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

Produced by Aberdeen HTA Group

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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.

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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)

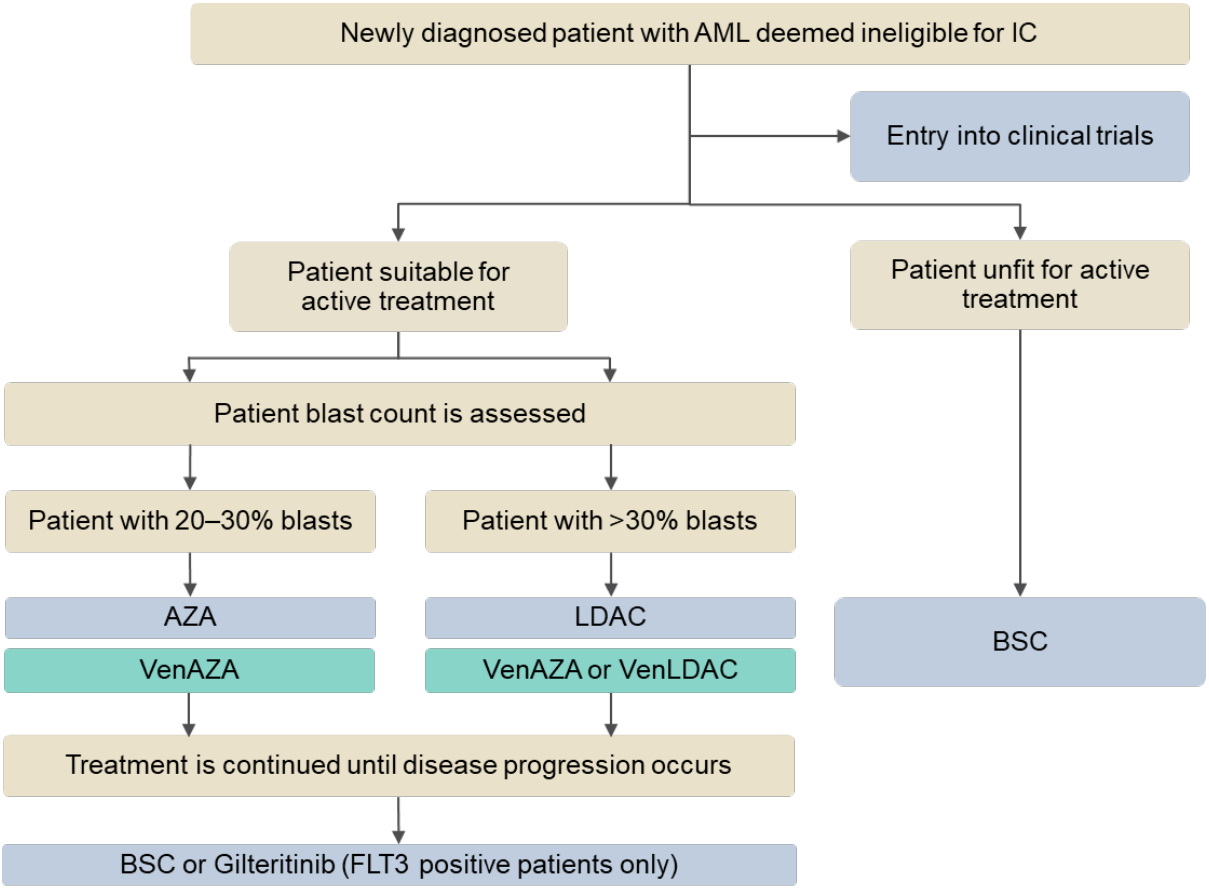
- In combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy
- Monotherapy is indicated for the treatment of CLL:
    - in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed 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: ○ Blast cell count 20-30%: AZA ○ Blast cell count >30%: LDAC • VenLDAC comparators: ○ 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

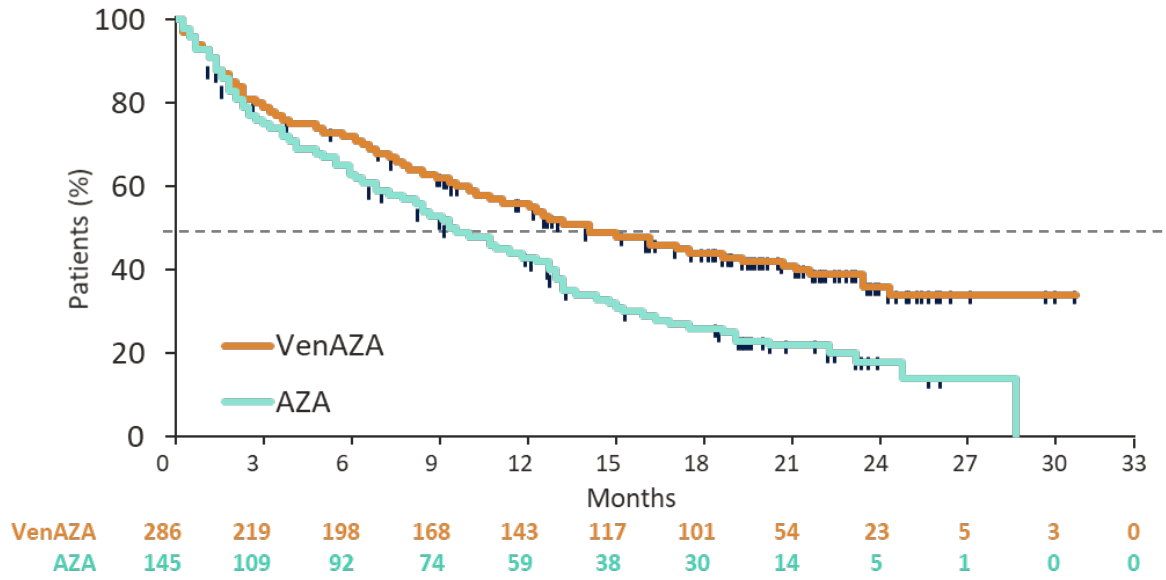
2018. Results from a second interim analysis (IA2) are presented for all outcomes (including CR + CRi) in VIALE-A for 431 randomised patients (VenAZA: n = 286; AZA: n = 145) with a median follow-up of 20.5 months, representing a cut-off date of 4th January 2020.

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.

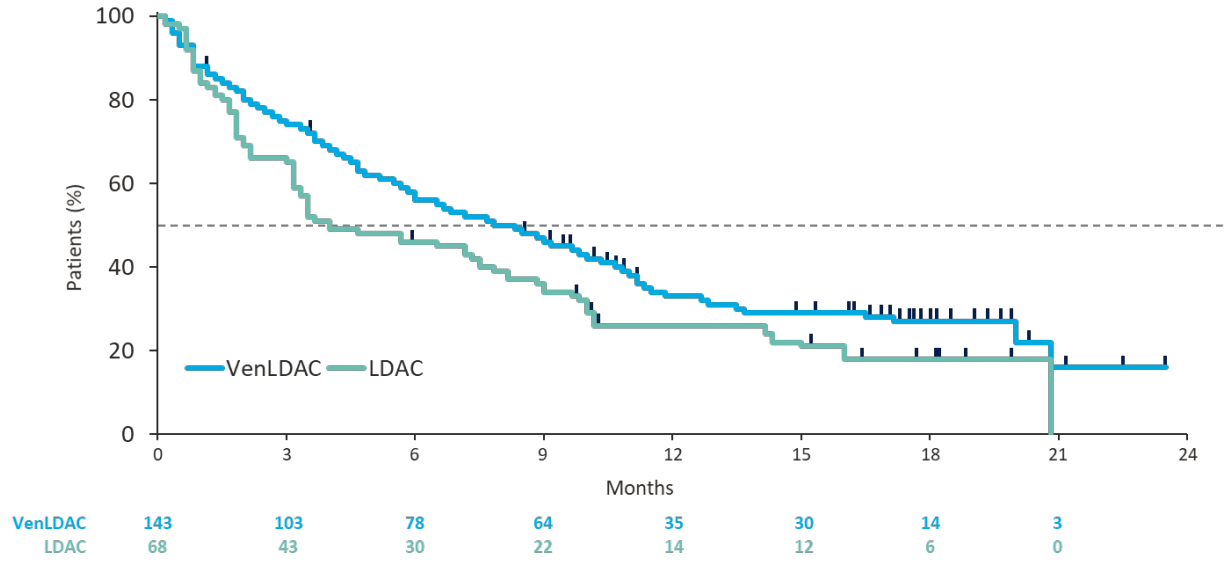
- **Transfusion independence:** Red blood cell (RBC) and platelet transfusion independence occurred in [redacted] of the participants in the VenAZA group and [redacted] of those in the AZA group. Rates of conversion from baseline RBC and platelet transfusion dependence to independence during the course 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 (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)
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.

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