapy and have not had personal experience of this. I have a close relative in [redacted] who also has AML and has been given Venetoclax and Azacytdine as a first line treatment. She praises the treatment and also finds the side effects easily managed by herself at home and plans around the cycles. She has told me that she thinks the treatment is doing wonders for her, and she can still go sailing on the weekends, she has moved house recently and looks after her grandchildren.
8. If there are disadvantages for patients of **current NHS treatments** for acute myeloid leukaemia when intensive chemotherapy is unsuitable (for example how the treatment is given or taken, side effects of treatment etc) please describe these	8. If the current treatment puts patients at risk of developing debilitating side effects and long hospital stays then this is a huge disadvantage to patients and their families. I know that the treatment is not intended to cure patients but only extend their life. Whilst this is also a valuable option for a patient facing limited options it would also be better if there was something else which might extend life whilst also helping them maintain overall general physical and mental wellness.

Advantages of this treatment	
9a. If there are advantages of venetoclax over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others?	9a. I am still alive. For me this is the stand alone benefit. I am really not sure whether I would still be alive today if it was not for Venetoclax. I feel that I might actually continue with a long durable remission and have already had 2 extra years of my life, and my children have had their [redacted] for this time. If Venetoclax was not available, then I probably would have had another round of chemotherapy to try and become MRD negative and I am not sure of how well I would have tolerated this or even how effective it would have been as I had not become MRD negative after undergoing such intense treatment. Another important benefit is the reduced level of toxicity and minimal side effects of the treatment which I believe can be managed by the patient. This then filters down to a patient's overall quality of life and the impact on families and carers. If a patient is able to be at home whilst on active treatment and manage their side effects easily and not have to be hospitalised for infections and other complications, then they will sleep better, eat better and generally be able to live their own life and feel more in control and be less of a burden on those around them. Long hospital stays are both disorientating and can be very frightening. The food is horrible and does not seem to be very nutritious, and it is difficult to get enough rest. Quality of life is extremely important for patients. I base quality on life on my ability to carry out normal activities, my mental wellbeing and ability to cope with anxiety and uncertainty, my general overall feeling of wellness and where I am actually spending my time. It is terrifying to have cancer especially one which is so insidious and erupts so rapidly. When you are unsure of how much time you might have left, being somewhere familiar or where you able to continue most of your normal activities, and if you are able to look after yourself with minimal care from others is very important. I felt like I had my independence and some control over my life whilst on this treatment compared to being in hospital. I imagine some

	people would be able to work depending on their jobs, or easily study. If you have responsibilities such as looking after your own children or grandchildren then it is possible whilst on Venetoclax. This is priceless and something that any parent or grandparent would consider a very important part of their lives and if options are given to patients in these categories, then a treatment like Venetoclax in my opinion would be the better option. As a patient I also began to look normal again, with my hair growing back and I was able to eat and maintain a better healthier weight. I started to look less like a cancer patient, which for my children was a relief. It also helped my confidence in general.
9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	9a.Overall quality of life. AML is such a devastating disease and swipes your life away from under your feet, so having a treatment available which can keep most aspects of your life in place whilst being treated is far better for the patients and also their families. The diagnosis is very frightening and physiologically and emotionally it is very difficult to deal with. If you can have a treatment which has a somewhat predictable cycle then you can plan your life around these cycles and mentally this also helps you feel a sense of certainty and having some control over your treatment. If side effects are minimal or only experienced in bursts then it makes your life easier to live, and without as much disruption to yourself and those close to you. Being able to take the treatment yourself also reduces the impact of anyone you live with or are close to and minimises the time you have to spend going to hospitals. Being well enough to still do the things you enjoy or still carry out your responsibilities also helps the people around you. If you can continue to live your life then your mental and emotional wellbeing increases and it also alleviates the burden on your loved ones.

9c. Does venetoclax help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	9c. I do think that if side effects are very minimal, and manageable by the patient, then as a patient you do not feel as much like a cancer patient as you might when you are made unwell because of the treatment. If treatment is making you feel completely devastated, then this impacts of every aspect of your life and your emotional wellbeing. It is extremely difficult to find the energy you might need to combat side effects however if these can be significantly reduced, then you will be able to maintain an overall wellness that in turn must have a more lasting effect on your ability to cope with the disease and help your body process the treatment and have the strength to continue living.
Disadvantages of this treatment	
10. If there are disadvantages of venetoclax over current treatments on the NHS please describe these? For example, are there any risks with venetoclax? If you are concerned about any potential side effects you have heard about, please describe them and explain why.	10.There could be some patients might find the lack of contact with a hospital a little difficult and might prefer more support. I was having weekly blood tests at my local hospital, so I did not fee like I needed any more contact than this. I had a good line of communication with my medical team and felt like they were just a phone call away. Some patients might find injecting themselves to be difficult if they are having cytarabine. I understand that azacytidine is given in hospital. I don't believe from my experience that there are any major risks with the treatment. I was very aware that Neutropenia could propose a risk to me however I took steps at home and if ever I was out with others to minimise any chance of compromising myself with an infection. It was clearly explained to me by my medical team. In my experience my nausea did worsen progressively each month when I was giving myself the cytarabine injections although this did not start until around the 6th cycle. Once I stopped the injections, I felt a shift in my energy levels and fatigue. The cytarabine slowed me down for a few days a month and made me feel a little woozy. However, I was able to plan for this and pace myself and make sure I was prepared for that part of the cycle. This short time of feeling a little unwell every

	month was mentally and physically tolerable because the rest of each month I felt generally well and therefore the majority of time I felt better than worse.
Patient population	
11. Are there any groups of patients who might benefit more from venetoclax or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Anyone who needs a treatment which is less toxic and offers fewer side effects which can be self managed. Anyone who lives a long way from a major hospital who can't make it into a hospital easily. Anyone who has family commitments which require them to be at home, or spend more time at home with their family would benefit as their own quality of life would mean that they are available for others. Patients who like me had basically run out of options and need to try something new. Patients who would struggle to inject themselves due to dexterity difficulties would need some assistance or someone else at home to help them. Any patients who have any cognitive impairments I expect would manage if they had ways to remind themselves to take their medication.
Equality	
12. Are there any potential equality issues that should be taken into account when considering acute myeloid leukaemia and venetoclax? Please explain if	I don't think there would be any issues.

you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. Do you have any general comments on the key issues in the ERG report (listed in table 1 and summarised in section 1.5)?	Issue 1 Cure Assumption As a patient I think we all aim for remission and then hopefully to be considered as cured. I am now at the 2-year point and beginning to feel confident that I have a better chance of long term survival which I would say is the same a cure in many ways. This is very important emotionally and mentally for patients to be able to feel like they have reached a point at which they can kind of cross over. An extension to life is also something which is definitely worth it. Issue 4. Quality of life whilst on treatment, This treatment with its routine and cycles makes treatment more predictable and helps patients maintain their normal activities and function at a level which is close to normal. As a patient who had this treatment, I can confirm that any side effects could be self-managed, and only experienced for a few days a month therefore there was more time when I felt well physically and mentally than not.

18. Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

19. In up to 5 sentences, please summarise the key messages of your statement:

- Venetoclax has extended my life when I had few other options or options which were risky.
- Venetoclax is far less toxic and side effects can be self-managed which meant I could be with my family.
- Venetoclax helped me maintain a better quality of life and a routine which was manageable.
- Venetoclax can get patients into remission which could not only extend their life but also potentially lead to long term survival
- Venetoclax helps patients look and feel less like cancer patients and therefore improves mental and emotional states and a sense of normality for themselves and those around them.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

NICE National Institute for Health and Care Excellence

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 21 July 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Leukaemia Care**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Cure assumptions applied to those on VenAZA and VenLDAC who are in remission at 2 years	NO	Clinical experts have indicated that this would be considered a potentially curative option for AML. This is an innovative treatment that is different to other options currently available to the group in this respect.
Key issue 2: Uncertainty regarding the justification for using general population mortality to adjust the curves used to estimate transition probabilities to progressive disease health state	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: Inconsistent assumptions related to modelling of time on treatment and subsequent treatment	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 4: Impact of adverse events on quality of life	**YES/NO**	The patient expert suggested that this treatment had a significant impact on [redacted] quality of life that may not have been captured in the modelling, including being able to do more of [redacted] usual daily activities.
Key issue 5: Potential for wastage of venetoclax	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Key issue 6: The distribution of subsequent treatments by treatment arm	**YES/NO**	Discussions with our patient expert suggest that the patients feel much better in terms of fitness and ability to undertake daily activities following treatment. This could mean that many patients would be fitter at the point of relapse after venetoclax combinations than those who have other treatments that are less likely to be effective initially, and also fitter that they were prior to treatment. Hence their eligibility for treatments may have changed in this time.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Use of venetoclax dosage in NHS	Related to issue 1	**No**	Clinical experts have suggested that the dosage and scheduling may differ in the NHS than in the trial. We would like to see if this has impacted upon
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 21 July 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Royal College of Pathologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Cure assumptions applied to those on VenAZA and VenLDAC who are in remission at 2 years	Yes	There are 2 lines of evidence that support the cure assumption. 1. Stem cell Transplantation: The majority of individuals eligible for the therapy in this TA are unlikely to be transplant candidates since they are deemed to be unfit for intensive chemotherapy. However, in the published Ven/Aza studies with longest follow-up around 20% of individuals did go on to receive a stem cell transplant (Pollyea et al, American Journals of Hematology, Sept 2020, DOI: 10.1002/ajh.26039), with good outcomes (75% still alive at time of publication) but with notably short follow-up. This situation my arise due to the fact that a subset of patients are unfit at presentation, but following therapy recover and are deemed to be fit enough for transplant. Indeed, the absence of intensive induction chemotherapy may well facilitate maintaining a good performance status in these individuals. This is in keeping with real world experiences of patients who received azacitidine as initial first line therapy (with 20-30% blasts) who may subsequently be suitable for either more intense therapy or transplantation. The number of potentially transplant eligible patients is similar to the numbers who underwent transplantation in the ADMIRAL study (25%) using gilteritinib (where a cure assumption was accepted) and will include patients with lower risk disease than the flt3 + patients treated with

		gilteritinib (therefore potentially with a lower relapse risk) although a higher risk population (due to presumed prior poor performance status since not given intensive chemo). While this is a plausible assumption the cost models do not include transplantation as an option. 2. Evidence of prolonged remissions/cure in patients off therapy Evidence for prolonged remission off therapy was recently presented at the European society for haematology. https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/325183/chong.chyn.chua.treatment.free.remission.28tfr29.after.ceasing.venetoclax-based.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dvenetoclax The data presented is small numbers but a significant duration (median follow-up was 55 months) of follow-up that gives confidence in the durability of the findings. 25 patients were included and 13 stopped therapy (reasons for stopping were patient or clinician choice). Median treatment free remission was 45 months in the study. The number of patients who remained off therapy in the subgroup with NPM1 or IDH1 mutations was 7/8. The proportion of patients who relapsed was higher in those who were on therapy than those that were off therapy, therefore continuing therapy did not appear in this small study to provide additional protection against relapse. Although these are small numbers these provide support that long term survival off therapy (and thus the cure assumption) is plausible, however this needs to be assessed in a prospective study.
Key issue 2: Uncertainty regarding the justification for using general population mortality to adjust the curves used	**Yes**	Patients who are deemed “cured” are likely to be comprised of those both post-transplant cure and patients who become MRD negative on treatment and cease all therapy. Therefore, I would suggest the former group are likely to have some residual morbidity post-transplant above that of the general population, the latter are likely to have similar mortality to the general population if they are truly cured.

to estimate transition probabilities to progressive disease health state		
Key issue 3: Inconsistent assumptions related to modelling of time on treatment and subsequent treatment	**yes**	This issue is complicated by the possibility that some patients may be cured and some not. Patients may relapse whether or not they remain on venetoclax after 2 years. But some may still be cured. Subsequent treatments are likely to be supportive/hydroxycarbamide in most cases, but it is plausible some patients who have had longer remissions would be reinduced with ven/aza (if off therapy post 2 years) or ven/ldac or an intensive regime or gilteritinib if flt3+. Longer follow-up and detail on the subsequent therapies that patients actually received who participated in the VIALE studies if available may be helpful here.
Key issue 4: Impact of adverse events on quality of life	**No**	It seems reasonable to remove impact of adverse events from EQ-5D data since there was no clear difference in adverse events between groups, but similarly I don't therefore understand why not leave this in (since it should have no overall effect) . Impact of SAEs may be significant on HRQoL given hospitalisation and recovery times.
Key issue 5: Potential for wastage of venetoclax	Yes	Patients will occasionally be advised to stop venetoclax during a cycle due to toxicity. There is no reason that these venetoclax packs cannot be carried forward to subsequent cycles. Some wastage may occur at the end of therapy however due to progressive disease. See other comments below regarding dosage. Most patients would not be in receipt of a dosage more than 100mg daily with our current practice. 7 days of waste of 100mg tablets at progression would seem a reasonable estimate.
Key issue 6: The distribution of subsequent treatments by treatment arm	**Yes**	A large series of mostly intensively treated patients with AML (pre TKI era) indicates that about 15% acquire an ITD at relapse (and therefore be eligible for gilteritinib). Comorbidities within the group of patients addressed in this TA are likely to be higher than average such that this treatment is not always appropriate at relapse. From our own local data (total 51 patients treated with Ven/LDAC or Ven/Aza - notably a slightly different population as per the

		interim NICE guidance) 3/10 patients (30%) who relapsed acquired a flt3 itd at relapse. This hints that the rate of flt3 positive patients post relapse is a bit higher after ven based regimens but the numbers are too small to reliably inform this TA. As stated above a small subset of patients may be fit enough to receive transplant which is not accounted for. Similarly a small number of patients may be fit enough at this stage for an intensive induction chemotherapy cycle. Nonetheless the majority would receive supportive care or hydroxycarbamide as suggested.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: **Cost assessment of aza/ven or ldac/ven not assessed according to current use (in HMRN data, according to interim NICE guidance**	no		The current interim guidance and the current practise in the UK is to use azole based prophylaxis for prevention of fungal infection (with Posaconazole or itraconazole) in AML patients. This is standard practise in all patients with AML regardless of therapy. Azoles are strong CYP3A inhibitors and therefore as per the dose reduction recommendations in the VIALE trials the dose of venetoclax prescribed in the vast majority of uk patients treated to date is 100mg. Pharmocokinetic studies have been undertaken to confirm this dose reduction is required to maintain the steady state of venetoclax at that expected without azole. In fact the SmPC data indicates even lower dosages of venetoclax when receiving such concomitant drugs (recommended 70mg) . In line with this is also common practise to reduce the duration of venetoclax to 21, 14 or even 7 days to minimise toxicity once the patients enter remission. All of the costings appear to have been based on the 400mg dosing (Ven/Aza) or 600mg (Ven/LDAC) for 4 weeks adjusted only to 0.5 for the venetoclax dose. Significant cost reductions are likely/inevitable therefore compared to that shown by the company in this TA for the venetoclax component.

			It is unlikely there were no patients on the study that received these therapies and therefore the lower dose of venetoclax. It would be helpful if the company to clarify this (and provide any relevant data - is this where the 0.5 adjustment has been derived from?) . It is critical that the review consider this quite marked potential price differential compared to what is shown.
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 21 July 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Cure assumptions applied to those on VenAZA and VenLDAC who are in remission at 2 years	Yes	A good proportion of AML patients are cured by conventional intensive chemotherapy. The rates and depth of responses (eradication of minimal residual disease) seen with VENAZA and VENLDAC are comparable to such established therapy. Randomised trials are now open and recruiting to compare conventional intensive chemotherapy approaches with venetoclax based therapy in younger AML patients as current data suggests they may be as effective with less toxicity. Whilst the duration of follow up in VIALE-A and VIALE-C does not yet conclusively demonstrate the cure assumption at 2 years it remains reasonable to conclude that a proportion of patients are cured and discussion is perhaps warranted whether this is at 2 or 3 years. Indeed within UK clinical practice many patients on VEN based therapies appear 'cured'. It has already been stated that optimal duration of therapy is yet to be established however there are many patients who have discontinued therapy for various reasons (early elite responses, toxicity, COVID, quality of life) and remain disease free years after cessation of therapy. Regular molecular monitoring of relapse in blood and marrow is completed after 2 years post consolidation as relapse risk is thin so low.
Key issue 2: Uncertainty regarding the justification for using general population mortality to adjust the curves used to estimate	No	Others are better placed to respond on whether this is the most appropriate model to utilise.

transition probabilities to progressive disease health state		
Key issue 3: Inconsistent assumptions related to modelling of time on treatment and subsequent treatment	No	The company base case assumes 3% of patients receive gilteritinib as a subsequent treatment following VENAZA and VENLDAC, with the remainder receiving hydroxycarbamide. The ERG's clinical advice was that a similar and higher proportion would be expected to receive gilteritinib as subsequent treatment in both arms**, our experts** agree with this. Estimated incidence at the time of disease progression/relapse would be for FLT3 mutation incidence of around 15%. A proportion of these patients at this point would have deteriorated clinically such that they would only receive best supportive care, mutation screening may not be undertaken by all clinical teams in a timely manner. As such an estimate use of 10% in all treatment arms may be more reasonable.
Key issue 4: Impact of adverse events on quality of life	No	We agree with the ERG and would prefer to see the observed data from the trials used in the model to estimate adverse event disutilities or be further informed of the rationale why adverse event disutilities were applied using a separate data source in a different patient group of relapse/refractory AML patients.
Key issue 5: Potential for wastage of venetoclax	No	We agree some wastage is inevitable. Consolidation cycles in UK clinical practice are 14 days in duration with each cycle being prescribed/issued one cycle at a time. To be consistent with TA642 (where cycles are 28 days duartion) wastage would at most be 7 days per patient.
Key issue 6: The distribution of subsequent treatments by treatment arm	No	The ERG's clinical advice was that a similar and higher proportion would be expected to receive gilteritinib as subsequent treatment in both arms.- as in response to key issue 3 we would agree (estimate 10%).

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: The EMA license for use of Venetoclax in AML.	NA	Yes	The EMA approved label for Venetoclax has been confirmed as “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”. The utilisation with LDAC has not been included which is a large part of TA1564. [redacted].
Additional issue 2: *The dose of venetoclax used is significantly less than the summary of product characteristics.*	NA	Yes	It is globally acknowledged by the AML community that the licensed dose is excessive- with concerns about neutropenia and associated delays in bone marrow recovery. In line with the ERG report we agree that posaconazole I standard of care in this population so generally patients receive 100mg (or 70mg) compared to the standard 400/600mg dose. In addition although 28 days of venetoclax is generally used for cycle 1- subsequent cycles are reduced in duration (generally 14 days). The data on the patients treated in NHS England has been collected and are undergoing analysis- planned submission for the annual scientific meeting of the American society for Haematology (ASH)- planned august 2021. Provisional findings indicate these dramatic dose and duration reductions reduce toxicity and do not impact on response rates and duration.
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 21 July 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Jazz Pharmaceuticals UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Cure assumptions applied to those on VenAZA and VenLDAC who are in remission at 2 years	**YES/NO**	We agree with the ERG's approach to remove the cure assumption for those in the venetoclax arms who remain in remission at two years because non-intensive treatments are not likely to be curative in this patient population. We also note the submissions from the professional organisations (Royal College of Pathologists and RCP-ACP-NCRI) mention that the interim COVID NICE guidance recommends off label use of venetoclax in the fit patient population. Again there is no promise of cure from venetoclax in this unlicenced population. The best chance of cure for the fit population is to receive an in-label, NICE-recommended therapy, for example those therapies mentioned by the Royal College of Pathologists in the professional organisation submission: "Fit patients are treated where possible on national clinical trials (AML18 and AML19) or with chemotherapy - daunorubucin and Ara-C with or without myelotarg or midostaurin depending on diagnostic features (TA545 and TA523 respectively), or Vyxeos (TA552)."
Key issue 2: Uncertainty regarding the justification for using general population mortality to adjust the curves used to estimate	**YES/NO**	We agree with the EGR's comment and although it is not clear if and how much of an effect it has on the ICER, we believe that applying general mortality rate to non-death transition is conceptually inaccurate.

transition probabilities to progressive disease health state		
Key issue 3: Inconsistent assumptions related to modelling of time on treatment and subsequent treatment	**YES/NO**	No comment
Key issue 4: Impact of adverse events on quality of life	**YES/NO**	No comment
Key issue 5: Potential for wastage of venetoclax	**YES/NO**	No comment
Key issue 6: The distribution of subsequent treatments by treatment arm	**YES/NO**	No comment

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	No comment
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	No comment
Additional issue N: Insert additional issue			No comment

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

wVenetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia unsuitable for intensive chemotherapy [ID1564]

ERG critique of the company's response to technical engagement

Produced by Aberdeen HTA Group

Authors Charlotte Kennedy[1]
Graham Scotland[1, 2]

1 Health Economics Research Unit, University of Aberdeen, UK
2 Health Services Research Unit, University of Aberdeen, UK

Correspondence to Graham Scotland
Health Economics Research Unit
University of Aberdeen
g.scotland@abdn.ac.uk

Date completed **04 August 2021**

Contains AIC/CIC

In their response to the technical engagement report the company addressed each of the issues raised in the ERG report and provided some revised economic analyses. This addendum to the ERG report provides a brief critique of the company response on each of the issues raised. It should be read in conjunction with the company's response document dated 21 July 2021.

Issue 1. Cure assumptions applied to those on VenAZA and VenLDAC who are in remission at 2 years

The company elaborate further on their arguments in support of a cure assumption being applied in the model for those who remain in remission at two years. Without going into the full details, these hinge on:

1. The ability of venetoclax to "provide rapid, deep, and durable remissions, which are closer to the achievements historically seen for IC treatments in younger/fitter patients".
2. The 66.4% of patients achieving complete remission (CR + CRi) on VenAZA being comparable to the rate of 40–60% that has previously been observed in older patients (>60 years) receiving treatment with intensive 7+3 regimens.[1, 2]
3. The significantly greater proportion of patients treated with VenAZA in VIALE A who achieved sustained deep remission (defined as MRD <0.001 and CR + CRi) compared with AZA alone (23.4% vs. 7.6%; [redacted]); MRD being a strong prognostic indicator for overall survival (OS) and risk of relapse, and, therefore, a potentially curative response (Ivey et al. 2016). [2, 3]
4. Evidence from VIALE A suggesting those patients who achieved MRD <0.001 and CR + CRi had longer duration of response (DoR), event free survival (EFS), and OS, regardless of when MRD negativity was achieved.[4]

Therefore, the company argue that it is reasonable to assume that VenAZA may offer IC ineligible patients clinical outcomes, which are more aligned to their IC eligible counterparts, including a possible cure for some patients.

Clinical expert and clinical organisation responses also seem to support the assumption that a cure is plausible and note experience in UK clinical practice which suggests that there "*are many patients who have discontinued therapy for various reasons (early elite responses, toxicity, COVID, quality of life) and remain disease free years after cessation of therapy*" (NCRI-ACP-RCP-RCR). The expert responses do, however, acknowledge the immaturity of the VIALE A and VIALE C data, and, therefore, the lack of conclusive evidence currently available to support the cure assumption being applied at 2 years. Thus, it is suggested that the optimal duration of treatment is yet to be established, but that "*it remains reasonable to conclude that*

a proportion of patients are cured and discussion is perhaps warranted whether this is at 2 or 3 years". The NCRI-ACP-RCP-RCR response further indicates that "*regular molecular monitoring of relapse in blood and marrow is completed after 2 years post consolidation as relapse risk is thin so low*".

The RCPath response on this issue provides a further line of evidence to support the cure assumption; that around 20% of individuals in the VenAZA studies with longest follow-up "*went on to receive a stem cell transplant with good outcomes (75% still alive at time of publication) but with notably short follow-up*[5]".The response notes that this may result from patients who are initially considered unfit, recovering sufficiently following treatment that they are subsequently deemed fit enough for transplant. The response further notes that "*This is in keeping with real world experiences of patients who received azacitidine as initial first line therapy (with 20-30% blasts) who may subsequently be suitable for either more intense therapy or transplantation*". This may, therefore, suggest that stem cell transplant may provide a relevant subsequent therapy in both arms of the model.

Based on the company and expert responses, the ERG accepts that a cure assumption is plausible for venetoclax and but believe it remains an uncertain assumption, particularly with respect to timing. Further, the response from the RCPath seems to indicate that stem cell transplant may be a relevant consideration in the population, potentially in both arms, and his has not been factored into the model. The ERG notes, however, that of patients enrolled in the VIALE-A trial, only 2/286 in the venetoclax arm and 1/145 in the placebo arm were reported to subsequently received a stem cell transplant after discontinuing study drug.[6] Zero patients in VIALE C were reported to receive a subsequent stem cell transplant.[7] Based on these frequencies, exclusion of transplantation costs is unlikely to have a material impact on the cost-effectiveness estimates.

Another piece of evidence offered in the RCPath response, is data comparing 13 patients who electively discontinued venetoclax after ≥12 months of treatment while in first remission (STOP cohort), with 12 patients who continued until disease progression (Continuation cohort).[8] The study found that following cessation, median treatment-free remission (TFR) was 45.8 months for the STOP cohort. It further

reported that 5 of the 12 patients relapsed following cessation of therapy in the stop cohort (only 1 of 8 in subgroup with NPM1 or IDH1 mutations), versus 6 of 13 in the continuation cohort. This limited data, therefore, appears to support the company's assumption that treatment with venetoclax can be stopped for those in remission at two years without negatively influencing outcomes, but it does not conclusively support a cure assumption from 2 years, whether or not treatment is stopped. The data indicates that of the 5 relapses observed in the stop cohort, 2 occurred beyond 36 months TFR. Of the 8 observed relapses in the continuation cohort, 5 occurred after >24 months of therapy. This, therefore, seems more in keeping with the ERG's clinical expert advice, that given the lack of observed data to conclusively support a cure assumption, scenarios that include an ongoing rate of relapse beyond 24 months should also be considered. This can be achieved in with company's model by selecting an appropriate time to relapse curve in combination with the company's revised approach to modelling treatment discontinuation form two years. Such an approach will ultimately assume that a proportion never do relapse. The EPayne and RCPath expert responses note further complications with respect to the pathway in that although some patients may relapse after 24 months following a prolonged remission, it is plausible that some of these patients "would be reinduced with ven/aza (if off therapy post 2 years) or ven/ldac or an intensive regime or gilteritinib if flt3+". However, such complexity of allowing curative treatment following progression is not possible in the company's model.

The company further acknowledge the uncertainty around the assumption that patients who remain in remission at two years (assumed cured) will have an overall survival outlook in line with that of the age matched general population and set this to be 20% above it in a scenario analysis based on expert clinical opinion. *The ERG agrees that this adjustment seems reasonable when a cure assumption is applied.*

Issue 2. Uncertainty regarding the justification for using general population mortality to adjust the curves used to estimate transition probabilities to progressive disease health state

The company acknowledge the ERGs concern and have provided a scenario analysis that removes this adjustment (included in their revised base case). On its own, it results in only a small increase in the ICERs.

The ERG is satisfied that the company has addressed the point.

Issue 3. Inconsistent assumptions related to modelling of time on treatment and subsequent treatment

The company has amended the model to allow patients to continue receiving venetoclax treatment upon entry to the cure state for up to one year. The amendment is applied using an exponential approach where it is assumed that 5% of all venetoclax patients would remain on treatment at the 3-year time point in the model. Previously, the company had assumed a higher ongoing treatment proportion (health state independent extrapolation), but with inconsistent assumptions which implied no one in the cure state would still be on treatment, whilst people with progressive disease would. Upon further consultation with 5 consultants, it was determined that:

- Patients would be extremely unlikely to remain on treatment beyond three years
- Patients who achieve CR+CRi can remain off treatment whilst maintaining the clinical benefits of achieving a deep remission
- The time in which patients continue first line treatment after achieving remission would vary depending on several factors such as patient and clinical preferences.
- Patients would remain on treatment for between 12-24 months after achievement of CR+CRI

The ERG finds the company correction and discussion agreeable and intuitive. The inclusion of the additional treatment state for cured patients alleviates previous concerns of the ERG where at the two-year time point, very few patients would receive subsequent treatment and the implication that patients who progress would continue to receive venetoclax. Furthermore, the ERG clinical expert corroborates the opinion of the company's clinical experts. Therefore, the ERG accepts this approach for time-on-treatment in the model.

Issue 4. Impact of adverse events on quality of life

The ERG had some concern that the company's approach of adjusting for adverse events when deriving treatment arm independent health state utilities, and applying AE disutilities separately from a different source, may potentially underplay the impact of the different treatment related adverse events on quality of life. Therefore, the ERG suggested that the company could have explored estimating treatment arm specific health state utilities, inclusive of any impacts of adverse events. The company have provided an analysis to address this, which shows no significant differences between the health state utility values by treatment arm, and values that directionally favour venetoclax combinations.

The ERG acknowledges the additional analysis which seems to support treatment independent health state utility values. However, it is not clear from this if these values also controlled for adverse events. The ERG intention was to estimate utility values by treatment arm without adjusting for adverse events, so that treatment arm specific utilities would reflect any differential impacts of adverse events between treatment arms. The ERG is unclear if this is the case with the values presented given the company description of the approach. Nevertheless, the impact of AEs is unlikely to be a model driver, and so the ERG accepts the company base case approach.

Issue 5. Potential for wastage of venetoclax

The company agrees that there is potential drug wastage which has not been accounted for in the initial company submission. Their response states that they expect the wastage to be minimal as patient tablet supplies are managed by splitting packs where necessary. Following precedence from TA642 and TA474, the company has assumed a 7-day tablet wastage of venetoclax for all patients who discontinue treatment or die within a treatment cycle in their revised base case. This is corroborated further by the NCRI-ACP-RCP-RCR response which indicates that wastage should be consistent with TA642 where "wastage would at most be 7 days per patient.". The RCPath and EPayne responses also support the 7-day tablet wastage assumption.

The ERG finds the company's revised approach to drug wastage reasonable and considers this issue resolved. The assumption of 7-days drug wastage results in only a small increase in the ICER.

Issue 6. The distribution of subsequent treatments by treatment arm

The ERG's clinical advice was that a similar and higher proportion of patients would receive gilteritinib as a subsequent treatment in both treatment arms. In the original company base case, all patients who received AZA/LDAC are ineligible to receive gilteritinib therapy and 3% of venetoclax patients could go on to receive gilteritinib. Given the discrepancy between the two approaches, the ERG advised that the company should seek additional clinical consultation of the expected distribution of subsequent treatments.

The company has sought further clinical advice which suggests that some AZA/LDAC patients would receive gilteritinib as a subsequent therapy. However, they suggest this would be lower than the proportion of patients who received venetoclax combinations as the first line therapy; In general, venetoclax patients achieve higher rates of CR+CRi so they are a fitter group of patients who would be more likely to be eligible to receive gilteritinib. Gilteritinib patients must be FTL3+ and able to tolerate the treatment. Clinical advice to the company suggested an alternative distribution of 5% and 3% for venetoclax combinations and AZA/LDAC patients, respectively. The company has applied this in their preferred base case at technical engagement. The company also explored a distribution of 15% and 10% of venetoclax combination and AZA/LDAC patients receive gilteritinib, respectively. The adjustment of subsequent treatments leads to an increase in the ICER due to the high acquisition cost of gilteritinib. However, it should be acknowledged that a PAS is available for gilteritinib.

The ERG finds the company's approach to address this uncertainty appropriate. Further consultation with the ERG clinical expert provides further corroboration for the distribution of 5% for venetoclax combinations and 3% for AZA/LDAC. The ERG does acknowledge that gilteritinib can act as a bridge to stem cell transplant which is costly. However, as very few patients received stem cell transplants within the VIALE

trials ([redacted] and [redacted] in both arms of VIALE A and VIALE C respectively)[6, 7] the ERG does not consider this would have a material impact on the analysis.

Additional issue – dose of venetoclax

In the company submission, the company based the costs of venetoclax on the licensed doses with adjustments for dose intensity based on dosing observed in the VIALE trials. They further noted that they reduced the dose intensity to 50% in combination with AZA on the advice of UK clinical experts they consulted. Expert responses during technical engagement indicate that due to interactions with concomitantly prescribed Azoles, the dose of venetoclax used in UK clinical practice is generally reduced to 100mg, and the number of doses per cycle is also often reduced from 28 days to an average 14 days. The responses refer to pharmacokinetic studies that confirm this dose reduction is required to maintain the steady state of venetoclax at that expected without azole. The response from NCRI-ACP-RCP-RCR further notes currently unpublished data on patients treated in NHS England that suggests these dramatic dose and duration reductions [redacted]

The ERG had not appreciated the inconsistency between the company's assumptions and UK clinical practice at the time the ERG report was submitted, and so did not make any corrections to this. However, the ERGs clinical expert concurs with the expert responses. Therefore, the ERG has now run scenarios that include these dose adjustments.

ERG scenario analysis results and discussion

The ERG provides the results of several scenarios upon an ERG revised company base case post technical engagement for each population in tables 1-3. The revision to the company's base case incorporates alternative adverse event costs of long stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis where day case admissions have been assumed in the company base case. The company provided the alternate adverse event costs at the clarification stage, the ERG believes that these costs more accurately reflect the resource use associated with these events. Furthermore, the ERG noticed a minor typographical error of the cost of subsequent treatment where 3% of gilteritinib in table 12 of the

company technical engagement response. This has been corrected for all scenarios presented by the ERG. Each scenario results in an increase in the ICER, particularly when the cure assumption is removed.

Following the discussion regarding the applicability of the cure assumption to this population (issue 1), the ERG believes a scenario where the cure assumption is removed is still relevant to consider on grounds of the data showing relapse beyond 24 and 36 months.[8] Significant uncertainty remains, however, where expert responses indicate that whilst it plausible that some patients do relapse after 24 months, they would be reinduced with venetoclax, AZA/LDAC or gilteritinib (EPayne, RCPath). The decision on whether the cure assumption should hold hinges on whether patients would continue to be at risk of relapse after 2 years of remission. Given that the treatment approach described in issue 3 is applied, the increase in incremental cost is due to the higher state and subsequent treatment cost of progressed disease. The smaller incremental QALY is due to the smaller QALY value attributed to the progressive disease state and its higher risk of mortality. Patients in the remission state of the model do not have a lower QALY value than that assumed when the cure assumption is applied.

Scenarios with alternate time-to-relapse curves and removal of the cure assumption are also explored. These curves were deemed plausible by clinical consultation to the company in the original submission and the ERG clinical expert. All these scenarios result in higher ICERs, as these curves indicate a higher rate of relapse in the longer term (over two years). The ERG also notes that company curve selections of other state transitions have been retained.

All scenarios are presented at 3 different dosage regimes of venetoclax. As described in the “Additional issue – dose of venetoclax” section, expert responses during technical engagement and the ERG clinical expert highlighted that 100mg per day would be prescribed in clinical practice in the UK due to interactions with concomitantly prescribed Azoles. Clinical consultation in the original company submission and the expert responses during technical engagement determined that for VenAZA at 50% dose intensity is appropriate. A scenario where 100mg per day

at 50% and [redacted] dose intensity for VenAZA and VenLDAC respectively is also explored.

Reflecting on the company's response, the ERG finds it difficult to determine which analysis represents its preferred modelling assumptions. Predominantly, whether there is sufficient evidence for a cure assumption in this population. VIALE-A and VIALE-C trial data lacks the maturity to offer conclusive evidence that would support a cure assumption being applied at 2 years. There is some evidence from a study of 25 patients that does suggest that treatment can be stopped for those in remission at 2 years without negatively influencing outcomes yet the same study reports patients who relapse after 2 years of therapy.[8] Furthermore, clinical expert and organization responses at technical engagement do support the plausibility of a cure with caveats that further evidence is required. The committee should refer to the accompanying confidential appendix for all ICERs inclusive of confidential discounts on subsequent treatments.

Table 1 ERG scenarios upon company base case post technical engagement – VenAZA versus AZA (20-30% blasts)

Scenario[A]		Incremental cost	Incremental QALYs	ICER
Licensed dose of Venetoclax[B] (50% DI)				
Company's base case post technical engagement		[redacted]	[redacted]	£24,596
ERG revised company base case post technical engagement[C]		[redacted]	[redacted]	£25,074
	Removal of cure assumption	[redacted]	[redacted]	£67,404
	Removal of cure assumption + log-logistic extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£68,011
	Removal of cure assumption + generalised gamma extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£78,626
100mg Venetoclax per day (100% DI)				
Company's base case post technical engagement		[redacted]	[redacted]	£16,747
ERG revised company base case post technical engagement[C]		[redacted]	[redacted]	£17,225
	Removal of cure assumption	[redacted]	[redacted]	£54,911
	Removal of cure assumption + log-logistic extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£55,424
	Removal of cure assumption + generalised gamma extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£64,586
100mg Venetoclax per day (50% DI)				
Company's base case post technical engagement		[redacted]	[redacted]	£13,017
ERG revised company base case post technical engagement[C]		[redacted]	[redacted]	£13,496
	Removal of cure	[redacted]	[redacted]	£48,976
	Removal of cure assumption + log-logistic extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£49,444
	Removal of cure assumption + generalised gamma extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£57,923

[A]*Subsequent treatment cost of AZA/LDAC treatment arms corrected to £563.06 from £536.06 in all scenarios.*[B]*400mg per day [QD].* [C]Alternate adverse event costs applied to company base case and subsequent ERG scenarios account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries. *Dose intensity (DI).*

Table 2 ERG scenarios upon company base case post technical engagement – VenAZA versus LDAC (>30% blasts)

Scenario[A]		Incremental cost	Incremental QALYs	ICER
Licensed dose of Venetoclax[B] (50% DI)				
Company's base case post technical engagement		[redacted]	[redacted]	£41,361
ERG revised company base case post technical engagement[C]		[redacted]	[redacted]	£41,557
	Removal of cure assumption	[redacted]	[redacted]	£63,919
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(>30%)	[redacted]	[redacted]	£88,588
100mg Venetoclax per day (100% DI)				
Company's base case post technical engagement		[redacted]	[redacted]	£34,975
ERG revised company base case post technical engagement[C]		[redacted]	[redacted]	£35,171
	Removal of cure assumption	[redacted]	[redacted]	£55,069
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(>30%)	[redacted]	[redacted]	£77,032
100mg Venetoclax per day (50% DI)				
Company's base case post technical engagement		[redacted]	[redacted]	£31,946
ERG revised company base case post technical engagement[C]		[redacted]	[redacted]	£32,142
	Removal of cure assumption	[redacted]	[redacted]	£50,871
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(>30%)	[redacted]	[redacted]	£71,556

[A]*Subsequent treatment cost of AZA/LDAC treatment arms corrected to £563.06 from £536.06 in all scenarios.*[B]*400mg per day [QD].* [C]Alternate adverse event costs applied to company base case and subsequent ERG scenarios account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries. *Dose intensity (DI).*

Table 3 ERG scenarios upon company base case post technical engagement – VenLDAC versus LDAC (>30% blasts)

Scenario[A]		Incremental cost	Incremental QALYs	ICER
Licensed dose of Venetoclax[B] (DI)				
Company's base case post technical engagement				£36,781
ERG revised company base case post technical engagement[C]				£36,652
	Removal of cure assumption			£77,743
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' – VenLDAC (>30%)			£105,325
	Removal of cure assumption + exponential extrapolation of time-to-relapse for patients in 'Remission' – VenLDAC (>30%)			£124,256
100mg Venetoclax per day (100% DI)				
Company's base case post technical engagement				£10,958
ERG revised company base case post technical engagement[C]				£10,829
	Removal of cure assumption			£23,341
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' – VenLDAC (>30%)			£36,256
	Removal of cure assumption + exponential extrapolation of time-to-relapse for patients in 'Remission' – VenLDAC (>30%)			£45,237
100mg Venetoclax per day (DI)				
Company's base case post technical engagement				£8,726
ERG revised company base case post technical engagement[C]				£8,597
	Removal of cure assumption			£18,638
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' – VenLDAC (>30%)			£30,284
	Removal of cure assumption + exponential extrapolation of time-to-relapse for patients in 'Remission' – VenLDAC (>30%)			£38,404

[A]*Subsequent treatment cost of AZA/LDAC treatment arms corrected to £563.06 from £536.06 in all scenarios.*[B]*600mg per day [QD].* [C]Alternate adverse event costs applied to company base case and subsequent ERG scenarios account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries. *Dose intensity (DI).*

References

1. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424-447.
2. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. New England Journal of Medicine 2020;383:617-629.
3. Ivey A, Hills RK, Simpson MA, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med 2016;374:422-33.
4. Pratz K, Jonas BA, Pullarkat V, et al. Measurable residual disease response in acute myeloid leukemia treated with venetoclax and azacitidine. Journal of Clinical Oncology 2021;39:7018-7018.
5. Pollyea, DA, Pratz, K, Letai, A, et al. Venetoclax with azacitidine or decitabine in patients with newly diagnosed acute myeloid leukemia: Long term follow-up from a phase 1b study. *Am J Hematol*. 2021; 96: 208– 217. https://doi.org/10.1002/ajh.26039
6. AbbVie. Data on File. VIALE-A Clinical Study Report.
7. AbbVie. Data on File. VIALE-C Clinical Study Report.
8. Chyn Chua C., Hammond, D., Kent, A., Soo Tiong, I., Ming Ong, D., Konopleva, M., Pollyea, D.A., DiNardo, C.D., Wei, A.H. (2021) 'Treatment free remission (TRF) after seasing venetoclax-based therapy in patients with acute myeloid leukemia, [E-Poster Presentation]. European Hematology Association 2021 Virtual Congress, 9-17 June 2021.
   Available at: https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/325183/chong.chyn.chua.treatment.free.remission.28tfr29.after.ceasing.venetoclax-based.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dvenetoclax (Accessed: 2 August 2021) (Accessible until: 15 August 2021)

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia unsuitable for intensive chemotherapy [ID1564]

Addendum to the ERG critique of the company's response to technical engagement

Produced by Aberdeen HTA Group

Authors Charlotte Kennedy[1]
Graham Scotland[1, 2]

1 Health Economics Research Unit, University of Aberdeen, UK
2 Health Services Research Unit, University of Aberdeen, UK

Correspondence to Graham Scotland
Health Economics Research Unit
University of Aberdeen
g.scotland@abdn.ac.uk

Date completed **06 September 2021**

Contains ■ information

This addendum provides the model-based mean and incremental life year estimates for the venetoclax combinations and the relevant comparators for the company post-technical engagement base case, and the ERG scenarios detailed in the ERG critique of the company response to technical engagement (Table 1). Probabilistic results are also provided for the company's post-technical engagement revised base case. These are provided in Table 2 and Figures 1-6.

Table 1 Discounted and undiscounted life years of scenarios presented in tables 1, 2 & 3 of the ERG response to technical engagement

Scenario	Discounted			Undiscounted		
	Total life years VenAZA/ VenLDAC	Total life years AZA/LDAC	Incremental	Total life years VenAZA/ VenLDAC	Total life years AZA/LDAC	Incremental
VenAZA vs. AZA (20-30% blasts)						
Company's base case post technical engagement	3.529	1.696	1.833	4.233	1.833	2.400
Removal of cure assumption	2.899	1.696	1.203	3.327	1.833	1.494
Removal of cure assumption + log-logistic extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	2.888	1.696	1.192	3.312	1.833	1.479
Removal of cure assumption + generalised gamma extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	2.780	1.696	1.084	3.164	1.833	1.331
VenAZA vs. LDAC (>30% blasts)						
Company's base case post technical engagement	2.940	0.798	2.142	3.544	0.839	2.705
Removal of cure assumption	2.319	0.798	1.512	2.658	0.839	1.819
Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(>30%)	1.969	0.798	1.171	2.172	0.839	1.333
VenLDAC vs. LDAC (>30% blasts)						
Company's base case post technical engagement	1.977	0.795	1.182	2.349	0.835	1.514
Removal of cure assumption	1.328	0.795	0.534	1.442	0.835	0.607
Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' – VenLDAC (>30%)	1.223	0.795	0.425	1.305	0.835	0.470
Removal of cure assumption + exponential extrapolation of time-to-relapse for patients in 'Remission' – VenLDAC (>30%)	1.173	0.795	0.378	1.240	0.835	0.405

Table 2 Probabilistic results of company base case post technical engagement with ERG correction to subsequent treatment cost[A]

Scenario	Life years			QALYs			Cost			ICER
	VenAZA/ VenLDAC	AZA/LDAC	Incremental	VenAZA/ VenLDAC	AZA/LDAC	Incremental	VenAZA/ VenLDAC	AZA/LDAC	Incremental	
VenAZA vs. AZA (20-30% blasts)	3.544	1.824	1.720	[redacted]	1.217	[redacted]	[redacted]	£102,581	[redacted]	£24,378
VenAZA vs. LDAC (>30% blasts)	2.916	0.853	2.062	[redacted]	0.559	[redacted]	[redacted]	£38,792	[redacted]	£40,872
VenLDAC vs. LDAC (>30% blasts)	1.902	0.849	1.052	[redacted]	0.557	[redacted]	[redacted]	£38,651	[redacted]	£39,949

[A]*Subsequent treatment cost of AZA/LDAC treatment arms corrected to £563.06 from £536.06 in all scenarios*

Figure 1 **Scatter plot of probabilistic results on the cost-effectiveness plane (VenAZA vs. AZA (20-30% blasts))**

Figure 2 **Cost-effectiveness acceptability curve (VenAZA vs. AZA (20-30% blasts))**

Figure 3 **Scatter plot of probabilistic results on the cost-effectiveness plane (VenAZA vs. LDAC (>30% blasts))**

Figure 4 **Cost-effectiveness acceptability curve (VenAZA vs. LDAC (>30% blasts))**

Figure 5 **Scatter plot of probabilistic results on the cost-effectiveness plane (VenLDAC vs. LDAC (>30% blasts))**

Figure 6 **Cost-effectiveness acceptability curve (VenLDAC vs. LDAC (>30% blasts))**

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia unsuitable for intensive chemotherapy [ID1564]

ERG scenarios around alternative cure timepoints

Produced by Aberdeen HTA Group

Authors Charlotte Kennedy[1]
Graham Scotland[1, 2]

1 Health Economics Research Unit, University of Aberdeen, UK
2 Health Services Research Unit, University of Aberdeen, UK

Correspondence to Graham Scotland
Health Economics Research Unit
University of Aberdeen
g.scotland@abdn.ac.uk

Date completed **10 September, 2021**

Contains AIC/CIC

Addendum to the ERG response to technical engagement

The following tables present the removal of the cure assumption at different time points in addition to the scenarios presented in the ERG response to technical engagement document. The scenarios explore the uncertainty of adjusting the time from which venetoclax patients who achieve remission are no longer at risk of relapse, achieve utility outcomes equal to that of the general population and are at risk of general population mortality with an SMR of 1.2. Similar to the removal of cure assumption presented in the ERG response to technical engagement document, these scenarios retain the company assumptions regarding treatment discontinuation. Where, from 2 years, patients discontinue treatment at a rate such that 5% of the total population would be receiving venetoclax by 3 years in the model.

The ERG would also like to note that these scenarios are presented upon the company base case with the following additions:

1. Post technical engagement the company model and response incorporated a minor error where the cost of subsequent treatment for AZA/LDAC was reported as £536.06. These scenarios use the correct cost of £563.06. Further information on how this is calculated can be seen in table 12 of the company technical engagement response form.
2. The ERG prefers the use of non-elective long-stay admission costs rather than day case costs for the following adverse events: atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia, and sepsis. The company provided these at the clarification stage.

The scenario which incorporates these additions is titled as “ERG revised company base case post technical engagement” in the proceeding tables.

Table 1 VenAZA versus AZA (20-30% blasts) - licensed dose[A] of Venetoclax (50% DI)

Scenario		Incremental cost	Incremental QALYs	ICER
ERG revised company base case post technical engagement		[redacted]	[redacted]	£25,074
	Cure assumed at 3 years	[redacted]	[redacted]	£40,433
	Cure assumed at 4 years			£51,327
	Cure assumed at 5 years			£58,008
	Removal of cure assumption			£67,404
	Removal of cure assumption + log-logistic extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£68,011
	Removal of cure assumption + generalised gamma extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£78,626

[A]400mg per day [QD]. Dose intensity (DI).

Table 2 VenAZA versus AZA (20-30% blasts) - 100mg QD dose of Venetoclax (100% DI)

Scenario		Incremental cost	Incremental QALYs	ICER
ERG revised company base case post technical engagement		[redacted]	[redacted]	£17,225
	Cure assumed at 3 years	[redacted]	[redacted]	£21,374
	Cure assumed at 4 years	[redacted]	[redacted]	£40,246
	Cure assumed at 5 years	[redacted]	[redacted]	£46,239
	Removal of cure	[redacted]	[redacted]	£54,911
	Removal of cure assumption + log-logistic extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£55,424
	Removal of cure assumption + generalised gamma extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£64,586

Dose intensity (DI).

Table 3 VenAZA versus AZA (20-30% blasts) - 100mg QD dose of Venetoclax (50% DI)

Scenario		Incremental cost	Incremental QALYs	ICER
ERG revised company base case post technical engagement		[redacted]	[redacted]	£13,496
	Cure assumed at 3 years	[redacted]	[redacted]	£25,946
	Cure assumed at 4 years	[redacted]	[redacted]	£34,981
	Cure assumed at 5 years	[redacted]	[redacted]	£40,647
	Removal of cure assumption	[redacted]	[redacted]	£48,976
	Removal of cure assumption + log-logistic extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£49,444
	Removal of cure assumption + generalised gamma extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(20-30%)	[redacted]	[redacted]	£57,923

Dose intensity (DI).

Table 4 VenAZA versus LDAC (>30% blasts) - Licensed dose[A] of Venetoclax (50% DI)

Scenario		Incremental cost	Incremental QALYs	ICER
ERG revised company base case post technical engagement		[redacted]	[redacted]	£41,557
	Cure assumed at 3 years	[redacted]	[redacted]	£49,044
	Cure assumed at 4 years			£54,276
	Cure assumed at 5 years			£57,731
	Removal of cure assumption			£63,919
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(>30%)			£88,588

[A]*400mg per day [QD]. Dose intensity (DI).*

Table 5 VenAZA versus LDAC (>30% blasts) - 100mg QD dose of Venetoclax (100% DI)

Scenario		Incremental cost	Incremental QALYs	ICER
ERG revised company base case post technical engagement		[redacted]	[redacted]	£35,171
	Cure assumed at 3 years	[redacted]	[redacted]	£41,744
	Cure assumed at 4 years	[redacted]	[redacted]	£46,357
	Cure assumed at 5 years	[redacted]	[redacted]	£49,424
	Removal of cure assumption	[redacted]	[redacted]	£55,069
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(>30%)	[redacted]	[redacted]	£77,032

Dose intensity (DI).

Table 6 VenAZA versus LDAC (>30% blasts) - 100mg QD dose of Venetoclax (50% DI)

Scenario		Incremental cost	Incremental QALYs	ICER
ERG revised company base case post technical engagement		[redacted]	[redacted]	£32,142
	Cure assumed at 3 years	[redacted]	[redacted]	£38,281
	Cure assumed at 4 years	[redacted]	[redacted]	£42,601
	Cure assumed at 5 years	[redacted]	[redacted]	£45,484
	Removal of cure	[redacted]	[redacted]	£50,871
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenAZA(>30%)	[redacted]	[redacted]	£71,556

Dose intensity (DI).

Table 7 VenLDAC versus LDAC (>30% blasts) - Licensed dose[A] of Venetoclax ([redacted]% DI)

Scenario		Incremental cost	Incremental QALYs	ICER
ERG revised company base case post technical engagement		[redacted]	[redacted]	£36,652
	Cure assumed at 3 years	[redacted]	[redacted]	£47,835
	Cure assumed at 4 years			£56,888
	Cure assumed at 5 years			£63,675
	Removal of cure assumption			£77,743
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenLDAC(>30%)			£105,325
	Removal of cure assumption + exponential extrapolation of time-to-relapse for patients in 'Remission' - VenLDAC(>30%)	[redacted]	[redacted]	£124,256

[A]600mg per day [QD]. Dose intensity (DI).

Table 8 VenLDAC versus LDAC (>30% blasts) – 100mg QD dose of Venetoclax (100% DI)

Scenario		Incremental cost	Incremental QALYs	ICER
ERG revised company base case post technical engagement		[redacted]	[redacted]	£10,829
	Cure assumed at 3 years	[redacted]	[redacted]	£14,178
	Cure assumed at 4 years			£16,904
	Cure assumed at 5 years			£18,961
	Removal of cure assumption			£23,341
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenLDAC(>30%)	[redacted]	[redacted]	£36,256
	Removal of cure assumption + exponential extrapolation of time-to-relapse for patients in 'Remission' - VenLDAC(>30%)	[redacted]	[redacted]	£45,237

Dose intensity (DI).

Table 9 VenLDAC versus LDAC (>30% blasts) – 100mg QD dose of Venetoclax ([redacted]% DI)

Scenario		Incremental cost	Incremental QALYs	ICER
ERG revised company base case post technical engagement		[redacted]	[redacted]	£8,597
	Cure assumed at 3 years	[redacted]	[redacted]	£11,268
	Cure assumed at 4 years	[redacted]	[redacted]	£13,447
	Cure assumed at 5 years	[redacted]	[redacted]	£15,095
	Removal of cure assumption	[redacted]	[redacted]	£18,638
	Removal of cure assumption + log-normal extrapolation of time-to-relapse for patients in 'Remission' - VenLDAC(>30%)	[redacted]	[redacted]	£30,284
	Removal of cure assumption + exponential extrapolation of time-to-relapse for patients in 'Remission' - VenLDAC(>30%)	[redacted]	[redacted]	£38,404

Dose intensity (DI).