Single Technology Appraisal

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Brancaster

2. **Company summary of information for patients (SIP)** from Brancaster

3. **Clarification questions and company responses**
   a. Clarification response
   b. Response to additional questions

4. **Expert personal perspectives** from:
   a. Dr Andrew King – clinical expert, nominated by Brancaster
   b. Professor Steven Knapper – clinical expert, nominated by Brancaster
   c. Adam Claxton – patient expert, nominated by Blood Cancer UK

5. **External Assessment Report** prepared by the School of Health and Related Research, University of Sheffield

6. **External Assessment Report – factual accuracy check**

7. **NICE Managed Access Feasibility Summary**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Company evidence submission

September 2025

File name	Version	Contains confidential information	Date
Brancaster evidence submission for HDC/IL-2 STA	**Final**	**No**	**04/09/2025**

Table of Contents

Tables and figures

Tables

Figures

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

1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation which includes adult acute myeloid leukaemia (AML) patients, who have a normal karyotype, have completed induction and consolidation treatment, are in first remission (CR1), are not considered suitable for allogeneic hematopoietic stem cell transplantation (allo-HSCT) and are 60 years old or younger.

The therapeutic indication approved in the marketing authorisation is "*Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection maintenance therapy is indicated* for *adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.*".

The proposed position in the treatment pathway therefore is narrower than the marketing authorisation because:

- This patient population of adult acute myeloid leukaemia (AML) patients, who have a normal karyotype, have completed induction and consolidation treatment, are in first remission (CR1), are not considered suitable for allogeneic hematopoietic stem cell transplantation (allo-HSCT) and are 60 years old or younger is the group in which the strongest evidence of benefit of histamine dihydrochloride (HDC) and interleukin-2 (IL-2) has clearly been shown. No clinical benefit has been found in patients over 60 years, which has led to the qualifying statement concerning efficacy and age (older than age 60) in the MHRA approved therapeutic indication.

Table 1 Decision problem summary

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with acute myeloid leukaemia who are in first remission.	Adult acute myeloid leukaemia (AML) patients who have undergone intensive therapy with induction and consolidation treatment, who are not considered suitable for allogeneic stem cell transplant, who are in first remission (CR1) and 60 years old or younger.	The eligibility criteria for patients in the pivotal Phase III RCT published by Brune, 2006 included patients who had undergone treatment with both induction and consolidation treatment and who were not considered suitable for allogeneic stem cell transplant. For this reason, we believe that the same patients should be considered for this technology appraisal. It is noted that NICE guidance will only be issued in accordance with the marketing authorisation. The approved indication for histamine dihydrochloride is '*for adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Histamine dihydrochloride (HDC) 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.*' The qualifying statement about age is based on the univariate analysis of Cox proportional hazards modeling of prognostic factors for leukaemia free survival (LFS) in the Brune, 2006 study population which revealed that no

			clinical benefit was seen in patients aged older than 60 years. In addition, post-hoc sub-group analyses by Nilsson, 2020 showed no LFS or OS benefit with HDC/IL-2 for patients with normal karyotype in CR1 who were 60 years or older. Since the indication clearly states that the efficacy of HDC has not been fully demonstrated in patients older than age 60, then this population should be excluded from the evaluation, in accordance with NICE guidelines.
Intervention	Histamine dihydrochloride with interleukin-2 as maintenance therapy.	Histamine dihydrochloride with interleukin-2 as maintenance therapy.	Not applicable – no difference to final scope.
Comparator(s)	Established clinical management without histamine dihydrochloride with interleukin-2 including but not limited to: • oral azacitidine for people who cannot have or do not want a haematopoietic stem cell transplant • midostaurin for people with an FLT3-mutation • sorafenib, after a stem cell transplant, for people with an FLT3-ITD mutation • quizartinib for people with an FLT3-ITD mutation	Best supportive care	The comparator used in the pivotal Phase III RCT published by Brune, 2006 was best supportive care and hence we believe that this should be considered as the main comparator within this appraisal. The full licensed indication for HDC/IL-2 in section 4.1 (“Therapeutic indications”) of the approved SmPC includes the qualifying statement: ‘*The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.*’ The approved indication clearly states that the evidence for the therapy is best supported in patients who are 60 years

	• cytarabine alone or in combination with other antineoplastic agents • best supportive care		old or less and hence should exclude those who are older than 60 years. The qualifying statement about age is based on the univariate analysis of Cox proportional hazards modeling of prognostic factors for LFS in the Brune, 2006 study population which revealed that no clinical benefit was seen in patients aged older than 60 years. In addition, post-hoc sub-group analyses by Nilsson, 2020 showed no benefit with HDC/IL-2 for patients with normal karyotype in CR1 who are 60 years or older. The clinical evidence supporting the patients who are 60 years old or less should therefore be evaluated within the context of this appraisal for HDC/IL-2. Interpretation of results from clinical trials of AML maintenance therapy should account for significant variability in the study populations with respect to age and disease features. Cross-trial comparisons should not be made where the study populations are dissimilar (Patel, 2021). **Oral azacitidine** It is acknowledged that oral azacitidine is recommended by NICE (TA827) for the maintenance treatment of AML patients who are in complete remission and cannot have or do not want a

			haematopoietic stem cell transplant. On this basis, it would seem a relevant comparator to HDC/IL-2. However, during interviews between May – August 2024 with 17 UK haematologists specialising in the treatment of AML patients, about the current maintenance treatment landscape and the use of oral azacitidine, it was mentioned by 15 out of 17 haematologists that the evidence from the pivotal QUAZAR randomised controlled study included only older AML patients who were ≥55 years and these UK haematologists were therefore curious why this was not reflected in the NICE recommendation. They also stated that there was limited use of oral azacitidine in the UK. This is supported by NHS Business Services Authority (NHSBSA) Secondary Care Medicines Data (SCMD): in March 2024, 840 azacitidine tablets were prescribed at a cost of £704,040, corresponding to treatment courses for approximately 60 patients; in March 2025, 908 tablets were prescribed at a cost of £761,034, corresponding to treatment courses for approximately 65 patients. A retrospective phase II trial published by Blum, 2017 using maintenance therapy with decitabine, a structurally

			and pharmacodynamically related analogue of azacitidine, in AML patients in CR1 after induction and consolidation treatment and who were <60 years old provided no benefit overall compared with historical controls. This data may have contributed to the rationale for assessing the efficacy of oral azacitidine in an older population of AML patients. Considering the approved indication for HDC/IL-2 immunotherapy is limited to AML patients in first remission who are 60 years or younger, we assessed the feasibility of collecting data on a similar group of patients (in other words, those who are 55-60 years of age) receiving oral azacitidine in the UK. From SCMD data and our discussions with the clinical experts we concluded that there is likely to be very little data available on the use of oral azacitidine in a similar group of patients where HDC/IL-2 is specifically indicated. If we used the data from the QUAZAR study for an indirect treatment comparison, then this is at best likely to produce high levels of uncertainty and at worst possibly even be misleading due to the differing ages and prognoses of the eligible patients.

			For these reasons, a formal indirect treatment comparison between oral azacitidine and HDC/IL-2 has not been conducted as it is likely to only produce high levels of uncertainty and possibly be misleading, as opposed to offering a meaningful comparison between the therapies. **<u>Midostaurin</u>** NICE has previously approved midostaurin as a maintenance treatment for AML patients with FLT3 mutations (TA523) and quizartinib for AML patients with FLT3-ITD mutations (TA1013). There are no comparative data published on the efficacy of HDC/IL-2 versus midostaurin as maintenance treatment in people with FLT3-mutation-positive AML or sorafenib/quizartinib for FLT3-ITD mutations. The clinical experts involved with the oral azacitidine appraisal (TA827) explained that most people with FLT3-mutation positive AML would have targeted treatment with midostaurin during induction, consolidation and maintenance treatment and would be unlikely to switch to oral azacitidine. We believe that it would be a similar situation with HDC/IL-2, where few

			patients would switch from midostaurin to HDC/IL-2 during maintenance. We note that midostaurin was considered a relevant comparator for people with FLT3-mutation positive AML in the oral azacitidine appraisal and an indirect treatment comparison was conducted. We note that the EAG also considered that survival analyses for this population are likely to be biased because of limitations associated with the indirect treatment comparison. The committee concluded that the results of the indirect treatment comparison comparing oral azacitidine with midostaurin were highly uncertain and considered this in its decision making. There are no data from the pivotal Phase III RCT published by Brune, 2006 on the genetic subtypes of patients recruited to the study and hence there are very limited data on the efficacy of HDC/IL-2 in AML patients with FLT3 mutations and FLT3-ITD mutations. For this reason, we have not attempted an indirect treatment comparison. As indicated above, without further data on the efficacy of HDC/IL-2 in genetic subtypes, the level of uncertainty in an

			indirect treatment comparison versus midostaurin is likely to be very high. HDC/IL-2 would therefore likely be of most benefit to patients whose AML does not have an FLT3-mutation or FLT3-ITD mutation. **Sorafenib** The conclusion above concerning midostaurin is also therefore true of sorafenib: without further data on the efficacy of HDC/IL-2 in genetic subtypes, the level of uncertainty in an indirect treatment comparison versus sorafenib is likely to be very high. **Quizartinib** The conclusion above concerning midostaurin is also therefore true of quizartinib: without further data on the efficacy of HDC/IL-2 in genetic subtypes, the level of uncertainty in an indirect treatment comparison versus quizartinib likely to be very high. **Cytarabine** In the NICE final appraisal document for oral azacitidine for maintenance treatment of AML after induction treatment, the NICE committee discussed the stakeholder comments that low dose cytarabine and subcutaneous azacitidine are not used routinely after induction and consolidation chemotherapy, but are

			used when intensive chemotherapy is unsuitable, and that very few people had maintenance treatment with low dose cytarabine and subcutaneous azacitidine. The committee therefore concluded that these treatments would not likely be used routinely as maintenance treatment in people who are in complete remission. The same rationale applies for the comparison with HDC/IL-2 where all patients have had prior intensive induction and consolidation chemotherapy and the indication is for maintenance treatment in patients who are in first complete remission (CR1).
Outcomes	• Leukaemia-free survival • Overall survival • Remission rate • Adverse effects of treatment • Health-related quality of life	• Leukaemia-free survival • Overall survival • Remission rate • Adverse effects of treatment • Health-related quality of life	Not applicable – no difference from final scope.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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. The availability and cost of biosimilar products of should be taken into account. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Cost-utility analysis using a three-state partitioned survival model based on leukaemia-free survival and overall survival.	

Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people who are eligible or ineligible for allogeneic stem cell transplant • people with or without an FLT3 mutation • people with or without an FLT3-ITD mutation	Adult AML patients who have undergone intensive therapy with induction and consolidation treatment, are not suitable for allogeneic stem cell transplant, have normal karyotype, are in CR1 and are less than 60 years old.	The pivotal Phase III RCT published by Brune, 2006 excluded patients who had prior allogeneic stem cell transplant (allo-SCT) and hence enrolled only patients who were considered ineligible for the therapy. Consequently, the main evidence supporting maintenance immunotherapy with HDC/IL-2 is in AML patients who are not considered suitable for allo-SCT. The pivotal Phase III RCT published by Brune, 2006 was conducted prior to routine genetic subtype testing and hence there are limited data on the efficacy of HDC/IL-2 within those patients with FLT3 mutations and FLT3-ITD mutations. There are post-hoc analyses data however on the efficacy of HDC/IL-2 in AML patients with normal karyotype in CR1 and less than 60 years old which indicate improved efficacy. For this reason, this population has been presented as the base case in the economic analysis.

Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The full licensed indication for HDC/IL-2 in section 4.1 ("Therapeutic indications") of the approved SmPC includes the qualifying statement: '*The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.*' The approved indication clearly states that the evidence for the therapy is best supported in patients who are 60 years old or less and hence should exclude those who are older than 60 years.	It is noted that NICE guidance will only be issued in accordance with the marketing authorisation. The full licensed indication for HDC/IL-2 in section 4.1 ("Therapeutic indications") of the approved SMPC includes the qualifying statement: '*The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.*' The approved indication clearly states that the evidence for the therapy is best supported in patients who are 60 years old or less and hence should exclude those who are older than 60 years. The qualifying statement about age is based on the univariate analysis of Cox proportional hazards modeling of prognostic factors for leukaemia free survival (LFS) in the Brune, 2006 study population which revealed that no clinical benefit was seen in patients aged older than 60 years. In addition, post-hoc sub-group analyses by Nilsson, 2020 showed no LFS or OS benefit with HDC/IL-2 for patients with normal karyotype in CR1 who are 60 years or older. Since the indication clearly states that the efficacy of HDC has not been fully demonstrated in patients older than age 60, then this population should be

			excluded from the evaluation, in accordance with NICE guidelines.

1.2 Description of the technology being evaluated

Table 2 Technology being evaluated

UK approved name and brand name	Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection (HDC) (with interleukin-2 (IL-2)). The company has decided to only use a generic name and not use a brand name.
Mechanism of action	Histamine dihydrochloride (HDC) when combined with interleukin-2 (IL-2) is an immunotherapy. The mechanism of action of HDC when combined with IL-2 for the treatment of AML is by modulating the immune response to effectively target residual leukaemic cells, particularly by enhancing the cytotoxic activity of natural killer (NK) cells and T cells (Martner, 2015). HDC inhibits release of immunosuppressive reactive oxidative species from myeloid-derived suppressor cells (MDSCs) and protects T and NK cells from inactivation. IL-2 promotes T and NK cell expansion, activation and cytotoxicity. HDC with IL-2 work together to uphold T and NK cell function to eradicate remaining or arising leukaemic cells. HDC/IL-2 act synergistically as the only form of immunotherapy approved for maintenance treatment in AML. Consistent with these effects, HDC with IL-2 has been found to be ineffective in the following groups: older patients (> 60 years) with aging immune systems (immunosenescence); patients likely to have increased residual disease having required more than one induction treatment to achieve remission, and in patients with abnormal tumour cell karyotype. Patients ideally start HDC/IL-2 therapy 6-8 weeks after their last chemotherapy, when their immune system has been reconstituted.
Marketing authorisation/CE mark status	Yes, the Marketing Authorisation for HDC was granted by the MHRA on Friday 1st August 2025. The Marketing Authorisation was approved under the MHRA national procedure.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication approved by the MHRA on 1st August 2025 is as follows, as set out in section 4.1 ("Therapeutic indications") of the SmPC: *Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection maintenance therapy is indicated for adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Histamine dihydrochloride 0.5*

	mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.
Method of administration and dosage	HDC should be administered in combination with IL-2, according to its indication in AML. The dosage of both active ingredients is summarised as follows: • HDC: It is administered through a subcutaneous injection twice daily 1 to 3 minutes after an injection of IL-2. Each 0.5 ml dose of HDC is administered slowly, over a period of 5 to 15 minutes. • IL-2: It is administered by subcutaneous injection twice daily prior to HDC injection. Each dose of IL-2 is 16,400 IU/kg (1 µg/kg). IL-2 is commercially available as a recombinant IL-2; Proleukin® (aldesleukin). HDC/IL-2 are administered in treatment cycles up to a maximum of 10 cycles, administered over a period of time up to 18 months. Each course consists of a 21-day (3-week) treatment period, followed by a non-treatment period that can be of three or six weeks in duration. In the case of cycles 1-3, each cycle consists of 3 weeks of treatment, followed by 3 weeks of no treatment. For cycles 4-10, each cycle consists of 3 weeks of treatment followed by 6 weeks of no treatment. For the full detailed method of administration and dosage, please refer to the approved SmPC (section 4.2 ("Posology and method of administration")) in Appendix A.
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	The NHS list price for a pack of 14 vials of HDC is £1,200 which is equivalent to one week's treatment. A 3-week cycle of treatment costs £3,600. The 18-month course of 10 treatments is £36,000. The NHS list price for an 18M unit vial of IL-2 is £636. A 3-week cycle of treatment costs £1,908 (3 vials). The 18-month course of 10 cycles is £19,080. The total cost of an 18-month course of 10 cycles of HDC/IL-2 is £55,080.
Patient access scheme (if applicable)	Not applicable.

1.3 Health condition and position of the technology in the treatment pathway

Acute myeloid leukaemia (AML) is a heterogeneous haematologic malignancy characterised by the clonal expansion of myeloid blasts, which are the precursor forms of cells that would mature into white blood cells (not lymphocytes), red blood cells or platelets. AML starts in the bone marrow but can also be detected in the blood or other tissues, including the lymph nodes, liver, spleen, central nervous system (the brain and spinal cord), and testes (ACS, 2019; Daver, 2019; Döhner, 2017).

AML is quite uncommon and accounted for less than 1% of all new cancer cases in the UK in 2017-2019. AML is estimated to have a UK annual incidence of around 2,900 new patients (Cancer Research UK, 2025).

AML is more common in older people and is rarer for people younger than 45 years and is more frequent in men than women (Kantarjian, 2016).

AML may arise *de novo* or be related to other treatments or previous diseases:

- *De novo* AML arises from a series of recurrent genetic alterations accumulated with age in haematopoietic stem cells, such as mutations, translocations, gene fusions, and other cytogenetic abnormalities (Ding, 2012; Welch, 2012).
- Secondary AML is usually induced by cytotoxic therapies used in the treatment of solid tumours or other haematologic malignancies, accounting for 5-20% of all AML cases. Approximately 1 in 10 patients diagnosed with myelodysplastic syndrome (MDS) progresses to AML (De Kouchkovsky, 2016; NCCN, 2023).

In the 1970s, the French-American-British (FAB) classification of AML was developed, and AMLs were classified into subtypes, from M0 to M7, according to the cell type from which the leukaemia develops and how mature the cells are. However, over time, numerous cytogenetic and molecular abnormalities have been identified that have implications for prognosis and treatment, so the World Health Organization (WHO) has developed a new AML classification of a more functional nature, including some of these prognostic factors (ACS, 2019; Döhner, 2022).

Prognostic factors for AML include age, presence of comorbidities, general health status (functional status), and genetic alterations (Saultz, 2016). In addition, response to treatment is also an important prognostic factor (Aurelius, 2019; Döhner, 2022). The karyotypes and mutations related to the prognosis of AML are shown in Table 3.

In general, younger patients, good functional status and certain genetic alterations (e.g., absence of mutation in the FTL3 gene) have a more favourable prognosis. In contrast, older patients, with impaired functional status, concomitant diseases, secondary AML and certain genetic alterations in leukaemic cells are associated with a poorer prognosis (Döhner, 2022).

Table 3 Cytogenetic and molecular abnormalities associated with AML prognosis

Forecast	Features
Favourable	- Cytogenetic abnormality of type t(8;21)(q22;q22) / RUNX1::RUNX1T1 - Cytogenetic abnormality of type inv(16)(p13.1q22) or t(16 ;16)(p13.1;q22) / CBFB::MYH11 - NPM1 mutation without FLT3-ITD mutation - CEBPA mutation within the bZIP framework
Intermediate	- NPM1 mutation and FLT3-ITD mutation - Absence of NPM1 mutation and FLT3-ITD mutation - t(9;11)(p21.3;q23.3); MLLT3::KMT2A - All other anomalies not classified as favourable or unfavourable
Unfavourable	- Cytogenetic abnormality of t(6;9)(p23.3;q34.1)*/DEK*::NUP214 - Cytogenetic abnormality of t(v;11q23.3)/KMT2A-rearranged - Cytogenetic abnormality of t(9;22)(q34.1;q11.2)*/BCR*::ABL1 - Cytogenetic abnormality of type t(8;16)(p11.2;p13.3)*/KAT6A*::CREBBP - Cytogenetic abnormality of type inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2*, *MECOM(EVI1*) - Cytogenetic abnormality of type t(3q26.2;v)*/MECOM*(*EVI1*)-rearranged - Cytogenetic abnormality of the -5 or del(5q); -7; -17/abn(17p) type - Complex karyotype, monosomal karyotype - *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2* mutation - TP53a mutation

Source: ACS, 2019; Döhner, 2022.

Figure 1 Relapse prevention using HDC/IL-2 in AML: treatment schema

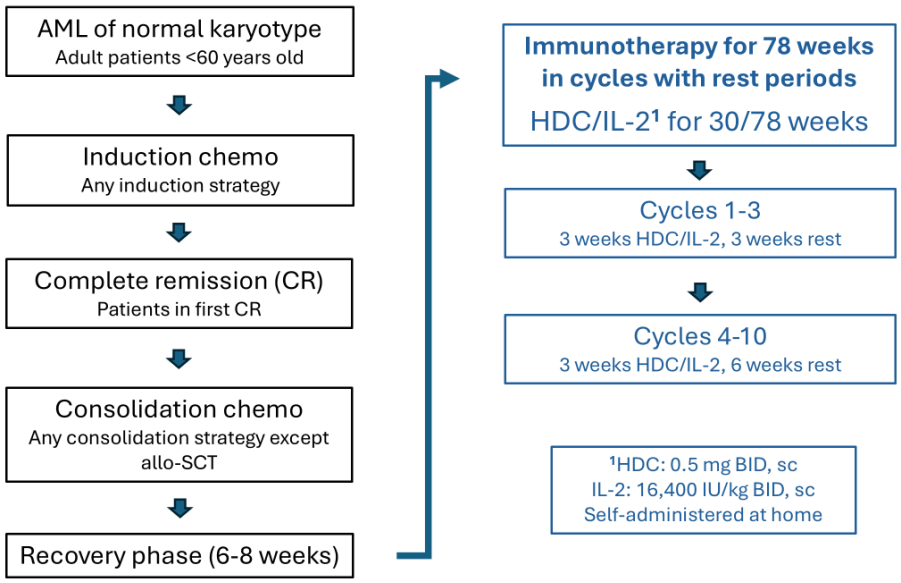


Figure 1 illustrates where immunotherapy with histamine dihydrochloride and interleukin-2 (HDC/IL-2) fits into the treatment pathway for patients with acute myeloid leukaemia (AML). After diagnosis with a blood test and bone marrow biopsy where the specific cytogenetics and molecular genetics are investigated the patient would normally be offered intensive induction therapy. Older and less fit patients may be offered a less intensive alternative treatment. The goal of induction therapy is to eradicate as many leukaemia cells as possible to achieve a 'complete remission', meaning the blood counts return to normal and there are no signs of leukaemia cells in the bone marrow.

After induction treatment and the patient is in complete remission a further consolidation treatment is normally given which aims to eliminate any remaining leukaemia cells that may not have been destroyed during induction and hence to prevent relapse.

HDC/IL-2 can then be offered as a maintenance immunotherapy after consolidation therapy to AML patients with normal karyotype who are in first complete remission and 60 years old or less and who are not considered suitable for allogeneic stem cell transplant. This would be offered to further reduce the possibility of disease relapse.

AML patients are typically managed by specialist haematological oncology services in secondary and tertiary care.

1.4 Equality considerations

It is noted that NICE guidance will only be issued in accordance with the marketing authorisation. The full licensed indication for HDC/IL-2 in section 4.1 ("Therapeutic indications") of the approved SmPC includes the qualifying statement: '*The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.*'

The approved indication clearly indicates that the evidence for the therapy is best supported in patients who are 60 years old or less and hence should exclude those who are older than 60 years.

The qualifying statement about age is based on the univariate analysis of Cox proportional hazards modeling of prognostic factors for leukaemia free survival (LFS) in the Brune, 2006 study population which revealed that no clinical benefit was seen in patients aged older than 60 years.

In addition, post-hoc sub-group analyses by Nilsson, 2020 showed no LFS or OS benefit with HDC/IL-2 for patients with normal karyotype in CR1 who are 60 years or older.

Since the indication clearly states that the efficacy of HDC has not been fully demonstrated in patients older than age 60, then this population should be excluded from the evaluation, in accordance with NICE guidelines.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

See appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.2 List of relevant clinical effectiveness evidence

Table 4 Clinical effectiveness evidence

Study	Interleukin-2 Plus Histamine Dihydrochloride in Treating Patients With Acute Myeloid Leukemia (NCT00003991), Brune, 2006
Study design	Open-label, international, multicentre, randomised controlled study
Population	Adult AML patients not considered suitable for allogeneic haematopoietic stem cell transplant (allo-HSCT) who are in complete remission (CR1 or CR2) after induction and consolidation treatment with an ECOG performance status of 0 or 1.
Intervention(s)	Histamine dihydrochloride with interleukin-2
Comparator(s)	Best supportive care
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem	• **Leukaemia-free survival (LFS)** • **Overall survival (OS)** • Remission rate • **Adverse effects of treatment** • Health-related quality of life
All other reported outcomes	Not applicable

Table 5 Clinical effectiveness evidence

Study	Post-hoc analyses from Interleukin-2 Plus Histamine Dihydrochloride in Treating Patients With Acute Myeloid Leukemia (NCT00003991), Nilsson, 2020
Study design	Open-label, international, multicentre, randomised controlled study
Population	Adult AML patients not considered suitable for allo-HSCT who are in complete remission (CR1) after induction and consolidation therapy, have a normal karyotype and are less than 60 years old
Intervention(s)	Histamine dihydrochloride with interleukin-2
Comparator(s)	Best supportive care
Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem	• **Leukaemia-free survival (LFS)** • **Overall survival (OS)** • Remission rate • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	Not applicable

2.3 Summary of methodology of the relevant clinical effectiveness evidence

Details of the randomised controlled trial, Interleukin-2 Plus Histamine Dihydrochloride in Treating Patients With Acute Myeloid Leukemia (NCT00003991), published by Brune, 2006 are as follows:

- Trial design: This was an open-label, randomised, multicentre phase 3 study. Patients were enrolled after the completion of induction and consolidation therapies and were randomly assigned to either a treatment or a control arm. Country-specific randomisation schedules were produced electronically based on

a block size of 4 and stratified by complete remission (CR) status, Complete remission was defined as less than 5% blasts in a normocellular bone marrow. The investigators received the treatment assignment from a centralised randomisation centre. Altogether 320 patients were enrolled in the study, 261 patients in the CR1 group and 59 in the subsequent CR group. Patients were followed up for a minimum of 3-years post randomisation.

- Eligibility criteria: Patients aged 18 years or older with *de novo* or secondary AML were eligible for enrollment. Inclusion criteria were verified CR; adequate renal, cardiac, and pulmonary functions; and a performance status (according to Eastern Cooperative Oncology Group [ECOG] criteria) of 0 to 1. Any previous induction or consolidation therapy was allowed with the exception of allogeneic – stem cell transplant; other exclusion criteria included active peptic ulcer, a history of recent asthma, or previous hypersensitivity reactions. Elapsed time from dates of CR and the completion of consolidation chemotherapy were not to exceed 6 and 3 months, respectively.

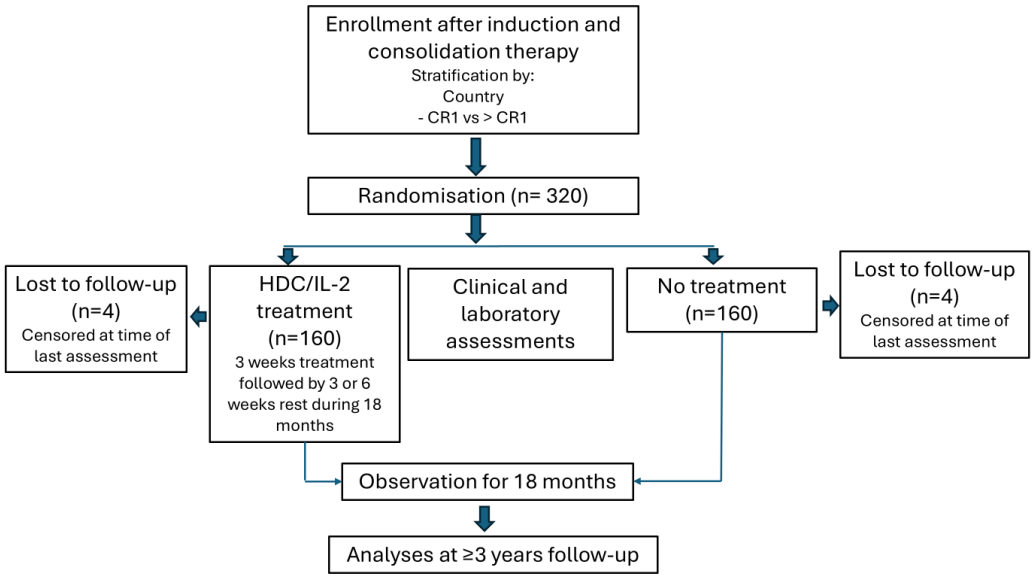
- Settings and locations where the data were collected: AML patients were enrolled at 100 centers in Australia, Canada, Europe, Israel, New Zealand, and the United States between June 1998 and October 2000. All patients were managed through secondary care services.

- Trial drugs and concomitant medications: The study scheme is presented in Figure 2. Patients in the treatment arm received 10 consecutive 3-week cycles of Histamine dihydrochloride (HDC)/IL-2, whereas patients in the control arm received best supportive care. The treatment continued for a total of 18 months or until the patients relapsed, died, discontinued therapy because of adverse events, withdrew consent, or became lost to follow-up. Cycles 1 to 3 comprised 3 weeks of treatment and 3 weeks off treatment, and in cycles 4 to 10 the off-treatment periods were extended to 6 weeks. In each cycle, patients in the treatment arm received HDC at 0.5 mg subcutaneous twice a day and human recombinant IL-2 (aldesleukin; 16 400 U/kg) subcutaneous twice a day. After 18 months of treatment (HDC/IL-2 arm) or observation (control arm), all patients were followed for at least 18 additional months until the study closure date on

October 31, 2003 (i.e. 3 years after enrollment of the last patient). To avoid acute toxicity, HDC was administered at a rate not exceeding 0.1 mg per minute. In the event of HDC-related side effects, the injection time was prolonged to 7 to 10 minutes; if toxicity persisted, the dose was reduced by 20%. Reduction of the IL-2 dose was prescribed in case of side effects or inconveniences related to this treatment. The first doses of study drugs were administered under the supervision of the investigator. Subsequent doses were administered by the patients at home. The dose of HDC was predicted to saturate 70% to 80% of phagocyte cell histamine H2 receptors (Dotevall, 1967, Lanas, 1994) and the dose of IL-2 had been shown previously to cause significant expansion of cytotoxic lymphocytes with documented antileukemic activity (Brune, 1996, Meropol, 1996). The doses and schedules were considered suitable for long-term treatment on the basis of the results obtained in a pilot study (Hellstrand,1997).

Treatment duration was chosen to maintain a protective level of immuno-stimulation during the high-risk phase that is during the initial 18 months post-consolidation of remission when > 85% of relapses would be expected.

Figure 2 Study scheme



- Outcomes used in the economic model or specified in the scope, including primary outcome: The primary trial endpoint was to determine the efficacy of post-consolidation maintenance treatment with HDC/IL-2 immunotherapy versus best supportive care on leukaemia-free survival (LFS, defined as the time from randomisation to relapse or death from any cause) in the intention-to-treat patient population. Pre-specified secondary endpoints included LFS at 6, 12, 24 and 36 months after randomisation, effects of treatment on LFS of patients in CR 1 and CR 1+, overall survival, safety, toxicity and quality of life.

Table 6 Baseline characteristics of the patients in the study

Inclusion criteria	**HDC/IL-2 N=160**	**Control N=160**
Sex, n (%)		
Men	84 (54)	86 (54)
Women	74 (46)	74 (46)
Age, years		
Global, median (range)	55 (18-81)	54 (18-84)
Patients older than 60 years, n (%)	66 (41)	59 (37)
CR, n (%)		
CR1	129 (81)	132 (82)
CR>1	31 (19)	28 (18)
FAB classification, n (%)		
M1/M1/M5/M6	60 (38)	56 (35)
M2/M3/M4	87 (54)	93 (58)
Functional status, n (%) [1].		
0	125(78)	114(71)
1	35(22)	46(29)
WBC count at diagnosis, x10^9 L, n (%)		
<20	97 (61)	111 (69)
20-100	51 (32)	36 (23)
>100	12 (7)	13 (8)
Karyotype, n (%) [2].		
Favorable	14 (9)	13 (8)
Intermediate	95 (59)	95 (59)
Adverse	10 (6)	7 (4)
Unknown	41 (26)	45 (28)
≤15% blastocysts after first induction.	147 (92)	144 (90)
History of hematologic cancer [3].	15 (9)	14 (9)
Pretreatment with high-dose cytarabine [4].	105 (66)	108 (68)
Pretreatment with autologous HSCT	22 (14)	17 (11)
Time from CR to randomization, days		

Inclusion criteria	HDC/IL-2 N=160	Control N=160
Global, median (range)	147 (6-727)	135 (4-553)
≤6 months, n (%)	117 (73)	125 (78)
>6 months, n (%)	43 (27)	35 (22)
Time from consolidation to randomization, days		
Global, median (range)	63 (20-545)	64 (14-468)
≤3 months, n (%)	125 (78)	122 (76)
>3 months, n (%)	34 (21)	35 (22)

Notes: [1]. Evaluated at the time of randomization; [2]. Classified according to the criteria of the Medical Research Council (Grimwade, 1998).; [3]. 12 patients (control) and 13 (HDC/IL-2) had myelodysplastic syndrome prior to AML. Two patients in each group had other previous hematologic malignancies; [4]. At least 2 g/m2 per day for 3 or more days during induction or consolidation.

Abbreviations: AML, acute myeloid leukemia; AML, acute myeloid leukemia; HCT, hematopoietic stem cell transplantation; HDC, histamine dihydrochloride; IL-2, interleukin-2; CR1, first remission; CR1+, subsequent remissions; WBC, white blood cells; WBC, white blood cells.

Source: Brune, 2006

The study arms were well balanced for demographics and potential prognostic factors such as age, sex, previous high-dose cytarabine treatment, previous autologous stem cell transplantation, leukaemic karyotypes, time from CR to inclusion, and frequency of antecedent haematologic disorder. Cox modeling did not reveal any imbalances between treatment and control arms.

In April 2024 members of the National Cancer Research Institute (NCRI) Acute Myeloid Leukaemia (AML) group were contacted to gain feedback on the evidence base supporting the use of HDC/IL-2 and where it might best fit into UK practice, since the RCT did not include any UK centres and there is therefore no personal experience with the therapy in the UK. From these conversations other UK haematological oncology peers specialising in the treatment of AML patients were recommended for approach. In February 2025 a remote scientific advisory board was convened including 7 experts who were available to attend from the group of 17 UK AML haematologists who had been spoken with previously. The views and opinions of these experts are represented in this submission.

Details of the post-hoc analysis of the randomised controlled trial, Interleukin-2 Plus Histamine Dihydrochloride in Treating Patients With Acute Myeloid Leukemia (NCT00003991), published by Brune, 2006, published by Nilsson, 2020 are as follows:

- Trial design: This was a post-hoc analysis of the randomised controlled trial, Interleukin-2 Plus Histamine Dihydrochloride in Treating Patients With Acute Myeloid Leukemia (NCT00003991), published by Brune, 2006.

- Eligibility criteria: The efficacy of HDC/IL-2 was assessed in CR1 patients with normal or aberrant karyotype AML who participated in the randomised phase III trial. The karyotypic features of leukemic cells were unknown in 36 of the 261 patients in CR1. Thus, data obtained from 225 CR1 patients with known karyotype were available for analysis of clinical outcome (LFS and OS).

- Settings and locations where the data were collected: As in the Brune, 2006 study summarised above.

- Trial drugs and concomitant medications: As in the Brune, 2006 study summarised above.

- Outcomes used in the economic model or specified in the scope, including primary outcome: The primary objective was to determine the efficacy of HDC/IL-2 maintenance immunotherapy versus control on the leukaemia-free survival (LFS) and overall survival (OS) in AML patients in CR1 with aberrant and normal karyotype. Efficacy was also assessed in younger patients (<60 years old) versus older patients (≥60 years old).

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Sample size calculation: For the Brune, 2006 study the number of subjects was initially based on hypothesised improvement in median LFS of 50% in subjects in CR1 in the HDC/IL-2 arm compared with control subjects. Ninety-six events in CR1 would be needed in each study arm to provide a statistical power of 80%, with a type I error rate of 0.05. For the hypothesized improvement in median LFS of 75% in subjects in subsequent CR, 51 events in each study arm would provide a statistical power of 80%, with a type I error rate of 0.05. In the initial protocol there were 2 primary endpoints; one for patients in CR1 and one for patients in subsequent CR. However, when a total of 320 subjects (261 in CR1 and 59 in CR >1) had been

enrolled, accrual of the necessary number of subjects in subsequent CR did not seem to be feasible. Therefore, further recruitment was terminated in October 2000, and in a protocol amendment the primary endpoint was changed to determination of LFS in the combined population of patients in CR1 and in subsequent CR (i.e. all patients randomly assigned into the trial). In October 2000, 320 patents had entered the study; these patients were to be followed for at least 3 years, and it was estimated that a sufficient number of events would occur before that time point.

Efficacy analyses: The primary efficacy analysis, duration of LFS, was thus conducted on the intent-to-treat population of all randomly assigned patients. The Kaplan-Meier procedure was used to estimate the LFS and overall survival distributions for all patients (n=320), as well as for the subgroups of patients in CR1 (n=261) and in subsequent CR (n=59). The LFS or survival estimates were compared using a log-rank test. For the log-rank comparisons, all events recorded until the closure date of the study were taken into account. Frequency analyses were performed by using the chi-square test or the Fisher exact test. All statistical analyses of efficacy (LFS and overall survival) were stratified by country and, if applicable, CR stratum (CR1 or CR >1). The efficacy analyses were performed according to the intent-to-treat principle, and all reported P values are 2-sided.

Cox modelling: Cox proportional hazards model regression analyses, stratified by country and CR status (CR1 and CR >1), were performed to assess the effects of possible confounding covariates on LFS. The Cox model included treatment and covariates identified as having a prognostic influence on outcome. The final model included the treatment effect and the variables selected in the univariate models.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Overall survival in the randomised controlled trial published by Brune, 2006 was not significantly affected by treatment, but it should be emphasised that the trial was not powered for differences in survival, and that an analysis of the time point selected for LFS (3 years after last enrollment) was not expected to yield significant results in terms of survival. In addition, the survival after a relapse was longer than that previously reported. Thus, although other investigators typically report a median time

from relapse to death of 4 to 5 months, the patients in the current trial lived for a median of at least 9 months in both arms, which further limited the possibility of establishing the putative effect of treatment on overall survival at the time of analysis. The reason for this discrepancy may be that the trial recruited patients after the completion of consolidation rather than immediately after CR.

The choice of comparator arm in this study was based on the notion that no treatment after the completion of consolidation was the current standard of care. The decision not to include additional conceivable comparators in the trial, the most apparent candidate being an IL-2 alone arm, was based on an assessment of the efficacy and toxicity reported in previous trials using monotherapy with IL-2 as maintenance therapy for patients with AML in CR. The available documentation about the putative efficiency of IL-2 to prevent relapse in AML was inconsistent at the onset of the present phase 3 trial, and severe toxicity from IL-2 treatment had been described.

Adult AML patients were recruited for inclusion into the Brune, 2006 randomised controlled trial (RCT) from 1998 to 2000. Consequently, there is a possibility that the induction and consolidation treatments used in the study are different to the treatments routinely used in a more contemporary setting and this might have impacted the relative outcomes. This point was raised by the majority of clinical experts we consulted whilst discussing the evidence base for HDC/IL-2.

Consolidation therapy forms the backbone of post-remission therapy for AML and is uniformly accepted as an integral part of therapy designed to achieve long-term survival. While there are several acceptable options for consolidation therapy, high-dose cytarabine is most widely used (Weigert, 2022). In the Brune, 2006 study the use of high-dose cytarabine treatment, as defined by at least 2 g/m^2 per day for 3 or more days during induction or consolidation, was well balanced between the two arms in the intention-to-treat population of the RCT (68% and 66% in the control arm and treatment arm respectively). This shows that most patients received intensive treatment using high-dose cytarabine which is what you would expect with modern intensive induction and consolidation treatment and that there was no bias in the

proportion of patients receiving high-dose cytarabine on either arm which might impact the efficacy outcome.

When looking at the subgroup of patients with normal karyotype, in CR1 and less than 60 years old, which is the subgroup being considered in the base case of the economic model, the use of high-dose cytarabine increased to 33/37 (89%) in the control arm vs 32/35 (91%) in the HDC/IL-2 arm (Data on file). Since this is a younger treatment subgroup, less than 60 years old, compared with the intention-to-treat population it is intuitive that more patients would have been fit to receive high-dose cytarabine during induction or consolidation therapy and this would more closely reflect the intensive treatment AML patients are likely to receive today in a more contemporary setting. In addition, the number of patients receiving high-dose cytarabine was well balanced between each arm and hence this is unlikely to have biased the efficacy data.

The performance of the control arm in the normal karyotype subgroup is close to what you might expect in that subgroup of patients treated in a more contemporary setting. In a recent study published by Potter et al (2025), which included data on a combination of two UK randomised controlled trials (UK AML 17 & 19), the 3-yr survival of AML patients with NPM1 and FLT3 mutations (N=140), a subset of normal karyotype AML, who were 60 years old or younger was 58% for the non-monitored group versus 69% for the monitored group. In the AML 19 study patients with NPM1 mutations who were MRD positive were excluded from the analysis, and this exclusion bias is likely to have had a beneficial effect on the outcomes. The control arm from the normal karyotype subgroup from Nilsson, 2020 showed a 3-yr survival of 58.7%.

In a different publication by Juliusson, 2020 which summarised real world experience from a large Swedish registry of AML patients the 3-yr survival of the patient subgroup (n=198) with an NPM1 mutation and less than 60 years old was 59.4% which again is very close to the 58.7% seen in the control arm of the Nilsson et al 2020 subgroup.

It would therefore seem apparent that the control group within the Nilsson, 2020 post-hoc analysis of the normal karyotype, CR1 and less than 60 years old showed

similar 3-year survival compared with similar groups of AML patients who have been treated in a more contemporary setting within UK trials and a Swedish real world evidence collection.

2.6 Clinical effectiveness results of the relevant studies

Clinical effectiveness results from the randomised controlled trial published by Brune, 2006 were as follows:

Patient characteristics:

Three hundred and twenty patients with AML in their first remission (CR1) or subsequent remission (CR >1) were enrolled. One hundred and sixty patients were randomly assigned to the HDC/IL-2 treatment arm and 160 to the control arm. Two hundred sixty-one patients were in CR1, and 59 were in subsequent CR. The 2 arms were evenly distributed with respect to prespecified prognostic factors.

Overall trial results:

Eight patients, 4 in each study arm, were lost to follow-up or withdrew their consent; these patients were censored at the time of last assessment. All other patients had an LFS follow-up exceeding 3 years. The median follow-up of living patients was 47.3 months (range, 1-68 months) in the control arm and 46.7 months (range, 1-66 months) in the HDC/IL-2 arm.

Primary endpoint: duration of leukemia-free survival (LFS) in the ITT population:

A total of 221 relapses occurred in the study; 102 in the treatment group and 119 in the control group. Kaplan-Meier survival curves demonstrated a significant increase in LFS on HDC/IL-2 treatment as shown in Figure 3, with a median (95% confidence interval [95% CI]) of 324 (266,550) days of LFS in the treatment group versus 264 (231, 341) in the control group (P<0.01). The primary study endpoint was therefore met.

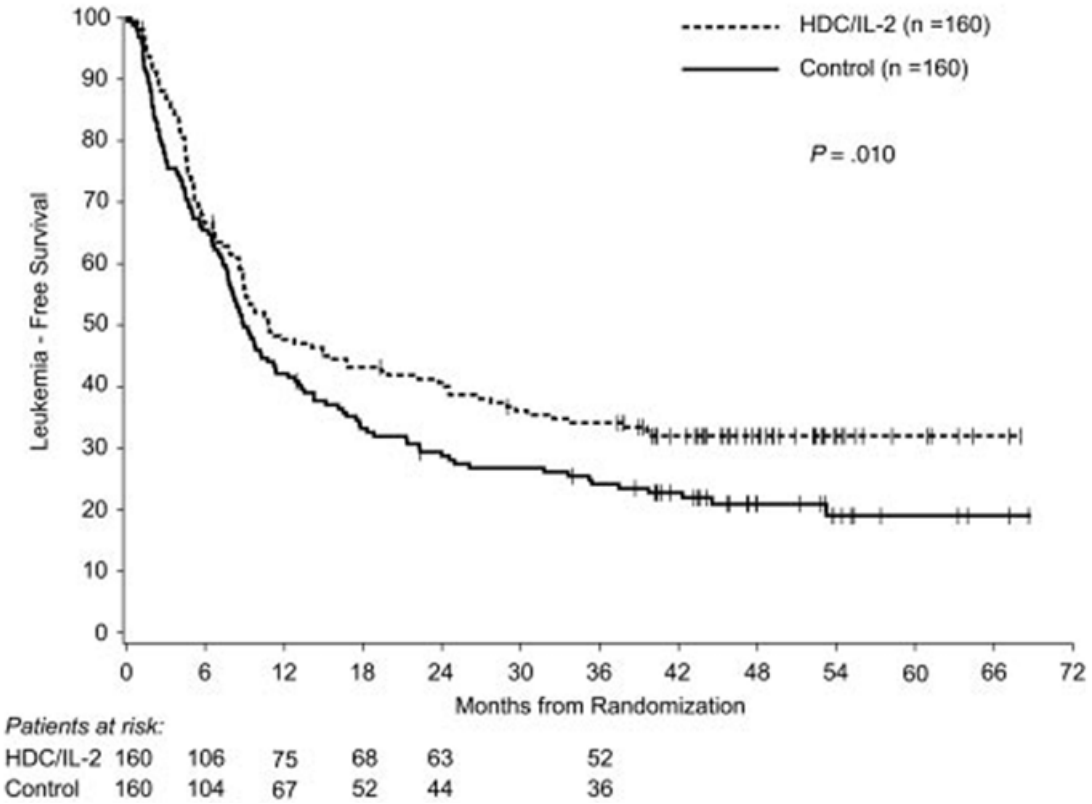
Table 7 LFS in the population by ITT (n=320)

	HDC/IL-2 N=160	Control N=160	p-value
LFS			
Median (95%CI), days	324 (266, 550)	264 (231, 341)	<0.01[1]
HR (95%CI)	0.71 (0,54-0,92)		
Proportion of patients with LFS ± SE, %.			
12 months	47.9 ± 4,0	41.5 ± 3,9	0.25
24 months	40.3 ± 3.9	28,8 ± 3,6	0.03
36 months	34.0 ± 3.8	24.7 ± 3.4	0.06

Note: [1]. Statistical analysis was performed using the Mantel-Cox test (*logrank test)*, stratified by country and CR.
Abbreviations: HDC, histamine dihydrochloride; CI, confidence interval; CI, confidence interval; IL-2, interleukin-2; HR, hazard ratio; ITT, internment to treat; LFS, leukemia-free survival; SE, standard error.
Source: Brune, 2006; Data on file, 2006.

Interestingly the separation of the Kaplan-Meier curves (Figure 3) was notable after 12-months and sustained for the duration of the follow up indicating that treatment with HDC/IL-2 was preventing relapse in some patients compared with the control arm.

Figure 3 Kaplan-Meier curves of LFS in the population by ITT (n=320)



Abbreviations: ITT: intention-to-treat; LFS: leukemia-free survival.
Source: Brune, 2006.

Duration of leukemia-free survival (LFS) in patients in first remission (CR1):

A total of 173 relapses occurred in the study in patients with CR1; 76 in the treatment group and 97 in the control group. Kaplan-Meier survival curves demonstrated a significant increase in LFS on HDC/IL-2 treatment as shown in Figure 4 in the group of patients with CR1, with a median (95% CI) of 450 (293,974) days of LFS in the treatment group versus 291 (232, 406) in the control group (P=0.01). Among patients with CR1, 46 patients in the treatment group and 27 in the control group remained in CR1 at the study cut-off date.

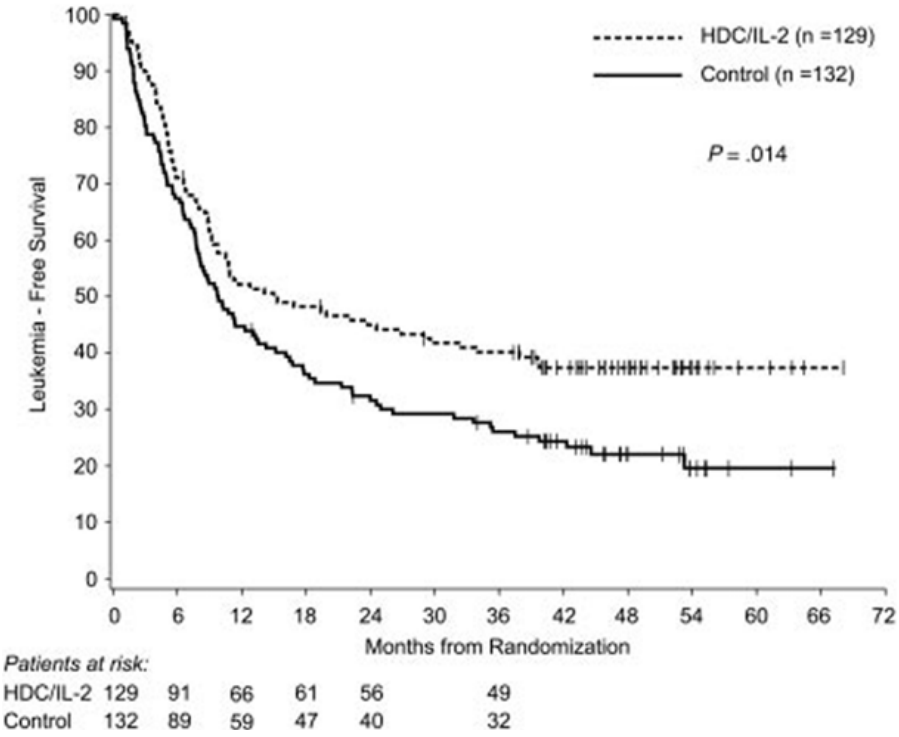
As with the ITT population, the Kaplan-Meier curves in Figure 4 for the CR1 subgroup (n=261) shows that treatment with HDC/IL-2 has a sustained improvement in LFS for the duration of the follow-up in comparison with the control arm. This indicates that the immunotherapeutic impact of HDC/IL-2 is preventing relapse in some patients.

Table 8 LFS in patients in CR1 (n=261)

	HDC/IL-2 N=132	**Control N=129**	**p-value**
LFS			
Median (95%CI), days	450 (293, 974)	291 (232, 406)	0.01[1]
HR (95%CI)	0.69 (0,51-0,93)		
Proportion of patients with LFS ± SE, %.			
12 months	52.5 ± 4,4	43.9 ± 4,3	0.17
24 months	44.7 ± 4.4	31.6 ± 4.1	0.03
36 months	39.9 ± 4.4	26.2 ± 3.8	0.02

Note: [1]. Statistical analysis was performed using the Mantel-Cox test (*logrank test)*, stratified by country and CR.
Abbreviations: HDC, histamine dihydrochloride; CI, confidence interval; IL-2, interleukin-2; LFS, leukemia-free survival; HR, hazard ratio; LFS, leukemia-free survival; CR1, first remission.
Source: Brune, 2006, Data on file, 2006

Figure 4 Kaplan-Meier curves of LFS in patients in CR1 (n=261)



Abbreviations: LFS: leukemia-free survival; CR1: first remission; HDC, histamine dihydrochloride; IL-2, interleukin-2
Source: Brune, 2006.

Cox Models

Univariate analysis of Cox proportional hazards modeling of potential prognostic factors for LFS in the study population revealed that age older than 60 years, adverse karyotype, AML of FAB classes M0/M1/M5/M6, percentage of bone marrow blasts exceeding 15% after first induction, and time from CR to random assignment of fewer than 6 months were associated with an adverse prognosis with respect to LFS. In addition, treatment with high-dose cytarabine during induction or consolidation treatments was associated with a longer duration of LFS. In the multivariate analysis, 2 factors, that is, age (≥60 versus <60) and karyotype (adverse versus other), were found to have a significant effect on LFS. The multivariate Cox proportional hazards model using the backward selection procedure demonstrated that the treatment effect observed was unaffected by demographic or prognostic factors. Thus, the multivariate analysis revealed a significant superiority of HDC/IL-2 within the population of all study patients with an adjusted P value of <0.01. An

analysis for the subgroup of patients in CR1 yielded a correspondingly adjusted P value of 0.01.

Duration of leukemia-free survival (LFS) in patients ≤60 years.

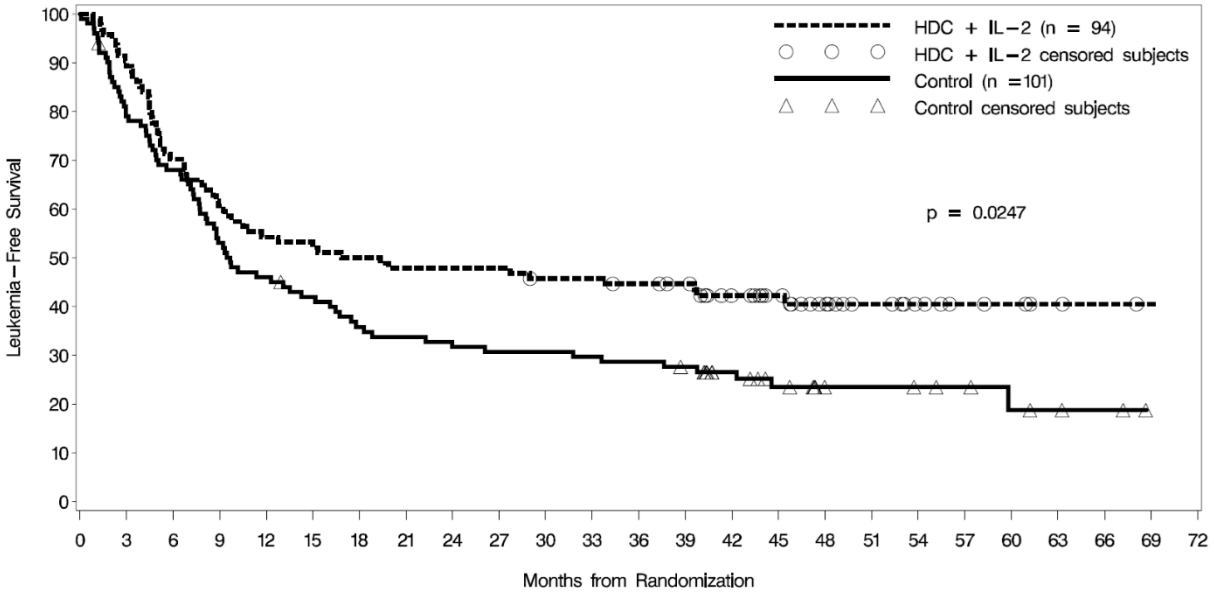
Sixty-three (63%) of patients in the treatment group and fifty-nine (59%) of patients in the control group were 60 years of age or younger. The log-rank test for LFS was statistically significant for patients at least 60 years old (p = 0.02), but not for patients older than 60 years (p = 0.35). The median LFS was 290 days for the control group and 543 days for the HCD/IL-2 treatment group in patients aged 60 years or younger. Kaplan-Meier estimates of LFS were statistically significant in favour of the treatment group at all time points up to 4 years (see Figure 5).

Table 9 LFS in patients in patients ≤60 years (n=195).

	HDC/IL-2 N=101	**Control N=94**	**p-value**
LFS			
Median (95%CI), days	543 (277, 2120)	290 (232, 484)	0.02[1]
Proportion of patients with LFS, %.			
12 months	54.3	46.0	0.25
24 months	47.9	31.7	0.02
36 months	44.7	28.7	0.02
48 months	40.5	23.5	0.01

Note: [1]. Statistical analysis was performed using the Mantel-Cox test (*logrank test)*, stratified by country and CR.
Abbreviations: LFS, leukemia-free survival. HDC, histamine dihydrochloride; CI, confidence interval; IL-2, interleukin-2;
Source: Brune, 2006; Data on file, 2006.

Figure 5 Kaplan-Meier curves of LFS in patients ≤60 years old (n=195)



Abbreviations: LFS: leukemia-free survival. HDC, histamine dihydrochloride; IL-2, interleukin-2;
Source: Data on file, 2006

Duration of leukemia-free survival (LFS) in patients in CR1 and ≤60 years.

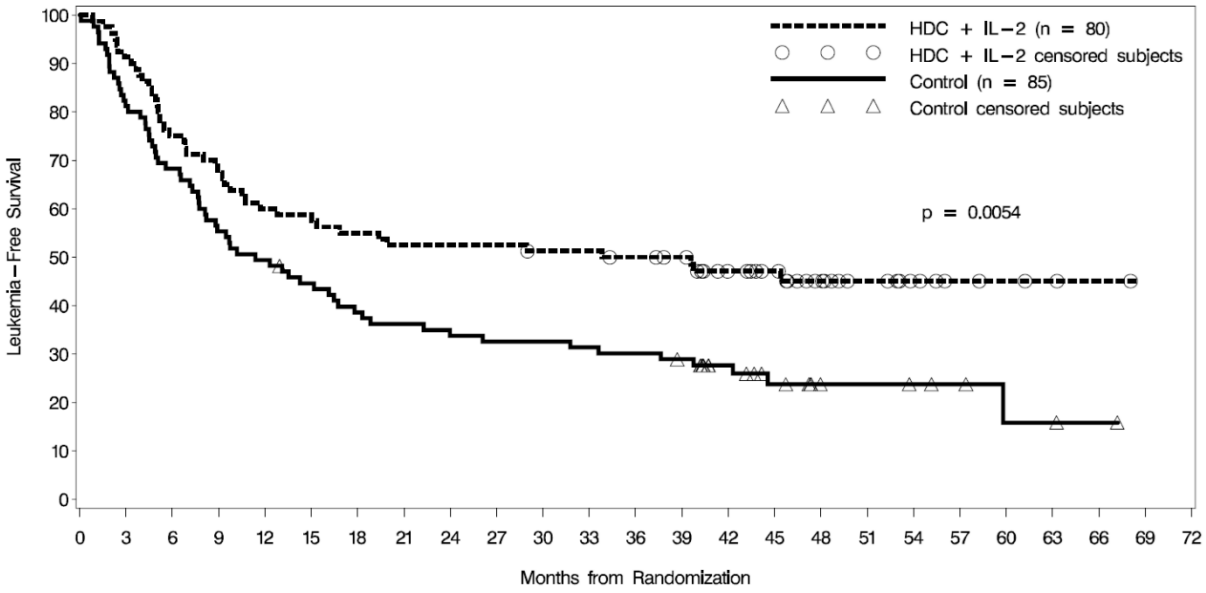
For the 80 patients treated with HDC/IL-2 who were in CR1 and ≤ 60 years of age, the Kaplan-Meier estimate of LFS at 36 months was 50% vs. 30% (p=0.01) for the 85 controls, or a relative improvement of 67% (Table 10). In addition, there was a statistically significant improvement in median LFS of 1015 days in the HDC/IL-2 arm compared with 341 days in the control arm (p=0.01) (Table 10 & Figure 6).

Table 10 LFS in patients in CR1 and ≤60 years (n=165)

	HDC/IL-2 N=80	**Control N=85**	**p-value**
LFS			
Median (95%CI), days	1015 (351, 2120)	341 (232, 534)	0.01[1]
Proportion of patients with LFS, %.			
12 months	60.0	49.4	0.16
24 months	52.5	33.8	0.01
36 months	50.0	30.2	0.01
48 months	45.1	23.8	0.01

Note: [1]. Statistical analysis was performed using the Mantel-Cox test (*logrank test)*, stratified by country and CR.
Abbreviations: LFS, leukemia-free survival; HDC, histamine dihydrochloride; CI, confidence interval; IL-2, interleukin-2; CR1, first remission.
Source: Data on file, 2006

Figure 6 Kaplan-Meier curves of LFS in patients in CR1 and ≤60 years (n=165)



Abbreviations: LFS: leukemia-free survival; CR1: first remission; HDC, histamine dihydrochloride; IL-2, interleukin-2
Source: Data on file, 2006

Overall survival (OS)

OS was superior in patients treated with HDC/IL-2 versus controls, although it did not reach statistical significance, neither for the overall ITT population (p=0.21) nor for patients in CR1 (p=0.16). Even so, the study was not designed to reach statistical significance for OS.

In the population of all patients, the median time between relapse and death was 9.0 and 9.5 months in the treatment and control arms, respectively. For patients in CR1, the median times from relapse to death were 9.2 (HDC/IL-2) and 9.5 (control) months.

Seven patients in the study, 4 in the control arm and 3 in the HDC/IL-2 treatment arm, died of AML without a previously captured relapse date. Four patients, all in CR1, died of causes unrelated to leukemia. Thus, 2 patients in the control arm died of unknown causes at 9 and 21 months after random assignment, respectively. In the treatment arm, the causes of death were pneumonia (at 28 months after randomisation), and multiorgan failure secondary to sepsis (at 40 months).

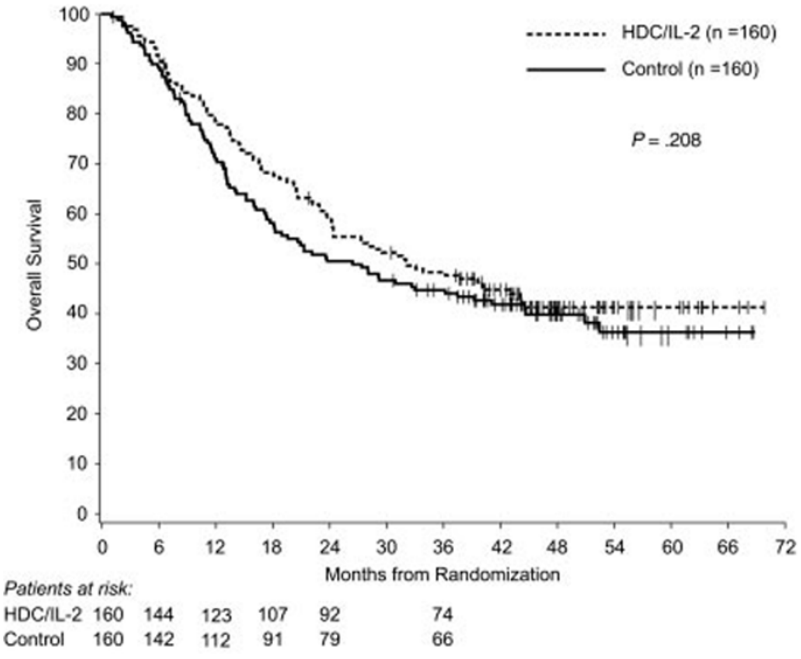
Table 11 OS in the ITT patient population (n=360) and in the subgroup of patients with CR1 (n=261)

	Population per ITT		Population with CR1	
	HDC/IL-2 N=160	Control N=160	HDC/IL-2 N=132	Control N=129
OS				
HR (95%CI); p	0.82 (0.61-1.11); p=0.21		0.78 (0.56-1.09); p=0.16	
Proportion of patients with OS ± SE, %.				
12 months	78 ± 3.3	70 ± 3.6	80 ± 3.5	73 ± 3.9
24 months	55 ± 4.0	51 ± 4.0	61 ± 4.3	53 ± 4.4
36 months	48 ± 4.0	44 ± 4.0	55 ± 4.4	46 ± 4.4

Note: [1]. Statistical analysis was performed using the Mantel-Cox test (*logrank test)*, stratified by country and CR.
Abbreviations: OS, overall survival; ITT, intention-to-treat; HDC, histamine dihydrochloride; IL-2, interleukin-2; CI, confidence interval; HR, hazard ratio; SE, standard error; IFR, hazard ratio.
Source: Brune, 2006

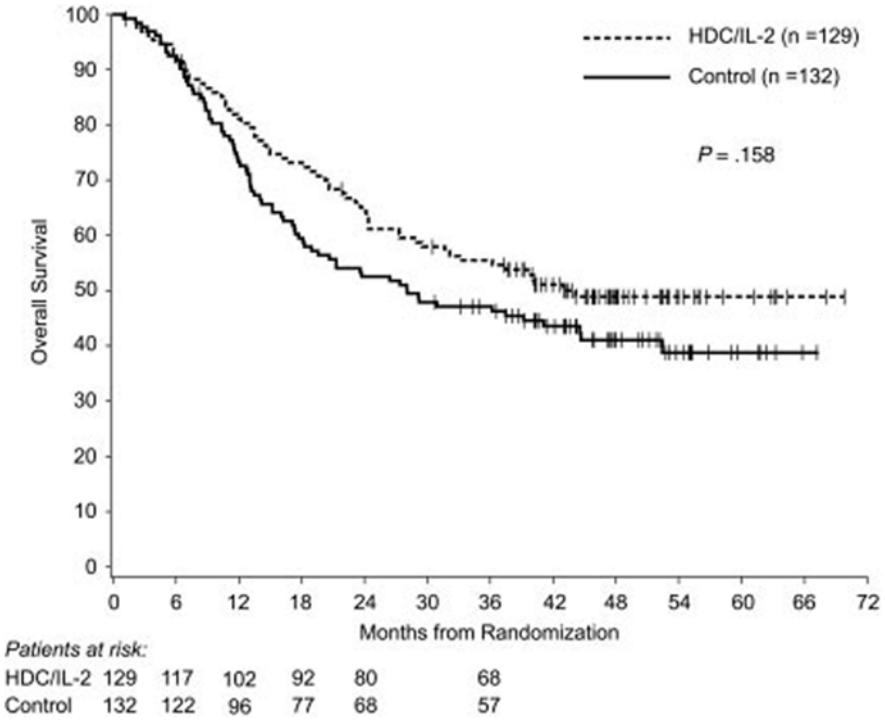
The median OS for the CR1 patients was encouraging; treated patients had a median OS of 1289 days versus 842 days for the best supportive care arm as illustrated in Figure 8 (data on file).

Figure 7 Kaplan-Meier curves of OS in the population by ITT (n=320)



Abbreviations: OS, overall survival; ITT, intention-to-treat; HDC, histamine dihydrochloride; IL-2, interleukin-2
Source: Brune, 2006

Figure 8 Kaplan-Meier curves of OS in patients in CR1 (n=261)



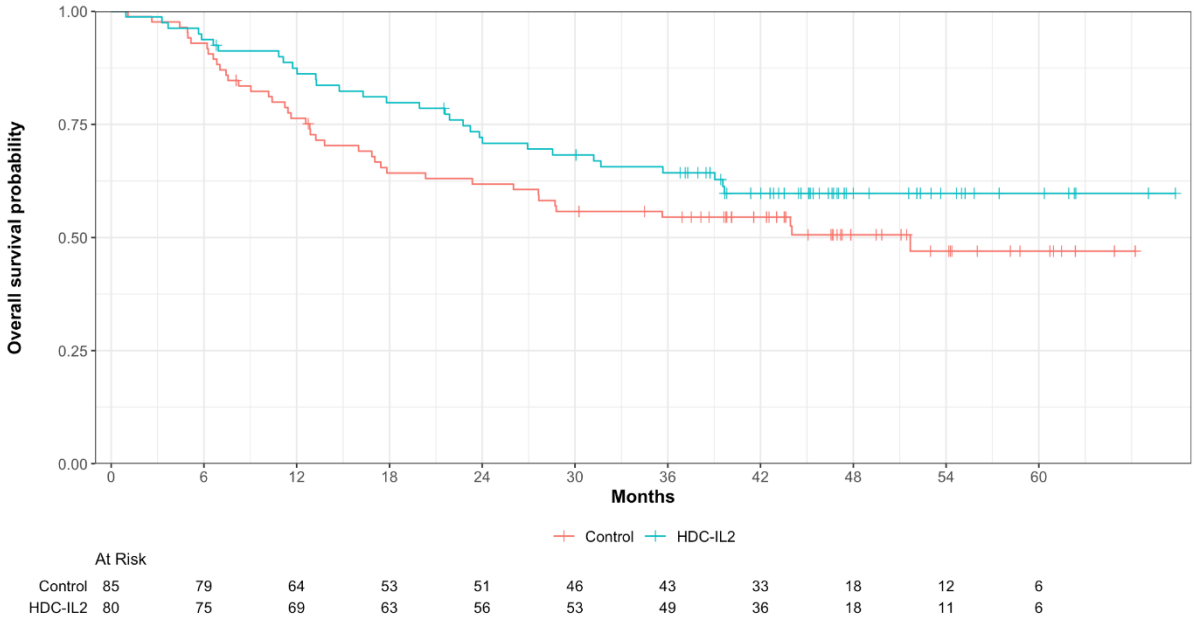
Abbreviations: OS, overall survival; CR1, first remission; HDC, histamine dihydrochloride; IL-2, interleukin-2; **Source:** Brune, 2006

Overall survival (OS) in patients in CR1 and ≤60 years.

OS was superior in patients treated with HDC/IL-2 versus controls in the CR1 and ≤60 years subgroup although it did not reach statistical significance (p=0.149). Even so, the study was not designed to reach statistical significance for OS. Median overall survival was 51.7 months in the control group and was not reached for the HDC/IL-2 treatment group during the follow-up period.

For the 80 patients treated with HDC/IL-2 who were in CR1 and ≤ 60 years of age, the Kaplan-Meier estimate of OS at 36 months was 64.3% vs. 54.5%for the 85 controls, or a relative improvement of 18% (see Figure 9).

Figure 9 Kaplan-Meier curves of OS in patients in CR1 and ≤60 years (n=165)



Abbreviations: OS, overall survival.: CR1, complete remission; HDC, histamine dihydrochloride; IL-2, interleukin-2
Source: Data on file

Clinical effectiveness results of the post-hoc analysis of the randomised controlled trial published by Nilsson, 2020 are as follows:

The basis of this post-hoc analysis was the finding in a multivariate analysis from the randomised controlled trial by Brune, 2006 that 2 factors, namely age (≥60 versus <60) and karyotype (adverse versus other) were found to have a significant effect on leukaemia free survival.

HDC/IL-2-treated patients with normal karyotype AML in CR1 displayed significantly improved LFS over control patients with a trend towards improved OS. Younger patients (<60 years) with normal karyotype AML in CR1 showed significantly improved LFS (P=0.006, HR=0.4) and OS (P=0.04, HR=0.43) vs. control patients (Table 12 and 13 and Figures 10 & 11). At 36-months after randomisation 65.6% of patients were leukaemia free on the HDC/IL-2 arm compared with 31.3% on the control arm (Table 12) and 76.5% were alive on the HDC/IL-2 arm compared to 58.7% on the control arm (Table 13).

The efficacy effects that can be seen in Kaplan-Meier curves for LFS and OS (Figures 10 & 11) show a sustained benefit for HDC/IL-2 treatment in the subgroup of AML patients (normal karyotype, CR1 & <60 years) over controls for the duration of the follow-up period. This statistically significant improvement in both LFS and OS indicates that the immunotherapeutic impact of HDC/IL-2 is helping to prevent relapse in this sub-group of AML patients.

It is noted that within the Kaplan-Meier plot presented in the post-hoc analyses published by Nilsson, 2020 a p-value of p = 0.009 demonstrates a significant improvement in leukaemia-free survival (LFS) for the subgroup of patients in first remission (CR1), with normal karyotype and under the age of 60 in the HDC/IL-2 treatment arm. No further statistical data is cited within this particular publication.

However, in the more recent post hoc analyses of HDC/IL-2 efficacy for AML remission maintenance published by Nilsson, 2025, this same subgroup is given a statistically significant p-value of p = 0.006, alongside several further statistical outputs including Hazard Ratios and 95% CI values (see Table 12).

The patient level data on file used for the health economic analysis accompanying this evidence submission has been used to calculate the p-value internally, and the output aligns with the results published in Nilsson, 2025; namely a p-value of p = 0.006. Accordingly, the p-value of p = 0.006 is considered the correct calculated value for this subgroup. Notably, both p-values are highly statistically significant.

For the avoidance of doubt, there is no difference, beyond rounding to specific decimal places, in the p-values cited for overall survival (OS) for this subgroup between the two cited publications.

These results show that the clinical benefit of HDC/IL-2 in terms of relapse prevention in AML is pronounced in patients harbouring leukemic cells of normal karyotype.

Table 12 LFS in patients with normal karyotype, CR1 and <60 years (n=72)

	HDC/IL-2 N=35	**Control N=37**	
LFS			

HR (95%CI); p	0.40 (0.20-0.79) p=0.006		
Proportion of patients with LFS, %.			
12 months	71.4	54.1	
24 months	65.6	37.0	
36 months	65.6	31.3	
48 months	65.6	28.4	
60 months	65.6	28.4	

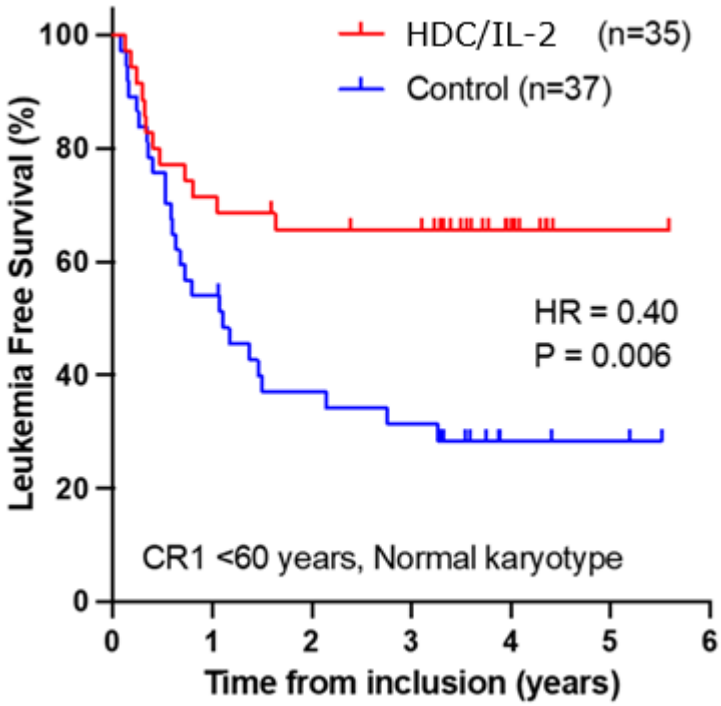
Abbreviations: HDC, histamine dihydrochloride; CI, confidence interval; , hazard ratio; IL-2, interleukin-2; OS, overall survival; HR, hazard ratio.
Source: Nilsson, 2025; Data on file

Table 13 OS in patients with normal karyotype, CR1 and <60 years (n=72)

	HDC/IL-2 N=35	**Control N=37**	
OS			
HR (95%CI); p	0.43 (0.18–1.01) p=0.04		
Proportion of patients with OS, %.			
12 months	94.3	73.0	
24 months	85.6	67.4	
36 months	76.5	58.7	
48 months	76.5	54.1	
60 months	76.5	54.1	

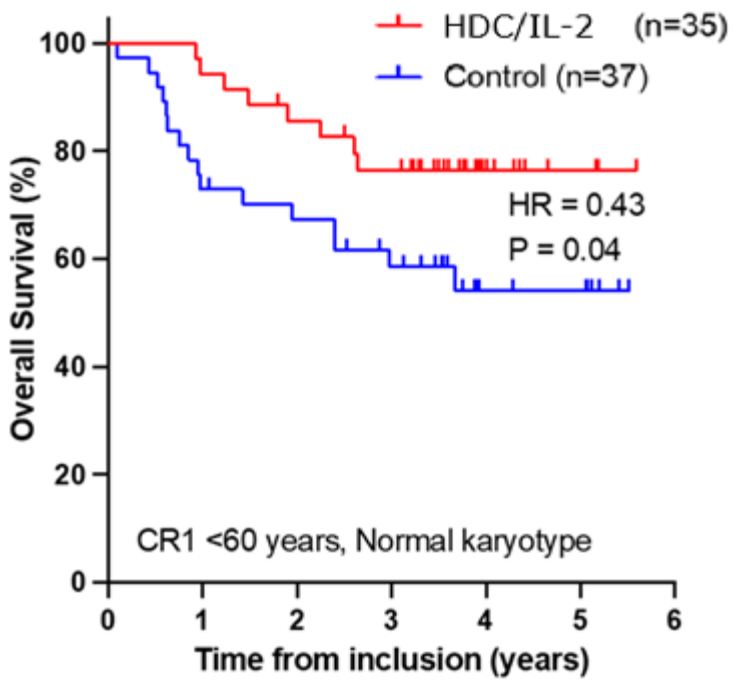
Abbreviations: HDC, histamine dihydrochloride; IL-2, interleukin-2; CR1, first remission; OS, overall survival.
Source: Nilsson, 2025, Data on file.

Figure 10 Kaplan-Meier curves of LFS in normal karyotype, CR1, <60 yrs (n=72)



Abbreviations: LFS, leukaemia-free survival.: CR1, complete remission; HDC, histamine dihydrochloride; IL-2, interleukin-2
Source: Nilsson, 2020, Data on file

Figure 11 Kaplan-Meier curves of OS in normal karyotype, CR1, <60 yrs (n=72)



Abbreviations: OS, overall survival.: CR1, complete remission; HDC, histamine dihydrochloride; IL-2, interleukin-2
Source: Nilsson, 2020, Data on file

2.7 Subsequent treatments used in the relevant studies

There are no data on what subsequent treatments patients received after relapse from the randomised controlled trial published by Brune, 2006. The investigators and authors were contacted to try and obtain these data and this information is not available.

2.8 Subgroup analysis

Pre-planned subgroup analyses in line with secondary endpoints were carried out on those patients in first remission (CR1) from the randomised controlled trial (RCT) published by Brune, 2006. These subgroup data are presented in section 2.6 (Figures 4 & 8, Tables 8 & 11).

The multivariate analyses from the RCT by Brune, demonstrated that treatment and age ≤ 60 were the 2 statistically significant determinants of improvement in LFS and these subgroup data are also presented in section 2.6 (Figure 5 & Table 9). The

efficacy results are also presented in those patients in CR1 and age ≤ 60 (Figures 6 & 9) in line with the approved indication.

A post-hoc analysis by Nilsson, 2020 published data on a subgroup of AML patients from the randomised controlled study by Brune, 2006 with normal karyotype, in CR1 and less than 60 years old has been presented in detail in section 2.6. The rationale for this evaluation was the finding in a multivariate analysis from the randomised controlled trial by Brune, 2006 that 2 factors, namely age (≥60 versus <60) and karyotype (adverse versus other) were found to have a significant effect on leukaemia free survival.

2.9 Meta-analysis

There is only one Phase III randomised controlled study published by Brune, 2006 and limited additional data published on the use of HDC/IL-2. Due to the limited published data on the use of HDC/IL-2, no meta-analysis has been carried out.

2.10 Indirect and mixed treatment comparisons

As identified by NICE in the final scope, it is acknowledged that there are alternative maintenance treatment stratagies for AML patients which have been recommended by NICE. These include:

- oral azacitidine for people who cannot have or do not want a haematopoietic stem cell transplant;
- midostaurin for people with an FLT3-mutation;
- sorafenib, after a stem cell transplant, for people with an FLT3-ITD mutation;
- quizartinib for people with an FLT3-ITD mutation; and
- cytarabine alone or in combination with other antineoplastic agents.

It is also understood that interpretation of results from clinical trials of AML maintenance therapy should account for significant variability in the study

populations with respect to age and disease features. Cross-trial comparisons should not be made where the study populations are dissimilar (Patel, 2021).

Oral azacitidine

Oral azacitidine is recommended by NICE (TA827) for the maintenance treatment of AML patients who are in complete remission and cannot have or do not want a haematopoietic stem cell transplant. On this basis it would seem a relevant comparator to HDC/IL-2.

However, during interviews with 17 UK haematologists specialising in the treatment of AML patients, about the current maintenance treatment landscape and the use of oral azacitidine, 15 out of 17 haematologists mentioned that the evidence from the pivotal QUAZAR randomised controlled study included only older AML patients who were ≥55 years and these UK haematologists were therefore curious why this was not reflected in the NICE recommendation. They also stated that there was limited use of oral azacitidine in the UK.

The feedback about the limited use of oral azacitidine in England is supported by NHS Business Services Authority (NHSBSA) Secondary Care Medicines Data (SCMD): in March 2024, 840 azacitidine tablets were prescribed at a cost of £704,040, corresponding to treatment courses for approximately 60 patients; in March 2025, 908 tablets were prescribed at a cost of £761,034, corresponding to treatment courses for approximately 65 patients.

A retrospective phase II trial published by Blum, 2017 using maintenance therapy with decitabine, a structurally and pharmacodynamically related analogue of azacitidine, in AML patients in CR1 after induction and consolidation treatment and who were <60 years old provided no benefit overall compared with historical controls. This data may have contributed to the rationale for assessing the efficacy of oral azacitidine in an older population of AML patients.

Considering the approved indication for HDC/IL-2 is limited to AML patients in first remission who are 60 years or younger, we assessed the feasibility of collecting data

on a similar group of patients (in other words, those who are 55-60 years of age) receiving oral azacitidine in the UK.

From our discussions with the clinical experts, we concluded that there is likely to be very little UK data available on the use of oral azacitidine in a similar group of patients where HDC/IL-2 is specifically indicated.

If we used the data from the QUAZAR study for an indirect treatment comparison, then this is at best likely to produce high levels of uncertainty and at worst possibly be even misleading due to the differing ages and prognoses of the eligible patients.

For these reasons a formal indirect treatment comparison between oral azacitidine and HDC/IL-2 has not been conducted as it is likely to only produce high levels of uncertainty and possibly be misleading, as opposed to offering a meaningful comparison between the therapies.

Midostaurin

NICE has previously approved midostaurin as a maintenance treatment for AML patients with FLT3 mutations (TA523) and quizartinib for AML patients with FLT3-ITD mutations (TA1013).

There are no comparative data published on the efficacy of HDC/IL-2 versus midostaurin as maintenance treatment in people with FLT3-mutation-positive AML or sorafenib/quizartinib for FLT3-ITD mutations.

The clinical experts involved with the oral azacitidine appraisal (TA827) explained that most people with FLT3- mutation positive AML would have targeted treatment with midostaurin during induction, consolidation and maintenance treatment and would be unlikely to switch to oral azacitidine.

We believe that it would be a similar situation with HDC/IL-2, where few patients with FLT3 mutation positive AML would switch from midostaurin to HDC/IL-2 during maintenance.

We note that midostaurin was considered a relevant comparator for people with FLT3-mutation positive AML in the oral azacitidine appraisal and an indirect treatment comparison was conducted.

We note that the EAG also considered that survival analyses for this population are likely to be biased because of limitations associated with the indirect treatment comparison.

The committee concluded that the results of the indirect treatment comparison comparing oral azacitidine with midostaurin were highly uncertain and considered this in its decision making.

There are no data from the pivotal Phase III RCT published by Brune, 2006 on the genetic subtypes of patients recruited to the study and hence there are very limited data on the efficacy of HDC/IL-2 in AML patients with FLT3 mutations and FLT3-ITD mutations.

For this reason, we have not attempted an indirect treatment comparison. As indicated above without further data on the efficacy of HDC/IL-2 in genetic subtypes the level of uncertainty in an indirect treatment comparison versus midostaurin is likely to be very high.

HDC/IL-2 would therefore likely be of most benefit to patients whose AML does not have an FLT3-mutation or FLT3-ITD mutation.

Sorafenib

The conclusion above concerning midostaurin is also therefore true of sorafenib: without further data on the efficacy of HDC/IL-2 in genetic subtypes, the level of uncertainty in an indirect treatment comparison versus sorafenib is likely to be very high.

Quizartinib

The conclusion above concerning midostaurin is also therefore true of quizartinib: without further data on the efficacy of HDC/IL-2 in genetic subtypes, the level of

uncertainty in an indirect treatment comparison versus quizartinib is likely to be very high.

Cytarabine

In the NICE final appraisal document for oral azacitidine for maintenance treatment of AML after induction treatment the NICE committee discussed the stakeholder comments that low dose cytarabine and subcutaneous azacitidine are not used routinely after induction and consolidation chemotherapy but are used when intensive chemotherapy is unsuitable, and that very few people had maintenance treatment with low dose cytarabine and subcutaneous azacitidine.

The committee therefore concluded that these treatments would not likely be used routinely as maintenance treatment in people who are in complete remission.

The same rationale applies for the comparison with HDC/IL-2 where all patients have had prior intensive induction and consolidation chemotherapy and the indication is for maintenance treatment in patients who are in first complete remission (CR1).

Uncertainties in the indirect and mixed treatment comparisons

The potential uncertainties about conducting indirect treatment comparisons have been described in section 2.10.

2.11 Adverse reactions

From the randomised controlled trial published by Brune et al. (2006), the safety population comprised all patients in the HDC/IL-2 treatment group who received at least 1 dose of study medication, and all randomised patients in the control group who completed the baseline visit (visit 2). Consequently 317 patients were included in the safety population, 157 in the HDC/IL-2 treatment arm and 160 in the control arm. In the treatment arm, patients received a median of 6 (range, 1-10) 3-week cycles of HDC/IL-2, and of 49 nonrelapsed patients, 45 (92%) completed all 10 scheduled cycles. All patients in the treatment arm and 95% of those in the control arm experienced adverse events (AEs). The events which were significantly more prominent in the HDC/IL-2 arm included IL-2–related side effects such as injection site reactions, fever, fatigue, and myalgia, along with side effects related to HDC

such as palpitations, flushing, and headache. There were no cases of grade 3 or 4 hypotension, nor were there any cases of capillary leakage syndrome or renal insufficiency. The incidence of AEs resulting in dose reduction or treatment interruption was 26%, the most common reasons being local inflammatory reactions at the injection sites (7.1%) or fever (5.1%). Thirteen patients (8.3%) in the HDC/IL-2 arm discontinued treatment because of AEs not related to relapse. The causes for discontinuation or early termination were neutropenia (n=3), asthenia, polyarthritis, acute congestive heart failure, bronchospasm, venous thrombosis/renal-cell cancer, hepatobiliary disorder, hypersensitivity with local reaction/flush, gastrointestinal hemorrhage, nausea/vomiting, and thrombocytopenia. The incidence of serious adverse events (SAEs) was 18.8% and 17.8% in the control and HDC/IL-2 arms respectively. Most SAEs were relapse related. Seven patients (4.5%) in the treatment arm had 9 treatment-related SAEs. These events were fever (n=3), congestive heart failure, dehydration, endocarditis, grand mal convulsion, polyarthritis, and aspergillosis. Patients with treatment related SAEs or dose modifications were not censored for any parameters of efficacy. There were no treatment-related deaths.

Table 14 Adverse events

	Control (n =160)			**HDC + IL-2 (n = 157)**			**P†**
Adverse Event	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4	
Blood							
Thrombocytopenia	13.8	9.4	0	13	16	1.3	.16
Eosinophilia	0	0	0	18	1.9	0	< .001
Neutropenia	5.0	3.1	0	6.4	5.7	0	.27
Leukopenia NOS	11	1.9	0	7.0	0.6	0.6	.20
Anemia	5.0	0.6	0	5.7	1.3	0	> .5
Cardiac							
Tachycardia NOS	1.3	0	0	14	0	0	< .001
Palpitations	1.9	0	0	8.3	0	0	.01
Gastrointestinal							
Nausea	9.4	0	0	31	1.3	0	< .001
Dyspepsia	3.8	0	0	15	0.6	0	< .001
Vomiting	5	0	0	15	0.6	0	.003
Diarrhea	10	0	0	18	1.9	0	.02
Abdominal pain	3.8	0	0	6.4	0	0	.32
General							

Fatigue	16	1.3	0	42	1.3	0	< .001
Pyrexia	16	1.3	0	41	2.5	0	< .001
Pain NOS	2.5	0	0	7.7	0	0	.04
Weakness	6.9	0	0	7.6	0	0	> .5
Chest pain	5.7	0.6	0	8.9	0	0	.40
Injection sites							
Erythema	NA	NA	NA	38	0	0	NA
Granuloma	NA	NA	NA	44	0	0	NA
Rigors	NA	NA	NA	18	0	0	NA
Pruritus	NA	NA	NA	22	0.6	0	NA
Infections							
Upper respiratory	14	0	0	18	0	0	.36
Sinusitis	5.7	0	0	5.8	0	0	> .5
Metabolic and nutrition							
Anorexia	3.1	0	0	8.3	0.6	0	.03
Musculoskeletal							
Myalgia	1.9	0	0	19	0	0	< .001
Arthralgia	14	0	0	23	1.3	0	.02
Back pain	12	0	0	13	0.6	0	> .5
Pain in limb	6.9	0	0	12	0	0	.13
Nervous system							
Headache	14	0	0	51	7	0	< .001
Dizziness	8.8	0	0	23	0.6	0	< .001
Dysgeusia	0	0	0	13	1.3	0	< .001
Psychiatric							
Insomnia	6.2	0	0	7.0	0.6	0	>.5
Depression	3.1	0.6	0	7.7	0.6	0	.10
Anxiety	8.8	0.6	0	5.1	0	0	.19
Respiratory							
Cough	14	0	0	27	0.6	0	.003
Pharyngitis	15	0	0	15	0.6	0	> .5
Nasal congestion	1.3	0	0	12	0	0	< .001
Dyspnea NOS	3.2	0	0	16	0.6	0	< .001
Rhinitis	1.9	0	0	5.7	0	0	.08
Rhinorrhea	2.5	0	0	6.3	0	0	.11
Epistaxis	2.5	0	0	5.7	0	0	.17
Sinus congestion	0.6	0	0	5.8	0	0	.01
Skin							
Rash NOS	4.4	0	0	12	0.6	0	.01
Sweating	1.3	0	0	9.5	0	0	< .001
Urticaria	0	0	0	5.1	0	0	.003
Vascular							
Flushing	0	0	0	87	1.3	0	< .001
Hypotension NOS	2.5	0	0	13	0	0	< .001

NOS = not otherwise specified; NA = not applicable.

*Data are presented as the percentage of the safety population reported by at least 5% of patients in any of the control or HDC/IL-2 arms.

†Statistical analysis using Fisher exact test.

2.12 Ongoing studies

There are no ongoing studies that are likely to provide additional evidence in the next 12 months.

2.13 Interpretation of clinical effectiveness and safety evidence

A recent publication by Wei, 2023 cites that "*For patients with AML in remission, hematopoietic stem cell transplantation (HSCT) is often the only potentially curative option, but many patients are not candidates for HSCT due to advanced age, poor performance status, comorbidities, patient preference, or favorable AML European Leukemia Net risk, particularly in younger patients. Thus, there is a need for effective maintenance therapies to prolong survival among HSCT-ineligible patients in complete remission*" (Wei, 2023). We believe that HDC/IL-2 immunotherapy has shown to provide an effective maintenance treatment option for younger AML patients ineligible for HSCT and in complete remission. The evidence of patient benefit is further improved in these AML patients with a normal karyotype.

The comparator used in the pivotal Phase III RCT published by Brune, 2006 was **best supportive care** and hence we believe that this should be considered as the main comparator within this appraisal. Please also refer to section 2.10 for a detailed discussion regarding the other comparators identified by NICE in the final scope and the potential uncertainties about conducting indirect treatment comparisons with these other comparators.

The primary endpoint from the pivotal RCT published by Brune, 2006 was met and showed that LFS was significantly prolonged in patients who received HDC/IL-2 compared with best supportive care (stratified log-rank test, P = 0.01, ITT population).

The impact of HDC/IL-2 on LFS was seen primarily in the CR1 patients. For CR1 patients, the median LFS was 291 days in the best supportive care arm versus 450 days for HDC/IL-2–treated patients. This was a clinically important improvement of 22.7 weeks in first remission, an increase of 55%. The log-rank test for treated versus controls was statistically significant, P = 0.011, and the Kaplan Meier estimate

of LFS at 3 years was 26% in the control group versus 40% in the HDC/IL-2 group (P = 0.02), or a 53% relative improvement over the best supportive care arm.

The study was not powered to demonstrate an overall survival advantage and statistical significance was not reached (P = 0.16) either for the intention-to-treat population or the CR1 remission status stratum (P = 0.12). The median OS for the CR1 patients was encouraging; treated patients had a median OS of 1289 days versus 842 days for the best supportive care arm.

Univariate analysis of Cox proportional hazards modeling of prognostic factors for leukaemia free survival (LFS) in the Brune, 2006 study population revealed that no clinical benefit was seen in patients aged older than 60 years.

Resulting from the above data, the approved licensed indication for HDC/IL-2 is as follows '*Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection maintenance therapy is indicated* for *adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.'* Since the indication clearly states that the efficacy of HDC has not been fully demonstrated in patients older than age 60, then this population should be excluded from the evaluation, in accordance with NICE guidelines.

Adverse events (AEs) reported from the RCT were common, as expected, in AML patients being maintained in remission; many adverse events were associated temporally with clinical relapse. There were no treatment-related deaths. Only 13 of 157 patients in the HDC/IL-2 group discontinued treatment because of AEs not related to relapse. Overall, 96% (152/159) of patients in the control group and all patients in the HDC/IL-2 group reported at least 1 adverse event of any severity. The frequencies of grade 3 or 4 AE's, and of those events classified as serious AEs (SAE's), were similar in the 2 arms (43% of controls versus 52% of HDC/IL-2 patients reported grade 3 or 4 events and 18% versus 19% reported SAEs). HDC/IL-2 recipients reported more flushing, injection site reactions, headache, fatigue, pyrexia, and nausea. The most common AEs of grade 3 or 4 severity in the HDC/IL-

2 group included thrombocytopenia (17%), headache (6%), and neutropenia (6%). The most frequent treatment-related serious adverse event was pyrexia (4 patients).

A post-hoc analysis by Nilsson et al (2020) from the pivotal RCT by Brune et al (2006) showed a profound treatment effect in those AML patients with normal karyotype in CR1 who were less than 60 years old. This subgroup of patients treated with HDC/IL-2 showed significantly improved LFS (P=0.006, HR=0.4) and OS (P=0.04, HR=0.43) vs. control patients. At 36-months after randomisation 65.6% of patients were leukaemia free on the HDC/IL-2 arm compared with 31.3% on the control arm and 76.5% were alive on the HDC/IL-2 arm compared to 58.7% on the control arm. The clinical evidence for this subgroup supports the base case in our economic submission.

The impressive efficacy effects in the subgroup of AML patients (normal karyotype, CR1 & <60 years) demonstrated in the separated Kaplan-Meier curves for LFS and OS (Figures 10 & 11) show a sustained benefit for HDC/IL-2 treatment over controls for the duration of the follow-up period. This statistically significant improvement in both LFS and OS indicates that the immunotherapeutic impact of HDC/IL-2 is helping to prevent relapse in selected AML patients.

Explanations for the rationale of not including indirect treatment comparisons with other comparators identified in the final scope issued by NICE and which are approved by NICE for the maintenance treatment of AML patients has been described in section 1.1 (Table 1) and section 2.10 of this evidence submission.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

A systematic literature review was conducted to identify economic evaluations assessing the treatment of adult patients with AML in first complete remission. Full details of the search are provided in Appendix E. No UK economic analyses were identified that evaluated the use of histamine dihydrochloride and low-dose interleukin-2 in the target population, nor were any studies identified that specifically evaluated treatments exclusively in patients with AML in first complete remission in the UK. A summary of the identified economic evaluation studies in AML from a UK NHS perspective is provided in Table 15. A full summary of all identified models is provided in the Appendix E.

Table 15 Summary list of published cost-effectiveness studies of interventions for AML in the UK

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Witlox (TA827)	2023	PSM	67.9	• Oral azacitadine: Not reported (commercial in confidence) • BSC: Not reported	• Oral azacitadine: Not reported (commercial in confidence) • BSC: Not reported	32,480
Russel-Smith	2021	Cohort STM	61.2	• Gemtuzumab ozogamicin + standard of care: 5.29199 QALYs • Standard of care: 4.29971 QALYs	• Gemtuzumab ozogamicin + standard of care: £135,545 • Standard of care: £122,088	13,544
Tremblay	2018	PSM	47.9 (median)	• Midostaurin: 7.79 QALYs • Standard of care: 6.32 QALYs	• Midostaurin: £267,325 • Standard of care: £213,253	36,826

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PSM, partitioned survival model; QALYs, quality-adjusted life years; STM, state transition model.

3.2 Economic analysis

A *de novo* economic model was developed for the present submission. While previously published economic analyses identified in the SLR adopted similar model structures for AML maintenance treatments, the models could not be adapted to the present analysis as they were not available in the public domain. A summary of the *de novo* economic model is presented in Table 16.

Table 16 Summary of the economic model

Aspect	Details	Justification
Population	Adults with AML, in first complete remission, aged under 60 years of age, with normal karyotype, ineligible for allogeneic stem cell transplantation	Aligned with the approved indication for histamine dihydrochloride and low-dose interleukin-2.
Model framework	Partitioned survival model	The choice of modelling approach was informed in part by the precedent set in TA523 and particularly TA827, both of which employed partitioned survival models with similar health states in patients with AML. The chosen approach is also consistent with the method used in the majority of oncology appraisals reviewed by NICE.
Model structure	Three health states (leukaemia-free, progressed disease, and death).	A model structure with three health states utilises the key primary (LFS) and secondary (OS) endpoints from the Brune *et al.* randomised controlled trial and the Nilsson *et al.* follow-up study in the normal karyotype population. Furthermore, the structure is consistent with approaches accepted in previous AML technology appraisals.
Discounting options	Cost and effectiveness outcomes at 3.5% *per annum*.	In line with the NICE reference case.
Perspective	NHS and PSS.	In line with the NICE reference case.
Treatment arms within executable model	• Histamine dihydrochloride and low-dose interleukin-2 • Standard of care	Aligned with the treatment options investigated in the pivotal RCT (Brune *et al.* 2006) and follow-up study in the normal karyotype population (Nilsson *et al.* 2020).

Clinical efficacy and safety	Data were obtained from: • Brune *et al.* 2006 RCT • Nilsson *et al.* 2020 follow-up study • UK general population mortality	The Brune *et al.* RCT and the Nilsson *et al.* follow-up study are the most robust primary sources of evidence for the efficacy and safety of histamine dihydrochloride and low-dose interleukin-2 in the target population.

Abbreviations: AML, acute myeloid leukemia; BSC, best supportive care; LFS, leukemia-free survival; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PSS, Personal Social Services; RCT, randomised controlled trial; TA, technology appraisal.

Patient population

The base case analysis was conducted in adults with AML, in first complete remission, aged under 60 years of age, with normal karyotype, and who were not eligible for allogeneic stem cell transplantation. This population was selected to align with the approved indication for histamine dihydrochloride and low-dose interleukin-2, which notes that "Histamine dihydrochloride 0.5mg/0.5ml solution for injection maintenance therapy is indicated for adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Histamine dihydrochloride 0.5mg/0.5ml solution for injection has not been fully demonstrated in patients older than age 60."

The mean baseline age of this target population as enrolled in the Brune *et al.* RCT was 44.2 years (43.0 years in the standard of care arm [n=37] and 45.5 years in the histamine dihydrochloride and low-dose interleukin-2 arm [n=35]). Across both arms in the Brune *et al.* RCT target population, 50% were male and 50% were female (54% [20/37] male in the standard of care arm and 46% [16/35] male in the histamine dihydrochloride and low-dose interleukin-2 arm). For the purposes of calculating the dose of interleukin-2 and in the absence of bodyweight data from the Brune *et al.* RCT, a mean patient bodyweight of 78.45 kg was adopted based on the 2021 Health Survey for England.

Model structure

The *de novo* economic model was structured as a partitioned survival model (PSM) with three mutually exclusive and jointly exhaustive partitions: leukaemia free, progressed disease, and death. The partitions were chosen based on clinical trajectories and treatment pathways described in AML guidelines (Döhner et al.

2022) and because they enabled direct use of clinical evidence from the primary (LFS) and secondary (OS) endpoints of the pivotal Brune *et al.* RCT (Brune *et al.* 2006) and the follow-up study reporting at least 36 months of follow-up in the normal karyotype population (Nilsson *et al.* 2020). In the RCT, and therefore also in the PSM, LFS was defined as the time from randomisation to relapse or death from any cause.

Furthermore, the PSM structure is aligned with previous Cost Utility Analyses (CUAs) for AML and oncology more broadly and has been the most commonly used model structure in previous NICE appraisals (NICE DSU, TSD 19, 2017).

Alternative model structures were considered but discounted. A state transition Markov or semi-Markov modelling framework was not considered to offer any advantages over a PSM and may have required the implementation of tunnel states to appropriately reflect time-dependencies in event rates that are implicitly captured in a PSM. To have been credible, it was considered that a discrete event simulation (DES) framework would have needed arm-specific evidence on heterogeneous pathways after relapse. Furthermore, the relative complexity of a DES would have added unquantifiable structural uncertainty without improving decision relevance beyond what can already be captured adequately in a PSM with leukaemia free, progressed disease, and death partitions.

In the absence of data on subsequent treatments after from the Brune *et al.* RCT and Nilsson *et al.* follow-up period, the only downstream treatment option captured in the model was post-progression best supportive care. This was modelled in line with best supportive care in the oral azacitadine technology appraisal, with proportions of the population assumed to be receiving hydroxycarbamide (15%), ciprofloxacin (30%), posaconazole (15%), fluconazole (15%), and tranexamic acid (15%). The exclusion of allogeneic stem cell transplantation from the subsequent treatment modelling was justified on the grounds that patients were ineligible for stem cell transplantation at the point of enrolment in the Brune *et al.* RCT.

A comparison of the model with economic analyses conducted as part of previous NICE technology appraisals is presented in Table 17.

Table 17 Features of the economic analysis compared with previous submitted analyses

Factor	Previous evaluation, TA523	Previous evaluation, TA827	Current evaluation, chosen values	Current evaluation, justification
Time horizon	54 years	30 years	60 years	For the target population, this covers patient lifetimes and would therefore be anticipated to capture the full extent of costs and benefits to patients.
Model structure	Partitioned survival model	Partitioned survival model	Partitioned survival model	Partition endpoints aligned with the primary and secondary endpoints of the Brune *et al.* RCT. Common approach to modelling AML.
Treatment waning effect?	No waning	No waning	No waning	There was no evidence to suggest any waning of the treatment effect in the Nilsson *et al.* follow-up data and the omission of waning is aligned with previous AML models.
Source of utilities	SLR and TTO study conducted to identify utility values	QUAZAR AML-001 trial for RFS health state; Joshi *et al.* 2019 for relapse heath state	Tremblay *et al.* 2018	Precedent for use of utility set in previous AML appraisals; relapse utility preferred by EAG in TA827.
Source of costs	BNF, NHS Reference Costs, PSSRU	eMIT, NHS Reference Costs, PSSRU	2023/24 National Cost Collection; eMIT, British National Formulary	Aligned with NHS and PSS cost perspective.

Abbreviations: AML, acute myeloid leukaemia; BNF, British National Formulary; eMIT, electronic market information tool; NHS, National Health Service; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; RCT, randomised controlled trial; SLR, systematic literature review; TTO, time trade-off.

Intervention technology and comparators

The intervention arm was histamine dihydrochloride and low-dose interleukin-2 (HDC/IL-2) in addition to standard of care versus standard of care alone. Clinical outcomes and adverse event rates in the standard of care arm were informed by outcomes from the Brune *et al.* RCT, while resource utilisation and costs were informed by a 2022 technology appraisal of oral azacitidine for maintenance treatment of AML after induction therapy (NICE TA827, 2022).

3.3 Clinical parameters and variables

Overall survival

Overall survival was modelled in both arms using parametric models fitted to the time-to-event data in adults with AML, in first complete remission, aged under 60 years of age, with normal karyotype. Several analyses were conducted on the time-to-event data to test for proportionality of hazards between the control and HDC-IL2 arms, including log-log plots (Figure 12), Cox–Snell residual plots (Figure 13), and Schoenfeld residuals plots (Figure 14).

Figure 12 Log-log plot of overall survival

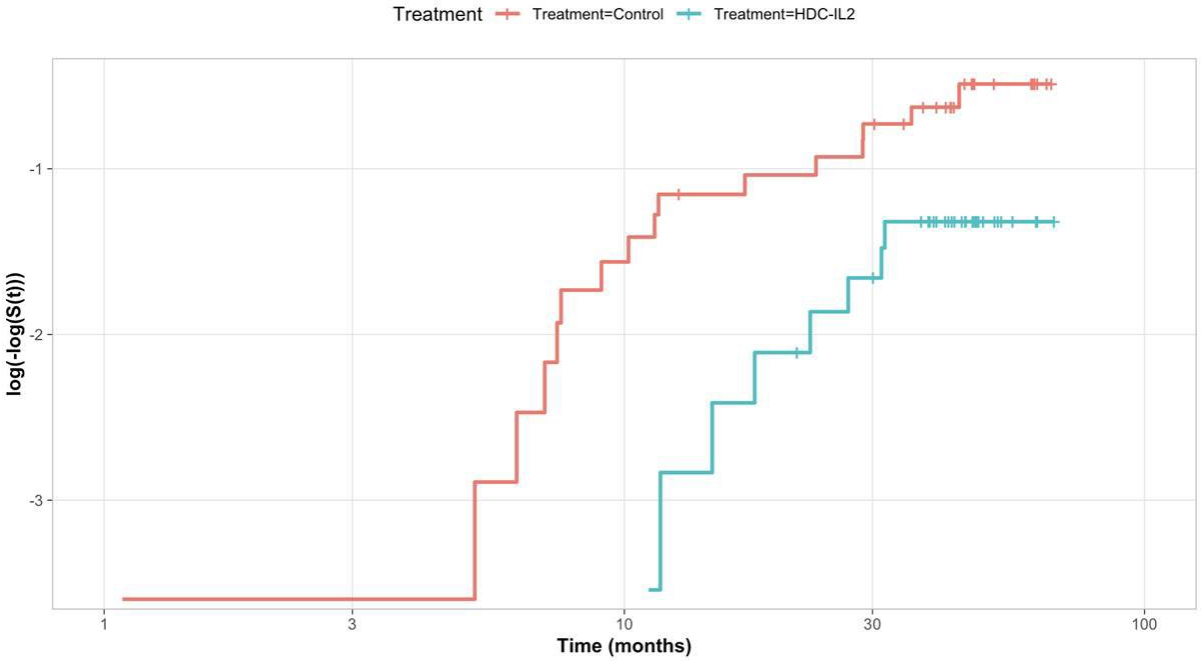
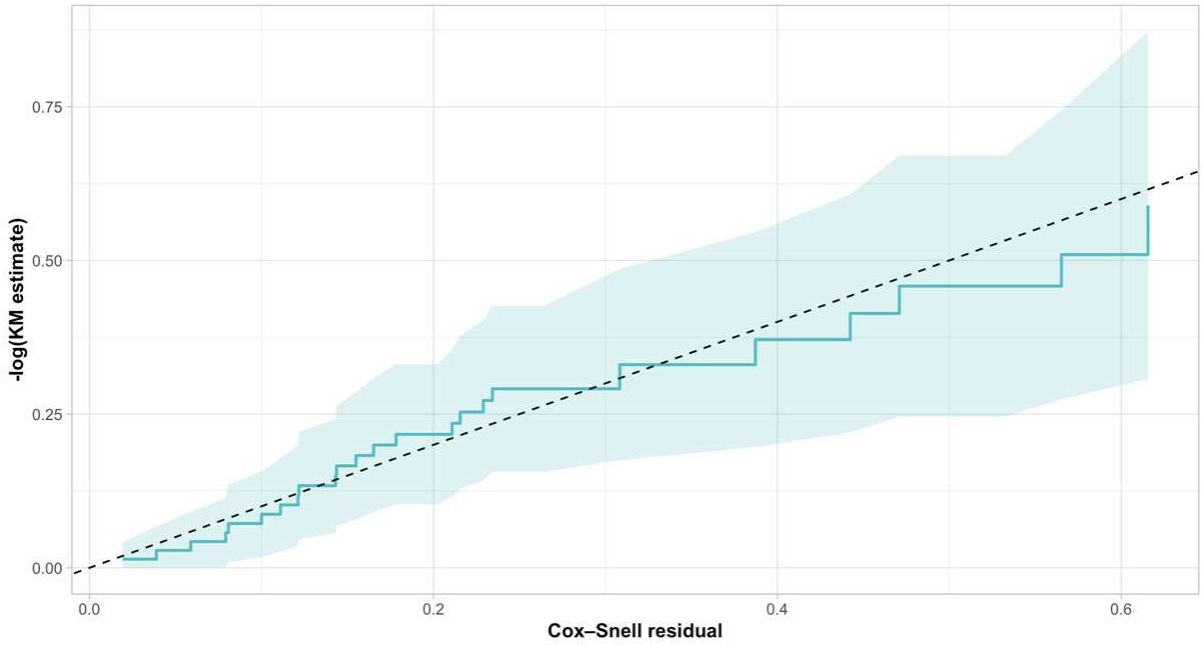
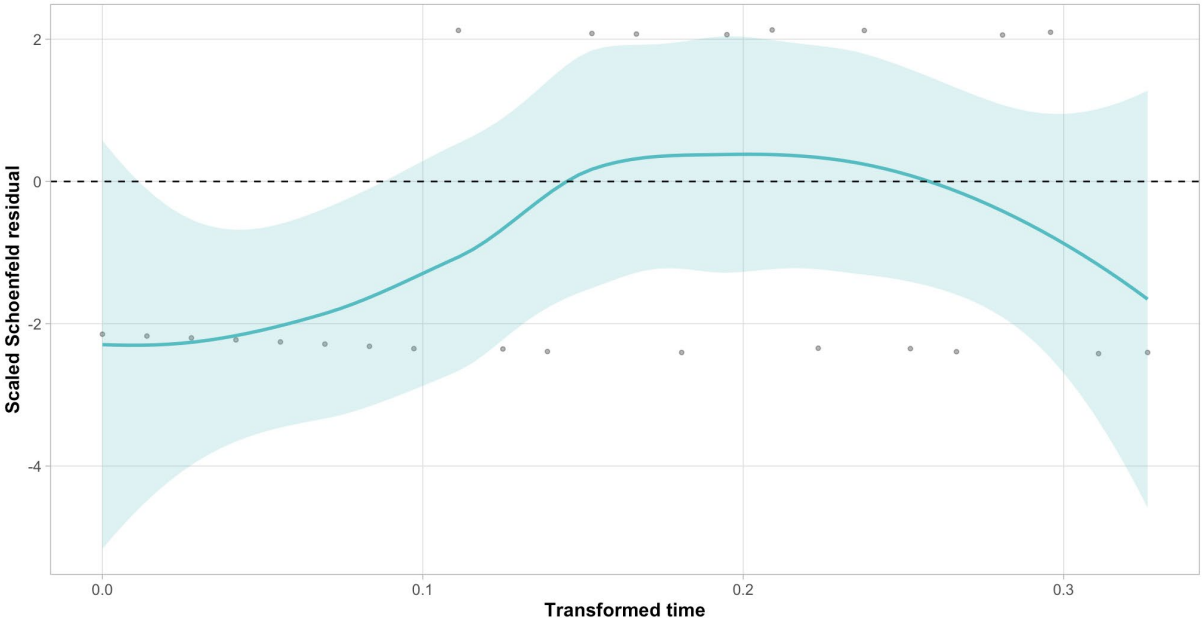


Figure 13 Cox-Snell residual plot and 95% confidence intervals of overall survival



Notes: Dashed line represents perfect proportionality of hazards.

Figure 14 Scaled Shoenfeld residuals of a Cox regression model fit to the overall survival data

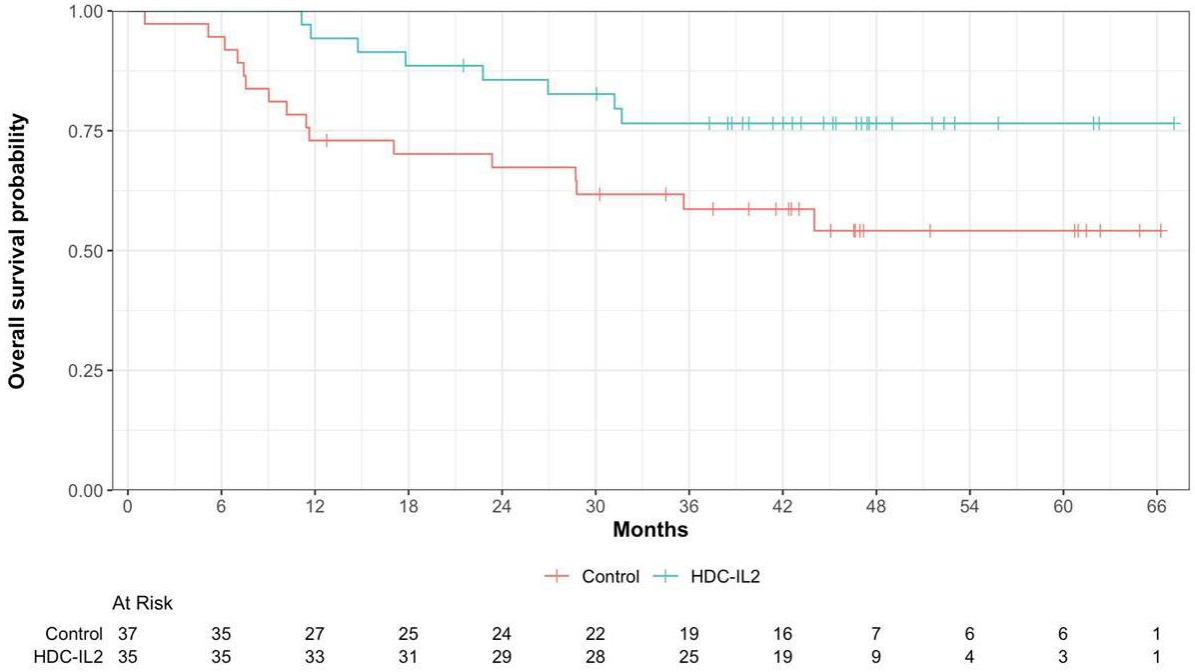


All diagnostic analyses and plots suggested that the proportional hazards assumption was not violated and combined parametric models were therefore fitted

with a treatment arm covariate rather than deriving separate parametric models for each treatment arm. The Shoenfeld residual plot (Figure 14) appeared to show a downward trend after an initial increase, but the p value of 0.15 for the treatment covariate indicated that the proportional hazard assumption could not be rejected. In particular, the p value of 0.15 for the treatment covariate in the Schoefeld residual analysis indicated that the proportional hazard assumption could not be rejected.

A Kaplan-Meier plot of overall survival showing the number at risk is presented in Figure 15.

Figure 15 Kaplan-Meier plot of overall survival and numbers at risk



To extrapolate overall survival beyond the maximum follow-up period in the Brune *et al.* RCT, the following parametric models were fitted to the OS time-to-event data using the `flexsurvreg` function in R: Weibull, exponential, gamma, log logistic, log normal, Gompertz, and generalised gamma. The model fits within the observed follow-up period are presented in Figure 16, with the extrapolations over 60 years presented in Figure 17.

Figure 16 Parametric model fits to overall survival data within the observed follow-up period

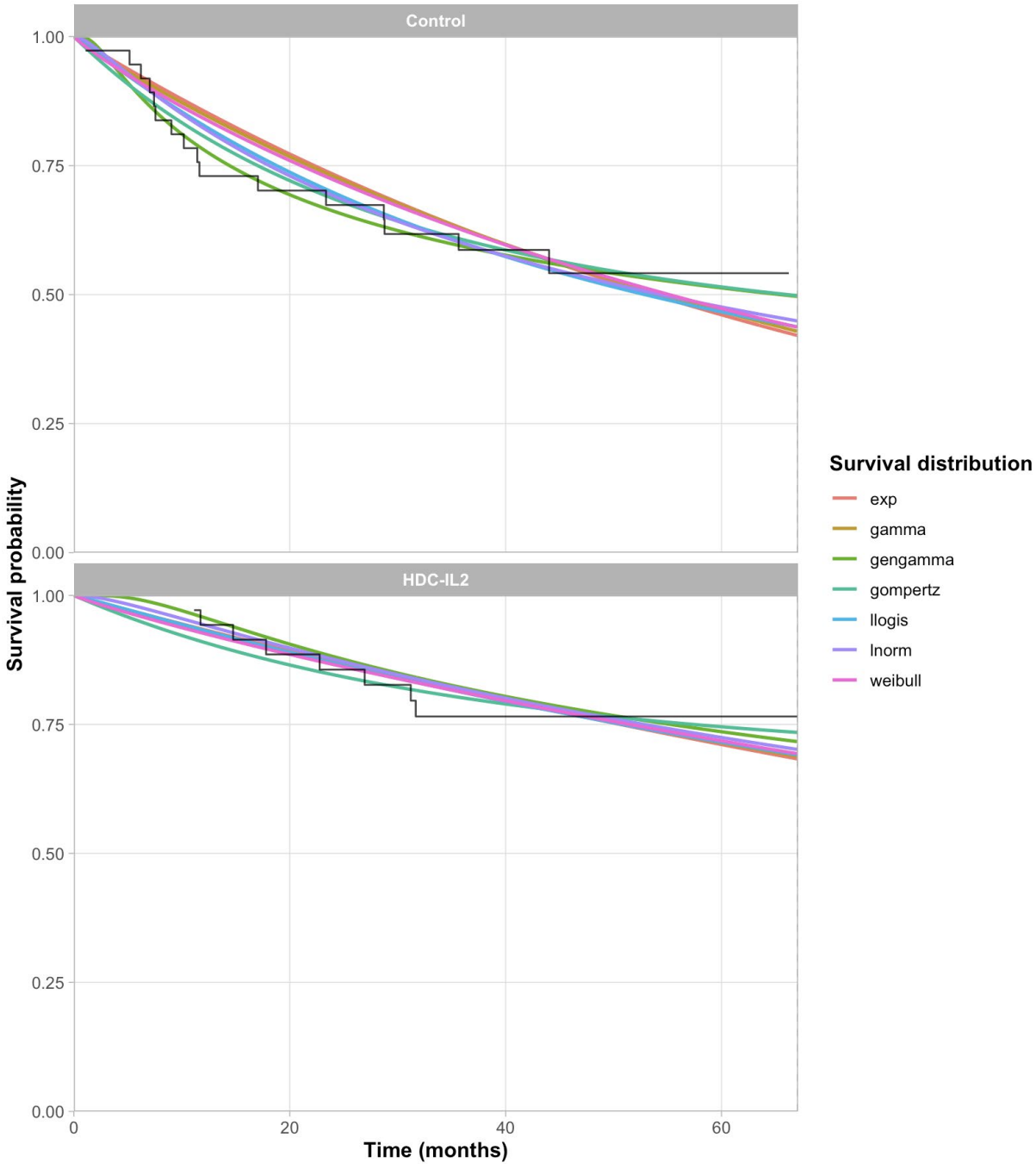
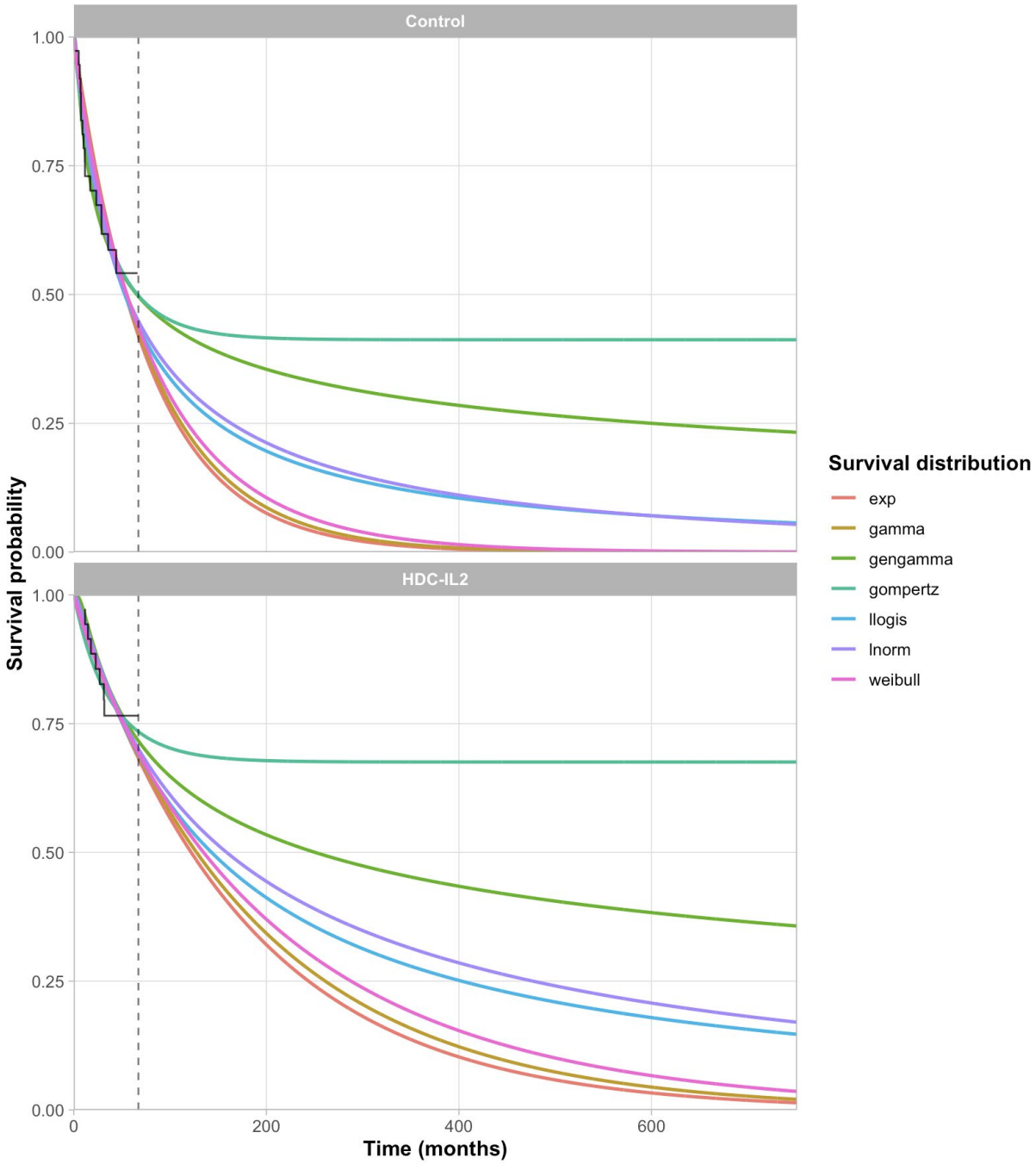


Figure 17 Parametric model fits to overall survival data and extrapolations up to 60 years (720 months)

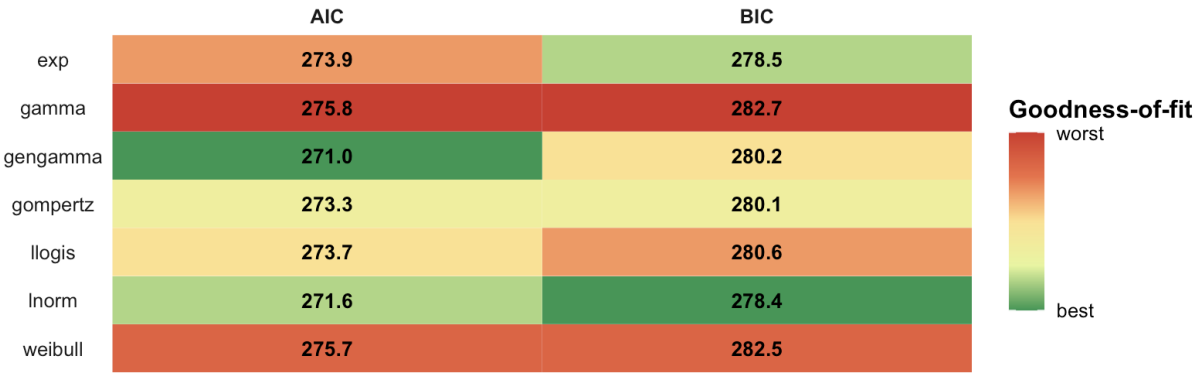


Notes: Dashed line marks end of observed follow-up (67.1 months).

The statistical goodness-of-fit of each model was assessed using the Akaike and Bayesian Information Criteria (AIC and BIC, respectively). The AIC and BIC criteria for each underlying survival distribution are presented in Figure 18. The generalised

gamma function was the best fit by AIC, while the lognormal fit was the best fit by BIC.

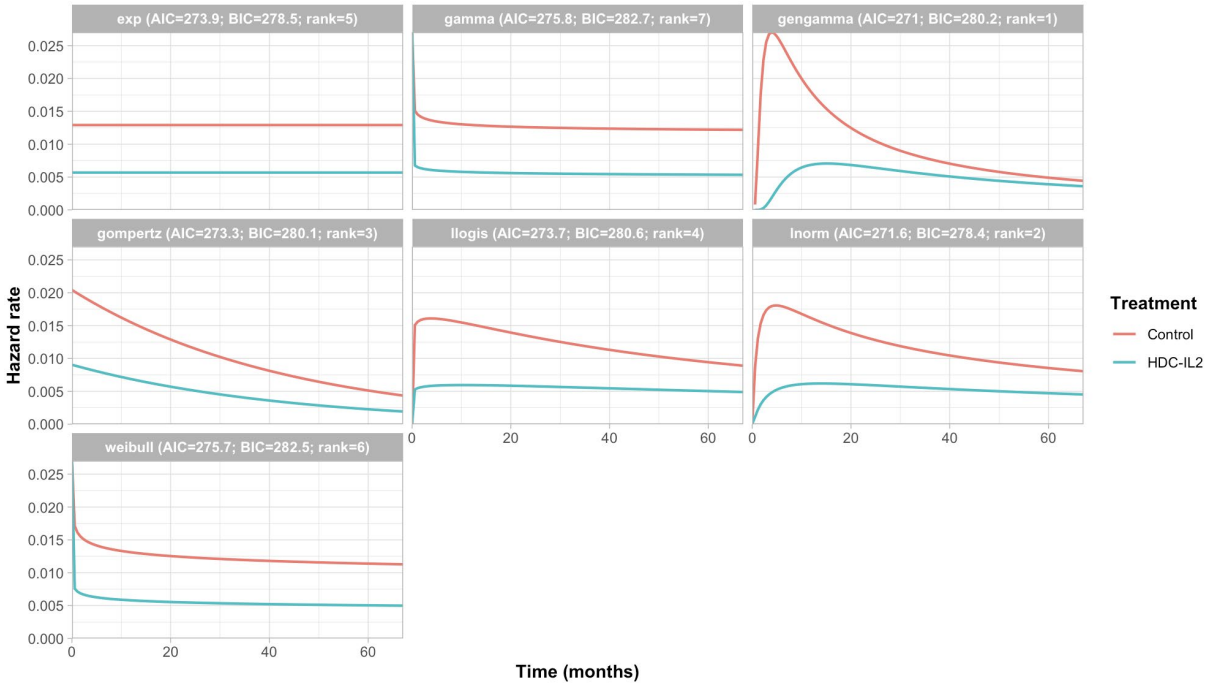
Figure 18 Statistical goodness-of-fit criteria for the fitted models of overall survival



Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Plots of the predicted instantaneous hazards from each of the fitted parametric models of overall survival are presented in Figure 19.

Figure 19 Modelled instantaneous hazards for each of the fitted overall survival parametric models



Based on the survival extrapolations, the Gompertz, generalised gamma, log logistic and log normal models yielded clinically implausible survival estimates over the extrapolation period, leaving the exponential, Weibull, and gamma distributions as only clinically plausible models for the purposes of extrapolation. As the gamma and Weibull models were ranked as the worst fit by AIC and BI, the exponential model was selected for use in the base case analysis. The exponential model was ranked the second best fit by BIC and fifth best fit by AIC.

Overall survival adjustment for age- and sex-match general population hazard

Within the economic model, additional functionality was incorporated into the survival modelling to ensure that the mortality hazard in any given cycle would not exceed the corresponding hazard in the age- and sex-matched general population based on life tables for England and Wales obtained from the ONS (ONS, 2023).

Leukaemia-free survival

As with overall survival, leukaemia-free survival was modelled in both arms using parametric models fitted to the time-to-event data in adults with AML, in first complete remission, aged under 60 years of age, with normal karyotype. The same diagnostic analyses were conducted on the time-to-event data to test for proportionality of hazards between the control and HDC-IL2 arms, including log-log plots (Figure 20), Cox–Snell residual plots (Figure 21), and Schoenfeld residuals plots (Figure 22).

Figure 20 Log-log plot of leukaemia-free survival

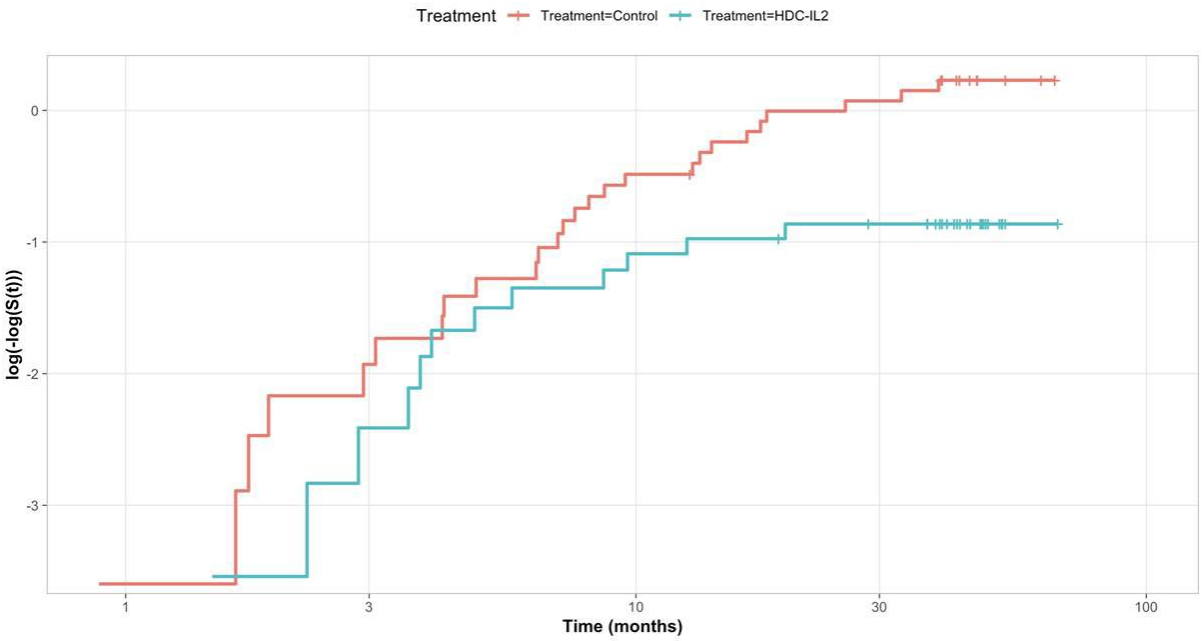
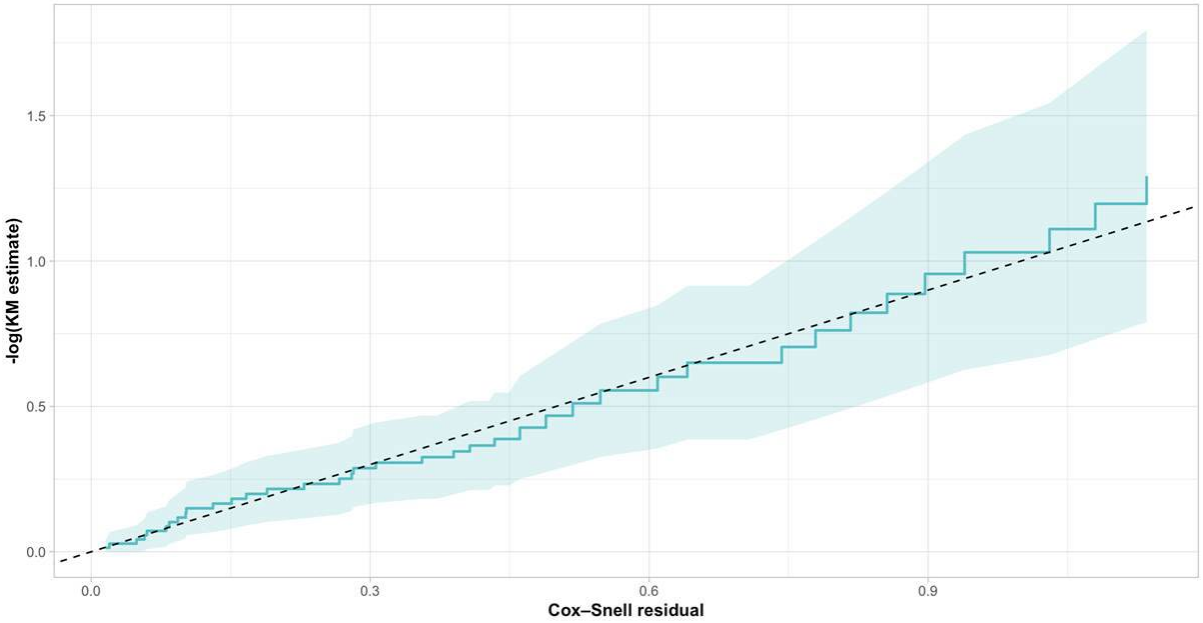
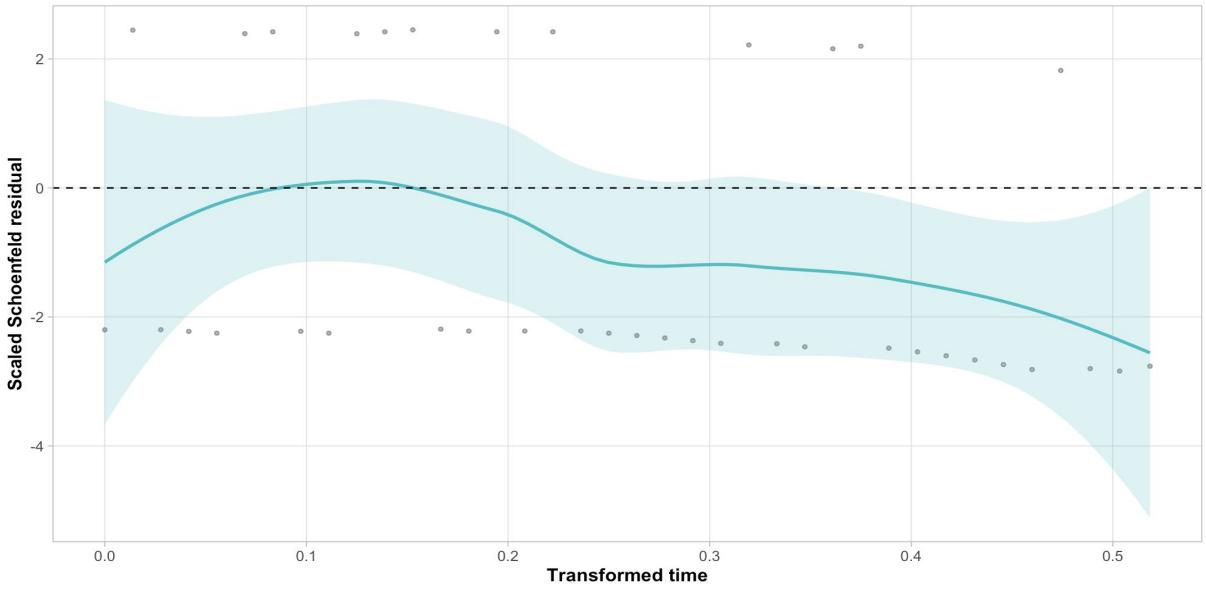


Figure 21 Cox-Snell residual plot and 95% confidence intervals of leukaemia-free survival



Notes: Dashed line represents perfect proportionality of hazards.

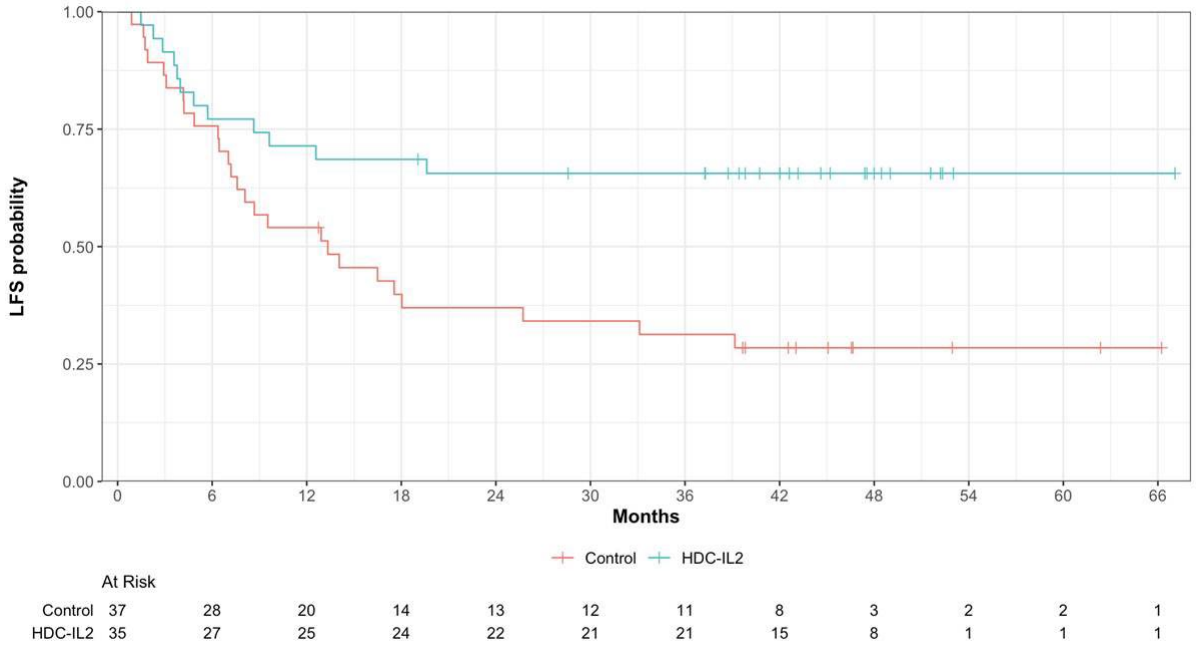
Figure 22 Scaled Shoenfeld residuals of a Cox regression model fit to the leukaemia-free survival data



As with overall survival, all diagnostic plots suggested that the proportional hazards assumption was not violated and combined parametric models were therefore fitted with a treatment arm covariate rather than deriving separate parametric models for each treatment arm. The plot of Schoenfeld residuals from a Cox model of LFS including a treatment covariate appeared to show a downward trend after an initial increase, but the p-value of 0.076 for the treatment covariate indicated that the proportional hazard assumption could not be rejected.

A Kaplan-Meier plot of leukaemia-free survival showing the number at risk is presented in Figure 23.

Figure 23 Kaplan-Meier plot of leukaemia-free survival and numbers at risk



To extrapolate leukaemia-free survival beyond the maximum follow-up period in the Brune *et al.* RCT, the following parametric models were fitted to the OS time-to-event data using the flexsurvreg function in R: Weibull, exponential, gamma, log logistic, log normal, Gompertz, and generalised gamma. The model fits within the observed follow-up period are presented in Figure 24, with the extrapolations over 60 years presented in Figure 25.

Figure 24 Parametric model fits to leukaemia-free survival data within the observed follow-up period

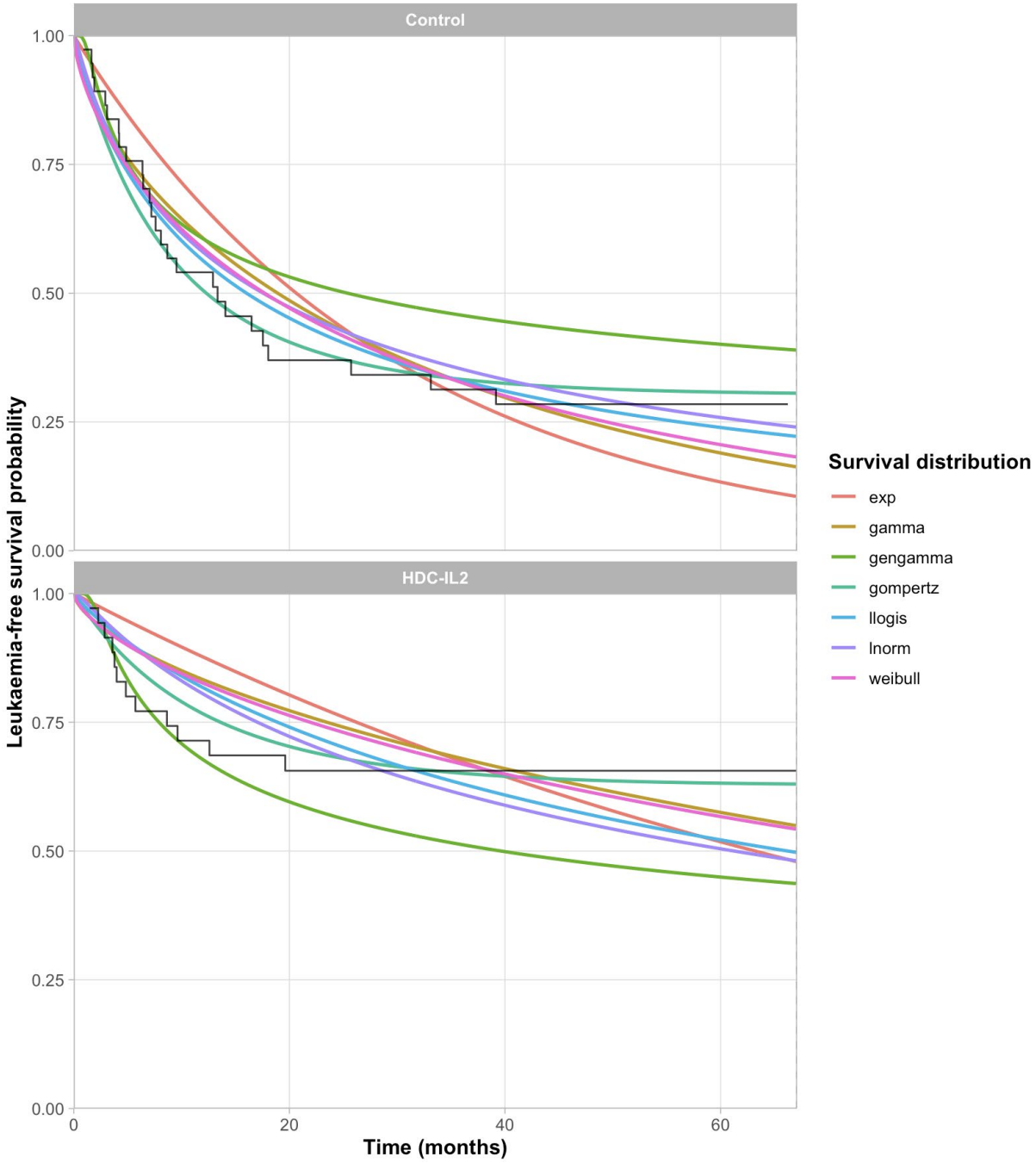
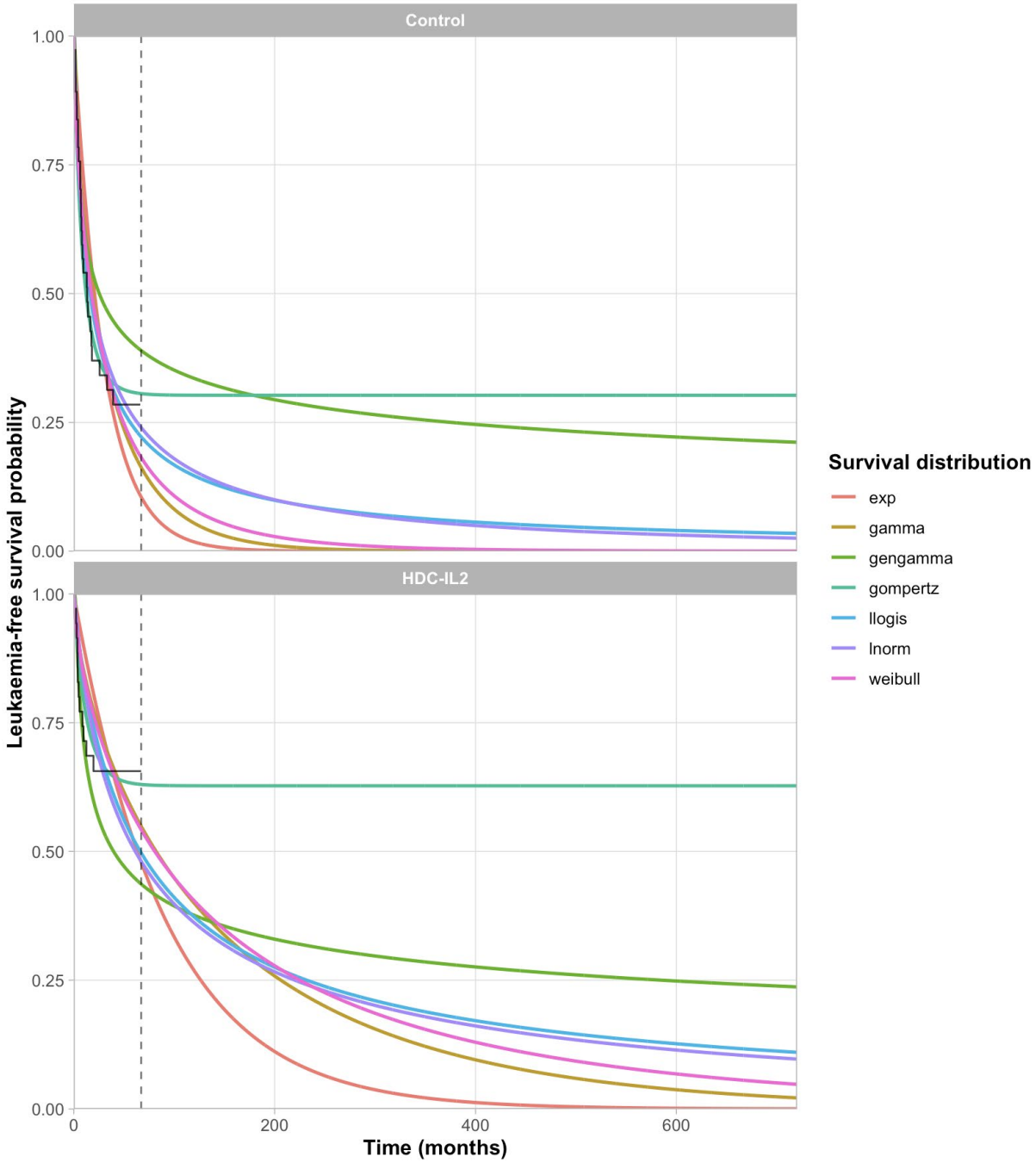
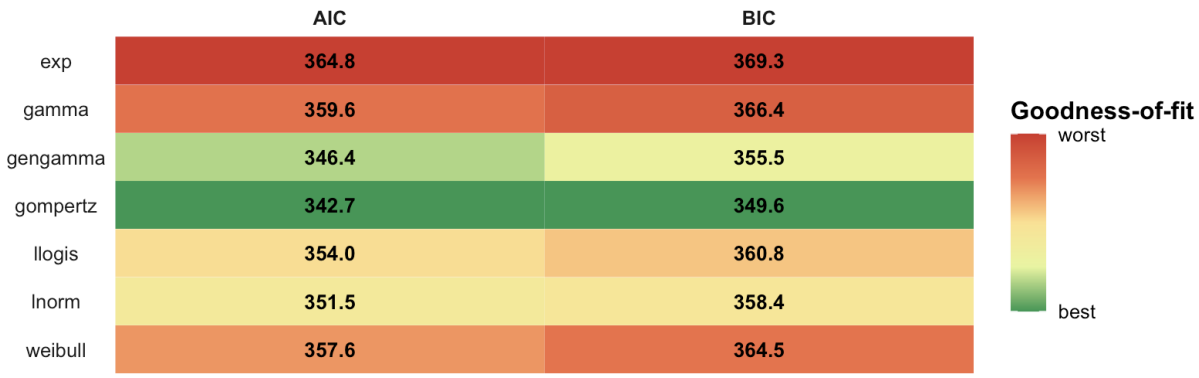


Figure 25 Parametric model fits to leukaemia-free data and extrapolations up to 60 years (720 months)



The statistical goodness-of-fit of each model was assessed using the Akaike and Bayesian Information Criteria (AIC and BIC, respectively). The AIC and BIC criteria for each underlying survival distribution are presented in Figure 26. The Gompertz fit was the best fit by both AIC and BIC.

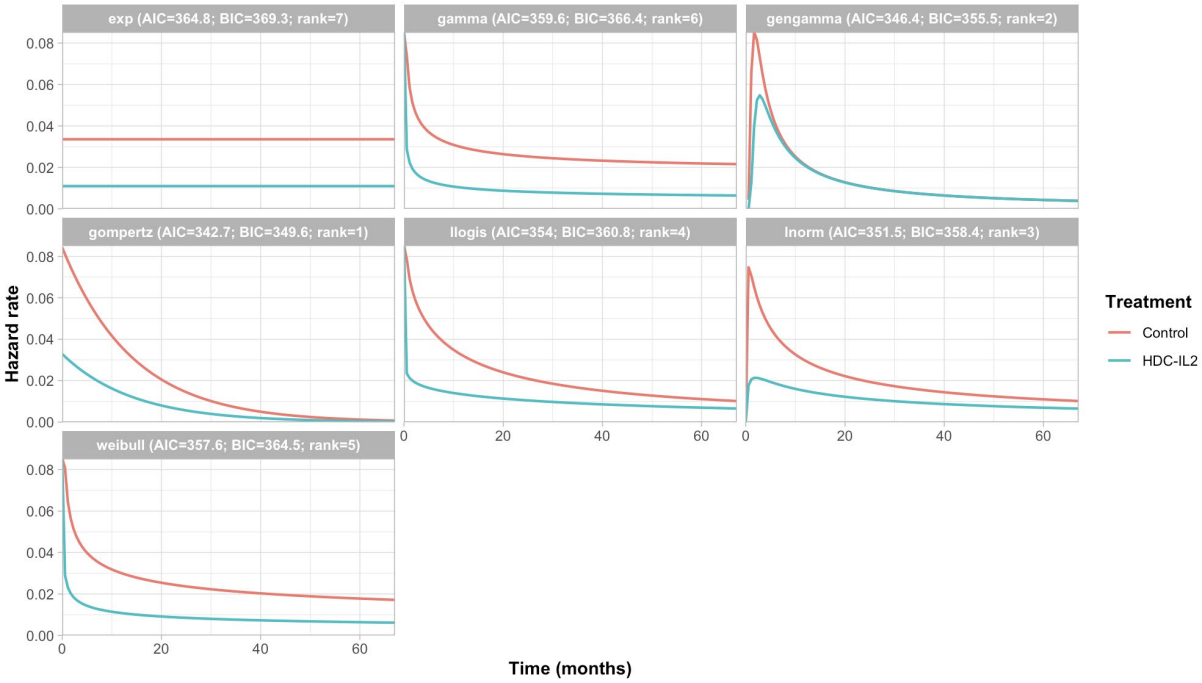
Figure 26 Statistical goodness-of-fit criteria for the fitted parametric models of leukaemia-free survival



Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Plots of the predicted instantaneous hazards of leukemia-free survival from each of the fitted parametric models are presented in Figure 27.

Figure 27 Modelled instantaneous hazards for each of the fitted leukaemia-free survival parametric models



Based on the leukaemia-free survival extrapolations and the selected overall survival model, the Gompertz, generalised gamma, log logistic, lognormal, and Weibull models yielded clinically implausible estimates of leukaemia-free survival over the

extrapolation period, leaving the exponential and gamma distributions as the only clinically plausible models for the purposes of extrapolation. With the exponential model selected as the basis of the overall survival modelling, the exponential model provided the most conservative fit from the perspective of histamine dihydrochloride and low-dose interleukin-2 and was therefore selected for use in the base case analysis.

Treatment discontinuation

As data on time to treatment discontinuation were not available in the individual patient-level data from the Brune *et al.* RCT, treatment discontinuation was modelled in line with two factors: 1) the proportion of patients remaining in the leukaemia-free partition (i.e. those free of relapse) and 2) the AE-related discontinuation rate observed in the overall Brune *et al.* RCT population. This approach was in line with the treatment discontinuation rules specified in the Brune *et al.* RCT protocol.

In the Brune *et al.* RCT, thirteen patients (8.3%) in the HDC/IL-2 arm discontinued treatment because of AEs not related to relapse. As these AE-related discontinuation events were assumed to be driven by treatment initiation, the discontinuation was captured in the first cycle of the model, with patients then being exposed to the same partition membership models as in the standard of care arm for the remainder of the analysis. The full cost of one cycle of histamine dihydrochloride and low-dose interleukin-2 (including dispensing) was captured in all patients in the first cycle of the model, with treatment discontinuations then affecting costs in subsequent model cycles.

3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

The Brune *et al.* clinical trial recorded EORTC QLQ-C30 and the aggregate data have been presented previously (Wallhult *et al.* 2007); however, the individual patient-level data were not available for use in the present analysis, despite attempts to obtain them from coauthors of the Brune *et al.* RCT manuscript and the Wallhult *et al.* abstract. As the data in the Wallhult *et al.* analysis were not presented by health

state, they could not be used directly in the health economic model and alternative values were therefore sought.

Mapping

As individual patient-level data from the EORTC QLQ-C30 could not be obtained from the Brune *et al.* RCT, no mapping techniques were employed to derive generic outcome measure-based health state utility values from these data.

Health-related quality-of-life studies

Appendix F documents the methodology and findings of systematic searches for relevant health-related quality-of-life data.

Adverse reactions

Adverse event disutilities were not captured separately in the analysis as a 0.02 decrement in the health state utility values was applied in patients receiving treatment with histamine dihydrochloride and low-dose interleukin-2 verus those not receiving treatment, corresponding to an average annual loss of approximately one week in perfect health in those patients receiving treatment. This was considered to be conservative from the perspective of histamine dihydrochloride and low-dose interleukin-2 given the low incidence rates of Grade 3 and 4 adverse events in the Brune *et al.* RCT.

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

In the base case analysis, in the absence of data utility values were taken from a previous cost-utility analysis comparing midostaurin with standard of care in patients with AML in the UK (Tremblay *et al.* 2018). The on- and off-treatment utilities were used , and the post-progression utility was ultimately preferred by the external assessment group (EAG) in the technology appraisal of oral azacitadine for maintenance treatment of acute myeloid leukaemia after induction therapy (NICE, TA827). Specifically, while on-treatment in the LFS partition, a utility of 0.81 was applied, versus 0.83 off-treatment in the same partition. A health state utility value 0.53 was applied in the PD state.

As health state utility data were unavailable from the Brune *et al.* RCT and there was uncertainty around the comparability of the populations enrolled in the Brune et al. RCT and the target population of the Tremblay *et al.* (2018) analysis, three scenario analyses were conducted around the choice of the health state utility values. Scenarios 1 and 2 were informed by the utility value sets utilised and discussed in TA827, while scenario 3 was informed by a more recent cost-utility analysis identified through the quality of life literature searches (Appendix F). All three scenarios relied on sets of utility values that had been used together in previous cost-utility analyses published by Joshi *et al.* (2019), Stein *et al.* (2019), and Russell-Smith *et al.* (2021) for scenarios 1, 2, and 3, respectively.

Table 18 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	Standard deviation	Primary and secondary references	Justification
Base case analysis				
Pre-progression utility, on treatment	0.81	0.081	Tremblay *et al.* 2018 (SD assumed) from Batty *et al.* 2014	Aligned with EQ-5D-based off-treatment remission utility, while capturing toxicity effects
Pre-progression utility, off treatment	0.83	0.083	Tremblay *et al.* 2018 (SD assumed) from Leunis *et al.* 2014	Measured EQ-5D value in line with NICE reference case
Post-progression utility	0.51	0.053	Tremblay *et al.* 2018 (SD assumed) from Pan *et al.* 2010	Preferred by the EAG in TA827 of oral azacitadine
Scenario analysis 1: Joshi *et al.* 2019				
Pre-progression utility, on treatment	0.89	0.15	Joshi *et al.* 2019	Scenario analysis used in TA827
Pre-progression utility, off treatment	0.89	0.15	Joshi *et al.* 2019	
Post-progression utility	0.51	0.46	Joshi *et al.* 2019	
Scenario analysis 2: Stein *et al.* 2019				
Pre-progression utility, on treatment	0.87	0.087	Stein *et al.* 2019	Scenario analysis used in TA827
Pre-progression utility, off treatment	0.87	0.087	Stein *et al.* 2019	
Post-progression utility	0.62	0.062	Stein *et al.* 2019	
Scenario analysis 3: Russell-Smith *et al.* 2021				
Pre-progression utility, on treatment	0.74	0.074	Russell-Smith *et al.* 2021 from NICE TA399	Recent analysis of AML treatments in the UK setting
Pre-progression utility, off treatment	0.74	0.074	Russell-Smith *et al.* 2021 from NICE TA399	
Post-progression utility	0.568	0.057	Russell-Smith *et al.* 2021 from NICE TA399	

Abbreviations: EAG, external assessment group; EQ-5D, EuroQoL 5D; NICE, National Institute for Health and Care Excellence; SD, standard deviation.

3.5 Cost and healthcare resource use identification, measurement and valuation

Appendix G describes how relevant cost and healthcare resource data were identified in the systematic literature reviews.

Intervention and comparators' costs and resource use

The cost of treatment with histamine dihydrochloride and low-dose interleukin-2 was modelled in line with list prices from the British National Formulary for interleukin-2 and from Brancaster Pharma for histamine dihydrochloride (Table 19).

Dosing of histamine dihydrochloride and low-dose interleukin-2 was modelled over ten 21-day cycles of treatment over an 18-month period in those patients remaining on treatment (Section 3.3). Cycles 1 to 3 comprised 3 weeks of treatment and 3 weeks off treatment, with the off-treatment periods extended to 6 weeks for cycles 4 to 10. In each cycle, patients in the active treatment arm receive histamine dihydrochloride at 0.5 mg subcutaneously twice a day and human recombinant IL-2 (aldesleukin) 16,400 U/kg subcutaneously twice daily. In the model, IL-2 costs were calculated based on a mean weight of 78.45 kg, informed by the weighted average bodyweight from the NHS Health Survey for England 2021.

While histamine dihydrochloride and low-dose interleukin-2 can be administered subcutaneously by the patient at home, it was assumed that the patient would attend an outpatient appointment for the first administration in each cycle. An additional cost of one subcutaneous treatment administration of GBP 249.64 was therefore captured in each treatment cycle in line with the administration costs modelled in the technology appraisal of oral azacitadine. The cost of administration was informed by the 2023/24 National Cost Collection outpatient procedure cost code SB12Z "Deliver Simple Parenteral Chemotherapy at First Attendance" (Table 19).

Table 19 Costs of histamine dihydrochloride and interleukin-2

Item	Cost (GBP)	Source
HDC	3,600.00 per cycle	Brancaster Pharma (GBP 1,200 per pack of 14 vials)
IL-2 (per 18 m IU pack)	636.00	British National Formulary

Item	Cost (GBP)	Source
Subcutaneous treatment administration	249.64	NICE TA827 and 2023/24 National Cost Collection (Outpatient Procedures: Deliver Simple Parenteral Chemotherapy at First Attendance [SB12Z]; Service Code 303)

Abbreviations: GBP, pounds sterling; HDC, histamine dihydrochloride; IL-2, interleukin-2; IU, international units; NICE, National Institute for Health and Care Excellence.

Health-state unit costs and resource use

Unit costs of routine disease management (haematology and nurse visits, blood counts, transfusions, bone marrow biopsies), post-progression best supportive care, and end-of-life costs are presented in Table 20.

Table 20 Unit costs of disease management and best supportive care after progression

Item	Cost (GBP)	Source
Disease management		
Haematologist visit	204.32	NICE TA827 and 2023/24 National Cost Collection (Outpatient Care: Clinical Haematology Consultant-Led Non-Admitted Face-to-Face Attendance, Follow-up [WF01A]; Service Code 303)
Nurse visit	108.90	NICE TA827 and 2023/24 National Cost Collection (Community Health Services: Specialist Nursing, Cancer Related, Adult, Face to face [N10AF]; Service Code 03)
Complete blood count/lab test	2.98	NICE TA827 and 2023/24 National Cost Collection (Directly Accessed Pathology Services: Haematology [PATH05]; Service Code 999)
Chemistry and liver panel	1.53	NICE TA827 and 2023/24 National Cost Collection (Directly Accessed Pathology Services: Clinical Biochemistry [PATH04]; Service Code 999)
Red blood cell transfusion, platelet transfusion	386.96	NICE TA827 and 2023/24 National Cost Collection (Outpatient Procedures: Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over [SA44A]; Service Code 303)
Bone marrow aspirate/biopsy	775.46	NICE TA827 and 2023/24 National Cost Collection (Admitted Patient Care: Diagnostic Bone Marrow Extraction Daycase [SA33Z])

Item	Cost (GBP)	Source
Best supportive care after progression (per cycle costs)		
Hydroxycarbamide	3.91	NICE TA827 and eMIT July 2025
Ciprofloxacin	1.15	
Posaconazole	114.75	
Fluconazole	1.95	
Tranexamic acid	2.72	

Abbreviations: eMIT, electronic market information tool; GBP, pounds sterling; NICE, National Institute for Health and Care Excellence.

Additional details on the derivation of the per-cycle pharmacy costs of best supportive care after progression are presented in Table 21.

Table 21 Derivation of per-cycle, post-progression best supportive care costs

	Dose, mg	Doses per cycle	mg per tablet	Pack size	Pack price (GBP)	Cost (GBP) per	
						Dose	Cycle
Hydroxycarbamide (dose is mg/kg)	40	7	500	100	8.90	0.56	3.91
Ciprofloxacin	500	14	250	10	0.41	0.08	1.15
Posaconazole	400	21	100	96	131.14	5.46	114.75
Fluconazole	200	21	200	7	0.65	0.09	1.95
Tranexamic acid	1,000	21	500	60	3.88	0.13	2.72

Abbreviations: GBP, pounds sterling.

Adverse reaction unit costs and resource use

Adverse event incidence rates are presented in Table 7. These represent the frequency of Grade 3/4 adverse events reported in the Brune *et al.* RCT and were captured in the first cycle of the model only. The incidence rates of each adverse event are presented in Table 22, while the split between inpatient and outpatient treatment and the assumed costs of each are presented in Table 23.

Table 22 Grade 3/4 adverse event incidence rates from the Brune *et al.* randomised controlled trial

	HDC/IL-2, %	SOC, %
Fatigue	1.3%	1.3%
Nausea	1.3%	0.0%

	HDC/IL-2, %	SOC, %
Vomiting	0.6%	0.0%
Diarrhoea	1.9%	0.0%
Anaemia	1.3%	0.6%

Abbreviations: HDC/IL-2, histamine dihydrochloride and low-dose interleukin-2; SOC, standard of care.

Table 23 Cost and resource use assumption associated with Grade 3/4 adverse events

	Treated as outpatients, %	Non-elective short stay inpatient cost (GBP)	Day case cost (GBP)	Weighted cost (GBP)	Source
Fatigue	95.0%	864.11	515.66	533.08	2023/24 National Cost Collection Acute Sector Admitted Patient Care: SA25M AML with CC code 0-1
Nausea	100.0%	864.11	515.66	515.66	
Vomiting	95.0%	515.48	379.59	386.39	2023/24 National Cost Collection Acute Sector Admitted Patient Care: FD01J Gastrointestinal infections without interventions, with CC score 0-1
Diarrhoea	95.0%	515.48	379.59	386.39	
Anaemia	90.0%	490.98	367.81	380.13	2023/24 National Cost Collection Acute Sector Admitted Patient Care: SA04L Iron deficiency anaemia with CC score 0-1

Abbreviations: GBP, pounds sterling.

Miscellaneous unit costs and resource use

An end-of-life cost of GBP 5,481 was captured in the proportion of the cohort entering the death partition in the model in each cycle based on an average end-of-life healthcare cost from four different cancer types as reported by Round *et al.*

(2015; Table 24). This was derived from a 2014 value of GBP 4,254 inflated to 2024 values using the NHS Cost Inflation Index from the Personal Social Services Research Unit.

Table 24 End-of-life costs

Item	Cost (GBP)	Source
End-of-life cost	5,391	Round *et al.* 2015

3.6 Severity

The technology was conservatively modelled as not meeting the criteria for a severity weight to be applied.

The York QALY Shortfall Calculator was used to derive estimates of remaining QALYs without AML in a whole population sample age- and sex-matched to the overall AML population in the Brune *et al.* RCT (median age 57 years; 54% male). This population would be anticipated to experience an average of 13.70 additional QALYs based on an adjusted, limited-dependent, variable mixture model (ALDVMM) of 2014 HSE data (the York QALY Shortfall Calculator reference case; Schneider *et al.* 2021 and Hernandez-Alava *et al.*). In the base case economic analysis in the sub-group with AML in first complete remission, aged under 60 years of age, with normal karyotype, patients in the standard of care arm were expected to experience a futher 3.48 QALYs when discounted at 3.5% *per annum* or 4.08 undiscounted QALYs. Relative to the general population matched to the overall Brune *et al.* RCT population, this would correspond to an absolute shortfall of 10.40 QALYs or a proportional shortfall of 75.92%, which would not qualify for a severity weight.

The same analysis was then also conducted in the population in first complete remission, under 60 years of age, and with normal karyotype (mean age 44.2 years. 50% male), corresponding to the base case economic analysis. This population would be anticipated to experience an average of 17.62 additional QALYs using the same reference case analysis as in the overall AML population in the Brune *et al.* RCT. The absolute shortfall in this population may qualify

Table 9 Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Brune *et al.* population at randomisation		
Sex distribution	54% male	Section 2.2
Starting age	57 years	Section 2.2
First complete remission population, <60 years of age, normal karyotype		
Sex distribution	50% male	Section 3.2
Starting age	44.2 years	Section 3.2

3.7 Uncertainty

The economic analysis relied on efficacy from a predefined subgroup of the Brune *et al.* RCT (2006), specifically people with AML with normal karyotype, in CR1, and aged <60 years (histamine dihydrochloride plus low-dose interleukin-2 n=35; standard of care n=37). The small sample size and correspondingly wide confidence interval around the LFS and OS estimates results in heightened uncertainty relative to broader AML populations. Nevertheless, this subgroup remains the most appropriate for the decision problem because it matches the population in whom maintenance with histamine dihydrochloride plus low-dose interleukin-2 is already established; Nilsson *et al.* (2020) reported that the treatment effect appears greatest in patients with normal karyotype in CR1 under 60 years, supporting the face validity of using this subgroup to inform relative effectiveness in contemporary practice. The era in which the trial was conducted may also introduce some uncertainty around comparisons with modern standard of care as AML management and supportive care have changed since 2006 (for instance, with broader molecular risk stratification and changes in consolidation/transplant pathways). On this basis, the use of Brune *et al.* is justifiable despite its age, while acknowledging that any absolute survival gains for standard care may have shifted over time.

As in many health economic analyses, model uncertainty arises from extrapolating trial outcomes beyond the observed follow-up period and mapping them to long-term quality-adjusted survival estimates. Results are sensitive to the choice of parametric survival functions and to assumptions about the maintenance of the treatment effect over time, background mortality, and post-relapse pathways, the latter of which were

not modelled owing to lack of data. Key structural assumptions included that subsequent treatments after relapse across both arms would consist of best supportive care only. Directionally, improvements in standard care since 2006 could attenuate the incremental benefit of histamine dihydrochloride plus low-dose interleukin-2 if baseline outcomes have improved. Scenario and sensitivity analyses (alternative parametric forms) are therefore essential to characterise uncertainty; in these, histamine dihydrochloride plus low-dose interleukin-2 remained cost-effective, although the magnitude of benefit varied with changes to these assumptions.

3.8 Managed access proposal

A managed access proposal is not being made for histamine dihydrochloride and low-dose interleukin-2.

3.9 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A summary of the base inputs is presented in Table 25.

Table 25 Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Time horizon (years)	60	N/A	N/A
Age (years)	44.2	Not sampled	Section 3.2
Proportion male	50%	Not sampled	Section 3.2
Baseline weight (kg)	78.45	Not sampled	Section 3.2
Treatment discontinuation rate from adverse events	8.3%	Not sampled	Section 3.3
Pre-progression utility on-treatment	0.89	SD = 0.09 (beta distribution)	Section 3.4
Pre-progression utility off-treatment	0.89	SD = 0.09 (beta distribution)	Section 3.4
Post-progression utility	0.53	SD = 0.05 (beta distribution)	Section 3.4
OS model	Exponential model	Variance-covariance matrices	Section 3.3
LFS model	Exponential model	Variance-covariance matrices	Section 3.3
Fatigue, HDC/IL-2	1.30%	SD = 0.13% (beta distribution)	Section 3.5
Nausea, HDC/IL-2	1.30%	SD = 0.13% (beta distribution)	Section 3.5
Vomiting, HDC/IL-2	0.60%	SD = 0.06% (beta distribution)	Section 3.5
Diarrhoea, HDC/IL-2	1.90%	SD = 0.19% (beta distribution)	Section 3.5
Anaemia, HDC/IL-2	1.30%	SD = 0.13% (beta distribution)	Section 3.5
Fatigue, SoC	1.30%	SD = 0.13% (beta distribution)	Section 3.5
Nausea, SoC	0.00%	SD = 0.00% (beta distribution)	Section 3.5
Vomiting, SoC	0.00%	SD = 0.00% (beta distribution)	Section 3.5
Diarrhoea, SoC	0.00%	SD = 0.00% (beta distribution)	Section 3.5
Anaemia, SoC	0.60%	SD = 0.06% (beta distribution)	Section 3.5
HDC price	3,600.00	Not sampled	Section 3.5
IL-2 price	636.00	Not sampled	Section 3.5
IL-2 dose per kg/day (IUs)	32,800	Not sampled	Section 3.5

Assumptions

The economic model uses a PSM with three mutually exclusive health states (leukaemia-free survival, progressed disease, and death) to compare histamine dihydrochloride plus low-dose interleukin-2 with standard of care in adults with acute myeloid leukaemia. As with any PSM, health state occupancy over time is governed

by the area under the OS and LFS curves, with the proportion experiencing progressed disease derived as OS minus LFS at each time point. In the base case analysis, standard parametric models were fit to Kaplan–Meier data from the trial, with the base case model selected based on clinical plausibility and goodness of statistical fit. Mortality rates were also constrained so as to never fall below the rates observed in an age- and sex-matched population in England and Wales. This structure assumes that long-term risks captured in the extrapolated OS and LFS curves adequately reflect the disease course and competing risks, and that treatment effects are fully mediated through these endpoints.

In the base case analysis, the treatment effect was assumed to be durable over time in line with the models of LFS and OS; the Brune *et al.* RCT follow-up period extended to 60 months; beyond this time, outcomes are projected using the chosen parametric forms and the base case maintains the modelled relative treatment effect implied by those fits.

Subsequent allogeneic stem-cell transplantation was not explicitly modelled because patients were ineligible for transplant at baseline and data on use post-relapse was not available from the Brune *et al.* RCT. Omitting transplant costs and benefits would be expected to be conservative for histamine dihydrochloride plus low-dose interleukin-2, as any differential transplant use would likely result in higher costs in the comparator arm on account of the higher relapse rate.

Health-state utility values were sourced from Tremblay *et al.* (2018), with the choice of the Tremblay *et al.* relapse health state utility value being specifically aligned with the approach preferred by the EAG in the technology appraisal of oral azacitadine. Utilities used in Tremblay *et al.* were applied in the leukaemia-free and progressed disease partitions as detailed in Section 3.4, with mortality valued at zero. Uncertainty arising from the choice of utility inputs and the choice of extrapolation models has been explored in deterministic and probabilistic sensitivity analyses, and scenario results are presented alongside the base case.

3.10 Base-case results

Base-case incremental cost-effectiveness analysis results

Results from the deterministic base case analysis are presented in Table , with the corresponding net health benefit (NHB) results at willingness-to-pay thresholds of GBP 20,000 and GBP 30,000 per QALY presented in Table . The base case analysis showed that would result in an incremental cost-effectiveness ratio of GBP 25,810 per QALY versus the standard of care in patients with AML in first complete remission, aged under 60 years of age, with normal karyotype, and who were not eligible for allogeneic stem cell transplantation.

Table 26 Base-case results

Technologies	Total costs (GBP)	Total LYG	Total QALYs	Incremental costs (GBP)	Incremental LYG	Incremental QALYs	ICER versus baseline (GBP/QALY)	ICER incremental (GBP/QALY)
Standard of care	46,654	5.37	3.54					
HDC/IL-2	129,100	9.47	6.74	82,446	4.10	3.19	25,810	25,810

Abbreviations: GBP, pounds sterling; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 27 Net health benefit

Technologies	Total costs (GBP)	Total QALYs	Incremental costs (GBP)	Incremental QALYs	NHB at GBP 20,000 (QALYs)	NHB at GBP 30,000 (QALYs)
Standard of care	46,654	3.54	82,446	3.19	-0.928	+0.446
HDC/IL-2	129,100	6.74				

Abbreviations: GBP, pounds sterling; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

3.11 Exploring uncertainty

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to explore the impact of model parameter uncertainty on the results. One thousand model iterations were performed to yield a joint distribution of incremental costs and QALYs, characterising the uncertainty of the cost-effectiveness results. During PSA, survival (LFS and OS) model parameters were sampled based on the Cholesky decomposition of the covariance-variance matrices of the selected LFS and OS models to ensure the generation of correlated random samples. For utility values, beta distributions were used to restrict samples to between 0 and 1. Treatment costs were not varied during the PSA.

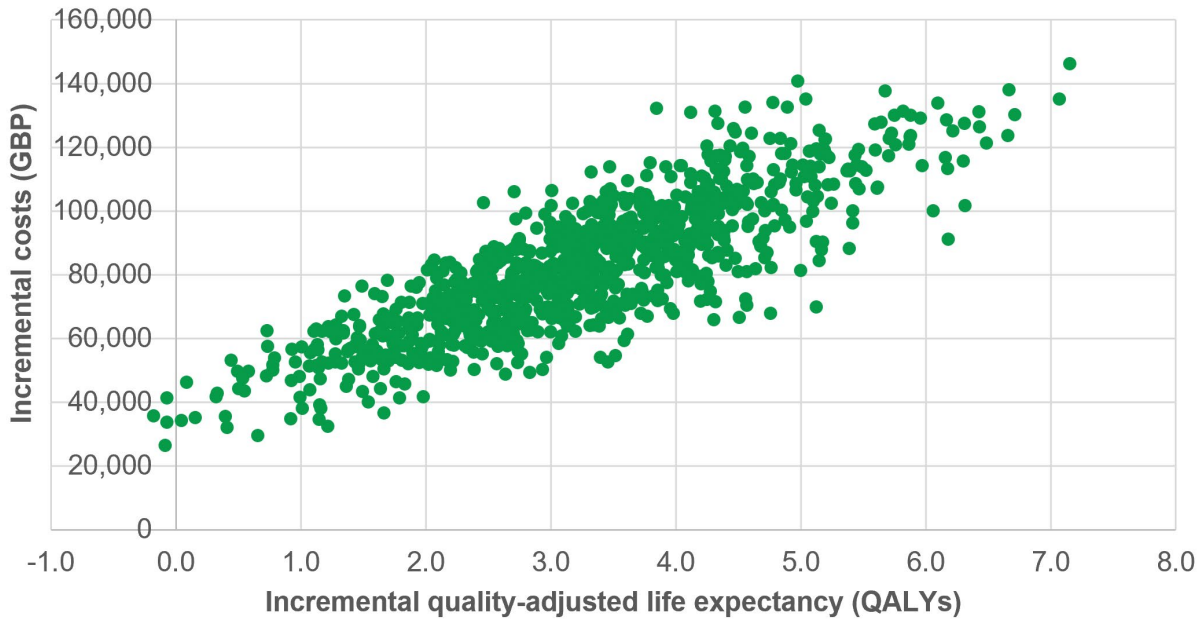
Total costs, QALYs and the incremental cost per QALY gained with histamine dihydrochloride and low-dose interleukin-2 versus standard of care are presented in Table 28. An incremental cost-effectiveness plane scatter plot and cost-effectiveness acceptability curve were generated to illustrate the degree of variability and uncertainty in the results graphically, as presented in Figure 28 and Figure 29. In the PSA, 99.6% of results fell in the northeast quadrant of the cost-effectiveness plane, representing increased costs and quality-adjusted life expectancy with histamine dihydrochloride and low-dose interleukin-2 versus standard of care. At a willingness-to-pay threshold of GBP 30,000 per QALY, there was a 73.8% likelihood of HDC/IL-2 being cost effective versus standard of care. Variation between deterministic and probabilistic analyses was relatively small, with the ICER differing by GBP 2,157 per QALY (GBP 27,967 per QALY in the probabilistic sensitivity analysis versus GBP 25,810 per QALY in the deterministic base case).

Table 28 Probabilistic sensitivity analysis results for histamine dihydrochloride and low-dose interleukin-2 versus standard of care

Technology	Mean cost (95% CrI), £	Mean QALYs (95% CrI)	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Standard of care	47,259 (28,349–70,165)	3.609 (2.451–5.055)		
HDC/IL-2	129,714 (98,988–168,236)	6.837 (4.653–9.292)		
Incremental	82,455 (44,298–126,053)	3.227 (0.923–5.755)	27,967 (17,103–53,390)	27,967 (17,103–53,390)

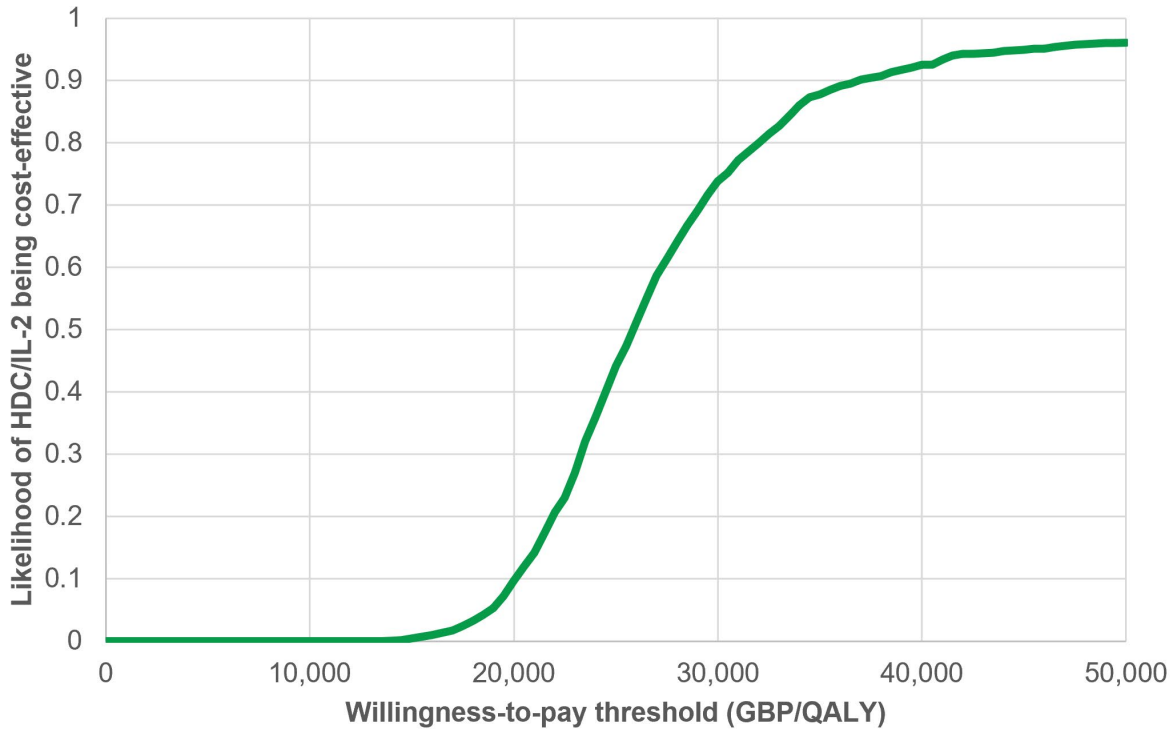
Abbreviations: CrI, Credible interval; ICER, Incremental costeffectiveness ratio; QALYs, Qualityadjusted life years.

Figure 28 Incremental cost effectiveness scatterplot showing incremental costs and QALYs with histamine dihydrochloride and low-dose interleukin-2 versus standard of care from 1,000 model iterations



Abbreviations: GBP, pounds sterling; QALYs, Qualityadjusted life years.

Figure 29 Cost effectiveness acceptability curve for histamine dihydrochloride and low-dose interleukin-2 versus standard of care showing the likelihood of cost effectiveness over a range of willingness to pay thresholds spanning GBP 0 per QALY gained to GBP 50,000 per QALY gained



Abbreviations: GBP, pounds sterling; HDC/IL-2, histamine dihydrochloride and low-dose interleukin-2; QALY, quality-adjusted life years.

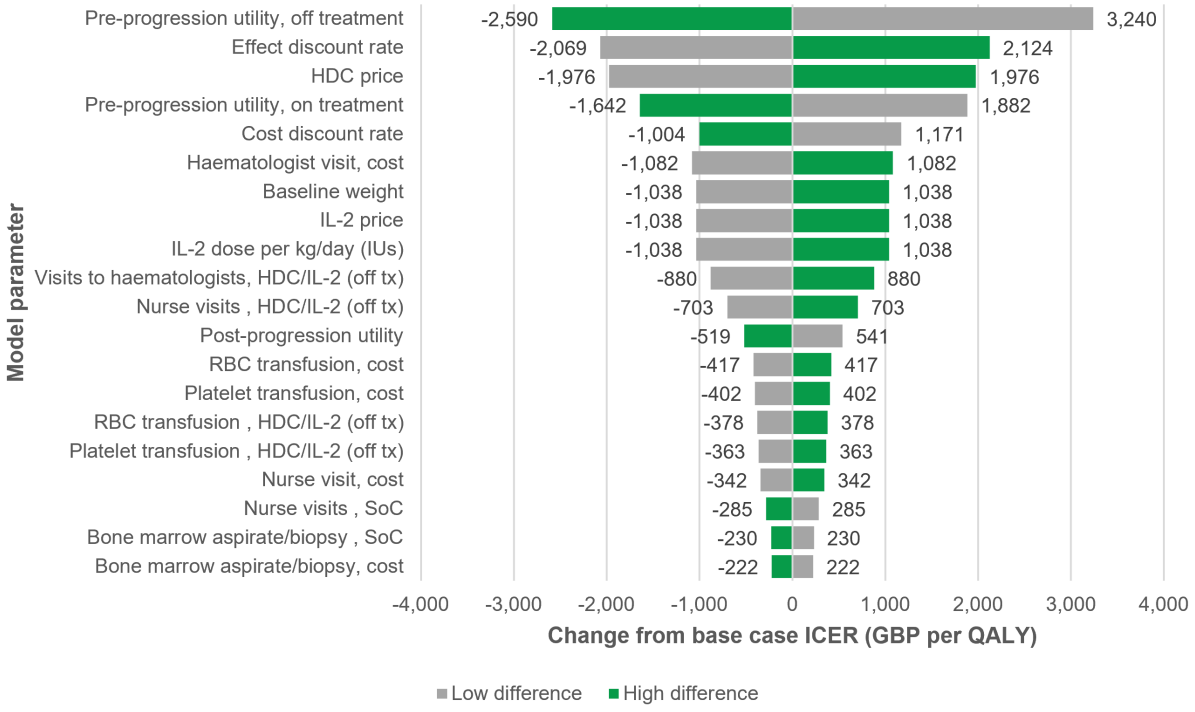
Deterministic sensitivity analysis

With the exception of the LFS and OS model parameters, which were only varied in the PSA, all model parameters were included in the deterministic sensitivity analysis (DSA). In the DSA, each parameter was individually varied up and down by 20% from its base case value, and the ICER for the low and high analyses was recorded. The base case ICER value was then subtracted from each to give the change from the base case, and the analyses were sorted in descending order of change and used to generate a Tornado diagram to illustrate the parameters with the largest effect on model outcomes (Figure 30). The absolute ICER values from each analysis are presented in Table 29.

None of the results from the DSA yielded an ICER greater than GBP 30,000 per QALY gained. The five parameters with the largest effect on the ICER were the pre-

progression off-treatment health state utility value, the effect discount rate, the price of histamine dihydrochloride, the pre-progression on-treatment health state utility value, and the cost discount rate. The pre-progression off-treatment health state utility value was the utility value responsible for the largest contribution to quality-adjusted life expectancy in the histamine dihydrochloride and low-dose interleukin-2 arm (Appendix I) and the magnitude of its effect on the ICER (in the absence of changes to the utilities in the standard of care arm) was therefore expected. Similarly, the pre-progression on-treatment utility, while contributing a smaller proportion to cumulative quality-adjusted life expectancy than the off-treatment utility, is responsible for the quality of life experienced in the first 18 cycles of the model where discounting has either no effect or a small effect.

Figure 30 Tornado diagram of the 20 parameters to which the model was most sensitive, ranked by the change from the base case ICER



Abbreviations: GBP, pounds sterling; HDC, histamine dihydrochloride; ICER, incremental cost-effectiveness ratio; HDC/IL-2, histamine dihydrochloride and low-dose interleukin-2; QALY, quality-adjusted life year; RBC, red blood cell; SoC, standard of care.

Table 29 Results of deterministic sensitivity analyses around the 20 parameters to which the model was most sensitive, ranked by the change from the base case ICER

Model parameter	Low (-20%)	High (+20%)	Low difference	High difference
Pre-progression utility, off treatment	29,050	23,220	3,240	-2,590
Effect discount rate	23,741	27,934	-2,069	2,124
HDC price	23,834	27,786	-1,976	1,976
Pre-progression utility, on treatment	27,692	24,168	1,882	-1,642
Cost discount rate	26,981	24,806	1,171	-1,004
Haematologist visit, cost	24,728	26,892	-1,082	1,082
Baseline weight	24,772	26,848	-1,038	1,038
IL-2 price	24,772	26,848	-1,038	1,038
IL-2 dose per kg/day (IUs)	24,772	26,848	-1,038	1,038
Visits to haematologists, HDC/IL-2 (off tx)	24,930	26,690	-880	880
Nurse visits, HDC/IL-2 (off tx)	25,107	26,513	-703	703
Post-progression utility	26,351	25,291	541	-519
RBC transfusion, cost	25,393	26,227	-417	417
Platelet transfusion, cost	25,408	26,212	-402	402
RBC transfusion, HDC/IL-2 (off tx)	25,432	26,188	-378	378
Platelet transfusion, HDC/IL-2 (off tx)	25,447	26,173	-363	363
Nurse visit, cost	25,468	26,152	-342	342
Nurse visits, SoC	26,095	25,525	285	-285
Bone marrow aspirate/biopsy, SoC	26,040	25,580	230	-230
Bone marrow aspirate/biopsy, cost	26,032	25,588	222	-222

Abbreviations: GBP, pounds sterling; HDC, histamine dihydrochloride; ICER, incremental cost-effectiveness ratio; HDC/IL-2, histamine dihydrochloride and low-dose interleukin-2; QALY, quality-adjusted life year; RBC, red blood cell; SoC, standard of care.

Scenario analysis

The results of scenario analyses are presented in Table 30. Scenario analyses included:

- Symmetrically changing the discount rates to 0% and 6% *per annum*.
- Changing the time horizon of the analysis to between 10 and 50 years inclusive in 10 year intervals.
- Selecting alternative parametric models for the extrapolation of LFS and OS to gamma, Gompertz, log logistic, log normal, Weibull, and generalised gamma.

- Alternative health state utility values as detailed in Section 3.4.

Scenario analyses showed that the model was sensitive to very short time horizons, with a 10-year time horizon pushing the ICER up to GBP 38,033 per QALY gained (from GBP 25,810 per QALY gained in the base case analysis).

Table 30 Scenario analysis results

Analysis	LYG			QALYs			Costs (GBP)	ICER (GBP/QALY)		
	SoC	HDC/IL-2	Δ	SoC	HDC/IL-2	Δ	SoC	HDC/IL-2	Δ	
Base case	**5.37**	**9.47**	**4.10**	**3.54**	**6.74**	**3.19**	**46,654**	**129,100**	**82,446**	**25,810**
Analysis parameters										
No discounting	6.45	13.51	7.06	4.16	9.28	5.12	57,659	167,106	109,447	21,382
Discounting costs and effects at 6% *per annum*	4.82	7.85	3.02	3.23	5.68	2.45	41,188	114,028	72,840	29,704
Time horizon 10 years	4.56	6.21	1.65	3.11	4.69	1.58	37,974	98,695	60,721	38,417
Time horizon 20 years	5.25	8.36	3.11	3.48	6.08	2.61	45,329	118,102	72,774	27,924
Time horizon 30 years	5.35	9.12	3.76	3.53	6.54	3.00	46,457	125,448	78,992	26,311
Time horizon 40 years	5.37	9.39	4.02	3.54	6.69	3.15	46,627	128,160	81,533	25,914
Time horizon 50 years	5.37	9.47	4.10	3.54	6.73	3.19	46,652	129,020	82,368	25,818
LFS extrapolations										
Gamma	5.37	9.47	4.10	3.63	7.32	3.69	45,107	120,534	75,426	20,456
Gompertz	8.50	13.71	5.21	6.61	11.09	4.48	53,295	141,060	87,765	19,606
Log logistic	5.86	9.81	3.95	4.28	7.50	3.22	43,268	122,506	79,238	24,586
Lognormal	5.79	9.74	3.95	4.27	7.41	3.14	42,252	122,337	80,085	25,519

Analysis	LYG			QALYs			Costs (GBP)	ICER (GBP/QALY)		
Weibull	5.37	9.56	4.19	3.70	7.37	3.67	43,875	120,505	76,630	20,903
Generalised gamma	8.48	10.39	1.91	6.77	7.74	0.97	50,315	121,119	70,804	73,128
OS extrapolations										
Gamma	5.51	9.79	4.28	3.62	6.90	3.29	48,071	132,223	84,152	25,612
Gompertz	10.48	15.10	4.62	6.25	9.72	3.47	97,222	184,811	87,590	25,245
Log logistic	7.03	11.17	4.14	4.42	7.63	3.21	63,068	145,845	82,777	25,771
Lognormal	7.26	11.69	4.43	4.55	7.91	3.37	65,392	151,044	85,651	25,447
Weibull	5.74	10.22	4.48	3.74	7.13	3.39	50,356	136,489	86,133	25,396
Generalised gamma	9.59	13.34	3.75	5.78	8.79	3.01	88,469	167,407	78,938	26,255
Health state utility values										
Utility scenario 1: Joshi *et al.* 2019	5.37	9.47	4.10	3.62	7.04	3.42	46,654	129,100	82,446	24,122
Utility scenario 2: Stein *et al.* 2019	5.37	9.47	4.10	3.91	7.33	3.42	46,654	129,100	82,446	24,134
Utility scenario 3: Russell-Smith *et al.* 2021	5.37	9.47	4.10	3.45	6.38	2.93	46,654	129,100	82,446	28,130

Abbreviations: GBP, pounds sterling; HDC, histamine dihydrochloride; ICER, incremental cost-effectiveness ratio; HDC/IL-2, histamine dihydrochloride and low-dose interleukin-2; QALY, quality-adjusted life year; RBC, red blood cell; SoC, standard of care.

3.12 Subgroup analysis

No subgroup analyses were performed.

3.13 Benefits not captured in the QALY calculation

No effects on family or caregiver quality of life (QoL) were included in the base case due to lack of data specifically in the target population of patients with AML in first complete remission, aged under 60 years, with normal karyotype; however, there is consistent evidence that caregiver and family QoL is adversely affected, particularly during periods when patients are not receiving active anti-leukaemic treatment (e.g., "watch-and-wait" or when disease-directed therapy is forgone). Caregivers of people with AML experience substantial burden and psychological morbidity over the course of treatment, indicating high susceptibility to QoL "spillover" effects (Grover *et al.*, 2019; Tan *et al.* 2023). In haematologic cancers, caregiver QoL closely tracks patients' symptom burden and social well-being and phases of uncontrolled disease or uncertainty are therefore associated with worse caregiver outcomes (Nielsen *et al.*, 2024). Moreover, in other cancers, RCTs of early/integrated palliative care (an active supportive intervention) have been shown to improve caregiver outcomes (e.g., reduced depression and anxiety), implying that caregivers fare worse when such treatment is absent (El-Jawahri *et al.* 2017). Taken together, any reduction in relapse risk and prolonged periods of controlled disease with histamine dihydrochloride plus low-dose interleukin-2 would be expected to reduce caregiver burden during "no-treatment" phases, and excluding these spillovers likely biases the QALY results against histamine dihydrochloride plus low-dose interleukin-2 by omitting material family and caregiver QoL benefits.

3.14 Validation

Validation of cost-effectiveness analysis

The cost-effectiveness model was developed by one researcher and independently validated by a second researcher. Validation included systematic extreme-value testing (pushing all continuous inputs to plausible bounds) and binary testing of on/off parameters and structural switches to confirm stable and expected behaviour across scenarios. Similar tests, such as setting all health state utility values to 1 to

ensure that quality-adjusted life expectancy equaled life expectancy, were also conducted.

Survival models were also reimplemented and cross-validated by reproducing the OS and LFS curves in R: parametric models were re-fit to the individual patient-level data by a second researcher using `flexsurvreg` and modelled LFS and OS outcomes were cross-checked against the R model outputs generated via the `summary()` function at common time points. LFS and OS predictions were numerically consistent with the `flexsurvreg` `summary()` results, providing assurance that survival extrapolations and downstream cost-effectiveness results were implemented correctly.

3.15 Interpretation and conclusions of economic evidence

In the base-case cost-utility analysis (from the NHS and Personal Social Services perspective over a lifetime horizon using a partitioned survival model capturing leukemia-free survival, progressed disease and death), histamine dihydrochloride plus low-dose interleukin-2 was compared with standard of care in adults with AML in first complete remission, aged under 60 years of age, with normal karyotype. Resource use included drug acquisition/administration, monitoring and adverse-event management, plus disease management costs after progression. Costs and outcomes were aggregated over a lifetime time horizon in line with the NICE reference case. The model projected total costs of GBP 129,100 and 6.74 QALYs (9.47 life-years) with histamine dihydrochloride plus low-dose interleukin-2 versus GBP 46,654 and 3.54 QALYs (5.37 life-years) for standard of care. This in turn yielded increments of GBP 82,446, 3.19 QALYs and 4.10 life-years, corresponding to a base case ICER of GBP 25,810 per QALY gained.

The incremental costs were primarily driven by the acquisition and delivery of HDC/IL-2, partially offset by lower downstream management costs due to delayed/avoided relapse. The incremental QALY gain arose from a combination of longer time in remission and improved overall survival, with health-state utilities applied from the published literature. Results were most sensitive to the time horizon of the analysis, survival extrapolation choices, and utility inputs. Not explicitly modelling allogeneic transplant post-relapse (patients were ineligible at baseline) is

expected to be conservative for HDC/IL-2. Deterministic and probabilistic analyses exploring these uncertainties are presented alongside the base case. Under these assumptions, histamine dihydrochloride plus low-dose interleukin-2 would be cost-effective at a willingness-to-pay threshold falling between the cost-effectiveness thresholds commonly applied by NICE (GBP 20,000 to GBP 30,000 per QALY).

4 References

ACS. (2019). Acute Myeloid Leukemia (AML) in Adults. https://www.cancer.org/cancer/types/acute-myeloid-leukemia.html

Aurelius J, Möllgård L, Kiffin R et al. Anthracycline-based consolidation may determine outcome of post-consolidation immunotherapy in AML. Leukemia and Lymphoma 2019, 60(11), 2771–2778. https://doi.org/10.1080/10428194.2019.1599110/SUPPL_FILE/ILAL_A_1599110_SM2136.PDF

Batty N, Yin Y, Wetzler M. Decitabine is more cost effective than cytarabine and daunorubicin in elderly acute myeloid leukemia patients. J Cancer Res Ther. 2014;2(4):68-73. http://dx.doi.org/10.14312/2052-4994.2014-9

Blum W, Sanford BL, Klisovic R, et al. Maintenance therapy with decitabine in younger adults with acute myeloid leukemia in first remission: a phase 2 Cancer and Leukemia Group B Study (CALGB 10503). Leukemia 2017; 31: 34–39

Brune M, Hellstrand K. Remission maintenance therapy with histamine and interleukin-2 in acute myelogenous leukaemia. Br J Haematol. 1996;92:620-626.

Brune M, Hansson M, Mellqvist UH et al. NK cell-mediated killing of AML blasts: role of histamine, monocytes and reactive oxygen metabolites. Eur J Haematol. 1996;57: 312-319.

Brune M, Castaigne S, Catalano J et al. Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. Blood 2006, 108(1), 88–96. https://doi.org/10.1182/BLOOD-2005-10-4073

Cancer Research UK, https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml (accessed 29th August 2025)

Data on file. (2006). Clinical Study Report (CSR). Multicenter Randomized Open-Label Study to Evaluate the Safety and Efficacy of Immunotherapy with Subcutaneous Ceplene™ (Histamine Dihydrochloride) plus Proleukin™ (Interleukin-

2) Versus No Treatment in Patients with Acute Myeloid Leukemia in First or Subsequent Complete Remission (CR).

Daver N, Schlenk RF, Russell NH, Levis MJ.Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia. 2019;33(2):299–312. https://doi.org/10.1038/s41375-018-0357-9

De Kouchkovsky I, Abdul-Hay M. Acute myeloid leukemia: a comprehensive review and 2016 update. Blood Cancer Journal. 2016;6(7):e441–e441. https://doi.org/10.1038/bcj.2016.50

Ding L, Ley TJ, Larson DE et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature. 2012;*481*(7382):506–510. https://doi.org/10.1038/nature10738

Döhner H, Wei AH, Appelbaum F et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345–1377. https://doi.org/10.1182/blood.2022016867

Dotevall G, Walan A. Gastric secretion of acid after intravenous infusion of histamine in large doses. Acta Med Scand. 1967;181:439-444.

Dotevall G, Walan A, Weinfeld A et al. Gastric secretion of acid and intrinsic factor during histamine infusion in 14 cases of duodenal ulcer. Scand J Haematol. 1967;4:169-175.

El-Jawahri A, Greer JA, Pirl WF, Park ER, Jackson VA, Back AL, Kamdar M, Jacobsen J, Chittenden EH, Rinaldi SP, Gallagher ER, Eusebio JR, Fishman S, VanDusen H, Li Z, Muzikansky A, Temel JS. Effects of Early Integrated Palliative Care on Caregivers of Patients with Lung and Gastrointestinal Cancer: A Randomized Clinical Trial. Oncologist. 2017;22(12):1528-1534. https://doi.org/10.1634/theoncologist.2017-0227

Grimwade D, Walker H, Oliver F et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The

Medical Research Council Adult and Children's Leukaemia Working Parties. Blood. 1998;92(7):2322–2333.

Grover S, Rina K, Malhotra P, Khadwal A. Caregiver Burden in the Patients of Acute Myeloblastic Leukemia. Indian J Hematol Blood Transfus. 2019;35(3):437-445. doi: 10.1007/s12288-018-1048-4. https://doi.org/10.1007/s12288-018-1048-4

Hellstrand K, Mellqvist UH, Wallhult E et al. Histamine and interleukin-2 in acute myelogenous leukemia. Leuk Lymphoma. 1997;27:429-438.

Joshi N, Hensen M, Patel S, Xu W, Lasch K, Stolk E. Health State Utilities for Acute Myeloid Leukaemia: A Time Trade-off Study. Pharmacoeconomics. 2019;37(1):85-92.

Juliusson G, Jadersten M, Deneberg S et al. The prognostic impact of FLT3-ITD and NPM1 mutation in adult AML is age-dependent in the population-based setting. Blood Advances. 2020;4(6):1094-1101.

Kantarjian H. Acute myeloid leukemia-Major progress over four decades and glimpses into the future. American Journal of Hematology. 2016;91(1):131-145. https://doi.org/10.1002/ajh.24246

Lanas AI, Anderson JW, Uemura N et al. Effects of cholinergic, histaminergic, and peptidergic stimulation on pepsinogen secretion by isolated human peptic cells. Scand J Gastroenterol. 1994;29:678-683.

Leunis A, Redekop WK, Uyl-de Groot CA, Löwenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. Eur J Haematol. 2014 Sep;93(3):198-206.

Martner A, Rydström A, Riise RE et al. Role of natural killer cell subsets and natural cytotoxicity receptors for the outcome of immunotherapy in acute myeloid leukemia. Oncoimmunology. 2015;5:e1041701.

Meropol NJ, Porter M, Blumenson LE et al. Daily subcutaneous injection of low-dose interleukin 2 expands natural killer cells in vivo without significant toxicity. Clin Cancer Res. 1996;2:669-677.

Nielsen IH, Tolver A, Piil K, Kjeldsen L, Grønbæk K, Jarden M. Family caregiver quality of life and symptom burden in patients with hematological cancer: A Danish nationwide cross-sectional study. Eur J Oncol Nurs. 2024;69:102538. https://doi.org/10.1016/j.ejon.2024.102538

NCCN. (2023). National Comprehensive Cancer Network. Acute Myeloid Leukemia. Version 3. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1411

Nilsson MS, Hallner A, Brune M et al. Immunotherapy with HDC/IL-2 may be clinically efficacious in acute myeloid leukemia of normal karyotype. Hum Vaccines Immunother 2020;16:109–111.

Nilsson MS, Martner A, Wennström L et al. Histamine dihydrochloride and low-dose interleukin-2 in an emerging landscape of relapse prevention in acute myeloid leukemia. Ther Adv Hematol 2025,16:1–13.

ONS. Life Tables for England and Wales. 2023. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables

Pan F, Peng S, Fleurence R, Linnehan JE, Knopf K, Kim E. Economic analysis of decitabine versus best supportive care in the treatment of intermediate- and high-risk myelodysplastic syndromes from a US payer perspective. Clin Ther. 2010;32(14):2444-56.

Patel SA, Litzow MR and Cerny J. Targeted and cytotoxic therapies as maintenance treatment for non-transplant eligible patients with acute myeloid leukemia. Blood Rev 2021; 50: 100863.

Potter N, Jovanovic J, Ivey A et al. Molecular monitoring versus standard clinical care in younger adults with acute myeloid leukaemia: results from the UK NCRI AML17 and AML19 randomised, controlled, phase 3 trials. Lancet Haematol 2025; 12: e346–56.

Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med. 2015;29(10):899-907.

Russell-Smith TA, Brockbank J, Mamolo C, Knight C. Cost Effectiveness of Gemtuzumab Ozogamicin in the First-Line Treatment of Acute Myeloid Leukaemia in the UK. Pharmacoecon Open. 2021;5(4):677-691.

Saultz J, Garzon R. Acute Myeloid Leukemia: A Concise Review. Journal of Clinical Medicine 2016;5(3):33. https://doi.org/10.3390/jcm5030033

Stein EM, Yang M, Guerin A, Gao W, Galebach P, Xiang CQ, Bhattacharyya S, Bonifacio G, Joseph GJ. Assessing utility values for treatment-related health states of acute myeloid leukemia in the United States. Health Qual Life Outcomes. 2018;16(1):193.

Tan KR, Chan YN, Iadonisi K, Poor E, Betancur S, Jung A, Sagester K, Coppola S, Pergolotti M, Kent EE, Schwartz T, Richardson D, Bryant AL. Perspectives of caregivers of older adults with acute myeloid leukemia during initial hypomethylating agents and venetoclax chemotherapy. Support Care Cancer. 2023;31(1):95. https://doi.org/10.1007/s00520-022-07565-7

Tremblay G, Dolph M, Patel S, Brandt P, Forsythe A. Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom. Cost Eff Resour Alloc. 2018;16:33.

Wei AH et al. Long-term survival with oral azacitidine for patients with acute myeloid leukemia in first remission after chemotherapy: Updated results from the randomized, placebo-controlled, phase 3 QUAZAR AML-001 trial. Am J Hematol. 2023;98:E84–E87.

Weigert N, Rowe JM, Lazarus HM, et al. Consolidation in AML: abundant opinion and much unknown. Blood Rev. 2022;51:100873.

Welch, JS, Ley TJ, Link DC et al. The Origin and Evolution of Mutations in Acute Myeloid Leukemia. Cell. 2012;150(2):264–278. https://doi.org/10.1016/j.cell.2012.06.023

5 Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analysis

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

Appendix F: Health-related quality-of-life studies

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Clinical outcomes and disaggregated results from the model

Appendix I: Price details of treatments included in the submission

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Summary of Information for Patients (SIP)

September 2025

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date

NICE SIP Brancaster HDC-IL-2 STA	**Final**	**No**	**10/09/25**

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response: Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection (HDC) (with interleukin-2 (IL-2)). The company has decided to only use a generic name and not use a brand name.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response: HDC/IL-2 is used in adults who have been treated successfully with chemotherapy and are in their first complete remission (CR1), have a normal karyotype (no chromosomal disorders), are not considered suitable for allogeneic stem cell transplantation and are 60 years or younger, to treat a particular type of leukaemia called acute myeloid leukaemia (AML) which is a cancer of blood forming cells in the bone marrow. HDC/IL-2 is used to maintain the remission (the period during which there is no evidence of disease). It will help the patients' immune system attack any remaining cancer cells after a previous cancer treatment.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: The product was approved by the MHRA on 1st August 2025. The approved SmPC can be viewed here - https://mhraproducts4853.blob.core.windows.net/docs/3d8f67b5dbe23379660d6adca51fa833edc47d40

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response: None to declare

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Response: The condition being assessed is acute myeloid leukaemia (AML) which is a type of rare cancer that affects the blood and bone marrow. AML accounted for less than 1% of all new cancer cases in the UK in 2017-2019. AML is estimated to have a UK annual incidence of around 2,900 new patients. Survival rates from AML are one of the lowest for all forms of cancer, with an estimated survival rate of just over 15% after 5 years (1). AML leads to a range of severe symptoms: • Profound fatigue and weakness: This is one of the most common and debilitating symptoms and is caused by anaemia • Increased risk of severe infections: The bone marrow produces abnormal white blood cells (myeloblasts) that don't function properly, and it crowds out healthy white blood cells (neutropenia). This severely compromises the immune system, making patients highly susceptible to frequent, severe, and potentially life-threatening infections (e.g., pneumonia, sepsis). Fevers are common. • Easy bruising and bleeding: Low platelet counts (thrombocytopenia) lead to impaired blood clotting. This can cause frequent nosebleeds, bleeding gums, heavy menstrual periods, easy bruising, tiny red spots on the skin (petechiae), and a risk of serious internal bleeding (e.g., in the brain or lungs). • Shortness of breath: Due to anaemia, patients may experience breathlessness, even at rest or with minimal activity. • Bone and joint pain: The build-up of leukaemia cells in the bone marrow can cause significant pain in bones and joints.

- Weight loss and loss of appetite: These are general symptoms of cancer that contribute to overall weakness.
- Organ enlargement and dysfunction: Leukaemia cells can infiltrate organs like the liver and spleen, causing swelling, discomfort, and potentially impaired function.
- Neurological symptoms (if spread to CNS): In rare cases, AML can spread to the brain and spinal cord, leading to severe headaches, seizures, blurred vision, confusion, or balance problems.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response: The diagnostic process for acute myeloid leukaemia (AML) typically begins with a complete blood count, a routine blood test that measures the number of red blood cells, white blood cells, and platelets. In a person with AML, the results often show an abnormal number of white blood cells, including the presence of immature, cancerous cells called myeloblasts, and low counts of red blood cells and platelets.

If the blood test suggests leukaemia, a bone marrow aspiration and biopsy is performed. A doctor uses a long, thin needle to extract a sample of liquid bone marrow and a small piece of bone from the hip. This sample is then examined under a microscope. A diagnosis of AML is confirmed if at least 20% of the cells in the bone marrow are myeloblasts.

Additional tests are then conducted on the blood and bone marrow samples to determine the specific subtype of AML and to help guide treatment. These include:

- Immunophenotyping: A test that identifies specific proteins on the surface of the leukaemia cells to classify the type of AML.
- Genetic and molecular testing: These tests look for specific changes in the chromosomes or DNA of the leukaemia cells, which can predict the disease's prognosis and help doctors choose the most effective treatment.

The diagnosis of AML is often an abrupt and life-changing event. The disease progresses quickly, requiring patients to begin aggressive treatment, often within days of diagnosis, which leaves little time to process the news or prepare. This creates significant physical and psychological challenges.

There are no additional diagnostic tests required for treatment with histamine dihydrochloride (HDC) with interleukin-2 (IL-2).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

Figure 1 Relapse prevention using HDC/IL-2 in AML: treatment schema

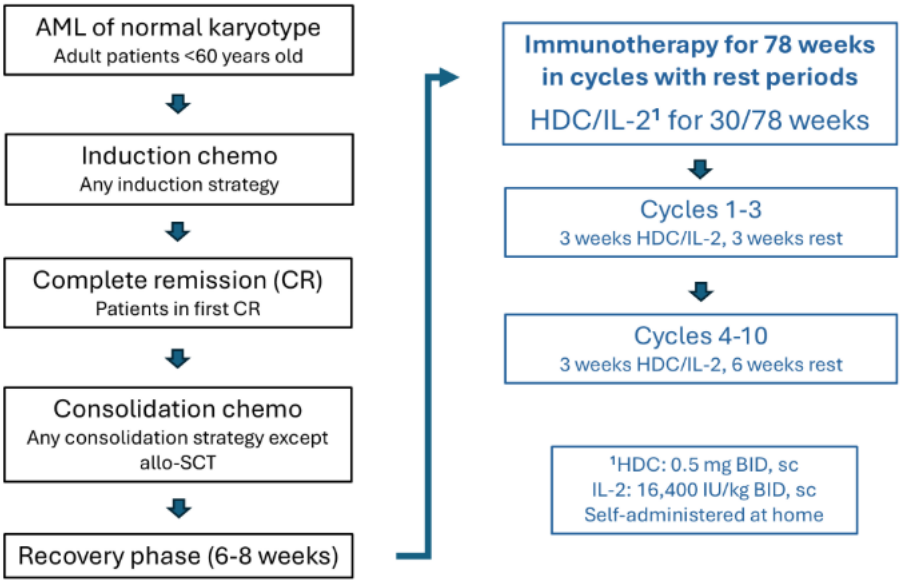


Figure 1 illustrates where immunotherapy with histamine dihydrochloride and interleukin-2 (HDC/IL-2) fits into the treatment pathway for patients with acute myeloid leukaemia (AML).

After diagnosis with a blood test and bone marrow biopsy where the specific cytogenetics and molecular genetics are investigated - these tests look for specific changes in the chromosomes or DNA of the leukaemia cells, which can predict the disease's prognosis and help doctors choose the most effective treatment - the patient would normally be offered intensive “induction therapy” (chemotherapy).

Older and less fit patients may be offered a less intensive alternative treatment.

The goal of “induction therapy” is to eradicate as many leukaemia cells as possible to achieve a ‘complete remission’, meaning the blood counts return to normal and there are no signs of leukaemia cells in the bone marrow.

After induction treatment and the patient is in complete remission a further consolidation treatment is normally given – this is also chemotherapy. At this stage, the patient’s doctors will perform a full assessment, looking at the genetic profile of the patient’s AML and response to treatment so far. The aim of this is to work out the risk of the leukaemia coming back in the future and aims to eliminate any remaining leukaemia cells that may not have been destroyed during induction and hence to prevent relapse. Without consolidation treatment, the AML is much more likely to come back

Allogeneic stem cell transplantation may be considered at this time depending on the fitness and prognosis of the patient.

HDC/IL-2 can then be offered as a maintenance immunotherapy after consolidation therapy to AML patients with normal karyotype who are in first complete remission and 60 years old or less

and who are not considered suitable for allogeneic stem cell transplant. This would be offered to further reduce the possibility of disease relapse.

HDC is contraindicated in the following circumstances:

- Patients with known allergy (hypersensitivity) to histamine or any of its ingredients.
- Patients with significantly compromised cardiac function
- Patients taking certain medications, including:
    - Steroids (e.g., prednisone, dexamethasone), which suppress immune function and reduce inflammation.
    - Clonidine, prescribed for high blood pressure.
    - H2-blockers (e.g., cimetidine, ranitidine, famotidine, nizatidine), used to treat stomach ulcers, indigestion, and heartburn.
- Patients who have received an allogeneic stem cell transplant (a type of bone marrow transplant) from a donor.
- During pregnancy or breastfeeding.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

In a study by LeBlanc T et al, 2015 (2) a semi-structured qualitative interview guide was developed to explore AML patients' experiences at diagnosis, satisfaction with clinical communication, factors related to prognostic understanding, and the treatment decision-making process. Thirty-three hospitalized patients with AML were enrolled within 7 days of starting a new treatment regimen, only those with high-risk AML due to either age >59, relapsed/refractory disease, or complex cytogenetics were interviewed. Interviews were audio recorded and transcribed for qualitative analysis.

Four themes emerged from this analysis, relating to: (1) uncertainty, (2) suddenness, (3) difficulty processing information, and (4) need for better communication. Patients frequently described uncertainty related to their prognosis, the number and nature of available treatments, and even the definition of the term "prognosis." In some cases this uncertainty was a source of hope, leaving open the possibility of a positive outcome. In other cases this uncertainty was crippling and frustrating. In terms of suddenness of the AML diagnosis, many patients described it as "overwhelming," "devastating," and "blindsiding," making them unable to process information and make a treatment decision. Many had not anticipated this severe change in health status. Compounding the suddenness for several patients was the need to travel far from home to be treated at a tertiary centre. Many patients found processing the complex information about their diagnosis and treatment options too difficult, which negatively impacted their understanding of available treatments. It was common for patients to separate options into either "do or die," when there were actually several available options of varying intensity and risk. Thus, patients perceived a lack of treatment choices and frequently exhibited negative coping behaviours, such

as cognitive distancing and denial. In terms of communication, most described their physicians as providing adequate information, yet sometimes described a mismatch between their needs and the type of information physicians provided. In the cases of mismatch, patients were less satisfied. Receiving bad news from a doctor they did not know stood out as a difficult and negative experience for many patients, and several described poor communication around the time of diagnosis.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:
Histamine dihydrochloride (HDC) when combined with interleukin-2 (IL-2) is an immunotherapy.

The mechanism of action of HDC when combined with IL-2 for the treatment of AML is by modulating the immune response to effectively target residual leukaemic cells, particularly by enhancing the cytotoxic activity of natural killer (NK) cells and T cells (3).

HDC inhibits release of immunosuppressive reactive oxidative species from myeloid-derived suppressor cells (MDSCs) and protects T and NK cells from inactivation.

IL-2 promotes T and NK cell expansion, activation and cytotoxicity. HDC with IL-2 work together to uphold T and NK cell function to eradicate remaining or arising leukaemic cells. HDC/IL-2 act synergistically as the only form of immunotherapy approved for maintenance treatment in AML.

Consistent with these effects, HDC with IL-2 has been found to be ineffective in the following groups: older patients (> 60 years) with aging immune systems (immunosenescence); patients likely to have increased residual disease having required more than one induction treatment to achieve remission, and in patients with abnormal tumour cell karyotype.

Patients ideally start HDC/IL-2 therapy 6-8 weeks after their last chemotherapy, when their immune system has been reconstituted.

A copy of the patient information leaflet can be found here:
https://mhraproducts4853.blob.core.windows.net/docs/f0de70133fbe07117522947c305684e814c3b9e6.

Healthcare professionals will be encouraged to consult the Summary of Product Characteristics (SmPC) that can be found here:
https://mhraproducts4853.blob.core.windows.net/docs/3d8f67b5dbe23379660d6adca51fa833edc47d40

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:
Yes.
During the treatment, the patient will always use interleukin-2 (IL-2) **and** Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection.
The mechanism of action and how the two products work synergistically is described in section 3a.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:
Histamine dihydrochloride (HDC) should be administered in combination with interleukin-2 (IL-2), according to its indication in AML. The dosage of both active ingredients is summarised as follows:

- HDC: It is administered through a subcutaneous injection twice daily 1 to 3 minutes after an injection of IL-2. Each 0.5 ml dose of HDC is administered slowly, over a period of 5 to 15 minutes.
- IL-2: It is administered by subcutaneous injection twice daily prior to HDC injection. Each dose of IL-2 is 16,400 IU/kg (1 µg/kg). IL-2 is commercially available as a recombinant IL-2; Proleukin® (aldesleukin).

HDC/IL-2 are administered in treatment cycles up to a maximum of 10 cycles, administered over a period of time up to 18 months. Each course consists of a 21-day (3-week) treatment period, followed by a non-treatment period that can be of three or six weeks in duration. In the case of cycles 1-3, each cycle consists of 3 weeks of treatment, followed by 3 weeks of no treatment. For cycles 4-10, each cycle consists of 3 weeks of treatment followed by 6 weeks of no treatment.

The first dose of HDC and IL-2 is administered in the hospital where the patient is instructed how to prepare and inject both IL-2 and HDC. Subsequent injections may be self-administered at home. Patients should remain seated for 20 minutes after injecting HDC.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

Details of the randomised controlled trial, Interleukin-2 Plus Histamine Dihydrochloride in Treating Patients With Acute Myeloid Leukemia (NCT00003991), published by Brune, 2006 (4) are as follows:

- Trial design: This was an open-label, randomised, multicentre phase 3 study. Patients were enrolled after the completion of induction and consolidation therapies and were randomly assigned to either a treatment or a best supportive care control arm. Patients were stratified by complete remission (CR) status, CR was defined as less than 5% blasts in a normocellular bone marrow. Altogether 320 patients were enrolled in the study, 261 patients in the CR1 group and 59 in the subsequent CR group. Patients were followed up for a minimum of 3-years post randomisation.
- Eligibility criteria: Patients aged 18 years or older with *de novo* or secondary AML were eligible for enrollment. Inclusion criteria were verified CR; adequate renal, cardiac, and pulmonary functions; and a performance status (according to Eastern Cooperative Oncology Group [ECOG] criteria) of 0 to 1. Any previous induction or consolidation therapy was allowed with the exception of allogeneic –stem cell transplant; other exclusion criteria included active peptic ulcer, a history of recent asthma, or previous hypersensitivity reactions. Elapsed time from dates of CR and the completion of consolidation chemotherapy were not to exceed 6 and 3 months, respectively.
- Settings and locations where the data were collected: AML patients were enrolled at 100 centers in Australia, Canada, Europe, Israel, New Zealand, and the United States between June 1998 and October 2000. All patients were managed through secondary or tertiary care services.

Details of the post-hoc analysis of the randomised controlled trial, Interleukin-2 Plus Histamine Dihydrochloride in Treating Patients With Acute Myeloid Leukemia (NCT00003991), published by Brune, 2006, published by Nilsson, 2020 (5) are as follows:

- Trial design: This was a post-hoc analysis of the randomised controlled trial, Interleukin-2 Plus Histamine Dihydrochloride in Treating Patients With Acute Myeloid Leukemia (NCT00003991), published by Brune, 2006.
- Eligibility criteria: The efficacy of HDC/IL-2 was assessed in CR1 patients with normal or aberrant karyotype AML who participated in the randomised phase III trial. The karyotypic features of leukemic cells were unknown in 36 of the 261 patients in CR1. Thus, data obtained from 225 CR1 patients with known karyotype were available for analysis of clinical outcome (LFS and OS).
- Settings and locations where the data were collected: As in the Brune, 2006 study summarised above.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

The primary endpoint of the Brune et al 2006 study (4) was duration of leukemia-free survival (LFS) in the intent-to-treat (ITT) population. Kaplan-Meier survival curves demonstrated a significant increase in LFS on HDC/IL-2 treatment with a median (95% confidence interval [95% CI]) of 324 days of LFS in the treatment group versus 264 in the best supportive care group ($P<0.01$). The primary study endpoint was therefore met. Interestingly the separation of the Kaplan-Meier curves was notable after 12-months and sustained for the duration of the follow up indicating that treatment with HDC/IL-2 was preventing relapse in some patients compared with the control arm.

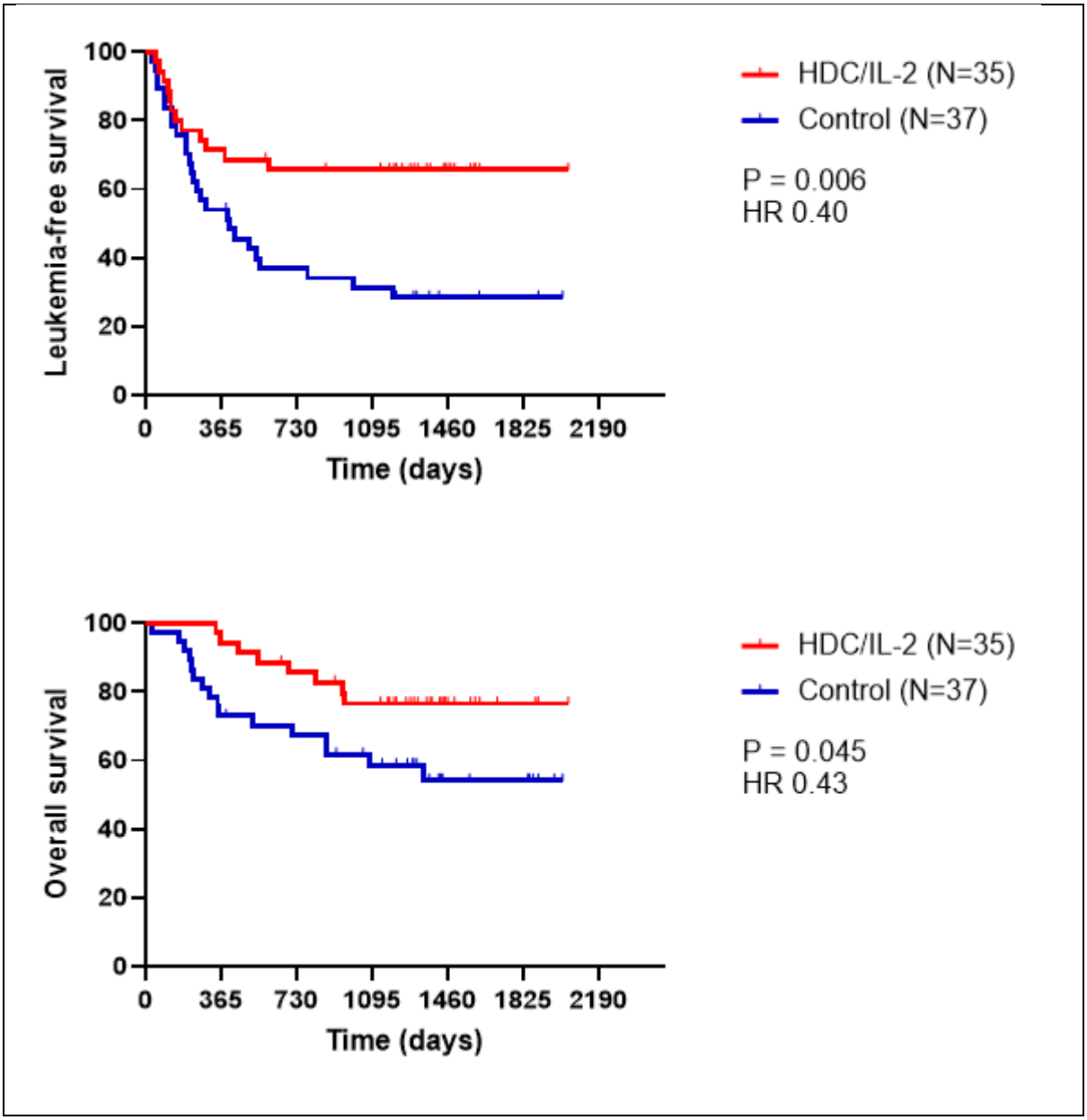
In a pre-planned analysis, the duration of leukemia-free survival (LFS) in patients in first complete remission (CR1) was evaluated (n=261). Kaplan-Meier survival curves demonstrated a significant increase in LFS on HDC/IL-2 treatment as shown in the group of patients with CR1, with a median (95% CI) of 450 days of LFS in the treatment group versus 291 in the control group (P=0.01). Among patients with CR1, 46 patients in the treatment group and 27 in the control group remained in CR1 at the study cut-off date. As with the ITT population, the Kaplan-Meier curves for the CR1 subgroup (n=261) shows that treatment with HDC/IL-2 has a sustained improvement in LFS for the duration of the follow-up in comparison with the control arm. This indicates that the immunotherapeutic impact of HDC/IL-2 is preventing relapse in some patients.

Leukaemia-free survival (LFS) was also evaluated in patients in patients in CR1 and who were 60 years or less (n=165). For the 80 patients treated with HDC/IL-2 who were in CR1 and ≤ 60 years of age, the Kaplan-Meier estimate of LFS at 36 months was 50% vs. 30% (p=0.01) for the 85 controls, or a relative improvement of 67%. In addition, there was a statistically significant improvement in median LFS of 1015 days in the HDC/IL-2 arm compared with 341 days in the control arm (p=0.01).

The study was not powered to demonstrate an overall survival (OS) advantage and statistical significance was not reached (P = 0.16) either for the intention-to-treat population or the CR1 remission status stratum (P = 0.12). The median OS for the CR1 patients was encouraging; treated patients had a median OS of 1289 days versus 842 days for the best supportive care arm.

A post-hoc analysis by Nilsson et al, 2020 (5) from the pivotal RCT by Brune et al 2006 (4) showed a profound treatment effect in those AML patients with normal karyotype in CR1 who were less than 60 years old. This subgroup of patients treated with HDC/IL-2 showed significantly improved LFS (P=0.006, HR=0.4) and OS (P=0.04, HR=0.43) vs. control patients. At 36-months after randomisation 65.6% of patients were leukaemia free on the HDC/IL-2 arm compared with 31.3% on the control arm and 76.5% were alive on the HDC/IL-2 arm compared to 58.7% on the control arm. The clinical evidence for this subgroup supports the base case in our economic submission.

The impressive efficacy effects in the subgroup of AML patients (normal karyotype, CR1 & <60 years) demonstrated in the separated Kaplan-Meier curves for LFS and OS show a sustained benefit for HDC/IL-2 treatment over controls for the duration of the follow-up period. This statistically significant improvement in both LFS and OS indicates that the immunotherapeutic impact of HDC/IL-2 is helping to prevent relapse in selected AML patients. The Kaplan-Meier curves are shown below.



3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information? Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).** Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.
Response: The Brune *et al.* clinical trial (3) recorded EORTC QLQ-C30 and the aggregate data have been presented by Wallhult *et al.* 2007 (6). Assessment of Quality of Life was performed using the validated EORTC-C30(v2) instrument at 8 pre-defined study visits: baseline; pre- and post-cycles 3, 5, and 8; and at 18 months. Comparisons were made between and within groups at baseline vs. each visit, pre- vs. post-treatment, and baseline vs. end of treatment (18 months).

At least one questionnaire was completed by 285 patients (89%). Patients in both study arms increased or maintained QoL status from baseline to last evaluation with respect to global health status, physical, cognitive and role functioning, and financial issues, as well as symptoms of fatigue, nausea/ vomiting, pain, diarrhea, and dyspnea. Comparisons of pre- vs. post-treatment QoL assessments showed transient increases in fatigue (P=0.008), nausea/vomiting (P=0.006), and appetite loss (P=0.005) in the treatment arm. In conclusion post-consolidation immunotherapy with HDC/IL-2 self-administered at home by AML patients was associated with transient gastrointestinal symptoms and fatigue but did not prevent recovery from induction/consolidation chemotherapy.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

Adverse events (AEs) reported from the randomised controlled study by Brune et al 2006 (4) were common, as expected, in AML patients being maintained in remission; many adverse events were associated temporally with clinical relapse. There were no treatment-related deaths. Only 13 of 157 patients in the HDC/IL-2 group discontinued treatment because of AEs not related to relapse. Overall, 96% (152/159) of patients in the control group and all patients in the HDC/IL-2 group reported at least 1 adverse event of any severity. The frequencies of grade 3 or 4 AE's, and of those events classified as serious AEs (SAE's), were similar in the 2 arms (43% of controls versus 52% of HDC/IL-2 patients reported grade 3 or 4 events and 18% versus 19% reported SAEs). HDC/IL-2 recipients reported more flushing, injection site reactions, headache, fatigue, pyrexia, and nausea. The most common AEs of grade 3 or 4 severity in the HDC/IL-2 group included thrombocytopenia (17%), headache (6%), and neutropenia (6%). The most frequent treatment-related serious adverse event was pyrexia (4 patients).

A copy of the patient information leaflet can be found here that details possible side effects under section 4:
https://mhraproducts4853.blob.core.windows.net/docs/f0de70133fbe07117522947c305684e814c3b9e6.

Healthcare professionals will be encouraged to consult the Summary of Product Characteristics (SmPC) that can be found here that sets out possible undesirable effects in section 4.8:
https://mhraproducts4853.blob.core.windows.net/docs/3d8f67b5dbe23379660d6adca51fa833edc47d40.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Response:

- The key benefit of histamine dihydrochloride (HDC) and low-dose interleukin-2 (IL-2) is to reduce the probability of relapse in AML patients who have undergone induction and consolidation treatment, are in first complete remission (CR1), are not suitable for allogeneic stem cell transplant and are 60 years or younger.
- The HDC/IL-2 treatment effect of preventing relapse is further improved in a subgroup of AML patients with normal karyotype, who are in CR1 and less than 60 years old.
- By preventing relapse patients can survive disease free for longer and avoid the debilitating effects of disease relapse on quality and length of life.
- The treatment has a finite course of 18-months and hence avoids the inconvenience and on-going adverse events experienced with treatments that need to be taken until relapse.
- After instruction and supervision by healthcare professionals in the hospital setting patients can self-administer the treatment at home.
- There is no requirement for additional diagnostic tests, monitoring or hospital admission.
- HDC/IL-2 work synergically as an innovative form of immunotherapy. This is the only approved form of immunotherapy which is specifically approved for the maintenance treatment of AML patients.
- The adverse events associated with HDC/IL-2 treatment are typically mild to moderate, transient and mostly due to fever and local inflammatory reactions that subsided or were ameliorated after reduction of the IL-2 dose. In the main randomised controlled trial (4) there was no treatment related mortality.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

- The main disadvantage of this treatment is the need to take two subcutaneous injections twice daily for each cycle which is three weeks on treatment.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by

patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

The *de novo* economic model was structured as a partitioned survival model (PSM) with three mutually exclusive and jointly exhaustive partitions: leukaemia free, disease progression, and death. The partitions were chosen based on clinical trajectories and treatment pathways described in AML guidelines (7) and because they enabled direct use of clinical evidence from the primary (LFS) and secondary (OS) endpoints of the pivotal Brune *et al.* RCT (4) and the follow-up study reporting at least 36 months of follow-up in the normal karyotype population (5).

The treatment has shown to significantly delay the time to AML disease relapse compared with best supportive care within the intent to treat population in a randomised controlled trial (4). In patients with complete first remission (CR1) the treatment effect further improves the delay to disease progression or relapse. The median overall survival for the CR1 patients was encouraging; treated patients had a median OS of 1289 days versus 842 days for the best supportive care arm although this was not statistically significant. A post hoc analysis (5) showed that in a subgroup of AML patients with normal karyotype, in CR1 and <60 years old HDC/IL-2 significantly improved both leukaemia free survival and overall survival compared to best supportive care. These improvements were sustained during the 3-year follow-up period.

The main outcomes feeding into the economic model are leukaemia free survival and overall survival from the subgroup of AML patients with normal karyotype, in CR1 and less than 60 years old. The follow-up within the pivotal randomised controlled trial (4) was a minimum of 3-years. The maximum follow-up period observed in the study extended to 60 months and within the model this was extrapolated to 60 years from the start of treatment.

The Brune *et al.* clinical trial (4) recorded EORTC QLQ-C30 and the aggregate data have been presented previously (6); however, the individual patient-level data were not available for use in the economic analysis, despite attempts to obtain them from the authors. In the economic base case analysis, in the absence of data utility values were taken from a previous cost-utility analysis comparing midostaurin with standard of care in patients with AML in the UK (8).

The on- and off-treatment utilities were used, and the post-progression utility was ultimately preferred by the external assessment group (EAG) in the technology appraisal of oral azacitadine for maintenance treatment of acute myeloid leukaemia after induction therapy (9). Specifically, while on-treatment in the leukaemia free survival partition, a utility of 0.81 was applied, versus 0.83 off-treatment in the same partition. A health state utility value 0.53 was applied in the disease progression state.

The cost of treatment with histamine dihydrochloride (HDC) and low-dose interleukin-2 (IL-2) was modelled in line with list prices from the British National Formulary for interleukin-2 and from Brancaster Pharma for HDC.Dosing of HDC/IL-2 was modelled over ten 21-day cycles of treatment over an 18-month period in those patients remaining on treatment. Cycles 1 to 3 comprised 3 weeks of treatment and 3 weeks off treatment, with the off-treatment periods extended to 6 weeks for cycles 4 to 10. In each cycle, patients in the active treatment arm receive HDC at 0.5 mg subcutaneously twice a day and human recombinant IL-2 (aldesleukin) 16,400 U/kg subcutaneously twice daily. In the model, IL-2 costs were calculated based on a mean weight of 78.45 kg, informed by the weighted average bodyweight from the NHS Health Survey for England 2021.

While HDC/IL-2 can be administered subcutaneously by the patient at home, it was assumed that the patient would attend an outpatient appointment for the first administration in each cycle. An additional cost of one subcutaneous treatment administration of GBP 249.64 was therefore captured in each treatment cycle in line with the administration costs modelled in the technology appraisal of oral azacitadine (9). The cost of administration was informed by the 2023/24 National Cost Collection outpatient procedure cost code SB12Z “Deliver Simple Parenteral Chemotherapy at First Attendance”.

HDC/IL-2 are given by subcutaneous injections twice daily during a 3-week cycle of treatment. The first administration of the treatment would be supervised under instruction by a suitably trained healthcare professional. Thereafter the patient can self-administer the therapy at home. There are no special requirements for monitoring the patient other than normal follow-up and access to specialist advice should adverse events occur.

As in many health economic analyses, model uncertainty arises from extrapolating trial outcomes beyond the observed follow-up period and mapping them to long-term quality-adjusted survival estimates. Results are sensitive to the choice of parametric survival functions and to assumptions about the maintenance of the treatment effect over time, background mortality, and post-relapse pathways, the latter of which were not modelled owing to a lack of data. Key structural assumptions included that subsequent treatments after relapse across both arms would consist of best supportive care only.

A probabilistic sensitivity analysis (PSA) was conducted to explore the impact of model parameter uncertainty on the results. One thousand model iterations were performed to yield a joint distribution of incremental costs and quality-adjusted life years (QALYs), characterising the uncertainty of the cost-effectiveness results. During PSA, survival (LFS and OS) model parameters were sampled to ensure the generation of correlated random samples. Treatment costs were not varied during the PSA.

An incremental cost-effectiveness acceptability curve was generated to illustrate the degree of variability and uncertainty in the results. The cost-effectiveness model was developed by one researcher and independently validated by a second researcher. Validation included systematic extreme-value testing (pushing all continuous inputs to plausible bounds) and binary testing of on/off parameters and structural switches to confirm stable and expected behaviour across scenarios. Similar tests, such as setting all health state utility values to 1 to ensure that quality-adjusted life expectancy equaled life expectancy, were also conducted.

Survival models were also reimplemented and cross-validated by reproducing the OS and LFS curves. Parametric models were re-fit to the individual patient-level data by a second researcher and modelled LFS and OS outcomes were cross-checked. LFS and OS predictions were numerically consistent, providing assurance that survival extrapolations and downstream cost-effectiveness results were implemented correctly.

The technology was conservatively modelled as not meeting the criteria for a severity weight to be applied.

Subsequent allogeneic stem-cell transplantation was not explicitly modelled because patients were ineligible for transplant at baseline and data on use post-relapse was not available from the Brune et al. RCT (4). Omitting transplant costs and benefits would be expected to be conservative for histamine dihydrochloride plus low-dose interleukin-2, as any differential transplant use would likely result in higher costs in the comparator arm on account of the higher relapse rate.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Histamine dihydrochloride (HDC) with interleukin-2 (IL-2) is a first-in-class immunotherapy that harnesses the immune system to effectively maintain remission in patients with AML. HDC unlocks activity of IL-2 in patients with AML by activating the immune system's T cells and NK cells. The combination therapy of histamine dihydrochloride and IL-2 meets a material, unmet need for effective maintenance treatment in AML care.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

- It is noted that NICE guidance will only be issued in accordance with the marketing authorisation. The full licensed indication for histamine dihydrochloride and interleukin-2 (HDC/IL-2) in section 4.1 ("Therapeutic indications") of the approved SMPC includes the qualifying statement: '*The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.*' The approved indication clearly states that the evidence for the therapy is best supported in patients who are 60 years old or less and hence should exclude those who are older than 60 years.

- The qualifying statement about age is based on the statistical analyses used (univariate analysis of Cox proportional hazards modeling of prognostic factors for leukaemia free survival (LFS), a regression model commonly used statistical in medical research for investigating the association between the survival time of patients and one or more predictor variables) in the Brune, 2006 study (4) population which revealed that no clinical benefit was seen in patients aged older than 60 years.

- In addition, post-hoc sub-group analyses by Nilsson, 2020 (5) showed no LFS or OS benefit with HDC/IL-2 for patients with normal karyotype in CR1 who are 60 years or older. Since the indication clearly states that the efficacy of HDC has not been fully demonstrated in patients older than age 60, then this population should be excluded from the evaluation, in accordance with NICE guidelines.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:
Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf
- Cancer Research UK. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml
- Leukaemia research charity | Leukaemia UK
- Leukaemia Care - The UK's leading leukaemia charity
- Blood Cancer UK | We're here to beat blood cancer

4b) Glossary of terms

Response:
AE – adverse event
SAE – serious adverse event
AML – acute myeloid leukaemia
CNS – central nervous system
CR – complete remission
CR1 – first complete remission
EORTC QLQ-C30 - The EORTC QLG Core Questionnaire is a 30-item instrument meant to assess some of the different aspects that define the quality of life of cancer patients.
GBP – Pounds Sterling (£)
HDC – histamine dihydrochloride
HR - Hazard Ratio (ratio of the rate at which the exposed group experiences an outcome to the rate at which the unexposed group experiences an outcome, and it provides the instantaneous risk at a given time rather than the cumulative risk over the length of a study)
LFS – leukaemia-free survival
IL-2 – interleukin-2
ITT – intention-to-treat
NK cells - Natural Killer cells (a type of white blood cell that forms part of the body's innate immune system)
OS – overall survival
PSA - probabilistic sensitivity analysis
PSM - partitioned survival model
QALY – quality-adjusted life year
QoL – quality of life
RCT – randomised controlled trial

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. Cancer Research UK. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml (accessed 8th September 2025)
2. LeBlanc TW, Fish LJ, Bloom CT, El-Jawahri A, Davis DM, Locke SC et al. Patient Experiences of Acute Myeloid Leukemia (AML): A Qualitative Study about Diagnosis, Illness Understanding, and Treatment Decision-Making. Blood 2015; 126 (23): 2119.
3. Martner A, Rydström A, Riise RE et al. Role of natural killer cell subsets and natural cytotoxicity receptors for the outcome of immunotherapy in acute myeloid leukemia. Oncoimmunology. 2015;5:e1041701.
4. Brune M, Castaigne S, Catalano J et al. Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. Blood 2006, 108(1), 88–96. https://doi.org/10.1182/BLOOD-2005-10-4073
5. Nilsson MS, Hallner A, Brune M et al. Immunotherapy with HDC/IL-2 may be clinically efficacious in acute myeloid leukemia of normal karyotype. Hum Vaccines Immunother 2020;16:109–111.
6. Wallhult E, Whisnant J, Rowe JM, Szer J, Bhagwat D, Hellstrand K et al. Impact on Quality of Life of Postconsolidation Immunotherapy with Histamine Dihydrochloride and Interleukin-2 in Acute Myelogenous Leukemia. Blood 2007;110 (11):4381.
7. Döhner H, Wei AH, Appelbaum F et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345–1377. https://doi.org/10.1182/blood.2022016867
8. Tremblay G, Dolph M, Patel S, Brandt P, Forsythe A. Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom. Cost Eff Resour Alloc. 2018;16:33
9. Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy.(2022). NICE technology appraisal guidance 827

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Clarification questions

October 2025

File name	Version	Contains confidential information	Date
Brancaster clarification questions responses	**Final**	**Yes**	**20/10/2025**

Section A: Clarification on effectiveness data

Decision problem

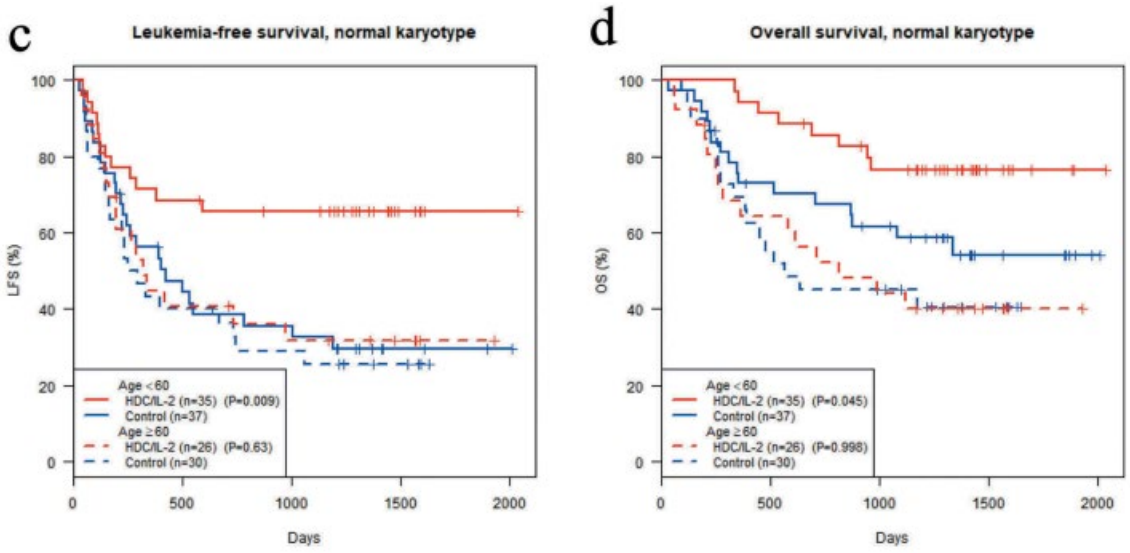
A1. PRIORITY. Company's submission (CS), Section 1.1, Table 1 (pages 9 and 19). The CS states *that "Since the indication clearly states that the efficacy of HDC has not been fully demonstrated in patients older than age 60, then this population should be excluded from the evaluation, in accordance with NICE guidelines."* Please clarify whether the wording in the marketing authorisation should be interpreted as signalling caution regarding use in people aged over 60 years rather than an outright exclusion of this group. In addition, please provide an estimate of the number of people expected to be treated with histamine dihydrochloride (HDC) with interleukin-2 (IL-2) in England per year?

The company maintains its position as set out in the CS that since the indication states that "the efficacy of HDC has not been fully demonstrated in patients older than age 60", then this population should be excluded from the evaluation, in accordance with NICE guidelines.

More specifically, the wording in the approved SmPC (section 4.1 'Therapeutic indications') and evidence provided in the CS confirms that the use of HDC/IL-2 in patients over 60 years is not supported and therefore the wording in the approved SmPC should be considered an exclusion of this group.

As noted in the CS, based on the evidence submitted, we believe that to prevent patients receiving HDC/IL-2 with little chance of benefit, those patients who are older than 60 should be excluded from the evaluation.

Please see below the Kaplan-Meier curves taken from the Nilsson et al 2020 study which demonstrate that there is no obvious benefit for HDC/IL-2 versus control in leukaemia-free survival or overall survival for those patients with a normal karyotype, who are in first complete remission (CR1) after induction and consolidation therapy and are 60 years or older.



For the avoidance of doubt, the use of HDC/IL-2 in patients over 60 years is not explicitly contraindicated, but should a prescriber consider the use of HDC-IL-2 in a patient aged, for example, 62 years, this would be considered “off-label” use and the decision and responsibility to prescribe in this manner would therefore lie with the prescribing healthcare professional on a case-by-case basis.

In line with the available evidence as set out in the CS, the intended population for whom HDC/IL-2 therapy is targeted is adult AML patients with normal karyotype, who have undergone induction and consolidation chemotherapy and are subsequently in first complete remission (CR1), are 60 years of age or less, and are considered ineligible for allogeneic stem cell transplantation. The company has carried out an evaluation of the estimated number of patients who could be treated with HDC/IL-2 per year in England based on this specific subgroup. In addition, we have excluded those patients with a FLT3 mutation who are expected to have maintenance treatment with a FLT3 inhibitor.

Taking into account this specific subgroup, and given these treatment assumptions regarding patients within this subgroup that have a FLT-3 mutation, the company estimates that only 50-100 adult AML people in England would be suitable for treatment with HDC/IL-2.

For further clarification, the intended population for whom HDC/IL-2 therapy is targeted is in line with approved indication (that is for adult AML patients in CR1 and who are 60 years of age or less), but in fact covers a narrower subgroup of patients

(those with normal karyotype). Expanding upon this point, the company would like to advise that a variation to update to the SmPC was submitted to the MHRA on 18 September 2025 and accepted for assessment by the MHRA on 23 September 2025. The variation covers a proposed update to section 5.1 of the SmPC ('Pharmacodynamic properties') and more specifically an update to the subsection 'Clinical efficacy and safety'. The variation is intended to add the relevant details, as presented in the post-hoc analyses by Nilsson et al. 2020, regarding the intended population for whom HDC/IL-2 therapy is targeted by the company, i.e. adult AML patients with normal karyotype, who have undergone induction and consolidation chemotherapy and are subsequently in first complete remission (CR1), are 60 years of age or less, and are considered ineligible for allogeneic stem cell transplantation; since it is this subgroup of patients that is expected to most benefit from HDC/IL-2 therapy.

The proposed additional wording to section 5.1 of the SmPC is as follows (please note that this wording has not yet been approved by the MHRA):

Clinical efficacy and safety

There have been 2 clinical studies to evaluate the use of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection in the maintenance of remission in adult AML patients.

Study AML-1 was exploratory, enrolling 39 AML patients in remission to determine the dose and feasibility of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection administered together with IL-2. Results of this pilot study were used to design and implement a multi-national phase 3 trial.

The randomised phase 3 trial (0201) compared Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection+IL-2 treatment to no treatment in 261 patients in first remission (CR1) and in another 59 patients in subsequent remission after relapse (CR>1). For CR1 patients, the median duration of leukaemia-free survival increased from 291 days (9.7 months) to 450 days (15 months) after Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection /IL-2 versus no maintenance treatment (Intention to Treat [ITT], p=0.01. n=261). The percentage of CR1 patients remaining leukaemia-free for 3 years was 40% after Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection+IL-2 versus 26% in patients not receiving this treatment (Hazard Ratio (HR) 0.69, 95% CI: 0.51–0.93, p=0.01).

This randomised phase 3 trial (0201) has since been further analysed focusing on patients in first remission (CR1), with normal karyotype and under the age of 60. The percentage of patients in this subgroup remaining leukaemia-free for 3 years was 65.6% after Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection+IL-2 versus 31.3% in patients not receiving this treatment (HR 0.40, 95% CI: 0.20–0.79, p=0.006), whilst overall survival was 76.5% after 3 years after Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection+IL-2 versus 58.7% in patients not receiving this treatment (HR 0.43, 95% CI: 0.18–1.01, p=0.04).

Figure 1: Kaplan-Meier curve of Leukaemia-Free Survival in patients in first remission (CR1), with normal karyotype and under the age of 60.

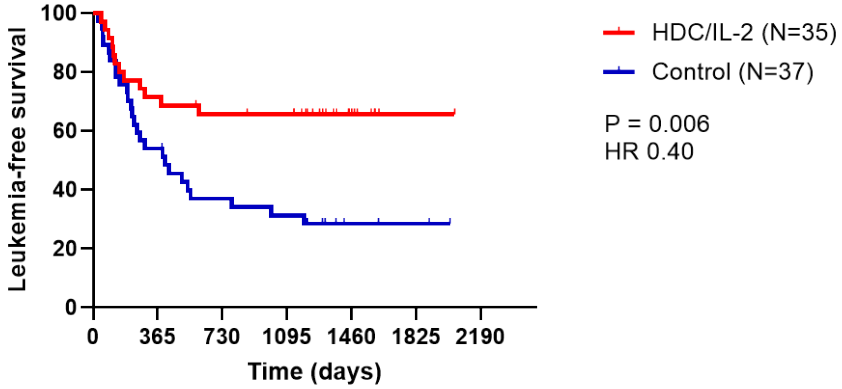
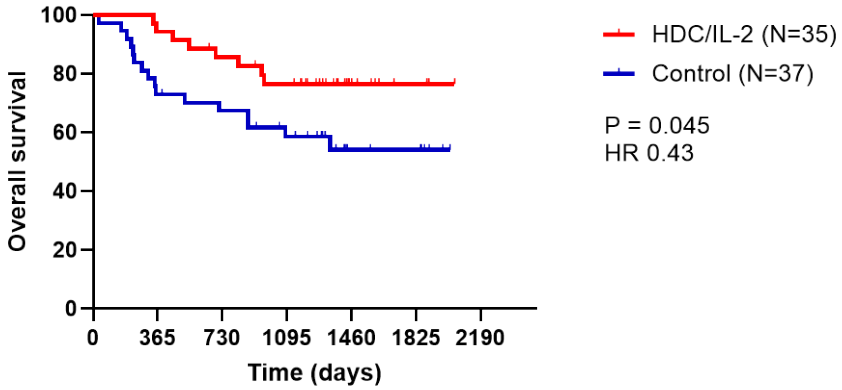


Figure 2: Kaplan-Meier curve of Overall Survival in patients in first remission (CR1), with normal karyotype and under the age of 60.



The company would like to confirm that it has selected this specific subgroup of patients that is appropriate for HDC/IL-2 therapy, despite the limited number of

patients (50-100 patients) that it therefore anticipates will be treated with HDC/IL-2 therapy as a consequence of this positioning.

A2. PRIORITY. CS, Section 1.1 (page 7), Table 1 (page 8) and Table 3 (page 24). In the CS, it is unclear whether the target population for this appraisal is restricted to acute myeloid leukaemia (AML) patients with a normal karyotype. For example, whilst the text on page 7 of the CS includes this restriction, the descriptions in Table 1 ('Population' and 'Comparators' sections) do not appear to reflect this. In addition, the wording of the marketing authorisation (CS, Appendix A) does not include this restriction either. Please clarify/confirm:

(a) If the target population for HDC/IL-2 is intended to be restricted to patients with a normal karyotype;

(b) What definition of 'normal karyotype' has been used to determine patient eligibility for treatment with HDC/IL-2 in the CS, as it does not appear to align with the karyotype categories presented in Table 3 of the CS and Brune *et al.* (2006).

(c) Whether the company is positioning histamine dihydrochloride for patients with AML who do not have a FLT3 mutation. In addition, based on the forecast categories and features presented in Table 3, please clearly specify in Table 1 below (adapted from CS Table 3) which patient groups will be considered eligible for treatment with HDC/IL-2 in England.

(d) Given that the AML landscape has changed considerably since the Brune *et al.* (2006) study was conducted, particularly with a shift toward more personalised and targeted therapies, and that the categories presented in CS Table 3 are no longer used in current UK clinical practice, please clarify how patients would be identified as eligible for treatment with HDC/IL-2 in current NHS practice?

Forecast	Features	Eligible for HDC/IL-2?

		(please indicate YES or NO in each row)
Favourable	t(8;21)(q22;q22) / RUNX1::RUNX1T1	Please note the answer to question A2. PRIORITY (b), with respect to eligibility with HDC/IL-2 for this and the other genetic subtypes listed in this table.
	inv(16)(p13.1q22) or t(16 ;16)(p13.1;q22) / CBFB::MYH11	
	CEBPA mutation within the bZIP framework	
	NPM1-positive and FLT3-ITD-negative	
Intermediate	NPM1-positive and FLT3-ITD-positive	
	NPM1-negative and FLT3-ITD-positive	
	t(9;11)(p21.3;q23.3); MLLT3::KMT2A	
	All other anomalies not classified as favourable or unfavourable	
Unfavourable	t(6;9)(p23.3;q34.1)*/DEK*::NUP214	
	t(v;11q23.3)/KMT2A-rearranged	
	t(9;22)(q34.1;q11.2)*/BCR*::ABL1	
	t(8;16)(p11.2;p13.3)*/KAT6A*::CREBBP	
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2*, *MECOM(EVI1*)	
	t(3q26.2;v)*/MECOM*(*EVI1*)-rearranged	
	the -5 or del(5q); -7; -17/abn(17p) type	
	Complex karyotype, monosomal karyotype	
	ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2 mutation	
	TP53a mutation	
Not included in ELN category	NPM1-negative and FLT3-ITD-positive	
	normal karyotype and FLT3-TKD mutation	
	normal karyotype and DDX41 mutation	

(a) The target population for HDC/IL-2 is intended to be restricted to patients with a normal karyotype.

As noted in our response to clarification question A1. PRIORITY, the target population is restricted to those adult AML patients:

- **With a normal karyotype**, which is narrower than the wording of the marketing authorisation and represents a subgroup where the efficacy of HDC/IL-2 has shown to be particularly effective. As noted in our response to clarification question A1. PRIORITY, the company has submitted a variation

to the MHRA to update the SmPC to address patients with “normal karyotype”;

- **In first complete remission (CR1),** which is in accordance with the wording of the marketing authorisation, occurring after induction and consolidation chemotherapy;

- **Who are 60 years of age or less**, which is in accordance with the wording of the marketing authorisation;

- **Who are considered ineligible for allogeneic stem cell transplant** - patients who have received an allogeneic stem cell transplant are explicitly contraindicated in the marketing authorisation.

(b) The following definition of “normal karyotype has been used to determine patient eligibility for treatment with HDC/IL-2 in the CS.

Normal karyotype is defined as a classification of AML in which the leukaemic cells appear to have a normal set of chromosomes when viewed under a microscope and karyotyping is established during the existing routine diagnostic protocols for AML (see response to (d) below). Normal karyotype is defined by the absence of large-scale chromosomal abnormalities, such as translocations, inversions, deletions, or gains, which are frequently found in other AML subtypes.

By contrast, Table 1 (adapted from CS Table 3) represents a risk classification by genetic subtypes at initial diagnosis in the 2022 recommendations from an international panel on behalf of the European Leukaemia Net (ELN).

The categories in Table 1 are a more recent risk classification system based on genetic subtypes rather than karyotype. The correlation between karyotype and genetic subtype is not exact in that the same genetic subtype could have normal karyotype or abnormal karyotype.

Table 1 is therefore not specifically relevant to the definition of “normal karyotype” vs. “abnormal karyotype”, which is determined from reviewing leukaemic cells

under a microscope (and occurs during the existing routine diagnostic protocols for AML as described in (d) below).

(c) The company is positioning HDC/IL-2 in patients who do not have a FLT3 mutation.

At the time when the Brune et al 2006 study was recruiting, molecular testing for genetic subtypes was not routine practice. Consequently, there are no data from the study on the efficacy of HDC/IL-2 within different genetic subtypes such as those patients with FLT3 mutations.

The company understands that patients with FLT3 mutations are likely to be given a FLT3 inhibitor, in line with NICE guidance (TA523 & TA1013); both recommendations are for use of such an FLT3 inhibitor (i.e. midostaurin and quizartinib) during induction, consolidation and maintenance treatment.

The clinical experts involved with the oral azacitidine appraisal (TA827) explained that most people with FLT-3 mutation positive AML would have targeted treatment with midostaurin during induction, consolidation and maintenance treatment and would be unlikely to switch to oral azacitidine. We believe that it would be a similar situation with HDC/IL-2, where few, if any, patients would switch from midostaurin or quizartinib to HDC/IL-2 during maintenance.

HDC/IL-2 would therefore likely be of most benefit to patients whose AML does not have an FLT3-mutation or FLT3-ITD mutation.

As above there are limited data on the efficacy of HDC/IL-2 according to genetic subtype and since the genetic subgroups in Table 1 are not directly correlated with karyotype status it is difficult to be clear about which of the genetic subtypes are normal or abnormal karyotype. For example, some AML genetic subtypes

such as NPM1 mutations are predominantly normal karyotype but a smaller percentage can also be abnormal karyotype.

(d) Patients would be identified as eligible for treatment with HDC/IL-2 in current NHS practice as follows.

We understand from discussions with clinical experts that the karyotype status is routinely assessed as part of the initial diagnostic workup for all patients with newly diagnosed AML in the UK. The definition of “normal” vs. “abnormal” karyotype is established and distinct.

HDC/IL-2 would therefore be eligible for the following NHS patients: adult AML patients with normal karyotype, who have undergone induction and consolidation chemotherapy and are subsequently in first complete remission (CR1), are 60 years of age or less, and are considered ineligible for allogeneic stem cell transplantation.

A3. CS, Section 1.2, Table 2. The CS describes the method of administration and dosage for HDC/IL-2 regimen which includes 4 subcutaneous injections (2 injections twice a day) at home, with each 0.5 ml dose of HDC being administered slowly, over a period of 5 to 15 minutes. The SmPC also suggests that following professional training, patients may self-administer HDC/IL-2 via subcutaneous injection. In relation to the HDC/IL-2 regimen:

(a) Please provide supporting evidence on the acceptability and feasibility of the HDC/IL-2 regimen for patients, caregivers, and healthcare professionals, considering the prolonged duration, frequent injections, and the burden of (potential) ongoing clinical supervision?

(b) Could this option be perceived as a benefit or barrier to the widespread adoption of HDC/IL-2 therapy? What alternative methods of administration were available for patients unable to self-administer at home?

(c) Please clarify how adherence and compliance were assessed in patients who self-administered HDC/IL-2 at home in the Brune *et al.* (2006) study? What

measures were in place to ensure correct administration and monitoring of ongoing use? Also, were any data collected on missed doses, incorrect administration, or the need for re-training? How might these factors impact the real-world effectiveness of the treatment?

(a) The supporting evidence on the acceptability and feasibility of the HDC/IL-2 regimen for patients, caregivers, and healthcare professionals, considering the prolonged duration, frequent injections, and the burden of (potential) ongoing clinical supervision is derived from the Brune *et al* 2006 study.

The evidence from the Brune *et al* 2006 study showed that the incidence of adverse events resulting in dose reduction or treatment interruption was 26%, the most common reasons being local inflammatory reactions at the injection sites (7.1%) or fever (5.1%).

In addition, the company spoke with Elizabeth Willhaut, Head Nurse (Section of Hematology and Coagulation) at Sahlgrenska University Hospital in Sweden who has had experience of supporting patients treated with HDC/IL-2. She confirmed that the patient would be instructed and trained on the administration of HDC/IL-2 for the first treatment in the first cycle within the hospital setting. Thereafter the patient would self-administer the treatment at home. She said that routinely the haematology nurse specialists would contact the patient 4 days into each cycle to find out how the administration was going, address any concerns about administration and discuss any related adverse events. She indicated that adverse events resulting in dose reduction or dose interruption were more likely to occur during the first 3 cycles of treatment, where there is 3-weeks off treatment between cycles compared with cycles 4-10 where there is 6-weeks off treatment between cycles.

In summary, clinical experience has shown that the HDC/IL-2 regimen is feasible and acceptable to patients in routine clinical practice.

(b) The company neither sees this option as a specific benefit or barrier to the widespread adoption of HDC/IL-2 therapy. It is a function of the therapy and as noted in the company response to clarification question A1. PRIORITY, the

number of patients expected to be eligible for HDC/IL-2 therapy is only 50-100 patients. The patient would need to be fully briefed on the details of HDC/IL-2 administration and motivated to proceed.

The company is aware that it is only on exceptional occasions that a patient was unable to self-administer. In these cases, a partner and/or carer has been able to assist with the procedure. The relatively younger age group of the treated population makes administration at home more feasible.

(c) From the clinical study report under section 11.3 (page 111 of 1042) on Measurements of Treatment Compliance, it states 'Treatment compliance was assessed at the end of each treatment cycle. The investigator judged where the patient had taken at least 80% of the required dose of IL-2 and HDC. By this measure, between 95% and 100% of patients took at least 80% of the required doses.' Please refer to Table 18.2 on page 398 of 1042 for further details.

A4. The EAG notes that the Scottish Medicines Consortium (SMC) evaluated HDC/IL-2 for use in NHS Scotland in 2011, and the SMC N. 666/10 document (available in https://scottishmedicines.org.uk/medicines-advice/histamine-dihydrochloride-ceplene-fullsubmission-66610/) states that *"SMC also had concerns that the outcomes for patients treated with standard care were poorer than might be expected with current practice and that adjustment for this would worsen the cost-effectiveness ratios."* Please comment on this statement and how changes in the AML treatment landscape (e.g., the introduction of personalised and targeted therapies, molecular risk stratification, and improvements in supportive care) may impact outcomes for patients receiving standard/best supportive care.

There is a high level of uncertainty in attempting to compare the outcomes of patients who have different baseline characteristics between different trials.

In the Wei *et al* 2020 study of oral azacitidine where AML patients were in first complete remission, ≥55 years old and who were not considered to be suitable for allogeneic stem cell transplant, the relapse-free survival at 12-months on the

treatment and placebo arms were 44.9% and 27.4%, respectively. The corresponding leukaemia-free survival for patients from the intent-to-treat population in the control arm from the Brune *et al* 2006 study at 12-months was 42%. Patients from the Wei *et al* 2020 study were recruited from May 2013 through October 2017 and those from the Brune *et al* study were recruited between June 1998 and October 2000. Given the caveats of comparing outcomes of patients with different baseline characteristics, it would seem that the results of relapse-free survival are not dissimilar between these studies which were conducted at different time points.

The performance of the control arm in the Nilsson *et al* 2020 post-hoc analysis in the normal karyotype subgroup is close to what you might expect in that subgroup of patients treated in a more contemporary setting. In the recent study published by Potter *et al* 2025, which included data on a combination of two UK randomised controlled trials (UK AML 17 & 19), the 3-yr survival of AML patients with NPM1 and FLT3 mutations (N=140), a subset of normal karyotype AML, who were 60 years old or younger was 58% for the non-monitored group versus 69% for the monitored group. In the AML 19 study patients with NPM1 mutations who were MRD positive were excluded from the analysis, and this exclusion bias is likely to have had a beneficial effect on the outcomes. The control arm from the normal karyotype subgroup from Nilsson *et al* 2020 showed a 3-yr survival of 58.7%.

In a different publication by Juliusson *et al* 2020 which summarised real world experience from a large Swedish registry of AML patients the 3-yr survival of the patient subgroup (n=198) with an NPM1 mutation and less than 60 years old was 59.4% which again is very close to the 58.7% seen in the control arm of the Nilsson *et al* 2020 subgroup.

It would therefore seem apparent that the control group within the Nilsson *et al* 2020 post-hoc analysis of the normal karyotype, CR1 and less than 60 years old showed similar 3-year survival compared with similar groups of AML patients who have been treated in a more contemporary setting within UK trials and a Swedish real world evidence collection.

Given the above there would seem to be little reason to consider any significant worsening of the cost-effectiveness ratios.

A5. PRIORITY. CS, Section 1.1, Table 1 (pages 10-13). Regarding the exclusion of oral azacitidine as a comparator from the company's analyses:

(a) Please provide clinical justification for this exclusion. As noted in the CS, the QUAZAR trial included only patients aged ≥55 years, however, there is no formal age restriction for oral azacitidine stated in the marketing authorisation or in the NICE recommendation (NICE TA827), which suggests that its use in appropriately selected younger adults (<55 years) could be clinically justified if they meet the criteria of the license indication;

(b) Please provide supporting evidence that the use of oral azacitidine in clinical practice in England is restricted to patients aged ≥55 years only.

(c) Please also comment on the potential overlap between the populations eligible for HDC/IL-2 and oral azacitidine (specifically patients aged between 55 and 60 years) if age restrictions are applied. In addition, please provide an estimate of the number of patients in England who may be eligible for both therapies.

(a) The clinical justification regarding the exclusion of oral azacitidine as a comparator from the company's analyses is that the published data available and the clinical experience does not allow for a meaningful indirect treatment comparison: the indicated patient population for HDC is 60 years or younger and the main evidence case for oral azacitidine as in Wei *et al* 2020 is in patients who are 55 or older.

The company is aware and understands that neither the marketing authorisation nor NICE recommendation for oral azacitidine includes an age restriction of treating AML patients only who are 55 years or older. However, at the same time, the company is unaware of any published data on the use of oral azacitidine as a maintenance treatment in AML patients who are in complete remission, who cannot have or do not want a haematopoietic stem cell transplant and who are less than 55 years old.

During interviews with 17 UK haematologists specialising in the treatment of AML patients, about the current maintenance treatment landscape and the use of oral azacitidine, 15 out of 17 haematologists mentioned that the evidence from the pivotal QUAZAR randomised controlled study included only older AML patients who were ≥55 years and these UK haematologists were therefore curious why this was not reflected in the NICE recommendation. They also stated that there was limited use of oral azacitidine in the UK.

The feedback about the limited use of oral azacitidine in England is supported by NHS Business Services Authority (NHSBSA) Secondary Care Medicines Data (SCMD): in March 2024, 840 azacitidine tablets were prescribed at a cost of £704,040, corresponding to treatment courses for approximately 60 patients; in March 2025, 908 tablets were prescribed at a cost of £761,034, corresponding to treatment courses for approximately 65 patients.

As a result of this, if the company used the data from the QUAZAR study for an indirect treatment comparison, then this is at best likely to produce high levels of uncertainty and at worst possibly even be misleading due to the differing ages and prognoses of the eligible patients.

These clinical considerations led to the decision by the company not to undertake an indirect treatment comparison for the original CS.

Further to these clarification questions, it is confirmed that the company, despite maintaining the above clinical reservations regarding the likely high levels of uncertainty, will be undertaking an indirect treatment comparison with oral azacitidine.

As discussed during the clarification questions call with NICE and the EAG and subsequently agreed in writing on Friday 3rd October by NICE, the company will provide an indirect treatment comparison analysis of HDC/IL-2 versus oral azacitidine as requested above which will be submitted by Monday 20th October at 5pm.

(b) The company is not aware of any published evidence or otherwise on the age of patients treated with oral azacitidine in England.

(c) Considering the approved indication for HDC/IL-2 is limited to AML patients in first complete remission who are 60 years or younger, we assessed the feasibility of collecting data on a similar group of patients (in other words, those who are 55-60 years of age) receiving oral azacitidine in England.

From our discussions with the clinical experts, we concluded that there is likely to be very little data available on the use of oral azacitidine in a similar group of English patients where HDC/IL-2 is specifically indicated.

As noted in the company's response to clarification question A1. PRIORITY, the company estimates that between 50-100 adult AML people in England would be suitable for treatment with HDC/IL-2 (adult AML patients with normal karyotype, who have undergone induction and consolidation chemotherapy and are subsequently in first complete remission (CR1), are 60 years of age or less, and are considered ineligible for allogeneic stem cell transplantation). Based on this estimate, it can be assumed that the potential overlap between the populations eligible for HDC/IL-2 and oral azacitidine (specifically patients aged between 55 and 60 years) would be very small.

A6. PRIORITY. CS, Section 1.1, Table 1 (pages 13-15). Regarding the exclusion of midostaurin and quizartinib as comparators from the company's analyses, please provide clinical justification for their exclusions, since the marketing authorisation for HDC/IL-2 does not exclude patients with FLT3 mutation.

The clinical justification regarding the exclusion of midostaurin and quizartinib as comparators from the company's analyses is that NICE has previously approved midostaurin as a maintenance treatment for AML patients with FLT3 mutations (TA523) and quizartinib for AML patients with FLT3-ITD mutations (TA1013).

There are no comparative data published on the efficacy of HDC/IL-2 versus midostaurin as maintenance treatment in people with FLT3 mutation-positive AML or sorafenib/quizartinib for FLT3-ITD mutations.

The clinical experts involved with the oral azacitidine appraisal (TA827) explained that most people with FLT3 mutation positive AML would have targeted treatment with midostaurin during induction, consolidation and maintenance treatment and would be unlikely to switch to oral azacitidine.

We believe that it would be a similar situation with HDC/IL-2, where few, if any, patients with FLT3 mutation positive AML would switch from midostaurin or quizartinib to HDC/IL-2 during maintenance.

We note that midostaurin was considered a relevant comparator for people with FLT-3 mutation positive AML in the oral azacitidine appraisal and an indirect treatment comparison was conducted.

We note that the EAG also considered that survival analyses for this population are likely to be biased because of limitations associated with the indirect treatment comparison.

The committee concluded that the results of the indirect treatment comparison comparing oral azacitidine with midostaurin were highly uncertain and considered this in its decision making.

There are no data from the pivotal Phase III RCT published by Brune, 2006 on the genetic subtypes of patients recruited to the study and hence there are very limited data on the efficacy of HDC/IL-2 in AML patients with FLT3 mutations and FLT3-ITD mutations.

For these reasons, we have not attempted an indirect treatment comparison. As indicated above without further data on the efficacy of HDC/IL-2 in genetic subtypes the level of uncertainty in an indirect treatment comparison versus midostaurin or versus quizartinib is likely to be very high.

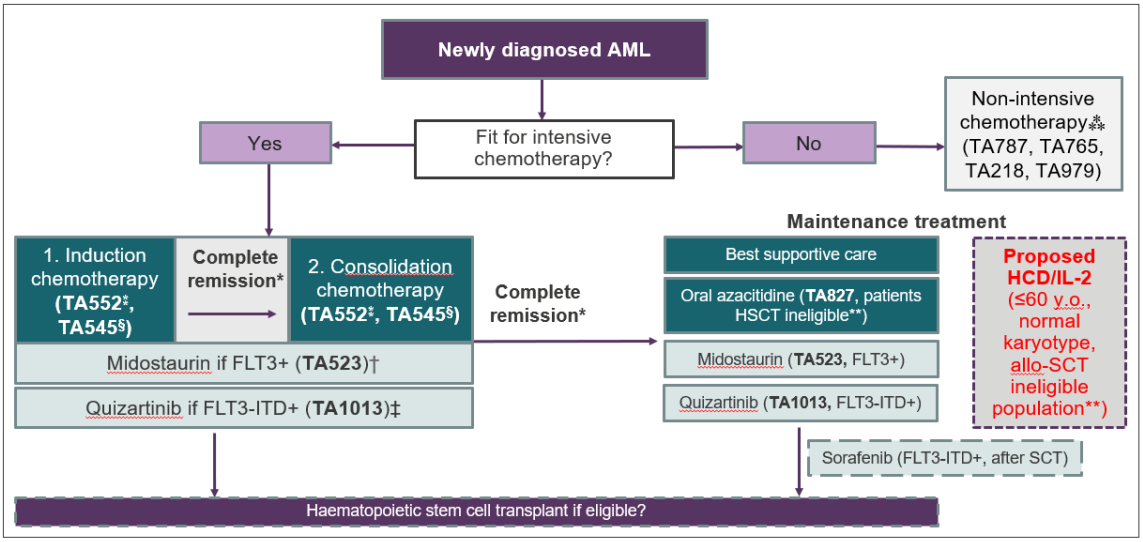
HDC/IL-2 would therefore likely be of most benefit to patients whose AML does not have an FLT3 mutation or FLT3-ITD mutation.

A7. CS, Section 1.3, Figure 1 (page 25). Please provide an updated figure which reflects the treatment pathway for patients with AML, including all treatments available along the pathway for the targeted population until patients reach the maintenance phase, and all the comparators currently available in the NHS (see Figure 1 as an example, adapted by the EAG from slide 5 of the NICE public committee slides in TA827). Please also clarify if the proposed positioning within the pathway shown in Figure 1 corresponds to the company's intended positioning.

The proposed positioning of HDC/IL-2 within Figure 1 below does correspond to the company's intended positioning.

As noted in the company's response to clarification question A1. PRIORITY, the intended population for whom HDC/IL-2 therapy is targeted is adult AML patients with normal karyotype, who have undergone induction and consolidation chemotherapy and are subsequently in first complete remission (CR1), are 60 years of age or less, and are considered ineligible for allogeneic stem cell transplantation.

Figure 1: Treatment pathway for AML in adults (adapted from TA827 slides)



*Complete remission or complete remission with incomplete blood count recovery.
‡ Liposomal cytarabine–daunorubicin for therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
§Gemtuzumab ozogamicin, with daunorubicin and cytarabine, for untreated de novo CD33+ AML patients, except acute promyelocytic leukaemia, in people ≥15 years
** Includes people eligible for HSCT but who choose not to undergo the procedure.
† Midostaurin given with standard daunorubicin plus cytarabine during induction therapy and high-dose cytarabine during consolidation therapy.
‡ Quizartinib given with standard cytarabine and anthracycline chemotherapy during induction therapy and standard cytarabine during consolidation therapy
⁂Venetoclax with low dose cytarabine (TA787), venetoclax with azacitidine (TA765), ivosidenib with azacitidine (IDH1 R132+ patients, TA979), azacitidine (HSCT ineligible patients, TA218)

Source: https://www.nice.org.uk/guidance/ta827/documents/1-3

Evidence Searches

A8. CS Appendix B, Table 2, line 5 (page 2) and Table 3, line 5 (page 3). Please explain the rationale behind the company's choice of intervention terms, which include terms for IL-2 and Mylotarg (gemtuzumab ozogamicin) while histamine dihydrochloride is searched for only by its brand name (Ceplene).

The intervention search terms were aligned with those used in a systematic literature review (SLR) conducted by the Cochrane Collaboration in 2015 (Mao *et al.* 2015). The abundance of terms and synonyms for IL-2 (including "receptors, interleukin 2"[MeSH] OR "interleukin-2"[tiab] OR "interleukin 2"[tiab] OR "interleukin2"[tiab] OR "IL-2"[tiab] OR "IL2"[tiab] OR "IL-2"[tiab] OR "proleukin"[tiab] OR "aldesleukin"[tiab]) — an integral part of the HDC/IL-2 intervention — combined with the brand name was considered sufficient to identify studies reporting on HDC/IL-2. Empirically, the searches identified all known studies and reports based on data from the pivotal Brune *et al.* (2006) RCT and additional terms were therefore not considered to be necessary.

A9. CS Appendix B, Table 3 (pages 3-5). The search string for EMBASE for the clinical systematic literature review (SLR) is presented in a format which makes it very difficult for the reader to follow. Please explain why this long string appears to contain clauses which EXCLUDE the phrase “randomised controlled”/”randomized controlled” when, according to the eligibility criteria in Table 1 (page 1), RCTs are eligible for inclusion.

The section of the search string referenced follows another initial NOT operator, which was designed to exclude study designs such as case-controls. To ensure that randomised controlled trials were not excluded when case-control was mentioned in the text, an additional NOT operator was used before “randomised controlled”/”randomized controlled”. The search string mentioned above was therefore part of a double negation and did not exclude randomised controlled trials from the search.

A10. CS, Appendices B, E and F. What searches for unpublished (grey) literature were conducted for each of the SLRs conducted, if any? Specifically, why did the company not search any registers of clinical trials, conference proceedings and international HTA websites?

Grey literature, clinical trial registers, and conference proceedings were not searched separately from the three primary databases (PubMed, EMBASE, and the Cochrane Library) on the grounds that:

- The Cochrane Library includes the Cochrane Central Register of Controlled Trials (CENTRAL), which in turn includes both published and unpublished sources, including CINAHL, ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform.
- EMBASE includes 5.5 million conference abstracts from 17,175 conferences (https://www.elsevier.com/en-gb/products/embase/content) in addition to more than 533,000 trials from ClinicalTrials.gov. Pertinently for the present review, conference materials covered by EMBASE include the ASH Annual Meeting, the American Society of Pediatric Hematology/Oncology, the Congress of the European Hematology Association (EHA), the Proceedings of the Society of Hematologic Oncology, HEMO, the Swiss Oncology and Hematology Congress (SOHC), and the Eurasian Hematology Oncology Congress, in addition to broader oncology conferences including the National Comprehensive Cancer Network (NCCN) Annual Conference and the European Society For Medical Oncology (ESMO) Congress.

The NICE website was searched for previous technology appraisals in AML during the preparation of Table 17 of the CS, although this search was conducted outside of the SLR. Individual international HTA websites were not searched specifically as part of the SLR, although results from international HTA websites were identified as part of targeted searches conducted during model conceptualisation and the SLR would be anticipated to pick up certain HTAs through journals such as Health Technology

Assessment and the International Journal of Technology Assessment in Health Care. As we also note in response to question B3, the documentation of economic analyses in, for instance, the SMC assessment of histamine dihydrochloride, was sparse and not sufficient to inform the parameterisation of the model for the present appraisal.

A11. CS, Appendices B, E and F. Please provide the source of the filters used to identify studies eligible for inclusion in each of the SLRs, including details of any modifications made to the published versions (e.g. the inclusion of unconventional terms such as “burdenliness” in the search terms in Appendix E Table 2 for the economic SLR).

We have included the sources of each component of the search terms in the revised tables presented below for Appendices B, E, and F, in Table 1, Table 2 and Table 3, respectively. The term “burdenliness” and similar terms came from an automated expansion of the “burden?” wildcard term to allow the search to be run using PubMed’s native term proximity operator, while the “burden?” term itself originated from Box 20.2.d in Chapter 20 of the Cochrane Handbook.

Table 1 Search terms reported in Appendix *B* including references for individual components of the search term

#	Search term	Source	PubMed hits
1	"Leukemia, Myeloid, Acute"[Mesh]	Mao 2015	69,165
2	"leukemia, myeloid"[MeSH Terms:noexp] AND "Acute Disease"[MeSH Terms:noexp]	Mao 2015	6,493
3	("acut*"[Title/Abstract] OR "akut*"[Title/Abstract] OR "agud*"[Title/Abstract] OR "aigu*"[Title/Abstract]) AND ("myelo*"[Title/Abstract] OR "mielo*"[Title/Abstract] OR "nonlympho*"[Title/Abstract] OR "myeloid*"[Title/Abstract] OR "myelocytic*"[Title/Abstract]) AND ("leukem*"[All Fields] OR "leukaem*"[All Fields] OR "leuc*"[All Fields])	Mao 2015	79,077
4	#1 OR #2 OR #3		109,186

#	Search term	Source	PubMed hits
5	"receptors, interleukin 2"[MeSH Terms] OR "interleukin-2"[Title/Abstract] OR "interleukin 2"[Title/Abstract] OR "interleukin2"[Title/Abstract] OR "IL-2"[Title/Abstract] OR "IL2"[Title/Abstract] OR "IL-2"[Title/Abstract] OR "TCGF"[Title/Abstract] OR "lymphokine"[Title/Abstract] OR "Il-b"[Title/Abstract] OR "ii b"[Title/Abstract] OR "proleukin"[Title/Abstract] OR "aldesleukin"[Title/Abstract] OR "mylotarg"[Title/Abstract] OR "ceplene"[Title/Abstract]	Mao 2015	95,268
6	#4 AND #5		1,157
7	"randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]	ISSG Search Filters Resource (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/rcts), based on chapter 4 of the Cochrane Handbook version 6.3 2022 (specifically, the technical appendix to this chapter)	1,716,534
8	"single-arm"[Title] OR "single arm"[Title]		4,177
9	"Epidemiologic Studies"[Mesh:NoExp] OR "Case-Control Studies"[Mesh] OR "Cohort Studies"[Mesh] OR case control[tw] OR cohort study[tw] OR cohort studies[tw] OR follow up study[tw] OR follow up studies[tw] OR observational study[tw] OR observational studies[tw] OR longitudinal[tw] OR retrospective[tw] OR cross sectional[tw] OR "Cross-Sectional Studies"[Mesh:NoExp]	SIGN, https://www.sign.ac.uk/what-we-do/methodology/search-filters/ date: 2023-05-04	4,352,991
10	#6 AND (#7 OR #8 OR #9)		183

Table 2 Search terms reported in Appendix E including references for individual components of the search term

#	Search term	Source	PubMed hits
1	"Leukemia, Myeloid, Acute"[Mesh]	Mao 2015	69,165
2	"leukemia, myeloid"[MeSH Terms:noexp] AND "Acute Disease"[MeSH Terms:noexp]	Mao 2015	6,493
3	("acut*"[Title/Abstract] OR "akut*"[Title/Abstract] OR "agud*"[Title/Abstract] OR "aigu*"[Title/Abstract]) AND ("myelo*"[Title/Abstract] OR "mielo*"[Title/Abstract] OR "nonlympho*"[Title/Abstract] OR "myeloid*"[Title/Abstract] OR "myelocytic*"[Title/Abstract]) AND ("leukem*"[All Fields] OR "leukaem*"[All Fields] OR "leuc*"[All Fields])	Mao 2015	79,077
4	#1 OR #2 OR #3		109,186
5	"Economics"[MeSH Terms:noexp] OR "Costs and Cost Analysis"[MeSH Terms] OR "economics, nursing"[MeSH Terms] OR "economics, medical"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms] OR "economics, hospital"[MeSH Terms] OR "economics, dental"[MeSH Terms] OR "Fees and Charges"[MeSH Terms] OR "Budgets"[MeSH Terms] OR "budget*"[Title/Abstract] OR "economic*"[Title/Abstract] OR "cost"[Title/Abstract] OR "costs"[Title/Abstract] OR "costly"[Title/Abstract] OR "costing"[Title/Abstract] OR "price"[Title/Abstract] OR "prices"[Title/Abstract] OR "pricing"[Title/Abstract] OR "pharmacoeconomic*"[Title/Abstract] OR "pharmaco economic*"[Title/Abstract] OR "expenditure"[Title/Abstract] OR "expenditures"[Title/Abstract] OR "expense"[Title/Abstract] OR "expenses"[Title/Abstract] OR "financial"[Title/Abstract] OR "finance"[Title/Abstract] OR "finances"[Title/Abstract] OR "financed"[Title/Abstract] OR "value for money"[Title/Abstract] OR "monetary value*"[Title/Abstract] OR "models,	Economic Evaluations & Models - PubMed from CADTH at https://searchfilters.cadth.ca/link/63	1,702,902

#	Search term	Source	PubMed hits
	economic"[MeSH Terms] OR "economic model*"[Title/Abstract] OR "markov chains"[MeSH Terms] OR "markov"[Title/Abstract] OR "monte carlo method"[MeSH Terms] OR "monte carlo"[Title/Abstract] OR "Decision Theory"[MeSH Terms] OR "decision tree*"[Title/Abstract] OR "decision analy*"[Title/Abstract] OR "decision model*"[Title/Abstract]		
6	"cost illness"[Title/Abstract:~2] OR "costliness illness"[Title/Abstract:~2] OR "costly illness"[Title/Abstract:~2] OR "cost disease"[Title/Abstract:~2] OR "costliness disease"[Title/Abstract:~2] OR "costly disease"[Title/Abstract:~2] OR "cost diseases"[Title/Abstract:~2] OR "costliness diseases"[Title/Abstract:~2] OR "costly diseases"[Title/Abstract:~2] OR "cost sickness"[Title/Abstract:~2] OR "costliness sickness"[Title/Abstract:~2] OR "burden illness"[Title/Abstract:~2] OR "burdenliness illness"[Title/Abstract:~2] OR "burdenly illness"[Title/Abstract:~2] OR "burden disease"[Title/Abstract:~2] OR "burdenliness disease"[Title/Abstract:~2] OR "burdenly disease"[Title/Abstract:~2] OR "burden diseases"[Title/Abstract:~2] OR "burdenliness diseases"[Title/Abstract:~2] OR "burdenly diseases"[Title/Abstract:~2] OR "burden condition"[Title/Abstract:~2] OR "burdenliness condition"[Title/Abstract:~2] OR "burdenly condition"[Title/Abstract:~2] OR "burden economic"[Title/Abstract:~2] OR "burdenliness economic"[Title/Abstract:~2] OR "burdenly economic"[Title/Abstract:~2] OR "cost of illness"[Title/Abstract] OR "health expenditures"[MeSH Terms] OR "out-of-pocket payment"[Title/Abstract:~2] OR "out-of-pocket expenditure"[Title/Abstract:~2] OR "out-of-pocket cost"[Title/Abstract:~2] OR "out-of-pocket spending"[Title/Abstract:~2] OR "out-of-pocket expenses"[Title/Abstract:~2] OR "expenditure health"[Title/Abstract:~3] OR	Aluko, 2022, Cochrane Handbook, Chapter 20, Box 20.2.d Translated from OvidSP (MEDLINE) to native PubMed syntax; expanded wildcards to allow use of PubMed native term proximity operator	121,446

#	Search term	Source	PubMed hits
	"expenditure direct"[Title/Abstract:~3] OR "expenditure indirect"[Title/Abstract:~3]		
7	#5 OR #6		1,745,641
8	#4 AND #7		1,677
9	#8 AND ("2015/01/01"[Date - Publication] : "3000"[Date - Publication])		982

Table 3 Search terms reported in Appendix F including references for individual components of the search term

#	Search term	Source	PubMed hits
1	"Leukemia, Myeloid, Acute"[Mesh]	Mao 2015	69,165
2	"leukemia, myeloid"[MeSH Terms:noexp] AND "Acute Disease"[MeSH Terms:noexp]	Mao 2015	6,493
3	("acut*"[Title/Abstract] OR "akut*"[Title/Abstract] OR "agud*"[Title/Abstract] OR "aigu*"[Title/Abstract]) AND ("myelo*"[Title/Abstract] OR "mielo*"[Title/Abstract] OR "nonlympho*"[Title/Abstract] OR "myeloid*"[Title/Abstract] OR "myelocytic*"[Title/Abstract]) AND ("leukem*"[All Fields] OR "leukaem*"[All Fields] OR "leuc*"[All Fields])	Mao 2015	79,077
4	#1 OR #2 OR #3		109,186
5	"Value of Life"[MeSH Terms] OR "Quality of Life"[MeSH Terms] OR "Quality of Life"[Title/Abstract] OR "Quality-Adjusted Life Years"[MeSH Terms] OR "quality adjusted life"[Title/Abstract] OR "qaly*"[Title/Abstract] OR "qald*"[Title/Abstract] OR "qale*"[Title/Abstract] OR "qtime*"[Title/Abstract] OR "life year"[Title/Abstract] OR "life years"[Title/Abstract] OR "disability adjusted life"[Title/Abstract] OR "daly*"[Title/Abstract] OR "sf36"[Title/Abstract] OR "sf 36"[Title/Abstract] OR "short form 36"[Title/Abstract] OR "shortform 36"[Title/Abstract] OR "short form36"[Title/Abstract] OR "shortform36"[Title/Abstract] OR "sf6"[Title/Abstract] OR "sf 6"[Title/Abstract] OR "short form	Economic - Health Utilities / Quality of Life - Standard - PubMed from CADTH at https://searchfilters.cadth.ca/link/65	1,239,187

#	Search term	Source	PubMed hits
	6"[Title/Abstract] OR "shortform6"[Title/Abstract] OR "sf6d"[Title/Abstract] OR "sf 6d"[Title/Abstract] OR "short form 6d"[Title/Abstract] OR "shortform 6d"[Title/Abstract] OR "sf six"[Title/Abstract] OR "sfsix"[Title/Abstract] OR "short form six"[Title/Abstract] OR "sf8"[Title/Abstract] OR "sf 8"[Title/Abstract] OR "short form 8"[Title/Abstract] OR "shortform8"[Title/Abstract] OR "sf12"[Title/Abstract] OR "sf 12"[Title/Abstract] OR "short form 12"[Title/Abstract] OR "shortform 12"[Title/Abstract] OR "short form12"[Title/Abstract] OR "shortform12"[Title/Abstract] OR "sf16"[Title/Abstract] OR "sf 16"[Title/Abstract] OR "sf20"[Title/Abstract] OR "sf 20"[Title/Abstract] OR "short form 20"[Title/Abstract] OR "hql"[Title/Abstract] OR "hqol"[Title/Abstract] OR "h qol"[Title/Abstract] OR "hrqol"[Title/Abstract] OR "hr qol"[Title/Abstract] OR "hye"[Title/Abstract] OR "hyes"[Title/Abstract] OR "healthy year equivalent*"[Title/Abstract] OR "healthy years equivalent*"[Title/Abstract] OR "pqol"[Title/Abstract] OR "qls"[Title/Abstract] OR "quality of wellbeing"[Title/Abstract] OR "quality of well being"[Title/Abstract] OR "index of wellbeing"[Title/Abstract] OR "index of well being"[Title/Abstract] OR "qwb"[Title/Abstract] OR "nottingham health profile*"[Title/Abstract] OR "sickness impact profile"[Title/Abstract] OR "health status indicators"[MeSH Terms] OR "health utilit*"[Title/Abstract] OR "health status"[Title/Abstract] OR "disutilit*"[Title/Abstract] OR "rosser"[Title/Abstract] OR "willingness to pay"[Title/Abstract] OR "standard gamble*"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "time tradeoff"[Title/Abstract] OR		

#	Search term	Source	PubMed hits
	"tto"[Title/Abstract] OR "hui"[Title/Abstract] OR "hui1"[Title/Abstract] OR "hui2"[Title/Abstract] OR "hui3"[Title/Abstract] OR "eq"[Title/Abstract] OR "euroqol"[Title/Abstract] OR "euro qol"[Title/Abstract] OR "eq5d"[Title/Abstract] OR "eq 5d"[Title/Abstract] OR "euroqual"[Title/Abstract] OR "euro qual"[Title/Abstract] OR "duke health profile"[Title/Abstract] OR "functional status questionnaire"[Title/Abstract] OR "dartmouth coop functional health assessment*"[Title/Abstract] OR ("utilit*"[Title/Abstract] AND ("valu*"[Title/Abstract] OR "measur*"[Title/Abstract] OR "health"[Title/Abstract] OR "life"[Title/Abstract] OR "estimat*"[Title/Abstract] OR "elicit*"[Title/Abstract] OR "disease"[Title/Abstract] OR "score*"[Title/Abstract] OR "weight"[Title/Abstract])) OR ("preference*"[Title/Abstract] AND ("valu*"[Title/Abstract] OR "measur*"[Title/Abstract] OR "health"[Title/Abstract] OR "life"[Title/Abstract] OR "estimat*"[Title/Abstract] OR "elicit*"[Title/Abstract] OR "disease"[Title/Abstract] OR "score*"[Title/Abstract] OR "instrument"[Title/Abstract] OR "instruments"[Title/Abstract]))		
6	#4 AND #5		2,076

Systematic literature review (SLR)

A12. CS Appendix B, Appendix E and Appendix F. Please provide full details of the SLR process, including the search strategy (already provided), inclusion and exclusion criteria (noting that the rationale for some criteria is unclear e.g. language restrictions; outcome definitions [the CS focuses on leukaemia-free survival (LFS) rather than

progression-free survival (PFS) as noted in Appendix B ,Table 1,] etc), data extraction methods, quality assessment approach, and data synthesis methods. In particular, please confirm whether study selection, data extraction, and quality assessment were conducted independently by at least two reviewers. If not, please justify the approach taken.

The inclusion and exclusion criteria, laid out using the Patients, Interventions, Comparators, Outcomes, Study Design (PICOS) structure, are detailed in Table 1 of each of the respective SLR appendices. Regarding the rationale for specific inclusion or exclusion criteria, we would note that:

- The English language restriction reflected the predominance of AML research in English-language journals indexed in the literature databases searched. The risk of the English language restriction resulting in pivotal data being excluded is lower than might be surmised through the language distribution of primary publications alone, owing to the common practice of high-impact non-English findings in oncology being republished, summarised, or editorialised in English (e.g., in English abstracts, conference proceedings), reducing the chance of omitting meaningful findings. To further reduce the risk of language selection bias, we:
    - Executed language-unrestricted searches.
    - Screened titles/abstracts of all records regardless of language and documented exclusions by language.
    - Included studies with sufficiently detailed English abstracts.
- The focus on progression-free survival (PFS) as an endpoint in the SLR was based on the rationale that PFS was considered to be a superset of LFS; PFS measures time to disease progression or death and is used regardless of whether the patient is in remission. Meanwhile, LFS in AML is typically defined only for patients in remission and measures time from randomization or remission to relapse or death (whichever comes first). LFS is therefore similar to relapse-free survival (RFS) or disease-free survival (DFS), both of

which were also considered to be subsets of PFS for the purposes of identifying studies during the SLR. The LFS terminology used in the CS was selected as the more-specific terminology to align with the terminology used in the publications of the pivotal Brune *et al.* (2006) RCT.

The effect of the language restriction on the number of included studies is quantified in the PRISMA flow diagrams, with one study (of 1,239 screened; 0.08%) being excluded from the clinical searches on the grounds of language, two studies (of 1,983 screened; 0.10%) being excluded from the cost-effectiveness search, and two studies (of 2,076 screened; 0.10%) being excluded from the health-related quality of life search.

We can confirm that study selection (both title and abstract screening and subsequent full-text screening) was conducted independently by two reviewers, with disagreements resolved by discussion. Data extraction and quality assessment were conducted in full by one reviewer with 20% of extracted values being checked by a second reviewer. When IPD were ultimately obtained from the pivotal RCT (Brune *et al.* 2006), numerous cross-checks (including curve tracing), were then made between the outputs of the IPD analyses conducted and the published materials identified through the SLR. See also the response to question B6.

A13. CS Appendix B, Appendix E and Appendix F. For completeness, please comment on the limitations and generalisability of restricting the company's SLRs to English-language publications.

We acknowledge that there is some risk of introducing bias with the use of language restrictions in SLRs; however, as we note in the response to A12 above, foreign language studies were not excluded in the search terms, only at the point of screening.

Furthermore, the effect of the language restriction on the number of included studies is quantified in the PRISMA flow diagrams, with one study (of 1,239 screened; 0.08%) being excluded from the clinical searches on the grounds of language, two

studies (of 1,983 screened; 0.10%) being excluded from the cost-effectiveness search, and two studies (of 2,076 screened; 0.10%) being excluded from the health-related quality of life search. Overall, only five studies of 5,298 were excluded on the basis of the English-language restriction, corresponding to an exclusion rate of <0.1%.

A14. CS Appendix B, Appendix E and Appendix F. As per the PRISMA 2020 checklist (see https://www.prisma-statement.org/prisma-2020-checklist), for all SLRs undertaken by the company, please provide a complete list of excluded studies (assessed at full text), along with the reasons for their exclusion. Where relevant, this should include any observational or single-arm studies that were identified but excluded, even if they were not considered necessary due to the availability of RCT-based evidence. Please also indicate whether any such studies could offer potentially relevant supplementary evidence.

Tables of the studies excluded at the full-text screening stage are presented for Appendices B, E, and F in Table 4, Table 5, and Table 6, respectively.

Table 4 Reasons for clinical full-text study exclusions

Year	Authors	Journal	Title	Reason for exclusion
2014	Petit A, Ducassou S, Leblanc T, Pasquet M, Rousseau A, Ragu C, Cachanado M, Nelken B, Bertrand Y, Michel G, Gandemer V, Cuccuini W, Dastugue N, Fenneteau O, Lapillonne H, Auvrignon A, Baruchel A, Leverger G	Blood	Relevance of a one-year maintenance therapy with interleukin-2 in the treatment of childhood acute myeloid leukemia: Results from the French multicenter, phase III, randomized controlled SFCE trial, ELAM02	Duplicate
2008	Baer MR, Kolitz JE, George SL, Caligiuri MA, Larson RA	Annals of hematology	Cancer and leukemia group B studies of recombinant interleukin-2 maintenance therapy in acute myeloid leukemia	Duplicate
2006	Baer MR, George SL, Caligiuri MA, Sanford BL, O'Loughlin L, Mrozek K, Kolitz JE, Powell BL, Moore JO, Stone RM, et al	Blood	Phase III study of immunotherapy with recombinant interleukin-2 (IL-2) versus no further therapy in acute myeloid leukemia (AML) patients 60 years in first complete remission (CALGB 9720)	Duplicate
2022	Mi R, Chen L, Wang X, Yin Q, Wang Z, Ma X, Xu Y, Chen S, Wang G, Yang H, Li Z, Wang H, Guo S, Zhao H, Song Q, Li W, Li J, Wei X	Ann Transl Med	A retrospective study on effectiveness of combined recombinant human interferon-α-1b, interleukin-2, and thalidomide for the treatment of acute myeloid leukemia in various disease states.	Intervention
2021	Gómez García LM, Escudero A, Mestre C, Fuster Soler JL, Martínez AP, Vagace Valero JM, Vela M, Ruz B, Navarro A, Fernández L, Fernández A, Leivas A, Martínez-López J, Ferreras C, De Paz R, Blanquer M, Galán V, González B, Corral D, Sisinni L, Mirones I, Balas A, Vicario JL, Valle P, Borobia AM, Pérez-Martínez A	Clin Lymphoma Myeloma Leuk	Phase 2 Clinical Trial of Infusing Haploidentical K562-mb15-41BBL-Activated and Expanded Natural Killer Cells as Consolidation Therapy for Pediatric Acute Myeloblastic Leukemia.	Intervention
2018	Petit A, Ducassou S, Leblanc T, Pasquet M, Rousseau A, Ragu C, Cachanado M, Nelken B, Bertrand Y, Michel G, Gandemer V, Cuccuini W, Fenneteau O, Lapillonne H, Auvrignon A, Baruchel A, Leverger G	Hemasphere	Maintenance Therapy With Interleukin-2 for Childhood AML: Results of ELAM02 Phase III Randomized Trial.	Intervention
2014	Curti A, Ruggeri L, Parisi S, Bontadini A, Dan E, Rizzi S, Motta MR, Trabanelli S, Ocadlikova D, Lecciso M, Giudice V, Urbani E, Papayannidis C, Martinelli G, Bonifazi F,	Blood	Donor Natural Killer (NK) Alloreactivity Predicts Long-Term Relapse-Free Survival in Acute Myeloid Leukemia Patients Undergoing Immunotherapy with NK Cells	Intervention

Year	Authors	Journal	Title	Reason for exclusion
	Bandini G, Fruet F, Lewis RE, Cavo M, Velardi A, Lemoli RM			
2014	Kolitz JE, George SL, Benson DM Jr, Maharry K, Marcucci G, Vij R, Powell BL, Allen SL, Deangelo DJ, Shea TC, Stock W, Bakan CE, Hars V, Hoke E, Bloomfield CD, Caligiuri MA, Larson RA	Cancer	Recombinant interleukin-2 in patients aged younger than 60 years with acute myeloid leukemia in first complete remission: results from Cancer and Leukemia Group B 19808.	Intervention
2014	Zhai X, Xuan L, Sun J, Fan Z, Zhang Y, Huang F, Jiang Q, Xu D, Wei Y, Zhou H, Liu Q	Blood	Autologous HSCT Followed By Immunotherapy and Maintenance Chemotherapy Compared with Allogeneic HSCT for Intermediate-Risk Molecules/Cytogenetics Acute Myeloblastic Leukemia in First Complete Remission	Intervention
2011	Lange BJ, Yang RK, Gan J, Hank JA, Sievers EL, Alonzo TA, Gerbing RB, Sondel PM	Pediatr Blood Cancer	Soluble interleukin-2 receptor α activation in a Children's Oncology Group randomized trial of interleukin-2 therapy for pediatric acute myeloid leukemia.	Intervention
2009	Willemze R, Suciu S, Mandelli F, Halkes SJM, Marie J-P, Labar B, Venditti A, Muus P, Mistrik M, Rotoli B, Magro D, Melillo L, Bron D, Fabbiano F, Selleslag DLD, Pastore D, Trisolini SM, Fazi P, Vandermaelen C, Baila L, Vignetti M, Amadori S, De Witte TM, Meloni G	Blood	Value of low dose IL-2 as maintenance following consolidation treatment or autologous transplantation in acute myelogenous leukemia (AML) patients aged 15-60 years who reached CR after high dose (HD-AraC) vs standard dose (SD-AraC) cytosine arabinoside during induction: Results of the AML-12 trial of EORTC and GIMEMA leukemia groups	Intervention
2008	Stone RM, DeAngelo DJ, Janosova A, Galinsky I, Canning C, Ritz J, Soiffer RJ	Am J Hematol	Low dose interleukin-2 following intensification therapy with high dose cytarabine for acute myelogenous leukemia in first complete remission.	Intervention
2008	Baer MR, George SL, Caligiuri MA, Sanford BL, Bothun SM, Mrózek K, Kolitz JE, Powell BL, Moore JO, Stone RM, Anastasi J, Bloomfield CD, Larson RA	J Clin Oncol	Low-dose interleukin-2 immunotherapy does not improve outcome of patients age 60 years and older with acute myeloid leukemia in first complete remission: Cancer and Leukemia Group B Study 9720.	Intervention
2001	Schiller G, Wong S, Lowe T, Snead G, Paquette R, Sawyers C, Wolin M, Kunkel L, Ting L, Li G, Territo M	Leukemia	Transplantation of IL-2-mobilized autologous peripheral blood progenitor cells for adults with acute myelogenous leukemia in first remission	Intervention
1999	Cortes JE, Kantarjian HM, O'Brien S, Giles F, Keating MJ, Freireich EJ, Estey EH	Cancer	A pilot study of interleukin-2 for adult patients with acute myelogenous leukemia in first complete remission	Intervention
1997	Blaise D, Attal M, Pico JL, Reiffers J, Stoppa AM, Bellanger C, Molina L, Nedellec G, Vernant JP, Legros M, Gabus	Leuk Lymphoma	The use of a sequential high dose recombinant interleukin 2 regimen after autologous bone marrow transplantation does	Intervention

Year	Authors	Journal	Title	Reason for exclusion
	R, Huguet F, Brandely M, Hercend T, Olive D, Maraninchi D		not improve the disease free survival of patients with acute leukemia transplanted in first complete remission.	
2023	McCloskey J, Liu H, Egan DN, Berdeja JG, Tsai SB, Kilcoyne A, Daly C, Koppisetti S, Krishnan R, Hariri R, Wang ES	Blood	Results of Cynk-001-AML-001: A Phase I Multi-Dose Study Evaluating the Safety, Tolerability, and Persistence of Cynk-001 in Adults with De Novo or Secondary Acute Myeloid Leukemia in Morphologic Complete Remission with Minimal Residual Disease or Relapsed/Refractory AML	Intervention
2014	Willemze R, Suciu S, Meloni G, Labar B, Marie JP, Halkes CJ, Muus P, Mistrik M, Amadori S, Specchia G, Fabbiano F, Nobile F, Sborgia M, Camera A, Selleslag DL, Lefrère F Sr, Magro D, Sica S, Cantore N, Beksac M, Berneman Z, Thomas X, Melillo L, Guimaraes JE, Leoni P, Luppi M, Mitra ME, Bron D, Fillet G, Marijt EW, Venditti A, Hagemeijer A, Mancini M, Jansen J, Cilloni D, Meert L, Fazi P, Vignetti M, Trisolini SM, Mandelli F, de Witte T	J Clin Oncol	High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: results of the EORTC-GIMEMA AML-12 trial.	Intervention
2011	Willemze R, Suciu S, Mandelli F, Halkes SJM, Marie J-P, Labar B, Venditti A, Muus P, Mistrik M, Camera A, Magro D, Melillo L, Bron D, Magrin S, Selleslag D, Pastore D, Trisolini S, Fazi P, Karrasch M, Vignetti M, Amadori S, De Witte TM, Meloni G	Blood	High dose (HD-AraC) vs standard dose cytosine arabinoside (SD-AraC) during induction and IL-2 vs observation after consolidation/autologous stem cell transplantation in patients with acute myelogenous leukemia (AML): Final report of the AML-12 trial of EORTC and GIMEMA leukemia groups on the value of low dose IL-2 maintenance	Intervention
2023	Li X, Mi R, Chen L, Wang L, Wei X	干扰素白细胞介素2联合来那度胺治疗微小残留病阳性老年急性髓系白血病1例并文献复习	Interferon, interleukin 2 combined with lenalidomide for elderly acute myeloid leukemia with minimal residual disease-positive: report of 1 case and review of literature	Language
2022	Zeng Q, Xiang B, Liu Z	Ann Hematol	Autologous hematopoietic stem cell transplantation followed by interleukin-2 for adult acute myeloid leukemia patients with favorable or intermediate risk after complete remission.	Outcome

Year	Authors	Journal	Title	Reason for exclusion
2019	Aurelius J, Möllgård L, Kiffin R, Ewald Sander F, Nilsson S, Thorén FB, Hellstrand K, Martner A	Leuk Lymphoma	Anthracycline-based consolidation may determine outcome of post-consolidation immunotherapy in AML.	Outcome
2000	Sievers EL, Lange BJ, Sondel PM, Krailo MD, Gan J, Tjoa T, Liu-Mares W, Feig SA	Cancer J Sci Am	Children's cancer group trials of interleukin-2 therapy to prevent relapse of acute myelogenous leukemia.	Outcome
1993	Ganser A, Heil G, Kolbe K, Maschmeyer G, Fischer JT, Bergmann L, Mitrou PS, Heit W, Heimpel H, Huber C, et al	Ann Hematol	Aggressive chemotherapy combined with G-CSF and maintenance therapy with interleukin-2 for patients with advanced myelodysplastic syndrome, subacute or secondary acute myeloid leukemia--initial results.	Outcome
2007	Kolitz JE, Hars V, DeAngelo DJ, Allen SL, Shea TC, Vij R	Blood	Phase III trial of immunotherapy with recombinant interleukin-2 (rIL-2) versus observation in patients < 60 years with acute myeloid leukemia (AML) in first remission (CR1): preliminary results from cancer and leukemia group B (CALGB) 19808	Outcome
2025	Khani-Eshratabadi M, Motallebzadeh Khanmiri J, Dashti MR, Esmaeili S, Moradi Sani Z, Daei A, Hedayat Hasanabadi M, Saberi Amarghan S, Younesi Moghaddam N, Baradaran B	Clinical and Experimental Medicine	Potential therapeutic roles of natural killer cells in acute myeloid leukemia: a systematic review study	Population
2023	Kulkarni U, Arunachalam AK, Palani HK, Nair RR, Balasundaram N, Venkatraman A, Korula A, Selvarajan S, Lionel S, Balasubramanian P, Maddali M, Abraham A, George B, Mathews V	Cell Transplantation	Haploidentical Natural Killer Cell Therapy as an Adjunct to Stem Cell Transplantation for Treatment of Refractory Acute Myeloid Leukemia	Population
2023	Wang ES, Liu H, Egan DN, Kilcoyne A, Stout B, Ruggeri Barbaro N, Daly C, Kilcoyne S, Hariri R, McCloskey J	Blood	Conditioning Impacts on Regulatory T-Cells (Tregs) in the Microenvironment of AML: Observations from the Phase 1 Cynk-001-AML-001 Trial	Population
2022	Berrien-Elliott MM, Becker-Hapak M, Cashen AF, Jacobs M, Wong P, Foster M, McClain E, Desai S, Pence P, Cooley S, Brunstein C, Gao F, Abboud CN, Uy GL, Westervelt P, Jacoby MA, Pusic I, Stockerl-Goldstein KE, Schroeder MA, DiPersio JF, Soon-Shiong P, Miller JS, Fehniger TA	Blood	Systemic IL-15 promotes allogeneic cell rejection in patients treated with natural killer cell adoptive therapy	Population
2021	Berdel AF, Rollig C, Wermke M, Angenendt L, Ruhnke L, Mikesch J-H, Hemmerle T, Wethmar K, Kessler T, Gerwing M,	Blood	A phase I trial of the antibody-cytokine fusion protein F16IL2 in combination with anti-CD33 immunotherapy for posttransplant AML relapse	Population

Year	Authors	Journal	Title	Reason for exclusion
	Hescheler D, Schäfers M, Hartmann W, Altvater B, Rossig C, Lenz G, Stelljes M, Rueter B, Neri D, Berdel WE, Schliemann C			
2021	Kim SA, Koh Y, Jung M, Hwang YK, Byun JM, Hong J, Shin D-Y, Kim I, Yoon S-S	Blood	A Pilot Study of MG4101, Allogeneic Natural Killer Cell, in Patients with Relapsed or Refractory Acute Myeloid Leukemia	Population
2019	Mi R, Chen L, Wei X, Wang X, Song Y	Blood	Combined Thalidomide and Recombinant Human Interferon-α-1b and Interleukin-2 for Acute Myeloid Leukemia of Various Disease Status: A Multi-Center Prospective Study	Population
2017	Ai H, Zhang YL, Wei XD, Yin QS, Wang P, Mi RH, Song YP	Journal of Leukemia and Lymphoma	Long-term survival of patients with relapsed/refractory acute myelogenous leukemia treated by thalidomide combined with interferon and interleukin 2: Report of two cases and review of literature	Population
2016	NA	clinicaltrials.gov	A Phase 1, Multicenter, Open-Label, Dose Escalating Safety Study of Human Cord Blood Derived, Culture Expanded Natural Killer Cell (PNK-007) Infusion With Subcutaneous Recombinant Human IL-2 (RHIL-2) in Adults With Relapsed and/or Refractory Acute Myeloid Leukemia (AML).	Population
2016	NA	clinicaltrials.gov	A Phase I/II Clinical Trial Testing the Safety and Feasibility of IL-21- Expanded Natural Killer Cells for the Induction of Relapsed/Refractory Acute Myeloid Leukemia	Population
2015	Friend R, Juskevicius R, Salmon L, Murthy HS, Xenakis J, Asch AS, Walker P	Blood	Phase II trial daily pulse interleukin-2 therapy with famotidine during marrow and lymphocyte recovery in acute myeloid leukemia: LJCC 0605	Population
2015	Greil J, Kunz J, Lang P, Claus M, Kulozik A	Bone Marrow Transplantation	Successful maintenance treatment with interleukin-2/ histamine dihydrochloride (IL-2/HDC) and sorafenib after haploidentical SCT for refractory relapse of AML	Population
2012	Walker PR, Kamdar MK, Asch AS	Journal of Immunotherapy	Phase II trial daily pulse interleukin-2 therapy during marrow/lymphocyte recovery in acute myeloid leukemia NCT#01289678	Population
2011	Yang LP, Perry CM	Drugs Aging	Spotlight on histamine dihydrochloride in acute myeloid leukaemia.	Population
2007	Wallhult E, Whisnant J, Rowe JM, Szer J, Bhagwat D, Hellstrand K, Nilsson BI, Brune ML	Blood	Impact on quality of life of postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myelogenous leukemia	Population

Year	Authors	Journal	Title	Reason for exclusion
2001	Cesaro S, Meloni G, Messina C, Pillon M, Proglia A, Lanino E, Caniggia M, Bagnulo S, Pession A, Locatelli F	Bone Marrow Transplant	High-dose melphalan with autologous hematopoietic stem cell transplantation for acute myeloid leukemia: results of a retrospective analysis of the Italian Pediatric Group for Bone Marrow Transplantation.	Population
1999	Boughton BJ, Simpson AW	Cytokines, Cellular and Molecular Therapy	Acute myeloblastic leukaemia: Graft-versus-host and graft-versus-leukaemia responses to autologous IL-2 activated lymphocytes in rapid and slow disease	Population
1997	Meloni G, Vignetti M, Pogliani E, Invernizzi R, Allione B, Mirto S, Sica S, Leoni F, Selleri C, Mandelli F	Cancer J Sci Am	Interleukin-2 therapy in relapsed acute myelogenous leukemia.	Population
1996	Meloni G, Vignetti M, Andrizzi C, Capria S, Foa R, Mandelli F	Leuk Lymphoma	Interleukin-2 for the treatment of advanced acute myelogenous leukemia patients with limited disease: updated experience with 20 cases.	Population
1996	Robinson N, Sanders JE, Benyunes MC, Beach K, Lindgren C, Thompson JA, Appelbaum FR, Fefer A	Blood	Phase I trial of interleukin-2 after unmodified HLA-matched sibling bone marrow transplantation for children with acute leukemia.	Population
1995	Bergmann L, Heil G, Kolbe K, Lengfelder E, Puzicha E, Martin H, Lohmeyer J, Mitrou PS, Hoelzer D	Leuk Lymphoma	Interleukin-2 bolus infusion as late consolidation therapy in 2nd remission of acute myeloblastic leukemia.	Population
1995	Spiekermann K, O'Brien S, Estey E	Cancer	Relapse of acute myelogenous leukemia during low dose interleukin-2 (IL- 2) therapy: Phenotypic evolution associated with strong expression of the IL- 2 receptor alpha chain	Population
1994	Neubauer A, Knigge O, Zimmermann R, Krahl D, Schmidt CA, Oertel J, Huhn D	Annals of hematology	Comparison of immunological and molecular markers when using interleukin-2 (IL2) alone or in combination with gamma-interferon (IFN) in the maintenance therapy of acute myeloid leukemia	Population
1994	Wiernik PH, Dutcher JP, Todd M, Caliendo G, Benson L	Am J Hematol	Polyethylene glycolated interleukin-2 as maintenance therapy for acute myelogenous leukemia in second remission.	Population
1991	Macdonald D, Jiang YZ, Swirsky D, Vulliamy T, Morilla R, Bungey J, Barrett AJ	British Journal of Haematology	Acute myeloid leukaemia relapsing following interleukin-2 treatment expresses the alpha chain of the interleukin-2 receptor	Population
1989	Gottlieb DJ, Brenner MK, Heslop HE, Bianchi AC, Bello-Fernandez C, Mehta AB, Newland AC, Galazka AR, Scott EM, Hoffbrand AV, et al	Br J Cancer	A phase I clinical trial of recombinant interleukin 2 following high dose chemo-radiotherapy for haematological malignancy: applicability to the elimination of minimal residual disease.	Population

Year	Authors	Journal	Title	Reason for exclusion
2015	Mao C, Fu XH, Yuan JQ, Yang ZY, Huang YF, YE QL, Wu XY, Hu XF, Zhai ZM, Tang JL	Cochrane Database of Systematic Reviews	Interleukin-2 as maintenance therapy for children and adults with acute myeloid leukaemia in first complete remission	Review
2011	Berry SM, Broglio KR, Berry DA	Cancer Invest	Addressing the incremental benefit of histamine dihydrochloride when added to interleukin-2 in treating acute myeloid leukemia: a Bayesian meta-analysis.	Review
2011	Buyse M, Squifflet P, Lange BJ, Alonzo TA, Larson RA, Kolitz JE, George SL, Bloomfield CD, Castaigne S, Chevret S, Blaise D, Maraninchi D, Lucchesi KJ, Burzykowski T	Blood	Individual patient data meta-analysis of randomized trials evaluating IL-2 monotherapy as remission maintenance therapy in acute myeloid leukemia.	Review
2011	Yang LP, Perry CM	Drugs	Histamine dihydrochloride: in the management of acute myeloid leukaemia.	Review
2010	Berry SM, Broglio KR, Berry DA	Blood	Incremental benefit of histamine dihydrochloride when added to interleukin-2 for remission maintenance in acute myeloid leukemia: A bayesian meta-analysis	Review
2009	Romero AI, Thorén FB, Aurelius J, Askarieh G, Brune M, Hellstrand K	Scand J Immunol	Post-consolidation immunotherapy with histamine dihydrochloride and interleukin-2 in AML.	Review
2010	Pautas C, Merabet F, Thomas X, Raffoux E, Gardin C, Corm S, Bourhis JH, Reman O, Turlure P, Contentin N, de Revel T, Rousselot P, Preudhomme C, Bordessoule D, Fenaux P, Terré C, Michallet M, Dombret H, Chevret S, Castaigne S	J Clin Oncol	Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study.	Unclear if first remission
2008	Lange BJ, Smith FO, Feusner J, Barnard DR, Dinndorf P, Feig S, Heerema NA, Arndt C, Arceci RJ, Seibel N, Weiman M, Dusenbery K, Shannon K, Luna-Fineman S, Gerbing RB, Alonzo TA	Blood	Outcomes in CCG-2961, a children's oncology group phase 3 trial for untreated pediatric acute myeloid leukemia: a report from the children's oncology group.	Unclear if first remission
2005	Willemze R, Suciu S, Mandelli F, de Witte T, Labar B, Marie J	Blood	High dose cytosine arabinoside (HD-AraC) vs standard dose AraC (SD-AraC) during induction, and stem cell transplantation followed by IL-2 or no maintenance in acute myelogenous leukemia (AML): first report on the AML-12 phase III trial of the EORTC-Leukemia Group (LG) and GIMEMA	Unclear if first remission

Table 5 Reasons for health economic study exclusions

Year	Authors	Journal	Title	Reason for exclusion
2022	McBride A, Huggar D, Copher R, Zhou Z-Y, Zichlin ML, Anderson A, Downes N, Brunner AM	Clinical Lymphoma, Myeloma and Leukemia	AML-430 A Surveillance, Epidemiology, and End Results (SEER)-Medicare Analysis of the Economic Burden Among Elderly Patients With Acute Myeloid Leukemia (AML) Treated With Hypomethylating Agents (HMA)	Duplicate
2016	Irish W, Ryan MP, Gache LM, Gunnarsson C, Bell T, Shapiro M	Value in Health	Acute myeloid leukemia: A retrospective claims analysis of resource utilization and expenditures for de novo patients from first-line induction to remission and relapse	Duplicate
2021	Pratz KW, Chai X, Xie J, Yin L, Nie X, Montez M, Iantuono E, Downs L, Ma E	Blood	Cost effectiveness analysis of venetoclax plus azacitidine versus azacitidine in newly diagnosed adult patients with acute myeloid leukemia who are ineligible for intensive chemotherapy from a United States payer perspective	Duplicate
2017	Umit EG, Baysal M, Kirkizlar O, Demir AM	Blood	Economic analysis of posaconazole prophylaxis in patients with acute myeloid leukemia undergoing remission induction chemotherapy from a hospital management perspective	Duplicate
2021	Chen C, Papademetriou E, Liu X, Potluri R	Clinical Lymphoma, Myeloma and Leukemia	AML-157: Economic Burden of Hospitalizations for Acute Myeloid Leukemia (AML) in Remission in the United States: A Retrospective Analysis of an Administrative Claims Database	Language
2022	Zhou M, An FR, Zhang Q, Dong Y, Qin H, Zhai ZM, Tao QS	Zhongguo Shi Yan Xue Ye Xue Za Zhi	[A Real-World Study of the Effect of rhG-CSF on Clinical Efficacy and Flow Cytometry MRD after Initial Induction Therapy for Acute Myeloid Leukemia].	Language
2016	Stein EM, Latremouille-Viau D, Guerin A, Shi S, Gagnon-Sanschagrin P, Bonifacio G, Joseph GJ	Blood	Real-world treatment patterns, healthcare resource utilization, and costs in patients with newly diagnosed acute myeloid leukemia (AML)	Outcome
2020	Tervonen T, Cutts K, Seo J, Nehme SA, La Torre I, Prawitz T, Chen C, Beach CL, Wang J	Blood	Patient Preferences for Maintenance Treatment of Acute Myeloid Leukemia: Results of a Discrete Choice Experiment	Outcome
2022	Tettero JM, Al-Badri WKW, Ngai LL, Bachas C, Breems DA, van Elssen CHMJ, Fischer T, Gjertsen BT, van Gorkom GNY, Gradowska P, Greuter MJE, Griskevicius L, Juliusson G, Maertens J, Manz MG, Pabst T, Passweg J,	Front Oncol	Concordance in measurable residual disease result after first and second induction cycle in acute myeloid leukemia: An outcome- and cost-analysis.	Outcome

Year	Authors	Journal	Title	Reason for exclusion
	Porkka K, Löwenberg B, Ossenkoppele GJ, Janssen JJWM, Cloos J			
2021	Russell-Smith TA, Brockbank J, Mamolo C, Knight C	Pharmacoecon Open	Cost Effectiveness of Gemtuzumab Ozogamicin in the First-Line Treatment of Acute Myeloid Leukaemia in the UK.	Outcome
2024	Alhajahjeh A, Patel K, Shallis RM, Podoltsev NA, Kewan T, Stempel JM, Mendez L, Huntington SF, Stahl M, Zeidan AM, Goshua G, Bewersdorf JP	Blood	Cost-Effectiveness of Allogeneic Hematopoietic Stem Cell Transplantation Versus Consolidation Chemotherapy for Patients with Intermediate Risk Acute Myeloid Leukemia	Population
2019	Choi M, Ravelo A, Keim H, Song J, Chai X, Betts K, Bui C	Journal of Managed Care and Specialty Pharmacy	Budget impact analysis of venetoclax combinations in treatment of newly diagnosed acute myeloid leukemia in adults who are ineligible for intensive induction chemotherapy	Population
2024	El-Zeiny A, Abdelfatah R, Abbassi M, Farid SF	Pharmaceutical Sciences	Idarubicin versus Doxorubicin in Acute Myeloid Leukemia: A Parallel Randomized Trial with Pharmacoeconomic Analysis	Population
2017	Hagiwara M, Sharma A, Chung KC, Delea TE	Journal of Clinical Oncology	Burden of acute myeloid leukemia (AML) in a U.S. commercially insured population	Population
2020	Havrilesky LJ, Lim S, Ehrisman JA, Lorenzo A, Alvarez Secord A, Yang JC, Johnson FR, Gonzalez JM, Reed SD	Gynecol Oncol	Patient preferences for maintenance PARP inhibitor therapy in ovarian cancer treatment.	Population
2021	Huggar D, Knoth RL, Copher R, Cao Z, Lipkin C, McBride A, LeBlanc TW	Blood	Healthcare resource utilization and costs in us patients with newly diagnosed acute myeloid leukemia treated with intensive induction chemotherapy	Population
2022	Imataki O, Ishida T, Kida JI, Uemura M, Fujita H, Kadowaki N	J Clin Med Res	Cost-Effectiveness Analysis of Transplantation-Ineligible Elderly Patients With Acute Leukemia Harboring a Molecular Target: Ph-Positive Acute Leukemia and FLT3-Mutated Acute Myeloid Leukemia.	Population
2015	Jiang H, Liang GW, Huang XJ, Jiang Q, Han S, Shi LW, Zhu HH	Leuk Res	Reduced medical costs and hospital days when using oral arsenic plus ATRA as the first-line treatment of acute promyelocytic leukemia.	Population
2017	Kansal A, Du M, Herrera-Restrepo O, Leipold R, Ryan RJ, Louie AC, Chung K	Blood	Cost-effectiveness of CPX-351 versus 7+3 regimen in the treatment of treatment-related acute myeloid leukemia (TAML) or aml with myelodysplasia-related changes (MRC)	Population

Year	Authors	Journal	Title	Reason for exclusion
2019	Kayal S, Sengar M, Jain H, Bonda A, George B, Kulkarni UP, Balasubramanian P, Bhurani D, Ahmed R, Biswajit D, Pk J, Batra A, Kumar S, Mishra K, Bhattacharyya J, Philip CC, Bhattacharyya M, Dasappa L, Govind Babu K, Saldanha SC, Sharma A, Lakshmanan J, Durairaj J, Rudravaram VV, Mathews V, Kapoor R	Blood	Induction Related Mortality in Acute Myeloid Leukemia: Multivariate Model of Predictive Score from the Indian Acute Leukemia Research Database (INwARD) of the Hematology Cancer Consortium (HCC)	Population
2022	Maziarz RT, Devine SM, Garrison LP, Agodoa I, Badaracco J, Gitlin M, Perales M-A	Blood	Estimating the Lifetime Medical Cost Burden of an Allogeneic Hematopoietic Cell Transplantation Patient and the Value of Addressing the Unmet Need	Population
2022	Muffly L, Young C, Xie B, Block A, Touya M, Pandya BJ	Blood	Real World Outcomes in Acute Myeloid Leukemia Patients Following Post Hematopoietic Stem-Cell Transplantation Maintenance Treatment with Midostaurin or Sorafenib: A US Retrospective Cohort Study	Population
2019	Panjabi S, Bychenkova A, McCloskey C, Nair S, Price K, Yucel E	Value in Health	PCN79 A TARGETED LITERATURE REVIEW (TLR) OF THE EPIDEMIOLOGY AND ECONOMIC BURDEN OF ACUTE MYELOID LEUKEMIA (AML)	Population
2022	Pratz KW, Chai X, Xie J, Yin L, Nie X, Montez M, Iantuono E, Downs L, Ma E	Pharmacoeconomics	Cost-Effectiveness Analysis of Venetoclax in Combination with Azacitidine Versus Azacitidine Monotherapy in Patients with Acute Myeloid Leukemia Who are Ineligible for Intensive Chemotherapy: From a US Third Party Payer Perspective.	Population
2019	Price K, Cao Z, Lipkin C, Robinson S, Profant DA	Blood	A Descriptive Study on Healthcare Utilization and Costs in Secondary Acute Myeloid Leukemia Patients Treated with CPX-351 Versus Those Treated with 7+3	Population
2021	Rodríguez-Rodríguez S, Guerrero-Torres L, Díaz-Huízar MJ, Pomerantz A, Ortíz-Vilchis MDP, Demichelis-Gómez R	Hematology, Transfusion and Cell Therapy	Cost-effectiveness of the regimen proposed by the International Consortium on Acute Promyelocytic Leukemia for the treatment of newly diagnosed patients with Acute Promyelocytic Leukemia	Population
2022	Saturnino LTM, Kuperman G, Gasca R, Larrosa J, Zapata N, Polanco A	Value in Health	POSC193 Economic Burden Associated to Acute Myeloid Leukemia in Mexico	Population
2020	Sierra J, Mareque M, Montesinos P, Guinea JM, Font P, Oyagüez I, Brockbank J, Candini D, Llinares J, Soto J, De La Fuente A	HemaSphere	Cost-effectiveness of gemtuzumab ozogamicin in combination with standard of care chemotherapy for first-line treatment of patients with CD33-positive acute myeloid leukemia in Spain	Population

Year	Authors	Journal	Title	Reason for exclusion
2020	Tabah A, Huggar D, Brady BL, Jariwala-Parikh K, Huey K, Copher RM, Leblanc TW	Clinical Lymphoma, Myeloma and Leukemia	AML-117: The Economic Burden of Relapse in Acute Myeloid Leukemia (AML): A Retrospective Analysis of US Commercial and Medicare Claims	Population
2017	Tikhonova IA, Hoyle MW, Snowsill TM, Cooper C, Varley-Campbell JL, Rudin CE, Mujica Mota RE	Pharmacoeconomics	Azacitidine for Treating Acute Myeloid Leukaemia with More Than 30 % Bone Marrow Blasts: An Evidence Review Group Perspective of a National Institute for Health and Care Excellence Single Technology Appraisal.	Population
2018	Tremblay G, Dolph M, Patel S, Brandt P, Forsythe A	Cost Eff Resour Alloc	Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom.	Population
2015	Van De Velde A, Beutels P, Anguille S, Gadisseur A, Schroyens W, Verlinden A, Smits E, Van Tendeloo V, Nijs G, Dom S, Cornille I, Berneman Z	Bone Marrow Transplantation	Cost analysis of dendritic cell therapy for acute myeloid leukemia patients	Population
2020	Ying C, Li Y, Yan L, Zhan H, Chen Y, Chen W	Value in Health Regional Issues	PCN26 Disease Burden of ACUTE Myelogenous Leukemia UNDER the Current Treatment Pattern in China	Population
2021	Zhou M, Yang H, Song Y, Marshall D, Griffin J, Saini L, Shah M	Journal of Managed Care and Specialty Pharmacy	Patient and Physician Perspectives on Treatment Attributes and the Humanistic and Economic Burden of Blood Transfusions in Patients with Acute Myeloid Leukemia (AML) Previously Treated with Hematopoietic Stem Cell Transplantation (HSCT)	Population
2019	Scory T, Shaw E, Cowling T, Peloquin F, Welch VL, Charaan M, Brown A	Blood	The Impact of Hematopoietic Stem Cell Transplantation on Work and Productivity Loss in Patients with Acute Leukemia: Results from a Rapid Review	Population
2019	Arenaza A, Diez R, Esteve J, Di Nicolantonio R, Gostkorzewicz J, Martínez C, Martínez Llinàs D, Martinez-Lopez J, Montesinos P, Moure-Fernández A, Sierra J, Vinent JL	Clinicoecon Outcomes Res	Cost-Effectiveness Of Midostaurin In The Treatment Of Acute Myeloid Leukemia With The FLT3 Mutation In Spain.	Unclear if first remission
2024	Borate U, Seiter K, Potluri R, Mazumder D, Chevli M, Prebet T, Gaugler L, Strocchia M, Vasconcelos A, Sieluk J	Adv Ther	Healthcare Utilization and Costs Among Patients with Acute Myeloid Leukemia Receiving Oral Azacitidine Maintenance Therapy Versus No Maintenance: A US Claims Database Study.	Unclear if first remission
2023	Borate U, Seiter K, Potluri R, Mazumder D, Heydendael W, Chevli M, Prebet T, Strocchia M, Vasconcelos A, Sieluk J	Value in Health	Healthcare Resource Utilization (HCRU) and Associated Costs Among Patients with Acute Myeloid Leukemia (AML) Treated with Oral Azacitidine as Maintenance and	Unclear if first remission

Year	Authors	Journal	Title	Reason for exclusion
			Those Eligible but Not Treated Using a US Claims Database	
2024	Boussi L, Burton H, Derkach A, Nemirovsky D, Ciervo J, Tallman MS, Stein EM, Cai S	Blood	Outpatient Vs Inpatient Hidac Consolidation for AML: The MSKCC Experience	Unclear if first remission
2021	Brunner AM, Huggar D, Copher R, Zhou Z-Y, Zichlin ML, Anderson A, Downes N, McBride A	Blood	Treatment Patterns and Economic Burden Among Elderly Patients with Acute Myeloid Leukemia Treated with Hypomethylating Agents: A SEER-Medicare Analysis	Unclear if first remission
2018	Cariou C, Tremblay G, Dolph M, Brandt PS, Forsythe A	Value in Health	Cost-effectiveness Model of Midostaurin (Mido) Versus Standard of Care (SoC) in Patients with Newly Diagnosed FLT3 Mutation-Positive (FLT3+) Acute Myeloid Leukemia (AML): A French Perspective	Unclear if first remission
2023	Catapia JRM, Vaswani PPM, Pajares CJV, Mo MC, Chen EBT, Bonifacio LB	Hematol Transfus Cell Ther	Economic burden of acute myeloid leukemia on patients in a resource-limited tertiary hospital in the Philippines.	Unclear if first remission
2021	Chen C, Papademetriou E, Kiendrebeogo Z, Potluri R	Blood	Economic burden of hospitalizations for patients with newly diagnosed acute myeloid leukemia in remission in the United States: Retrospective analysis of an administrative claims database	Unclear if first remission
2022	Choi M, Song J, Bui CN, Ma E, Chai X, Yin L, Betts KA, Kapustyan T, Montez M, LeBlanc TW	J Manag Care Spec Pharm	Costs per patient achieving remission with venetoclax-based combinations in newly diagnosed patients with acute myeloid leukemia ineligible for intensive induction chemotherapy.	Unclear if first remission
2017	Hörster L, Schlenk RF, Stadler M, Gabriel M, Thol F, Schildmann J, Vollmann J, Rochau U, Sroczynski G, Wasem J, Ganser A, Port M, Neumann A	Leuk Res	Cost-effectiveness of methods in personalized medicine. Results of a decision-analytic model in patients with acute myeloid leukemia with normal karyotype.	Unclear if first remission
2020	Immonen J, Wiik E, Vertuani S, Wolf M, Tukiainen M, Sainio T	Value in Health	PCN155 Healthcare Resource Use and Associated Costs in Patients Diagnosed with Acute Myeloid Leukemia in Hospital District of Southwest Finland	Unclear if first remission
2021	Pocock C, Montesinos P, Braun T, Kambhampati S, Oriol A, La Torre I, Skikne B, Beach C, Zhong J, Chen C, Ranjan S, Potluri R, Natalie Oliva E	HemaSphere	Estimated hospitalization-related costs with oral azacitidine (ORAL-AZA) vs placebo (PBO) for remission maintenance in patients with acute myeloid leukemia (AML) in Spain and the United Kingdom (UK)	Unclear if first remission
2023	Santoni NB, Antunes RMC, Pereira I, Pereira ACPR, Fernandes RA	Hematology, Transfusion and Cell Therapy	Resource Utilization and Costs Related to Acute Myeloid Leukemia Management: A Systematic Literature Review	Unclear if first remission

Table 6 Reasons for health-related quality of life study exclusions

Year	Authors	Journal	Title	Reason for exclusion
1985	Jehn U, Löwenberg B	Onkologie	[AML-7 study of the value of intensive remission induction in aged patients with acute myelocytic leukemia].	Language
1985	Jehn U, Zittoun R, Löwenberg B	Onkologie	[AML-6 and AML-7 studies on the treatment of acute myelocytic leukemia. Cyclic alternating chemotherapy during remission, and induction of remission and survival of elderly patients].	Language
2022	Ahmed M, Suero B, Cameron H, Chen C	Value in Health	POSB364 Systematic Literature Reviews (SLRS) of Economic Evaluations and Health Utility Studies of AML Treatments for Adults Receiving High Intensity Induction Therapy, with or without Maintenance Therapy	Outcome
2007	Appelbaum FR	Best Pract Res Clin Haematol	Hematopoietic cell transplantation from unrelated donors for treatment of patients with acute myeloid leukemia in first complete remission.	Outcome
2021	Bornhaeuser M, Schliemann C, Schetelig J, Rollig C, Kramer M, Glass B, Platzbecker U, Burchert A, Haenel M, Mueller LP, Klein S, Bug G, Beelen DW, Roesler W, Schaefer-Eckart K, Schmid C, Jost E, Lenz G, Tischer J, Spiekermann K, Pfirrmann M, Serve H, Stoelzel F, Alakel N, Ehninger G, Berdel WE, Stelljes M	Blood	Allogeneic Hematopoietic Cell Transplantation in Patients ≤ 60 Years with Intermediate-Risk Acute Myeloid Leukemia in First Remission - Results of the Randomized Etal-1 Trial-	Outcome
2020	Döhner H, Wei AH, Pocock C, Montesinos P, Dombret H, Ravandi F, Sayar H, Jang JH, Porkka K, Selleslag D, Sandhu I, Turgut M, Giai V, Ofran Y, Cakar MK, Botelho De Sousa A, Rybka J, Frairia C, Borin L, Beltrami G, Cermak J, Pfeilstöcker M, Thol F, Fieldmann G, Ossenkoppele GJ, La Torre I, Skikne B, Kumar K, Dong Q, Beach CL, Roboz GJ	Oncology Research and Treatment	The QUAZAR AML-001 maintenance trial: Results of a phase III international, randomized, double-blind, placebo-controlled study of oral CC-486 in patients with Acute Myeloid Leukemia (AML) in first remission	Outcome
2014	Kurosawa S, Yamaguchi H, Yamaguchi T, Fukunaga K, Yui S, Kanamori H, Usuki K, Uoshima N, Yanada M, Shono K, Ueki T, Mizuno I, Yano S, Takeuchi J, Kanda J,	Blood	Decision Analysis of Allogeneic Hematopoietic Stem Cell Transplantation Versus Chemotherapy in Cytogenetically Standard-Risk Acute Myeloid Leukemia in First Complete Remission: The Impact of FLT3-ITD Profile	Outcome

Year	Authors	Journal	Title	Reason for exclusion
	Okamura H, Tajima K, Inamoto Y, Inokuchi K, Fukuda T			
2013	Ling V, Burnett AK, Bradstock K, Seymour JF, Hills RK, Wei A	Br J Haematol	Utility of a clinical risk score to identify high-risk patients with de novo acute myeloid leukaemia in first remission after high-dose cytarabine (HiDAC) based induction chemotherapy.	Outcome
2020	Roboz G, Dohner H, Pocock C, Dombret H, Ravandi F, Jang JH, Selleslag D, Mayer J, Martens U, Liesveld J, Bernal T, Wang MC, La Torre I, Skikne B, Kumar K, Dong Q, Braverman J, Abi Nehme S, Beach C, Wei A	HemaSphere	Health-related quality of life with CC-486 in patients with acute myeloid leukemia (AML) in first remission following induction chemotherapy (IC): Results from the phase iii Quazar AML-001 trial	Outcome
2020	Roboz GJ, Dohner H, Pocock C, Dombret H, Ravandi F, Jang JH, Selleslag D, Mayer J, Martens UM, Liesveld J, Castillo TBD, Wang M-C, Torre IL, Skikne B, Kumar K, Dong Q, Braverman J, Nehme SA, Beach CL, Wei A	Journal of Clinical Oncology	Health-related quality of life (HRQoL) in the phase III QUAZAR-AML-001 trial of CC-486 as maintenance therapy for patients with acute myeloid leukemia (AML) in first remission following induction chemotherapy (IC)	Outcome
1988		Leuk Res	Survival in acute myeloblastic leukemia is not prolonged by remission maintenance or early reinduction chemotherapy. The Toronto Leukemia Study Group.	Population
2019	Bonifazi F, Solano C, Wolschke C, Sessa M, Patriarca F, Zallio F, Nagler A, Selleri C, Risitano AM, Messina G, Bethge W, Herrera P, Sureda A, Carella AM, Cimminiello M, Guidi S, Finke J, Sorasio R, Ferra C, Sierra J, Russo D, Benedetti E, Milone G, Benedetti F, Heinzelmann M, Pastore D, Jurado M, Terruzzi E, Narni F, Völp A, Ayuk F, Ruutu T, Kröger N	Lancet Haematol	Acute GVHD prophylaxis plus ATLG after myeloablative allogeneic haemopoietic peripheral blood stem-cell transplantation from HLA-identical siblings in patients with acute myeloid leukaemia in remission: final results of quality of life and long-term outcome analysis of a phase 3 randomised study.	Population
1975	Burge PS, Prankerd TA, Richards JD, Sare M, Thompson DS, Wright P	Lancet	Quality and quantity of survival in acute myeloid leukaemia.	Population
2021	Cutts K, Tervonen T, Seo J, Abi Nehme S, La Torre I, Chen C, Beach C, Wang J	HemaSphere	Patient preferences for maintenance therapy of acute myeloid leukemia: A discrete choice experiment subanalysis of patients in Germany and Italy	Population

Year	Authors	Journal	Title	Reason for exclusion
2021	Montégut C, Falandry C, Cinieri S, Montane L, Rousseau F, Joly F, Frindte J, Mosconi AM, Guerra-Alia E, Schauer C, Fujiwara H, Vergote IB, Parma G, Lindahl G, Anota A, Canzler U, Marmé F, Pujade-Lauraine E, Ray-Coquard I, Sabatier R	International Journal of Gynecological Cancer	Safety and quality of life of first-line maintenance olaparib plus bevacizumab in older patients with advanced ovarian cancer in the paola-1 trial	Population
2017	Retzler J, Smith AB, Chung KC	Value in Health	Health utilities in acute myeloid leukemia: A comprehensive literature review	Population
2014	Schultz KA, Chen L, Chen Z, Kawashima T, Oeffinger KC, Woods WG, Nicholson HS, Neglia JP	Pediatr Blood Cancer	Health conditions and quality of life in survivors of childhood acute myeloid leukemia comparing post remission chemotherapy to BMT: a report from the children's oncology group.	Population
2021	Zhou M, Yang H, Song Y, Marshall DA, Griffin JD, Saini L, Shah MV	HemaSphere	Patient and physician preferences for post-hematopoietic stem cell transplantation maintenance treatment of acute myeloid leukemia	Population
2018	Kayastha N, Wolf SP, Locke SC, Samsa GP, El-Jawahri A, LeBlanc TW	Support Care Cancer	The impact of remission status on patients' experiences with acute myeloid leukemia (AML): an exploratory analysis of longitudinal patient-reported outcomes data.	Unclear if first remission

A15. CS Appendix B, Section 1.3, pages 9-11. Although the Cochrane Risk of Bias 2 (RoB 2) tool has been used to critically appraise the Brune *et al.* (2006) study, it appears that the tool may not have been applied correctly. Please review and revise the assessment accordingly, including a judgment of the overall risk of bias; for guidance, see the current version of the RoB 2 tool (https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2).

The complete table showing the outcomes of the Cochrane Risk of Bias 2 tool for the Brune *et al.* 2006 RCT, now including the final "Overall risk of bias" row, is presented in Table 7.

Table 7 Cochrane Risk of Bias assessment of the Brune et al. 2006 randomised controlled trial

Risk of bias assessment criterion	**Brune *et al.* 2006**
Risk of bias arising from the randomization process	
Was the allocation sequence random?	Yes
Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No
Did baseline differences between intervention groups suggest a problem with the randomization process?	No
Were participants aware of their assigned intervention during the trial?	Yes
Risk-of-bias judgement	**Some concerns**
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No
If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk-of-bias judgement	**Low risk**
Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	
Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Risk of bias assessment criterion	**Brune *et al.* 2006**
If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No
If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk-of-bias judgement	**Low risk**
Risk of bias due to missing outcome data	
Were data for this outcome available for all, or nearly all, participants randomized?	Yes
If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA
If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk-of-bias judgement	**Low risk**
Risk of bias in measurement of the outcome	
Was the method of measuring the outcome inappropriate?	No
Could measurement or ascertainment of the outcome have differed between intervention groups?	No
If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No
If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk-of-bias judgement	**Low risk**
Risk of bias in selection of the reported result	
Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes
Is the numerical result being assessed likely to have been selected, on the basis of the results, from…	
... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No
... multiple eligible analyses of the data?	No
Risk-of-bias judgement	**Low risk**
Overall risk of bias	
Low / High / Some concerns	**Low risk**

Clinical effectiveness evidence

A16. PRIORITY. CS, Section 4, pages 106-107. Please provide a copy of the Clinical Study Report (CSR) for the *"Multicenter Randomized Open-Label Study to Evaluate the Safety and Efficacy of Immunotherapy with Subcutaneous CepleneTM (Histamine Dihydrochloride) plus ProleukinTM (Interleukin-2) Versus No Treatment in Patients with Acute Myeloid Leukemia in First or Subsequent Complete Remission (CR)."* trial (Data on file, 2006 in the reference list).

The clinical study report (CSR) for the *"Multicenter Randomized Open-Label Study to Evaluate the Safety and Efficacy of Immunotherapy with Subcutaneous CepleneTM (Histamine Dihydrochloride) plus ProleukinTM (Interleukin-2) Versus No Treatment in Patients with Acute Myeloid Leukemia in First or Subsequent Complete Remission (CR)."* was uploaded onto the NICE Docs platform at 12.49pm on Tuesday 2nd October.

A17. PRIORITY. CS, Section 2.3, Table 6 (pages 31-32). Regarding the baseline characteristics of patients included in the Brune *et al.* (2006) study, please provide:

(a) Karyotype breakdown for the subgroup of patients in CR1 and ≤60 years by treatment arm.

(b) A table with the baseline characteristics of the subgroup of normal karyotype, in CR1 and less than 60 years old, by treatment arm (N=35 in the histamine dihydrochloride and low-dose interleukin-2 arm and N=37 in BSC arm). Please comment on the impact of any imbalances in patient characteristics, where relevant.

(a) Please find in the table below the karyotype breakdown from the subgroup of patients on CR1 and ≤60 years by treatment arm:

Karyotype	**Control (n=85)**	**HDC/IL-2 (n=80)**
Favourable	7	11

Intermediate	40	36
Unfavourable	12	8
Other	13	13
Unknown or insufficient metaphases	13	12

We contacted one of the co-authors of the Nilsson *et al* 2020 publication, Professor Kristoffer Hellstrand, who was able to give us the baseline characteristics of the subgroup of normal karyotype, in CR1 and less than 60 years old as follows:

Baseline characteristic	**Control (n=37)**	**HDC/IL-2 (n=35)**
Age (mean, median)	43.0, 44.5	45.4, 46.0
Female/male (%)	46/54	40/60
ECOG performance status (0/1)	31/6	30/5
Prior auto-SCT (yes/no)	5/32	8/27
Prior high-dose cytarabine (yes/no)	33/4	32/3

There do not appear to be any obvious differences in baseline characteristics between the two arms of the subgroup of patients with normal karyotype, in CR1 and less than 60 years old. You would therefore expect that the similarity in baseline characteristics between the two arms would not unduly influence the outcomes on either the HDC/IL-2 or treatment arms.

A18. PRIORITY. CS, Section 2.3, Table 6 (page 31). The baseline characteristics of patients included in the Brune *et al.* (2006) study reports that approximately 12.2% of patients in the ITT population of the study (22 patients in the HDC/IL-2 and 17 patients in the control group) received previous treatment with autologous haematopoietic stem cell transplantation (auto-HSCT). Clinicians consulted by the

EAG mentioned that auto-HSCT has not been used in the UK in patients with AML for several years. Please clarify:

(a) What proportion of patients in the ≤60 years, normal karyotype and CR1 group had received previous treatment with auto-HSCT?

(b) How generalisable is the population in the Brune *et al.* (2006) study to current UK clinical practice, given that AML management has changed significantly over the past decade?

(c) How the differences between the study population in Brune *et al.* (2006) and the current UK AML patient population are expected to impact the study outcomes?

(a) Having contacted the co-author of the Brune et al 2006 study and the Nilsson et al 2020 post-hoc analyses, Professor Kristoffer Hellstrand, he confirmed that 5/37 patients in the control arm and 8/35 patients in the HDC/IL arm received prior autologous stem cell transplant within the normal karyotype subgroup.

(b) In the Brune *et al* 2006 study, 66% and 68% of patients in the treatment arm and control arm, respectively, received high dose cytarabine as defined by at least 2 g/m^2 per day for 3 or more days during induction or consolidation treatment. One might expect that a higher proportion of patients who are fit for induction and consolidation treatment would receive high-dose cytarabine in the UK today. It is also likely that the number of AML patients offered allogeneic stem transplant at first complete remission in the UK has increased significantly since the Brune *et al* 2006 study was conducted. The routine diagnostic tests for UK patients with suspected or newly diagnosed AML include cytogenetic testing to define the karyotype status and molecular genetic testing to detect specific gene mutations (e.g., *FLT3*, *NPM1*, *CEBPA*) that are important in determining the patient's prognosis and guiding the use of targeted therapy. The Brune *et al* 2006 study was conducted prior to the introduction of routine molecular genetic testing. However, patients with gene mutations who are thereby eligible for specific treatment, as exemplified by FLT3 inhibitors for those with FLT3 mutations, are expected to receive those targeted treatments to the exclusion of HDC/IL-2. The

remaining target population, eligible for HDC/IL-2, can be considered relatable to those described in the Brune *et al* 2006 study.

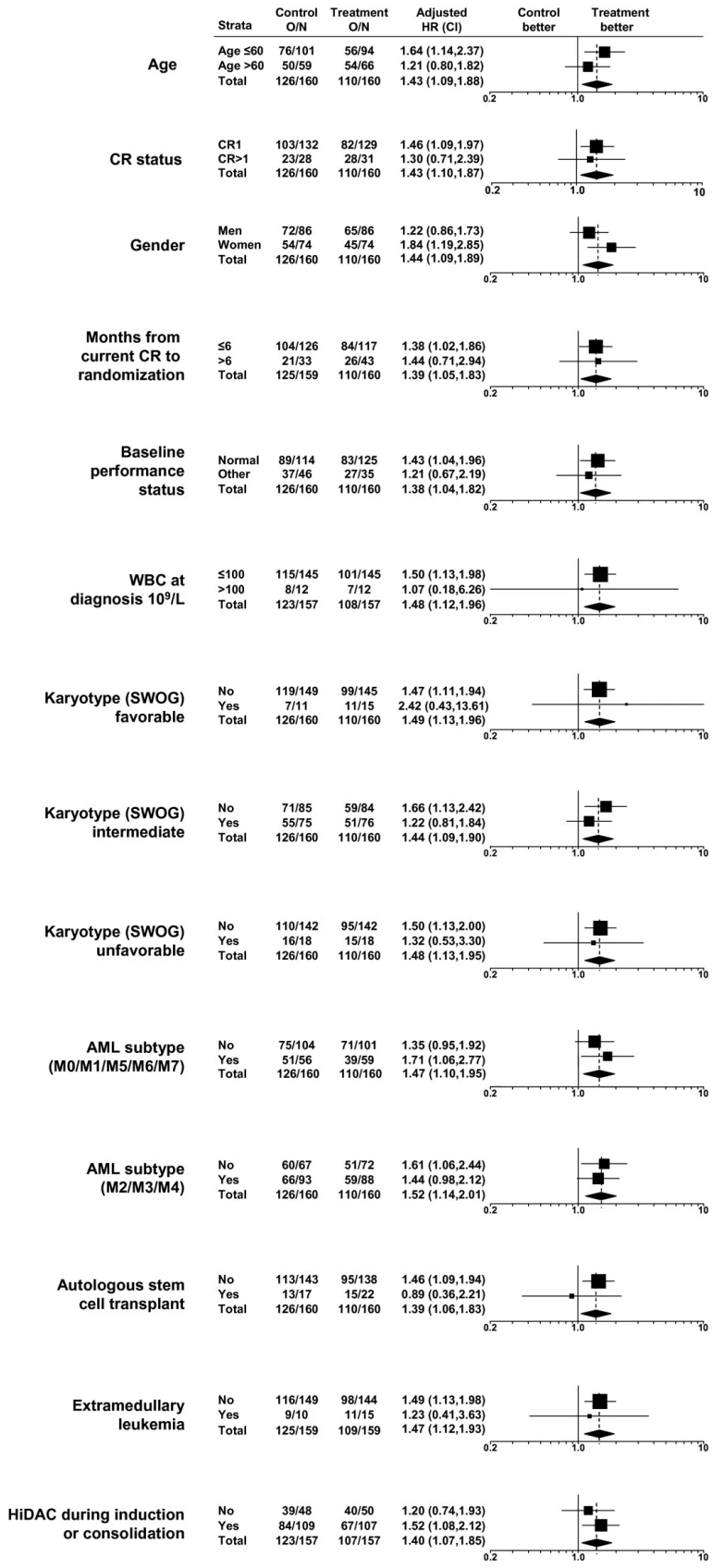
(c) Considering the above the impact of more patients receiving high-dose cytarabine at induction and consolidation may help to improve outcomes generally, although all patients would need to be in first complete remission in any case to be considered for treatment with HDC/IL-2. If more AML patients in the UK receive allogeneic stem cell transplant after induction and consolidation treatment at first complete remission, then this is likely to reduce the population of patients considered for maintenance immunotherapy with HDC/IL-2. It may also mean that the patients who are now not considered suitable for allogeneic stem cell transplant have a favourable risk compared with the Brune *et al* 2006 patient population. The implication of molecular testing is that those patients where there is an effective targeted treatment available, such as FLT3 inhibitors for those patients with FLT3 mutations, will tend to reduce the patient population considered suitable for HDC/IL-2

A19. CS, Section 2.3, page 29. The CS states that *"Settings and locations where the data were collected: AML patients were enrolled at 100 centers in Australia, Canada, Europe, Israel, New Zealand, and the United States between June 1998 and October 2000."* Please clarify how many patients from the UK were included in the study, given that the trial register on clinicaltrials.org (https://clinicaltrials.gov/study/NCT00003991) lists three study locations in the UK.

According to the clinical study report three patients were included in the study from the UK of which two patients were randomised to the control arm and one patient to the treatment arm.

A20. CS, Section 2.8, pages 50-51. Please present the forest plot for the subgroup analyses from the Brune *et al.* (2006) study (similar to Figure 1 in Buyse *et al*. 2011 - https://doi.org/10.1186/1745-6215-12-86) as this is not presented in the CS.

Please see forest plot reproduced from Buyse et al 2011 below.



Forest plots of leukemia-free survival (LFS) hazard ratios (HR) and their confidence intervals (CI) by baseline characteristics. O/N = event rate per arm

where O is the number of observed events (relapse or death) and N is the sample size. HR = hazard ratio, CI = confidence interval, CR = complete remission, CR1 = first complete remission, WBC = white blood cell, SWOG = Southwest Oncology Group, AML = acute myeloid leukemia, HiDAC = high-dose cytosine arabinoside.

A21. PRIORITY. CS, Section 2.3, page 32. In the economic analysis, the population was restricted to AML patients with normal karyotype in CR1 and less than 60 years old. Please clarify: (a) whether the population chosen for the economic model was based on the *post-hoc* analysis published by Nilsson *et al.* (2020); (b) how the age cut-off of 60 years, CR1, and normal karyotype were identified as factors potentially influencing prognosis and modifying treatment effects on outcomes, including the criteria used for the *post-hoc* analysis. Please also comment on the *post-hoc* nature of this analysis and the potential implications for the break in randomisation.

(a) Yes, the economic analysis was based on the *post-hoc* analysis published by Nilsson et al (2020).

(b) In the multivariate analysis from the Brune et al (2006) study, 2 factors, that is, age (≥60 versus <60) and karyotype (adverse versus other), were found to have a significant effect on leukaemia-free survival (LFS). A significant treatment effect was shown in those patients (n=261) in first complete remission (CR1) and not in the small subgroup of patients (n=59) in subsequent complete remission (CR>1). These findings provided the rationale for conducting a post-hoc analysis in the subgroup of patients with a normal karyotype, who are in CR1 and less than 60 years.

A22. CS, Section 2.3, Table 6 (page 31). Please clarify the definition of ‘normal karyotype’ used in Brune *et al.* (2006), since the baseline characteristics of patients reported in the trial and in CS Table 6 categorise karotypes only as ‘Favorable’, ‘Intermediate’, ‘Adverse’ and ‘Unknown’.

As noted under the company's response to clarification question A2. PRIORITY, "normal" karyotype refers to a form of AML where the chromosomes in the leukaemia cells appear normal under standard cytogenetic analysis (karyotyping) and is established during the existing routine diagnostic protocols for AML.

The classification of karyotypes as 'favorable', 'intermediate' and 'adverse' were described according to MRC criteria which were published by Grimwade et al (1998). Three prognostic groups were defined by cytogenetic abnormalities detected at presentation in comparison with the outcome of patients with normal karyotype on the basis of response to induction treatment, relapse risk, and overall survival, three prognostic groups were defined. AML associated with t(8;21), t(15;17) or inv(16) predicted a relatively favourable outcome. Whereas in patients lacking these favourable changes, the presence of a complex karyotype, -5, del(5q), -7, or abnormalities of 3q defined a group with relatively poor prognosis. The remaining group of patients including those with 11q23 abnormalities, +8, +21, +22, del(9q), del(7q) or other miscellaneous structural or numerical defects not encompassed by the favourable or adverse risk groups were found to have an intermediate prognosis.

Within the Brune et al (2006) study all normal karyotype patients were within the intermediate karyotype classification.

A23. PRIORITY. CS, Section 2.3, page 32. For transparency, please provide details of the clinicians involved in the April 2024 National Cancer Research Institute (NCRI) Acute Myeloid Leukaemia (AML) group meeting and the February 2025 Advisory Report meeting, along with minutes or transcripts from these meetings, and any documentation of subsequent communications with the company to support the CS. Please ensure the documentation includes all the questions posed to the experts.

Initially we contacted clinicians who were involved in the National Cancer Research Institute (NCRI) Acute Myeloid Leukaemia (AML) group individually from April 2024. To be clear this was not a group meeting but a series of individual meetings which were either held remotely or in-person from April 2024 to April 2025 and included

others who were recommended by their peers. The clinicians who we conducted these meetings with were:

[redacted]

The clinicians who attended the 2-hr remote advisory board meeting on Monday 3rd February 2025 are:

[redacted]

We will provide minutes from the advisory board meeting as a separate confidential document as requested.

During the development of our company submission, we did ask one of the co-authors of the Brune et al 2006 publication, Professor Kristoffer Hellstrand, for some clarification on the data for the normal karyotype subgroup. Although we did not contact the UK clinicians listed above to help directly with our company submission, we did use the information gained from our previous discussions to help with certain details.

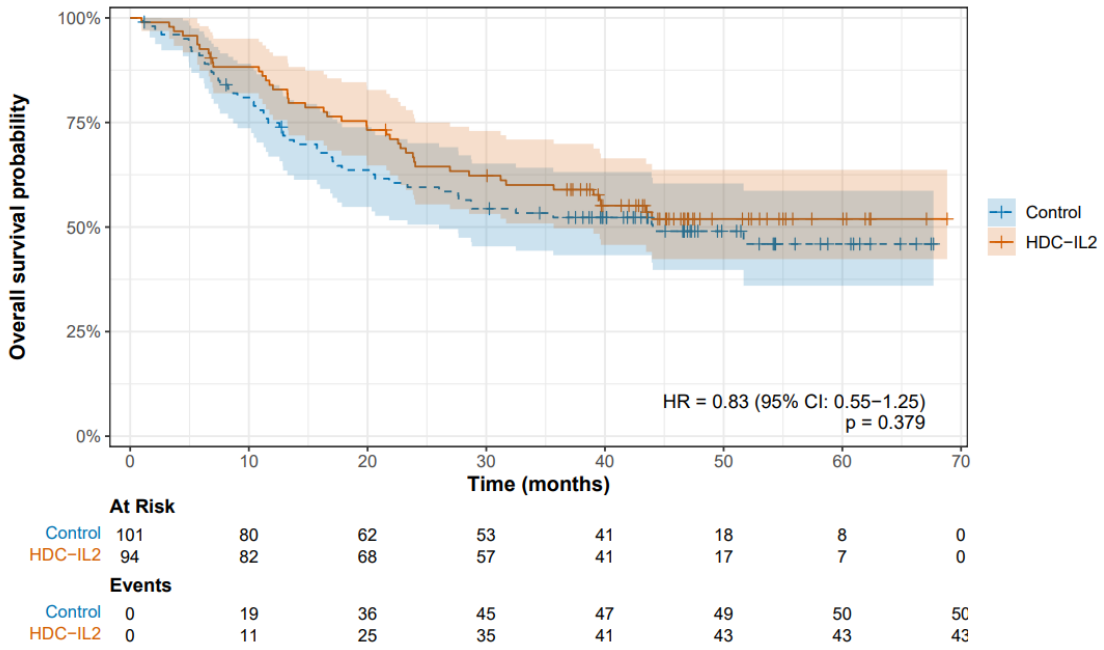
A24. CS Section 2.6. Please provide the hazard ratios (HRs) with corresponding 95% confidence intervals (CI) for all presented outcomes in the CS (e.g., Tables 7 to 13). Please also present the full results for OS (including the HRs) for the subgroups 'in patients ≤60 years' and 'in patients in CR1 and ≤60 years'.

Please see below a table with the hazard ratios and confidence intervals for leukaemia free survival (LFS) and overall survival (OS) for those patients from the Brune et al 2006 study who were 60 years old or less with or without first complete remission (CR1).

	Patients	HR [95% CI)	N
LFS	All ≤60 years old	0.66 [0.47-0.94]	195
	All ≤60 years old in CR1	0.58 [0.40-0.86]	165

OS	All ≤60 years old	0.83 [0.55-1.25]	195
	All ≤60 years old in CR1	0.71 [0.45-1.13]	165

Kaplan-Meier curves to show OS in patients ≤ 60 years (n=195)

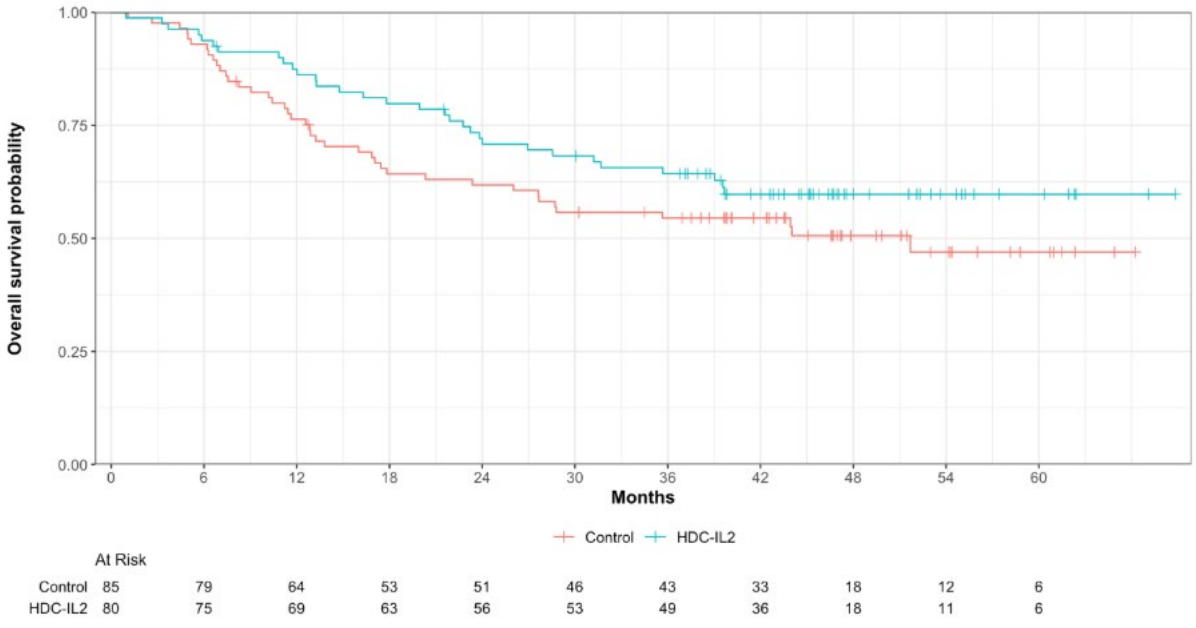


Overall survival (OS) in patients in CR1 and ≤60 years.

OS was superior in patients treated with HDC/IL-2 versus controls in the CR1 and ≤60 years subgroup although it did not reach statistical significance (p=0.149). Even so, the study was not designed to reach statistical significance for OS. Median overall survival was 51.7 months in the control group and was not reached for the HDC/IL-2 treatment group during the follow-up period.

For the 80 patients treated with HDC/IL-2 who were in CR1 and ≤ 60 years of age, the Kaplan-Meier estimate of OS at 36 months was 64.3% vs. 54.5%for the 85 controls, or a relative improvement of 18% (see Figure 9).

Kaplan-Meier curves of OS in patients in CR1 and ≤60 years (n=165)



Abbreviations: OS, overall survival.: CR1, complete remission; HDC, histamine dihydrochloride; IL-2, interleukin-2
Source: Data on file

A25. CS, Section 2.5, page 36. The CS states that *"In a recent study published by Potter et al (2025), which included data on a combination of two UK randomised controlled trials (UK AML 17 & 19), the 3-yr survival of AML patients with NPM1 and FLT3 mutations (N=140), a subset of normal karyotype AML, who were 60 years old or younger was 58% for the non-monitored group versus 69% for the monitored group."* The EAG has been unable to verify this statement. Please specify where in the Potter *et al.* (2025) publication this information is reported.

The information above from the Potter et al (2025) study is reported from Figure 2C on page e352 of the publication.

A26. CS, Section 2.5, page 36. The CS states that "*In a different publication by Juliusson, 2020 which summarised real world experience from a large Swedish registry of AML patients the 3-yr survival of the patient subgroup (n=198) with an NPM1 mutation and less than 60 years old was 59.4% which again is very close to the 58.7% seen in the control arm of the Nilsson et al 2020 subgroup."* Please comment on the comparability of the NPM1-mutated, <60 years subgroup from Juliusson (2020) with the target population, including any differences in treatment pathways or clinical practice that may affect relevance to the UK context.

The reason for selecting the Juliusson et al 2020 study population was that it consists of a large group of AML patients who have been treated in a more contemporary setting compared to the Brune et al study population and includes data on age and molecular status. Patients were recruited into the national Swedish registry from 2007. Most evaluated patients were treated with a high intensity treatment and high transplantation rates which more closely reflects current practice in the UK.

The subgroup of patients reported in the Juliusson et al study who were under the age of 60 and had an NPM1 mutation (n=198) was selected as the most relevant comparator to the subgroup of patients with normal karyotype, in first complete remission (CR1) and under the age 60 years from the Nilsson et al 2020 study. Mutations of NPM1 or FLT3-ITD are the most prevalent mutations within the group of normal karyotype AML, where mutated NPM1 comprises approximately 40–50% of cases and FLT3-ITD approximately 30–40% (Schlenk et al 2007). NPM1- and/or FLT3-ITD-mutated AML mutations account for >75% of all normal karyotype AML (Schlenk et al 2007).

Given the above, it was considered that comparing the 3-year survival in this sizeable population of AML patients with a similar disease profile and age, treated in a more contemporary setting, with the control arm of the subgroup of normal karyotype in CR1 who are under 60 years from the Nilsson et al 2020 study was relevant. The fact that the 3-year survival in the Swedish subgroup was very similar to the 3-year survival in the control arm of the subgroup within the Nilsson et al 2020

study (59.4% vs 58.7% respectively) indicates that the survival outcomes in this subgroup are generalisable in a contemporary setting.

A27. CS, Section 2.3, page 31. Please provide full details of the quality-of-life analysis reported in Brune *et al.* (2006) including, study design, measures used, data synthesis methods and key findings. If this information is not available, please explain why.

Having contacted one of the co-authors of the Brune et al 2006 publication it has not been possible to obtain the details of the quality-of-life data collected in the study.

From the published abstract by Wallhult et al 2007 the assessment of quality-of-life was performed in the Brune et al 2006 study using the validated EORTC-C30(v2) instrument at 8 pre-defined study visits: baseline; pre- and post-cycles 3, 5, and 8; and at 18 months. Data were analyzed as specified in the EORTC scoring manual for 9 scales (1 global, 5 functional, 3 symptom scales) and 6 single-symptom items. Comparisons were made between and within groups at baseline vs. each visit, pre- vs. post-treatment, and baseline vs. end of treatment (18 months).

At least one questionnaire was completed by 285 patients (89%). Patients in both study arms increased or maintained QoL status from baseline to last evaluation with respect to global health status, physical, cognitive and role functioning, and financial issues, as well as symptoms of fatigue, nausea/ vomiting, pain, diarrhoea, and dyspnea. Comparisons of pre- vs. post-treatment QoL assessments showed transient increases in fatigue (P=0.008), nausea/vomiting (P=0.006), and appetite loss (P=0.005) in the treatment arm.

Indirect treatment comparison

A28. PRIORITY. CS, Section 2.10, pages 52-53. In relation to an indirect treatment comparison (ITC) between HDC/IL-2 and oral azacitidine:

(a) Please list the relevant studies for oral azacitidine.

(b) Please present the results for the main outcomes (LFS, OS, AEs) from the relevant studies and any relevant subgroup analyses.

(c) Please conduct an indirect treatment comparison (ITC) analysis of HDC/IL-2 versus oral azacitidine using both naïve ITC and population-adjusted indirect comparison. Please comment on the generalisability of the results to the targeted population.

(a) Regarding the inclusion of oral azacitidine as a comparator, we would note that NHS England have stated that (emphasis added): *"Clinical opinion also felt that if histamine dihydrochloride with interleukin-2 were to be approved* ***they would not displace the market share of oral azacitidine****. This is due to the supporting literature suggesting that younger patients with favourable and intermediate risk leukaemias that are more likely to benefit from histamine dihydrochloride with interleukin-2, whereas it was mainly older and adverse risk patients who were enrolled in the QUAZAR trial, that was the confirmatory trial for oral azacitidine. This means that the* ***majority of use for the two interventions will be in non-overlapping populations****."*

Furthermore, we would add that NHS England reports that (emphasis added): *"Uptake of oral azacitidine has been* ***lower than anticipated as the clinical trial used for evidence enduring the appraisal only enrolled patients over the age of 55****, meaning there is no data confirming efficacy in younger patients rendering clinicians reluctant to use a drug with significant toxicity in patients where there is no clear evidence of benefit."*

Nevertheless, a rapid, reproducible, literature review was conducted as part of the present clarification response to identify RCTs (**S**tudy design) recording overall survival, leukaemia/relapse-free survival and/or incidence of adverse events (**O**utcomes) of oral azacitidine (**I**ntervention) versus placebo, best supportive care, or

watchful waiting (**C**omparator) in the maintenance treatment of patients with AML in first remission (**P**opulation). The comparator was selected on the grounds that no head-to-head comparisons of oral azacitidine versus HDC/IL-2 had been identified in the systematic literature review conducted during the preparation of the initial company submission.

The search terms were developed using a range of published search terms as detailed below:

- **Population terms:** Based on Mao *et al.* (2015).
- **Intervention terms:** Based on previously-published reviews by Hasegawa *et al.* (2023), Saiz-Rodríguez *et al.* (2021) and Wen *et al.* (2020).
    - **Maintenance terms:** Based on previously-published reviews by Songol *et al.* (2020) and Muchtar *et al.* (2013).
- **Comparator terms:** Based on previously-published reviews by Lee *et al.* (2015) and Ahmed *et al.* (2004).
- **Study design filter:** Based on Canada's Drug Agency/L'Agence des medicaments du Canada; available at: https://searchfilters.cda-amc.ca/link/108

Searches were run in the PubMed (including MEDLINE) and EMBASE databases via the Ovid interface on October 9, 2025. The search terms and the total number of hits across both databases are presented in Table 6.

Table 8 Search terms for randomized controlled trials of oral azacitidine versus placebo

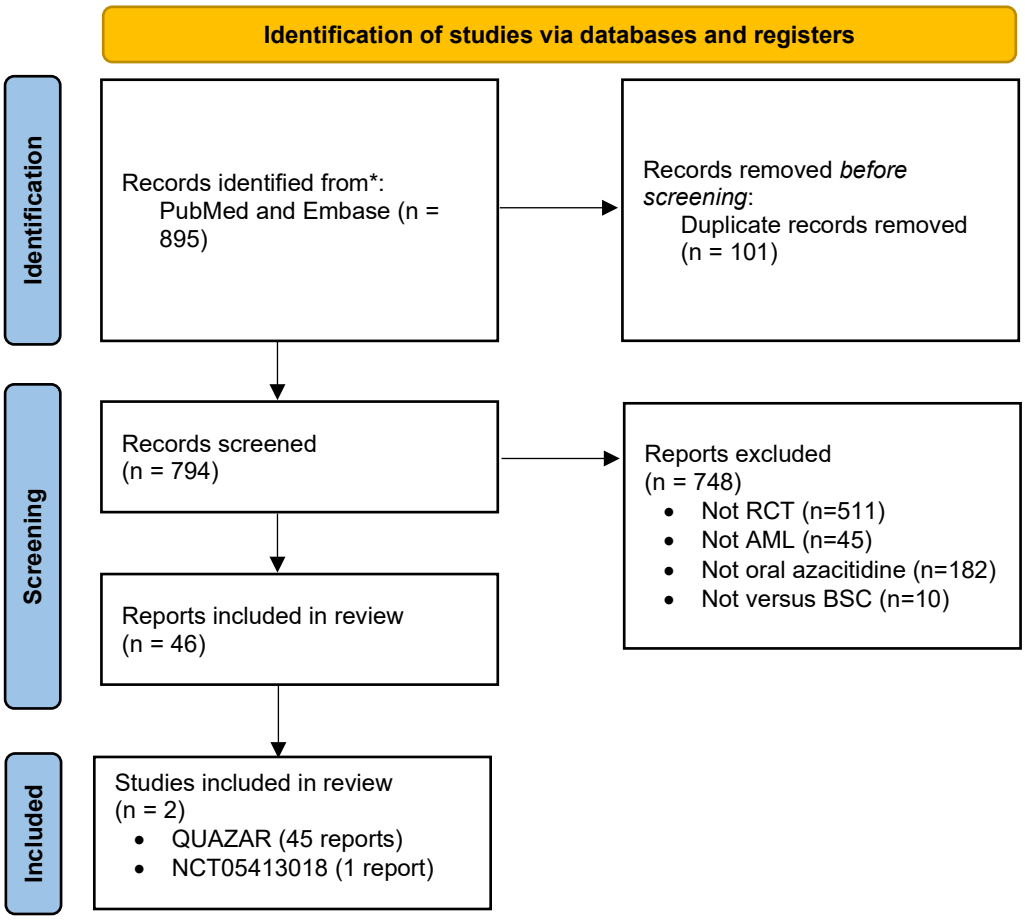
#	Term	Hits
1	exp Leukemia, Myeloid, Acute/	231,624
2	Leukemia, Myeloid/	47,502
3	Acute Disease/	347,133
4	2 and 3	7,350
5	((acut* or akut* or agud* or aigu*) and (myelo* or mielo* or nonlympho* or myeloid* or myelocytic*) and (leukem* or leukaem* or leuc*)).af.	293,303
6	1 or 4 or 5	322,733
7	exp Maintenance Chemotherapy/	6,862

#	Term	Hits
8	exp Drug Administration Schedule/	1,686,236
9	(mainten* or "stop-and-go" or "stop and go" or continu* or intermittent or meinten* or consolidat* or postconsolidat* or post-consolidat* or "post consolidation" or postremission or post-remission or "post remission" or remission).af.	5,598,996
10	7 or 8 or 9	7,099,845
11	("azacitidine" or "Onureg" or "cc-486").af.	32,748
12	exp Azacitidine/	32,011
13	exp Placebos/	558,785
14	placebo*.af.	946,208
15	exp Palliative Care/	235,147
16	(watch and wait).af.	5,947
17	((support* or optim* or palliat* or symptom*) and (care or caring or treat* or therap* or control or measure*)).af.	13,474,614
18	13 or 14 or 15 or 16 or 17	14,091,663
19	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	744,603
20	Randomized Controlled Trial/	1,764,156
21	exp Randomized Controlled Trials as Topic/	494,307
22	"Randomized Controlled Trial (topic)"/	302,301
23	Controlled Clinical Trial/	556,738
24	exp Controlled Clinical Trials as Topic/	509,791
25	"Controlled Clinical Trial (topic)"/	13,786
26	Randomization/	210,745
27	Random Allocation/	210,745
28	Double-Blind Method/	500,682
29	Double Blind Procedure/	314,375
30	Double-Blind Studies/	500,682
31	Single-Blind Method/	119,230
32	Single Blind Procedure/	83,583
33	Single-Blind Studies/	119,230
34	Placebos/	554,175
35	Placebo/	518,027
36	Control Groups/	124,380
37	Control Group/	124,380
38	(random* or sham or placebo*).ti,ab,hw,kf.	5,294,210
39	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	795,484
40	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	5,963
41	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.	3,572,544
42	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	155,202
43	allocated.ti,ab,hw.	236,510
44	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.	204,747

#	Term	Hits
45	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.	43,642
46	(pragmatic study or pragmatic studies).ti,ab,hw,kf.	2,020
47	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.	23,007
48	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.	43,404
49	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.	221,663
50	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	7,619,591
51	6 and 9 and (11 or 12) and 18 and 50	895
52	remove duplicates from 51	794

The titles and abstracts of the 794 unique retrieved records were screened by one reviewer, ultimately leaving 45 individual reports reporting on the QUAZAR study and one report on the ongoing randomized Phase II study of oral azacitidine as maintenance therapy in Chinese patients with AML in complete remission (NCT05413018; Figure 1).

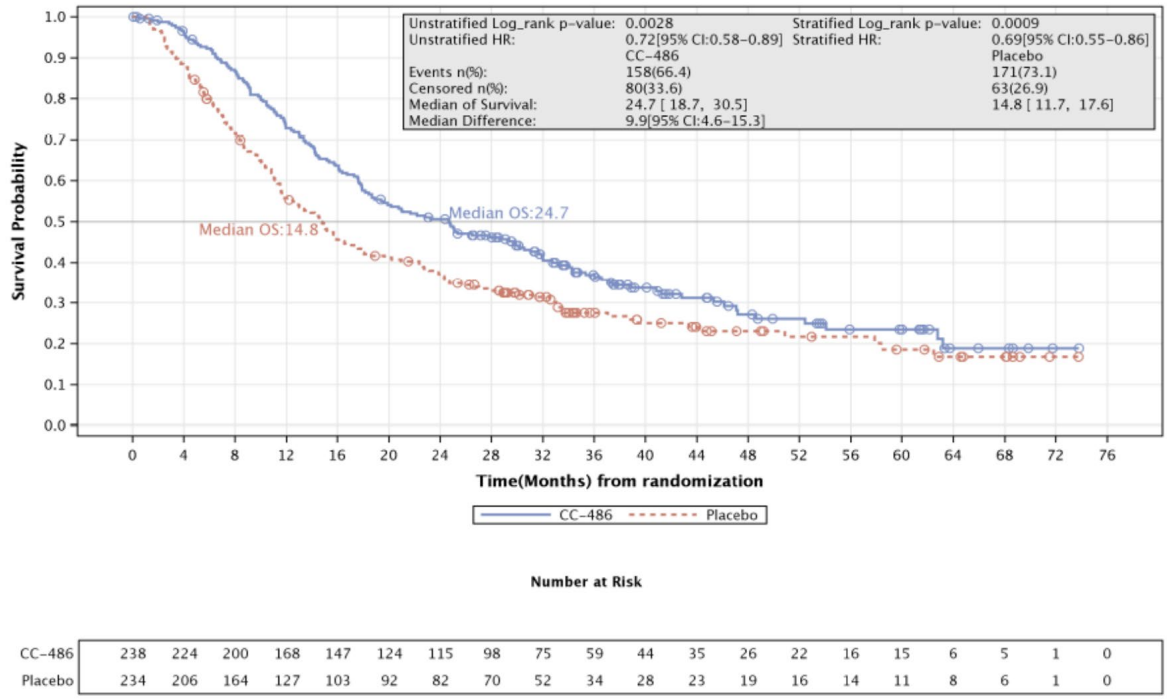
Figure 1 PRISMA flow diagram showing the numbers of records retrieved, duplicates removed, reasons for exclusion, and the final number of distinct studies identified



The Phase II RCT (NCT05413018) identified was not due to complete until March 2026 and data were therefore not available from the clinicaltrials.gov record. The only pivotal study of oral azacitidine, used as the basis of the economic modelling in the single technology appraisal (TA827), was QUAZAR AML-001 (NCT01757535). QUAZAR AML-001 was an international, multicentre, Phase 3, randomised, two-arm, double-blind, placebo-controlled, parallel group study. The study was conducted in patients with AML, aged 55 years or more, in complete remission after intensive chemotherapy with or without consolidation chemotherapy, and who were not candidates for HSCT. The study investigated the use of oral azacitidine 300 mg QD + best supportive care. The exclusion of patients aged under 55 years of age from the QUAZAR AML-001 RCT highlights the aforementioned key difference between the target populations for oral azacitidine and HDC/IL-2. The efficacy of azacitidine has been evaluated in studies of patients aged over 55 or, in some cases, specifically 60 years (Jaekel *et al.* 2017), while the wording in the approved HDC/IL-2 SmPC (section 4.1 'Therapeutic indications') confirms that the use of HDC/IL-2 in patients over 60 years is not supported. As confirmed in the response to question A1, this wording in the SmPC should be considered an exclusion of this group from eligibility for treatment with HDC/IL-2 on the grounds of there being no evidence of its efficacy.

(b) Overall survival and relapse-free survival from the QUAZAR AML-001 study are presented in Figure 1 and Figure 2, respectively. The most common Grade 3/4 TEAEs reported with oral azacitidine were neutropenia, thrombocytopenia, anaemia, and febrile neutropenia (Table 7). The incidence of serious treatment-emergent adverse events (TEAEs) reported in ≥1% of patients in either treatment arm is presented in Table 8.

Figure 2 Kaplan-Meier analysis of overall survival (data cut-off date, 15 July 2019) in the intention-to-treat population in the QUAZAR AML-001 randomised controlled trial

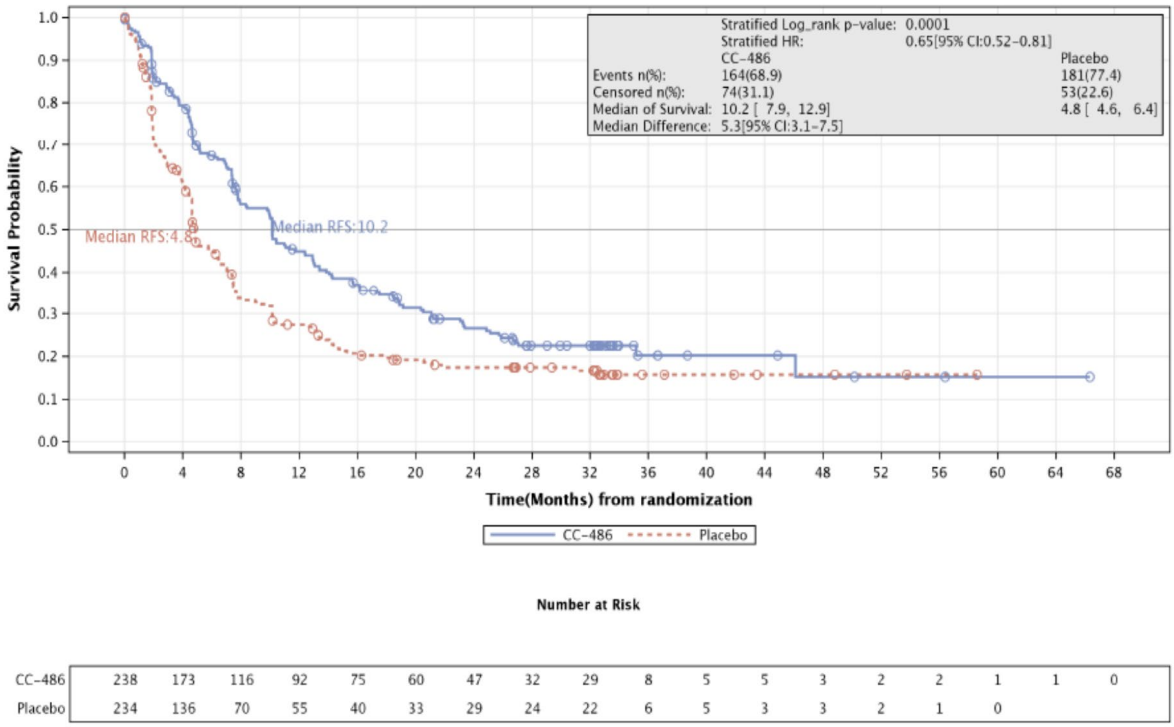


Number at Risk

CC-486	238	224	200	168	147	124	115	98	75	59	44	35	26	22	16	15	6	5	1	0
Placebo	234	206	164	127	103	92	82	70	52	34	28	23	19	16	14	11	8	6	1	0

Source: Reproduced from TA827.

Figure 3 Kaplan-Meier analysis of relapse-free survival in the intention-to-treat population in the QUAZAR AML-001 randomised controlled trial (15 July 2019 data cut-off)



Source: Reproduced from TA827.

Table 9 TEAEs reported in >10% of patients, QUAZAR AML-001 study (safety population)

Event	Oral azacitidine (N=236)		Placebo (N=233)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TEAEs, n (%)	231 (98)	169 (72)	225 (97)	147 (63)
Nausea	153 (65)	6 (3)	55 (24)	1 (<1)
Vomiting	141 (60)	7 (3)	23 (10)	0 (0)
Diarrhoea	119 (50)	12 (5)	50 (21)	3 (1)
Neutropenia	105 (44)	97 (41)	61 (26)	55 (24)
Constipation	91 (39)	3 (1)	56 (24)	0 (0)
Thrombocytopenia	79 (33)	53 (22)	63 (27)	50 (21)
Fatigue	70 (30)	7 (3)	45 (19)	2 (1)
Anaemia	48 (20)	33 (14)	42 (18)	30 (13)
Asthenia	44 (19)	2 (1)	13 (6)	1 (<1)
pyrexia	36 (15)	4 (2)	44 (19)	1 (<1)
Arthralgia	32 (14)	2 (1)	24 (10)	1 (<1)
Abdominal pain	31 (13)	2 (1)	16 (7)	0 (0)
Upper respiratory tract infection	31 (13)	1 (<1)	32 (14)	0 (0)
Decreased appetite	30 (13)	2 (1)	15 (6)	2 (1)
Cough	29 (12)	0 (0)	39 (17)	0 (0)
Febrile neutropenia	28 (12)	27 (11)	18 (8)	18 (8)
Back pain	28 (12)	3 (1)	23 (10)	2 (1)
Leukopenia	25 (11)	18 (8)	19 (8)	14 (6)
Pain in extremity	25 (11)	1 (<1)	12 (5)	0 (0)
Dizziness	25 (11)	0 (0)	21 (9)	0 (0)
Headache	23 (10)	0 (0)	26 (11)	1 (<1)
Peripheral oedema	21 (9)	0 (0)	24 (10)	1 (<1)

Table 10 Serious TEAEs reported in ≥1% of patients in either treatment arm in the QUAZAR AML001 study (safety population)

Event	Oral azacitidine (N=236)	Placebo (N=233)
Serious TEAEs, n (%)	79 (33)	59 (25)
Febrile neutropenia	16 (7)	9 (4)
Pneumonia	9 (4)	7 (3)
Pyrexia	5 (2)	1 (0.4)
Cellulitis	4 (2)	1 (0.4)
Sepsis	4 (2)	5 (2)
Influenza	3 (1)	0 (0)
Diarrhoea	3 (1)	0 (0)
Back pain	3 (1)	0 (0)
Atrial fibrillation	3 (1)	0 (0)
Cholecystitis	3 (1)	2 (1)

Event	Oral azacitidine (N=236)	Placebo (N=233)
Anaemia	2 (1)	3 (1)
Thrombocytopenia	2 (1)	3 (1)

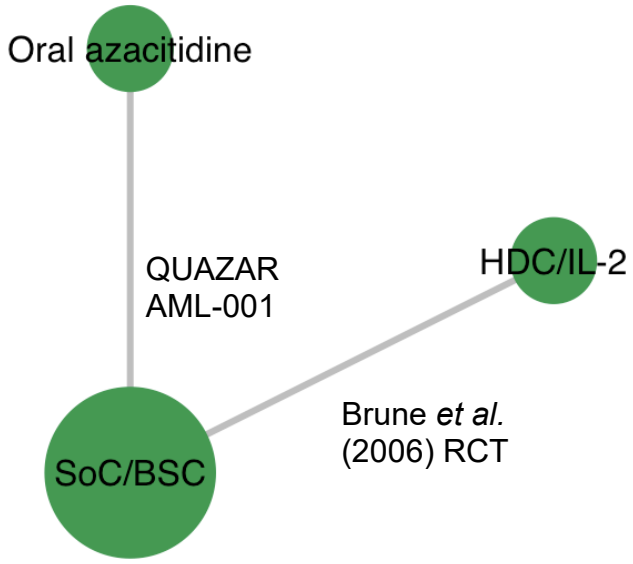
Table 11 Comparison of key outcomes in the full intention-to-treat trial populations enrolled in the QUAZAR AML-001 and Brune *et al.* 2006 randomised controlled trials

	QUAZAR AML-001 ITT population		Brune *et al.* (2006) ITT population	
	Best supportive care + placebo	Best supportive care + oral azacitidine	Standard of care	HDC/IL-2
Median OS (months)*	14.8	24.7	27.6	42.3
Median LFS/RFS (months)*	4.8	10.2	8.7	10.6

* Median OS and LFS in Brune *et al.* (2006) converted from days to months using a conversion factor of 365.25/12 (30.4375 days per month). LFS calculations based on a median LFS (95% confidence interval [95% CI]) of 324 (266,550) days in the HDC/IL-2 group versus 264 (231, 341) in the control group (P<0.01). OS calculations based on median OS of 1,289 days versus 842 days in the control group.

(c) Data from the QUAZAR AML-001 and Brune *et al.* (2006) RCTs enabled a simple network to be constructed via the standard of care/best supportive care arms of the respective trials (Figure 3) based on the assumption that the “standard of care” arm in the Brune *et al.* (2006) RCT would be comparable with the “supportive care according to local practice” reported in the QUAZAR AML-001 RCT. As reported in TA827, best supportive care in the QUAZAR AML-001 RCT may have included red blood cell and platelet transfusions; use of an ESA; antibiotic, antiviral, and/or antifungal therapy; nutritional support; and/or G-CSF for patients experiencing neutropenic infections.

Figure 4 Indirect treatment comparison network



Abbreviations: BSC, best supportive care; SoC, standard of care.

A naïve ITC using the Bucher *et al.* methodology across the respective trial ITT populations and the subgroups. The outcomes from this ITC are presented for the ITT population from the QUAZAR AML-001 RCT versus the ITT population and also the HDC/IL-2 target population (normal karyotype, CR1 and <60 years) from the Brune *et al.* (2006) RCT for OS and LFS/RFS in Table 12 and Table 13, respectively.

Table 12 Naïve indirect comparisons of overall survival with oral azacitidine versus HDC/IL-2 based on the QUAZAR AML-001 and Brune *et al.* (2006) randomised controlled trials

	HR	Lower 95% CI	Upper 95% CI	p
ITT populations				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13 Naïve indirect comparisons of leukaemia/relapse-free survival with oral azacitidine versus HDC/IL-2 based on the QUAZAR AML-001 and Brune *et al.* (2006) randomised controlled trials

	HR	Lower 95% CI	Upper 95% CI	p
ITT populations				
[redacted]				

The trial populations in QUAZAR AML-001 ITT population and Brune *et al.* (2006) are distinct, particularly with regard to the baseline age of the enrolled populations; the median age at baseline in the Brune *et al.* (2006) RCT was 54 years (range 18–84 years) in the control arm versus 68 (range 55-86 years) in QUAZAR AML-001. There are also substantial differences in baseline ECOG performance status between the trials, with 48% of the QUAZAR AML-001 ITT population in ECOG 0 at baseline versus 75% of patients in the Brune *et al.* (2006) RCT.

A matching-adjusted indirect comparison was attempted, but the individual patient-level data available from the Brune *et al.* (2006) RCT was restricted to study site, baseline age, sex, last known date of remission, date of relapse and censorship, date of death and censorship, karyotype at diagnosis, neutrophil counts, lymphocyte counts, eosinophil counts, and white blood cell count. The exclusion of patients from the Brune *et al.* (2006) subgroup aged over 60 years also resulted in difficulties in the assigment of suitable weights to balance by age, given the median age at baseline of 68 in the QUAZAR AML-001 study.

A29. CS, Section 2.10, pages 53-54. In relation to an ITC between HDC/IL-2 and midostaurin:

(a) Please list the relevant studies for midostaurin.

(b) Please present the results for the main outcomes (LFS, OS, AEs) from the relevant studies and any relevant subgroup analyses.

(c) Please conduct an ITC analysis of HDC/IL-2 versus midostaurin using both naïve ITC and population-adjusted indirect comparison. Please comment on the generalisability of the results to the targeted population.

The clinical justification regarding the exclusion of midostaurin as a comparator from the company's analyses is that NICE has previously approved midostaurin as a maintenance treatment for AML patients with FLT3 mutations (TA523).

There are no comparative data published on the efficacy of HDC/IL-2 versus midostaurin as maintenance treatment in people with FLT3-mutation-positive AML.

The clinical experts involved with the oral azacitidine appraisal (TA827) explained that most people with FLT3- mutation positive AML would have targeted treatment with midostaurin during induction, consolidation and maintenance treatment and would be unlikely to switch to oral azacitidine.

We believe that it would be a similar situation with HDC/IL-2, where few, if any, patients with FLT3 mutation positive AML would switch from midostaurin to HDC/IL-2 during maintenance.

We note that midostaurin was considered a relevant comparator for people with FLT3-mutation positive AML in the oral azacitidine appraisal and an indirect treatment comparison was conducted.

We note that the EAG also considered that survival analyses for this population are likely to be biased because of limitations associated with the indirect treatment comparison.

The committee concluded that the results of the indirect treatment comparison comparing oral azacitidine with midostaurin were highly uncertain and considered this in its decision making.

There are no data from the pivotal Phase III RCT published by Brune *et al* 2006 on the genetic subtypes of patients recruited to the study and hence there are very limited data on the efficacy of HDC/IL-2 in AML patients with FLT3 mutations.

For these reasons, we have not attempted an indirect treatment comparison. As indicated above without further data on the efficacy of HDC/IL-2 in genetic subtypes the level of uncertainty in an indirect treatment comparison versus midostaurin is likely to be very high.

HDC/IL-2 would therefore likely be of most benefit to patients whose AML does not have an FLT3 mutation or FLT3-ITD mutation.

A30. CS, Section 2.10, pages 54-55. In relation to an ITC between HDC/IL-2 and quizartinib:

(a) Please list the relevant studies for quizartinib.

(b) Please present the results for the main outcomes (LFS, OS, AEs) from the relevant studies and any relevant subgroup analyses.

(c) Please conduct an ITC analysis of HDC/IL-2 versus quizartinib using both naïve ITC and population-adjusted indirect comparison. Please comment on the generalisability of the results to the targeted population.

The clinical justification regarding the exclusion of quizartinib as a comparator from the company's analyses is that NICE has previously approved quizartinib as a maintenance treatment for AML patients with FLT3-ITD mutations (TA1013).

There are no comparative data published on the efficacy of HDC/IL-2 versus quizartinib as maintenance treatment in people with FLT3-ITD mutation positive AML.

The clinical experts involved with the oral azacitidine appraisal (TA827) explained that most people with FLT3 mutation positive AML would have targeted treatment with midostaurin during induction, consolidation and maintenance treatment and would be unlikely to switch to oral azacitidine.

We believe that it would be a similar situation with HDC/IL-2, where few, if any, patients with FLT3-ITD mutation positive AML would switch from quizartinib to HDC/IL-2 during maintenance.

There are no data from the pivotal Phase III RCT published by Brune *et al* 2006 on the genetic subtypes of patients recruited to the study and hence there are very limited data on the efficacy of HDC/IL-2 in AML patients with FLT3-ITD mutations.

For these reasons, we have not attempted an indirect treatment comparison. As indicated above without further data on the efficacy of HDC/IL-2 in genetic subtypes the level of uncertainty in an indirect treatment comparison versus quizartinib is likely to be very high.

HDC/IL-2 would therefore likely be of most benefit to patients whose AML does not have a FLT3-ITD mutation.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY. In line with clarification question A28, please clarify why oral azacitidine is not included as a comparator in the economic model. If the reason for its exclusion relates to data limitations, please explain this. Otherwise, please include this comparator in the economic model using the results of the ITC presented in question A28. Please ensure that oral azacitidine can be selected as a comparator in the economic analysis, and update the model results, accordingly, presenting a full incremental analysis and pairwise comparisons between HDC/IL-2 and BSC and oral azacitidine.

As discussed during the clarification questions call with NICE and the EAG and subsequently agreed in writing on Friday 3rd October by NICE, the company will provide a response to this question and an updated version of the economic model incorporating the results of an indirect treatment comparison by Monday 20th October at 5pm.

As noted in the responses to clarification questions A5 and A28, we would reiterate that the clinical justification regarding the exclusion of oral azacitidine as a comparator from the company's analyses is that the published data available and the clinical experience does not allow for a meaningful indirect treatment comparison: the indicated patient population for HDC is 60 years or younger and the main evidence case for oral azacitidine as in Wei *et al* 2020 is in patients who are 55 or older.

Nevertheless, oral azacitidine has been incorporated into the economic model as a comparator, with calculations performed on a new "Calculations Oral Aza" worksheet.

In the absence of publicly available information on a patient access scheme (PAS) discount for oral azacitidine, the per-pack cost of oral azacitidine has been taken from the British National Formulary at a price of £5,867 per pack of seven 300 mg tablets (only the 100 mg powder suspension form of oral azacitidine is listed in eMIT, which was not the dosage form administered in the QUAZAR AML-001 RCT). In the base case analysis versus oral azacitidine, the model captured the cost of 12 cycles of oral azacitidine treatment based on the median number of treatment cycles received as reported in the QUAZAR AML-001 RCT. This aligns with the median duration on treatment of 11.4 months as reported in TA827. The mean number of treatment cycles could not be identified in the public domain, but at least one patient in QUAZAR AML-001 received 80 cycles of treatment, suggesting that the median of 12 may be a conservative estimate of the treatment duration. In line with the HDC/IL-2 arm of the analysis, it was assumed that patients discontinuing due to adverse events would do so in the first cycle of the analysis; in the base case, this was 13% of patients in line with the proportion reported as discontinuing treatment due to adverse events in Wei *et al.* (2023). Further discontinuations after those driven by adverse events were modelled in line with the proportion of patients experiencing

relapse and therefore in the LFS partition, in line with the approach to modelling HDC/IL-2.

Differences in efficacy between HDC/IL-2 and oral azacitidine were modelled based on LFS and OS hazard ratios informed by the ITC presented in the response to clarification question A28. In the base case analysis, these were set to 0.88 in favour of oral azacitidine for OS and 0.92 in favour of oral azacitidine for LFS/RFS. The adverse event profiles were conservatively assumed to be the same for oral azacitidine and HDC/IL-2.

Results of economic analyses based on the revised model showing HDC/IL-2 versus standard of care and, in turn, oral azacitadine versus HDC/IL-2 on the basis of the naïve ITT ITC are presented in Table 14 and Table 15, respectively.

Table 14 Economic results for HDC/IL-2 versus standard of care in the revised economic model

	Quality-adjusted life expectancy (QALYs)	Costs (GBP)	ICER (GBP)
HDC/IL-2	6.741	127,658	
Standard of care	3.543	50,341	
Difference	**+3.197**	**+77,317**	**24,183**

Table 15 Economic results for oral azacitidine versus HDC/IL-2 in the revised economic model

	Quality-adjusted life expectancy (QALYs)	Costs (GBP)	ICER (GBP)
Oral azacitidine	[redacted]	[redacted]	[redacted]
HDC/IL-2	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]

B2. In line with clarification questions A29 and A30, please clarify why midostaurin and quizartinib are not included as comparators in the economic analysis. Please consider including these regimens as comparators in the economic model using the results of the ITC presented in questions A29 and A30, and update the results accordingly. If the reason for the exclusion relates to data limitations, please explain this.

The exclusion of midostaurin and quizartinib as comparators in the economic analysis was driven by the same rationale as that presented in the responses to A29 and A30.

Review of cost-effectiveness studies

B3. CS, Section 3.1, Pages 61-62. The CS states that *"No UK economic analyses were identified that evaluated the use of histamine dihydrochloride and low-dose interleukin-2 in the target population, nor were any studies identified that specifically evaluated treatments exclusively in patients with AML in first complete remission in the UK."* Please clarify:

(a) if the 3 studies reported in Table 15 of the CS have been used to inform the model structure or other parameters (except the health state utilities) of the current economic analysis submitted by the company.

(b) if the health economic analysis used to inform the Scottish Medicines Consortium (SMC) assessment (SMC N. 666/10 document, (available in https://scottishmedicines.org.uk/medicines-advice/histamine-dihydrochloride-ceplene-fullsubmission-66610/) has been identified by the SLR of economic studies, and if so, provide justification for this exclusion.

(a) The three studies reported in Table 15 of the CS were used to guide the choice of the model structure, with the choice of a partitioned survival model ultimately driven by the use of the same model structure in Tremblay *et al.* and particularly in Witlox *et al.* (2023), which had previously been assessed by NICE as part of the single technology appraisal of oral azacitadine (TA827) for maintenance treatment in patients with acute myeloid leukaemia after induction therapy. In addition to the choice of health state utility values, the TA827/Witlox *et al.* model was also used to identify appropriate resource utilisation estimates for best supportive care.

(b) The health economic analysis used to inform the SMC assessment wasn't identified through the economic searches conducted as part of the systematic literature review as these searches were restricted to PubMed, EMBASE, and the Cochrane Library (see also response to question A10); however, we became aware of the assessment through earlier, targeted searches to inform the model concept. The study was not subsequently included in the SLRs (e.g. by "hand searches") or similar because the documentation of the model is extremely sparse, with only a single page of the SMC report dedicated to the economic evaluation and we were unable to identify any further information in the literature pertaining to the model or the analysis.

Population baseline characteristics

B4. CS Section 3.2, page 64 and Section 3.5 (page 84). The CS (page 84) states that *"IL-2 costs were calculated based on a mean weight of 78.45 kg, informed by the weighted average bodyweight from the NHS Health Survey for England 2021."* Please clarify to which population in the NHS Health Survey for England this estimate relates to, and how it relates to the population eligible for HDC/IL-2.

The 78.45 kg estimate of mean weight was based on self-reported weight from the entire population surveyed in the NHS Health Survey for England, which reported mean weights of 85.1kg and 71.8kg for men and women, respectively (https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2021/part-4-trends). Weight data were unavailable from the pivotal Brune *et al.* (2006) RCT and bodyweight was similarly not reported in trials of other interventions for patients with AML in first remission such as the QUAZAR study of oral azacitidine (Wei *et al.* 2020) or the pivotal RCT of midostaurin (Stone et al. 2017). In the absence of any bodyweight data from these populations, the NHS Health Survey for England was used as a surrogate UK-specific estimate of average bodyweight, preferring specificity to the UK over specificity to an AML population in the wrong geography. In preparing the present response, we identified a UK-specific

study (Liu *et al.* 2024) that reported the distribution of people with AML across body mass index (BMI) strata:

Table 1

	IT (n = 4971)	NIT (n = 2388)	IU (n = 547)	Documented SACT (total of IT, NIT, and IU) (n = 7906)
BMI*				
Underweight (<18.5 kg/m^2)	96 (1.9%)	47 (2.0%)	11 (2.0%)	154 (1.9%)
Normal weight (18.5 to <25.0 kg/m^2)	1501 (30.2%)	596 (25.0%)	109 (19.9%)	2206 (27.9%)
Overweight (25.0 to <30.0 kg/m^2)	1586 (31.9%)	654 (27.4%)	138 (25.2%)	2378 (30.1%)
Obese (≥30.0 kg/m^2)	1236 (24.9%)	497 (20.8%)	79 (14.4%)	1812 (22.9%)
Unknown	552 (11.1%)	594 (24.9%)	210 (38.4%)	1356 (17.2%)

Abbreviations: IT, intensive treatment; IU, intensity unknown; NIT, nonintensive treatment; SACT, systemic anticancer therapy.

In 2022-23, the prevalence of overweight and obesity in the UK general population was 64.0%, with 26.2% of people estimated to be living with obesity (https://www.gov.uk/government/statistics/update-to-the-obesity-profile-on-fingertips/obesity-profile-short-statistical-commentary-may-2024). Focussing on the intensive treatment group from Liu *et al.* (2024) and distributing the proportion of patients with unknown BMI (11.1%) across the other weight categories (proportionally to the respective category's contributions to the known BMI categories) results in an estimate of 63.9% of intensively-treated people with AML falling into the overweight or obese BMI categories. Applying similar scaling to the non-intensively treated population yields an estimate of 64.2% of the population falling into the overweight or obese BMI categories. These both align well with the 64.0% of patients falling into the overweight or obese BMI categories in the general UK population. While this doesn't conclusively demonstrate that the estimate of 78.45 kg would also apply to the population eligible for treatment with HDC/IL-2, it suggests that the weight distribution of the population with AML is similar to the weight distribution of the general UK population. In the absence of bodyweight data from the published RCTs of maintenance treatments in patients with AML, the value from the NHS Health Survey for England is likely to serve as a reasonable surrogate.

Model structure

B5. PRIORITY. CS, Section 3.2, pages 64-66 and model 'Calculations HDC' and 'Calculations SoC' worksheets, column D. Please change the cycle length of the model

from monthly cycles to either 3-weekly or weekly cycles, to better represent the treatment schedule for HDC/IL-2. Update the parameters accordingly (e.g. survival estimates, costs etc).

Please see also the response to question B27, which details how the treatment schedule for HDC/IL-2 is incorporated into the model. In brief, the model captures the full cost of each treatment cycle in the model cycle in which the treatment cycle is initiated. This should align with the economic reality as a full treatment cycle of HDC/IL-2 can be dispensed to the patient at the start of each treatment cycle. The model does not make any downwards adjustment to the cost of HDC/IL-2 treatment to adjust for the portion administered in each model cycle. Furthermore, the number of treatment cycles captured by the model can be verified by inspecting columns AS and AW of the "Calculations HDC" worksheet to ensure that 10 cycles of treatment are being captured in those patients remaining on treatment (which is the case in the case base analysis). We would be open to further EAG discussion on the need for a cycle length adjustment, but retaining a monthly cycle length in the model has the additional benefit of years containing an integer multiple of model cycles, avoiding issues such as those flagged by the EAG in, e.g. TA881, where the year was assumed to be exactly 52 weeks (i.e. 364 days) long to ensure an integer number of weeks in each year.

Efficacy

B6. PRIORITY. Model, 'Extracted KM Data' worksheet. Please clarify which Kaplan-Meyer estimates were used to fit the parametric survival models for overall survival (OS) and LFS in both treatment groups. In the executable model tab 'Extracted KM Data', column C suggests there are 5 different data sources for each endpoint, specifically 2 different data sources for patients who are CR1 at randomisation, normal karyotype, and <60 years of age.

The “Extracted KM Data” sheet includes four sets of data that were extracted from charts in the Brune *et al.* (2006) and Nilsson *et al.* (2020) publications by tracing the Kaplan-Meier curves in the respective publications and simulating the time-to-event data using the Guyot *et al.* methodology (2012). These data were used exclusively for the purposes of validating that the individual patient-level data (IPD) was aligned with the data used as the basis of the publications, including alignment on the application of patient selection criteria and data analysis techniques. The fifth dataset, which was used to fit the parametric survival models for OS and LFS, is provided in the rows with “user_readable_title” column (Column C) values of “IPD CR1 at randomization, normal karyotype, <60 years”.

B7. PRIORITY. CS, Section 3.3, pages 67-80 and Model, ‘OS and LFS Parameters’ and ‘OS and LFS Models’ worksheets. For both OS and LFS extrapolation for the subgroup of patient in first complete remission, <60 years of age, with normal karyotype and ineligible for allogeneic stem cell transplantation (allo-SCT):

(a) Please confirm the parametric models fitted to the time-to-event data in the model were fitted jointly.

(b) Please comment on whether any of the standard parametric survival models provide a good fit to the observed data for both treatment groups (CS Figure 16 and Figure 24).

(c) Present the empirical/unsmoothed and smoothed hazard functions overlaying on the modelled instantaneous hazards for each of the fitted models.

(d) Fit independent standard parametric models for each treatment group for both OS and LFS, and present statistical goodness of fit and the empirical hazard overlaying on the modelled instantaneous hazards for each of the fitted models.

(e) Provide clinical assessment of the plausibility of the survival extrapolation in the extrapolated period for both OS and LFS. If none of the standard parametric models provide plausible long-term projections, please fit the data using flexible survival models.

(f) Incorporate the results of these OS and LFS survival analyses to the economic model, ensuring the model includes the additional functionality to use the results of the independently-fitted parametric (and flexible, if applicable) OS and LFS models.

(a) We can confirm that all the parametric models in the submitted model were fitted jointly.

(b) We have provided further side-by-side plots of the joint model fits to the OS and LFS data in Figure 1 and Figure 2. The visual fit of the OS models to the observed data (Figure 1) appears to be good when considering the relatively small numbers of patients at risk and the resulting size of the steps in the K-M curves. Statistically, the generalised gamma provided the best fit to the observed data, as presented in Figure 18 of the CS.

The visual fit of the LFS models to the observed data (Figure 2) is more mixed, with the generalised gamma model appearing to perform particularly poorly (despite ranking as second best fit by both AIC and BIC), while the Gompertz model has good visual fit to the observed LFS and ranks first by both AIC and BIC, although it provides an implausible estimate of long-term LFS.

Figure 5 Side-by-side presentation of OS model fits to the control and HDC/IL-2 arms

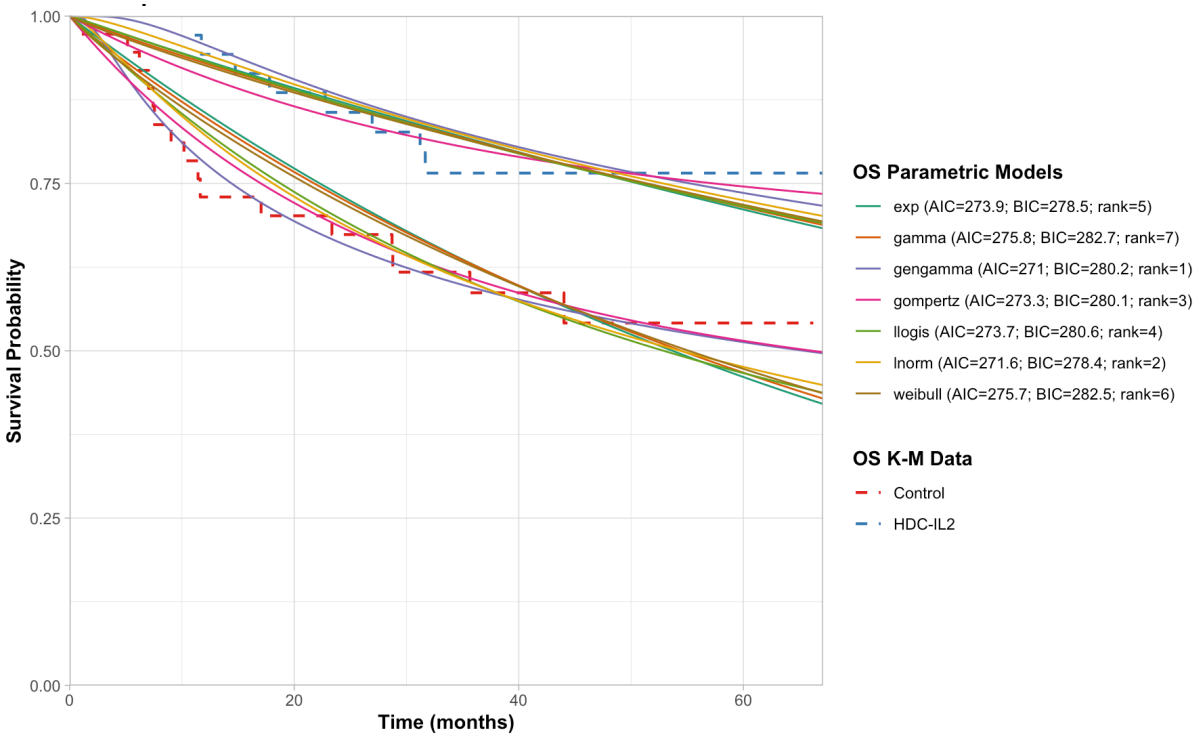
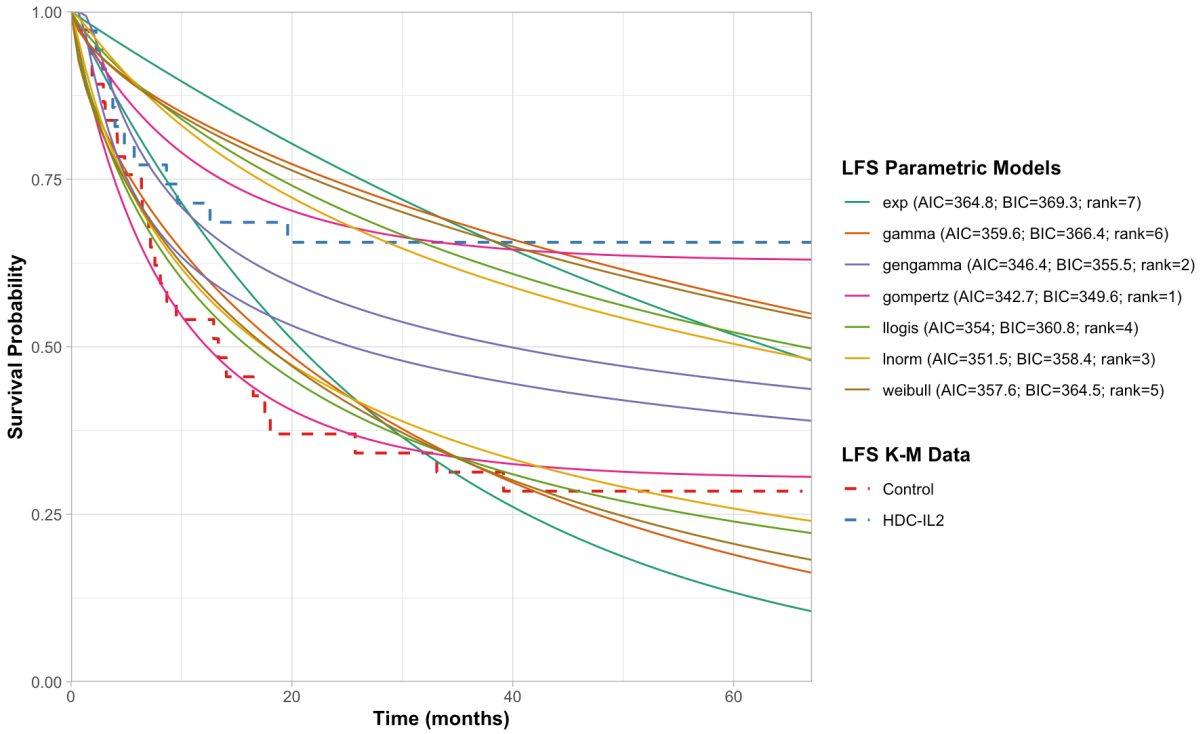


Figure 6 Side-by-side presentation of LFS model fits to the control and HDC/IL-2 arms



(c) Plots showing the empirical, smoothed, and modelled instantaneous hazards are presented in Figure 3 for LFS and Figure 4 for OS. The smoothed hazard functions

were estimated non parametrically based on B-splines from the perspective of generalized linear mixed models, using the default settings in the `bshazard` R package.

Figure 7 Empirical, smoothed, and modelled instantaneous hazards for each joint model fitted to the LFS data

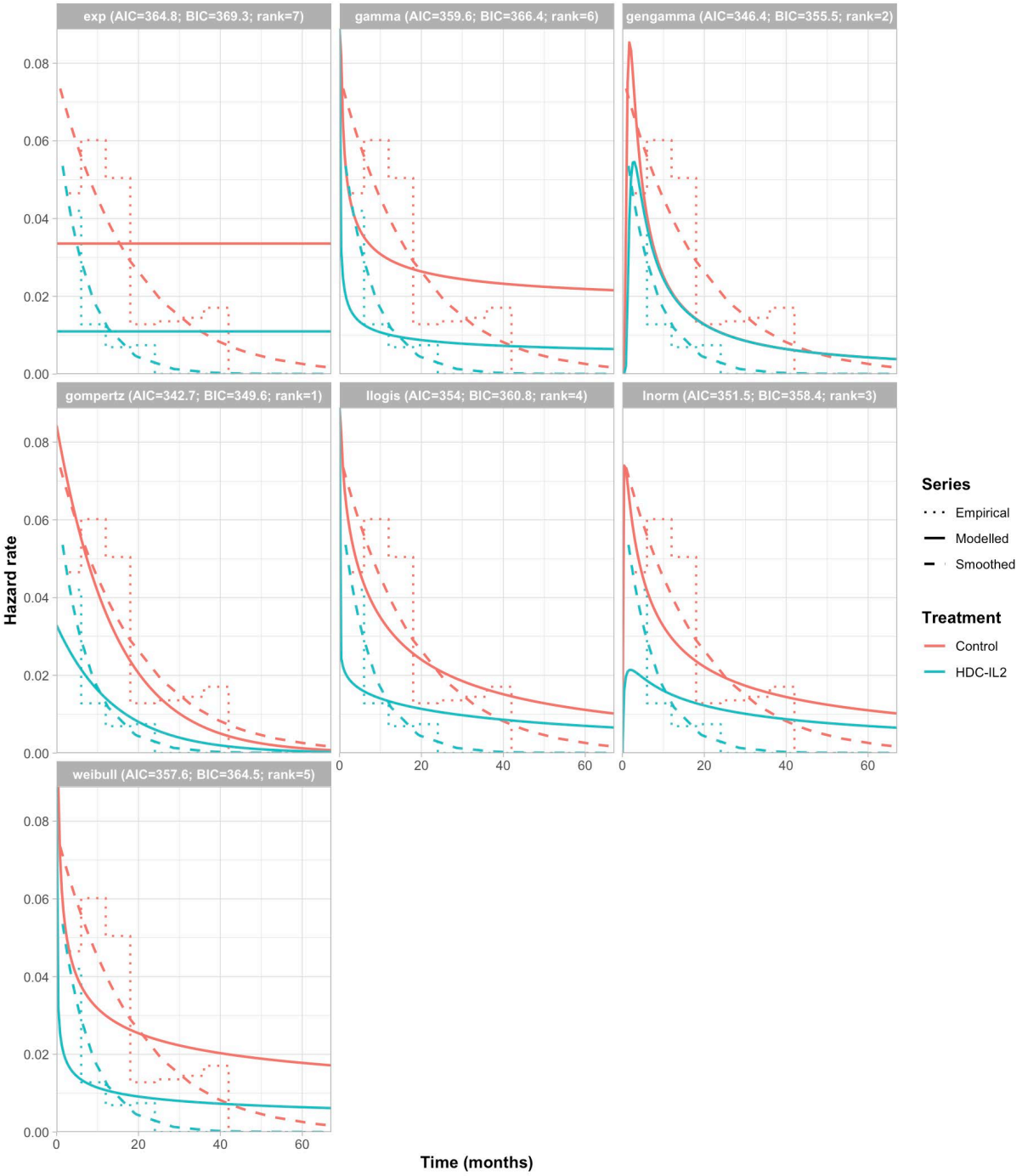
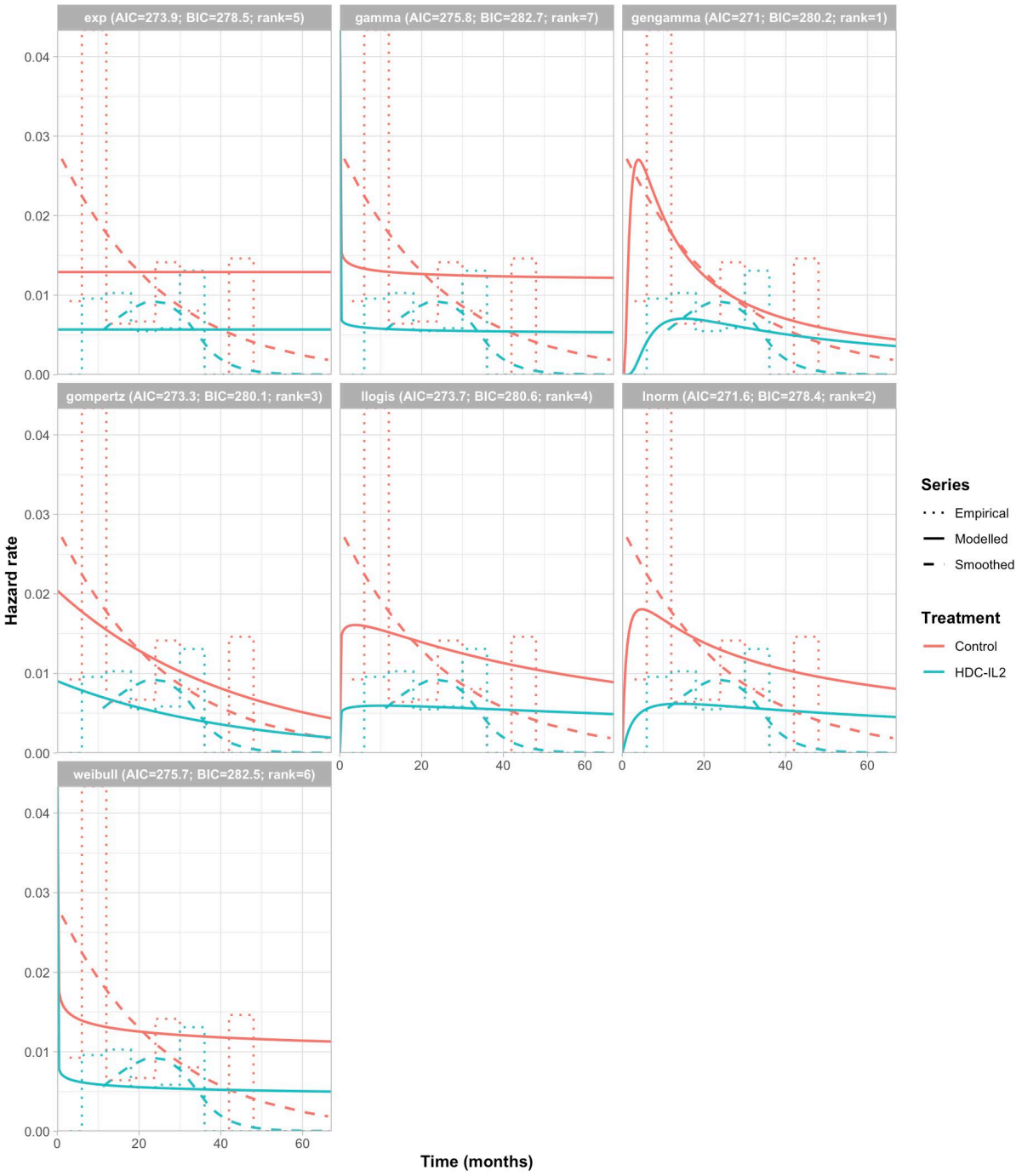


Figure 8 Empirical, smoothed, and modelled instantaneous hazards for each joint model fitted to the OS data



(d) Independent standard parametric models have been fitted to the LFS and OS data. The visual fits of the independent parametric models for LFS and OS within the observed follow-up period are illustrated in Figure 5 and Figure 6, respectively.

Figure 9 Independent parametric model fits to leukaemia-free survival data within the observed follow-up period

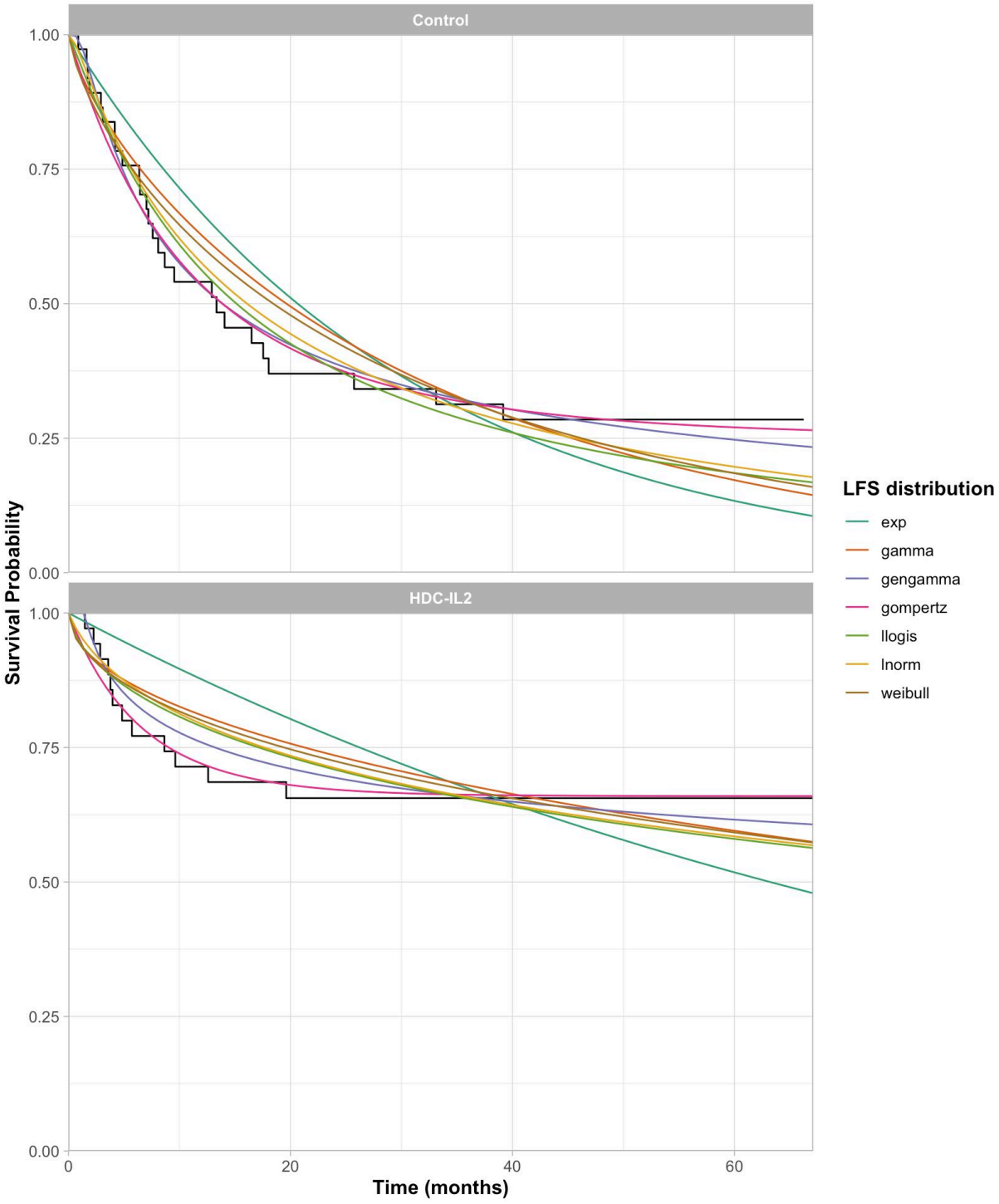
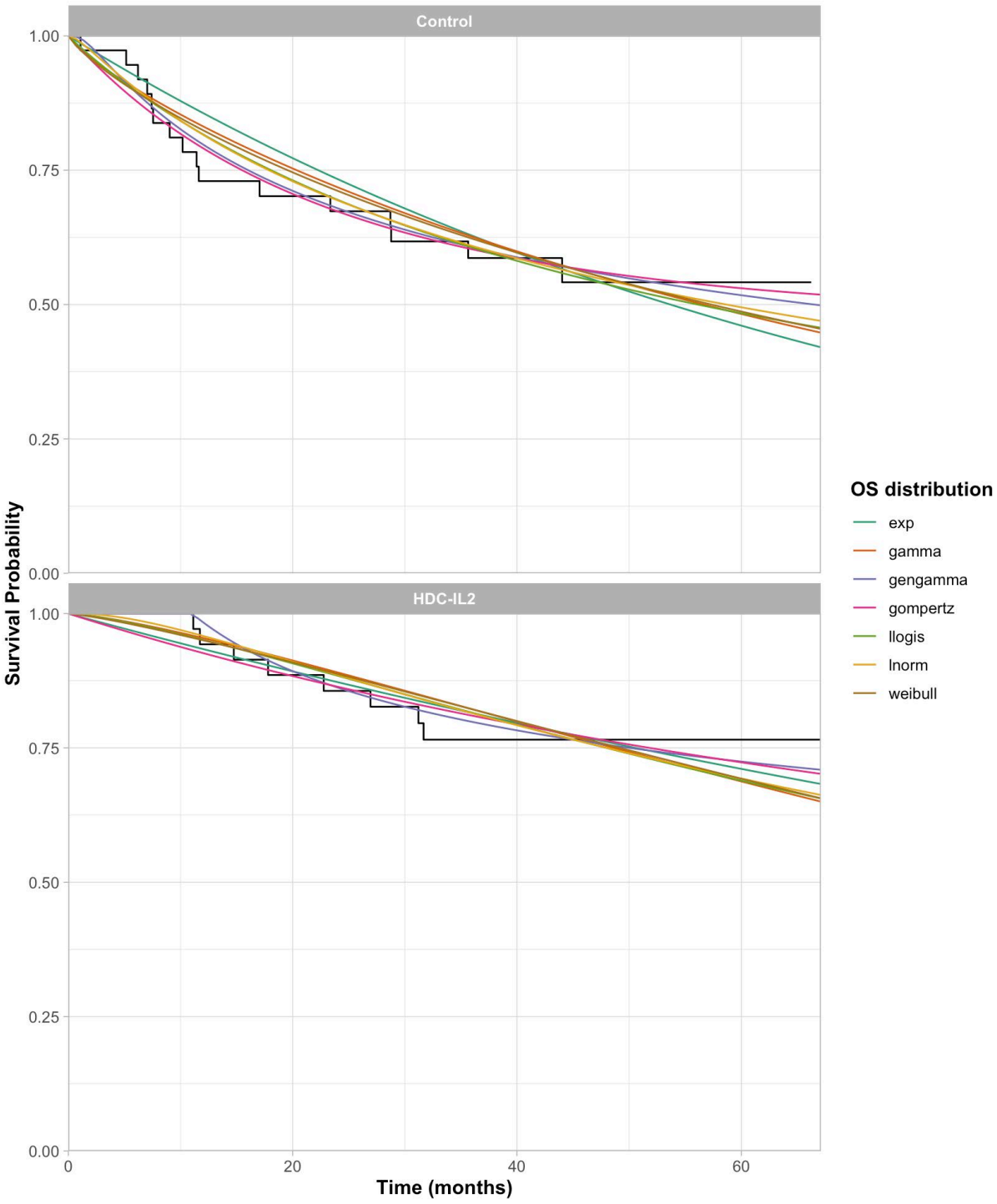


Figure 10 Independent parametric model fits to overall survival data within the observed follow-up period



(e) Extrapolations over 60 years are presented in Figure 7 and Figure 8 for LFS and OS, respectively. The OS models include some that are clinically plausible with, e.g. HDC/IL-2 overall survival of <25% after 200 months.

Figure 11 Independent parametric model fits to leukaemia-free survival data and extrapolations up to 60 years (720 months)

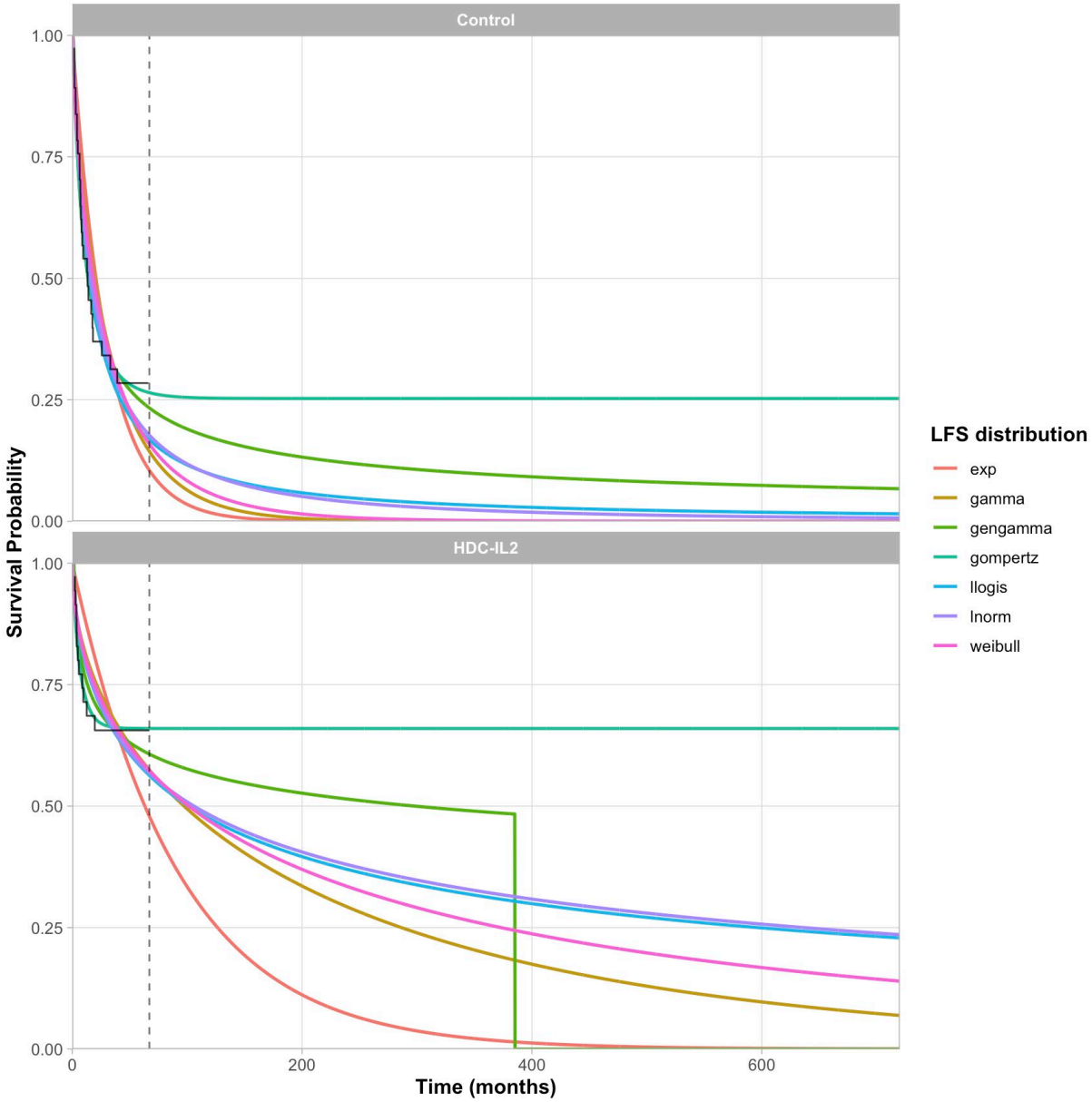
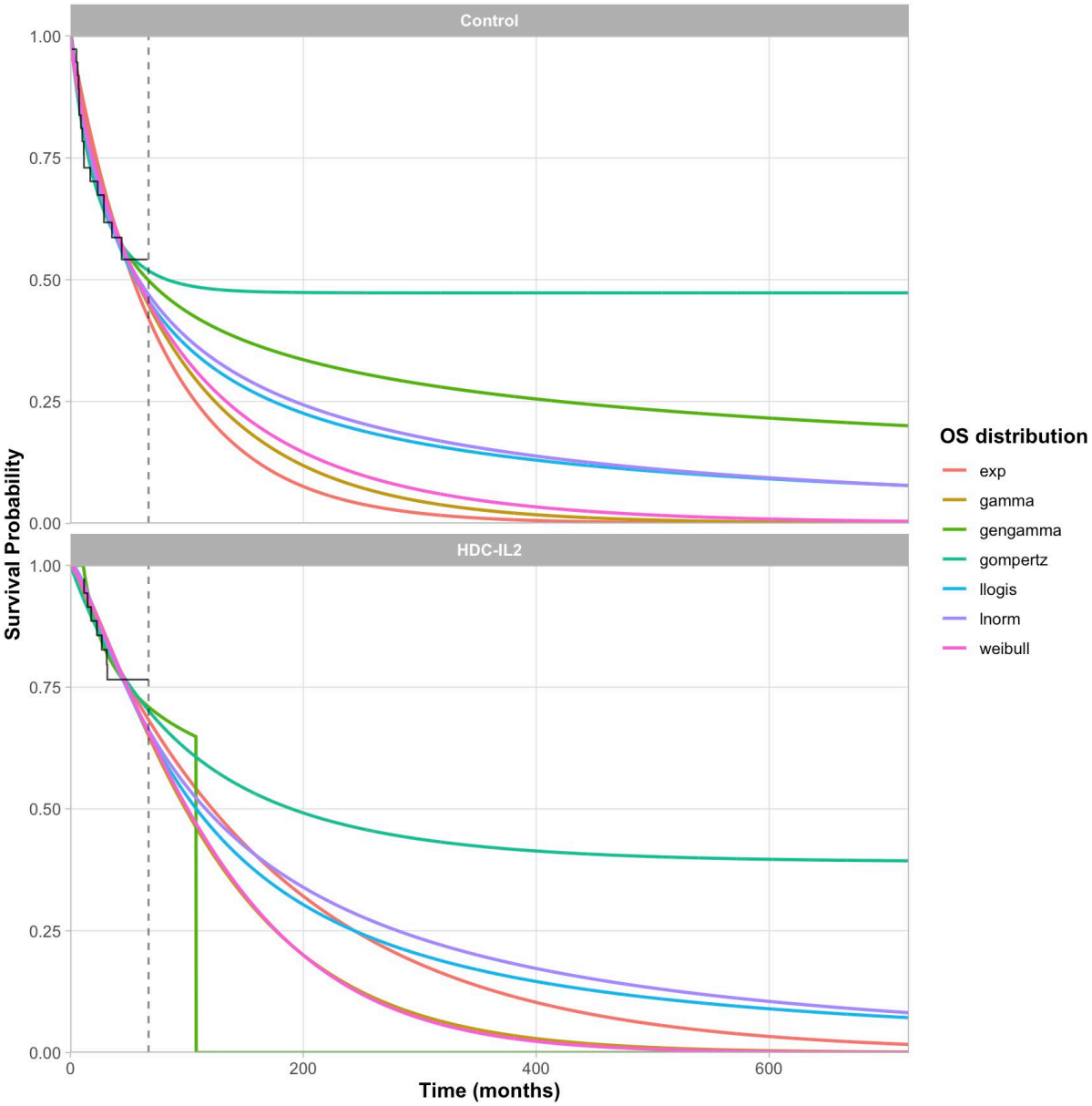


Figure 12 Independent parametric model fits to overall survival data and extrapolations up to 60 years (720 months)



Goodness-of-fit criteria are presented in Figure 9 and Figure 10 for the LFS model fits to the HDC/IL-2 arm and control arm, respectively, while Figure 11 and Figure 12 present goodness-of-fit criteria for the OS model fits to the HDC/IL-2 arm and control arm, respectively.

Figure 13 Statistical goodness-of-fit criteria for the fitted models of leukaemia-free survival with HDC/IL-2

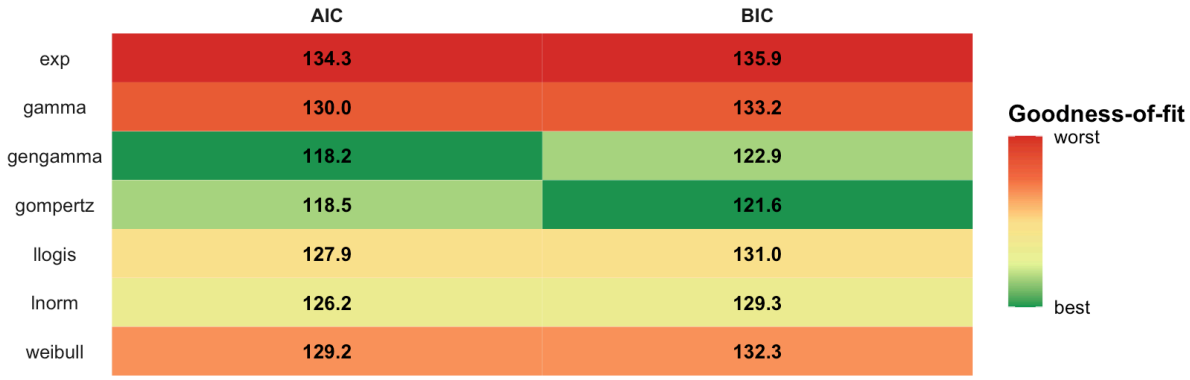


Figure 14 Statistical goodness-of-fit criteria for the fitted models of leukaemia-free survival with standard of care

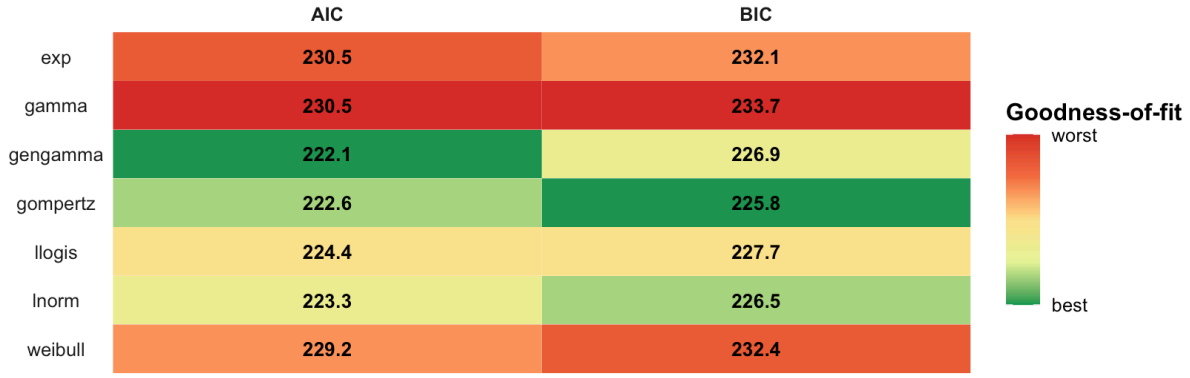
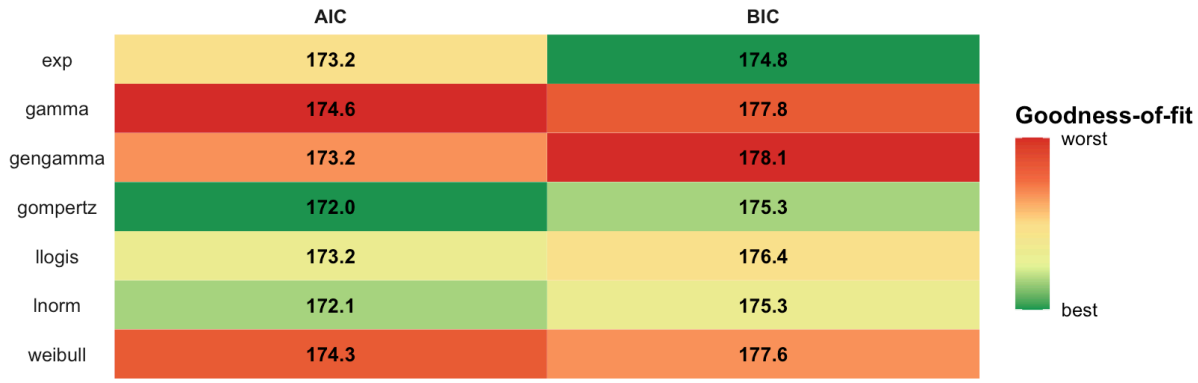


Figure 15 Statistical goodness-of-fit criteria for the fitted models of overall survival with HDC/IL-2

Figure 16 Statistical goodness-of-fit criteria for the fitted models of overall survival with standard of care



Plots of the empirical and smoothed hazards overlaid with the modelled instantaneous hazards for each of the independently fitted models are presented for LFS and OS in Figure 13 and Figure 14, respectively. The figures show the sum of the AIC and BIC values for the two independent models in the facet titles for each survival distribution.

Figure 17 Empirical, smoothed, and modelled instantaneous hazards for each independent model fitted to the LFS data

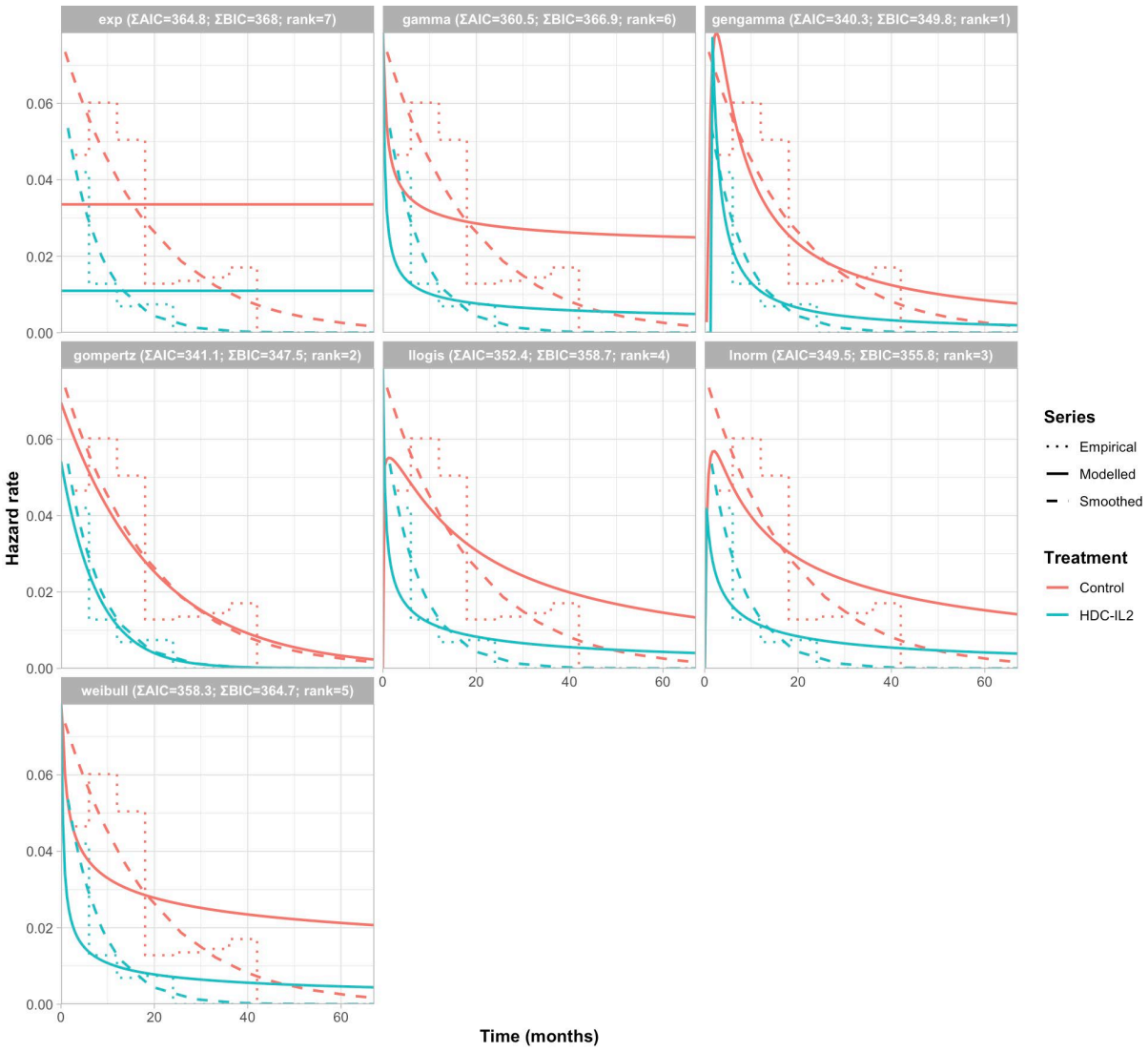
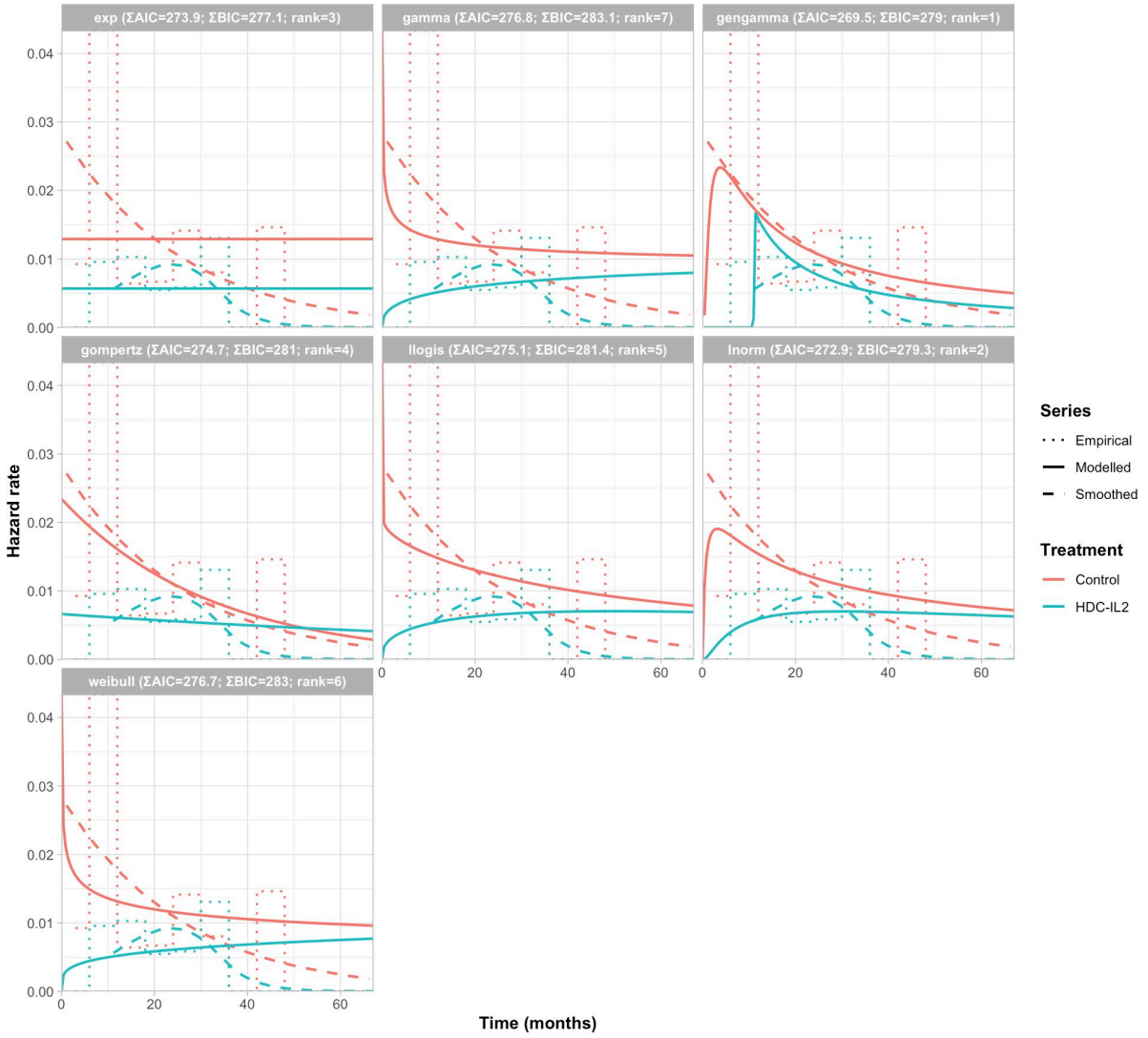


Figure 18 Empirical, smoothed, and modelled instantaneous hazards for each independent model fitted to the OS data



(f) We have incorporated the parameters for the independent models into the revised health economic model.

B8. CS, Section 3.3, pages 67-80 and Model, 'OS and LFS Parameters' and 'OS and LFS Models' worksheets. For both OS and LFS extrapolations for the subgroup of patient in first complete remission, <60 years of age, ineligible for allo-SCT, please:

(a) Fit independent standard parametric models for each treatment group for both OS and LFS, and present statistical goodness of fit and the

empirical/unsmoothed and smoothed hazard functions overlaying on the modelled instantaneous hazards for each of the fitted models.

(b) Provide clinical assessment of the plausibility of the survival extrapolation in the extrapolated period for both OS and LFS. If none of the standard parametric models provide plausible long-term projections, please fit the data using flexible survival models

(c) Incorporate the results of this analysis to the economic model, ensuring the model includes the additional functionality to use its results of the independently-fitted parametric (and flexible, if applicable) OS and LFS models.

(a) Independent standard parametric models for the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT have been fitted to the LFS and OS data. Goodness-of-fit criteria for these models are presented in Figure 15 and Figure 16 for the LFS model fits to the HDC/IL-2 arm and control arm, respectively, while Figure 17 and Figure 18 present goodness-of-fit criteria for the OS model fits to the HDC/IL-2 arm and control arm, respectively.

Figure 19 Statistical goodness-of-fit criteria for the fitted models of leukaemia-free survival with HDC/IL-2 in the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT

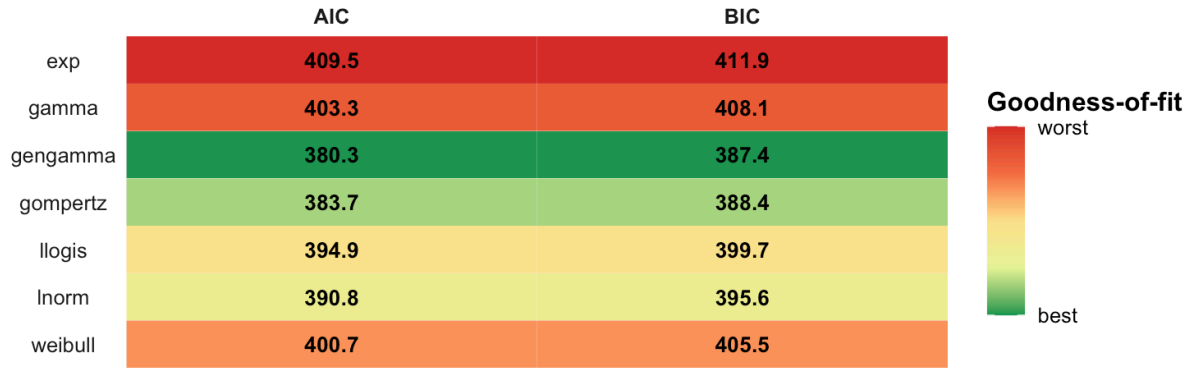


Figure 20 Statistical goodness-of-fit criteria for the fitted models of leukaemia-free survival with standard of care in the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT

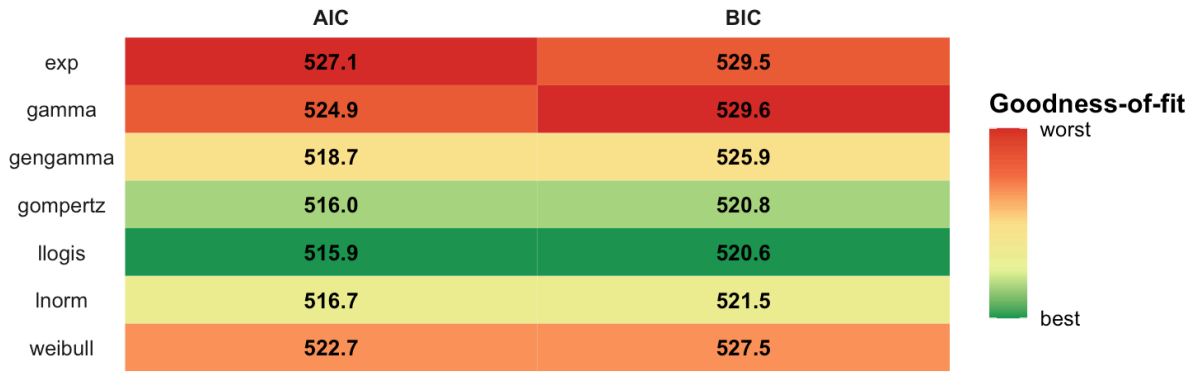


Figure 21 Statistical goodness-of-fit criteria for the fitted models of overall survival with HDC/IL-2 in the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT

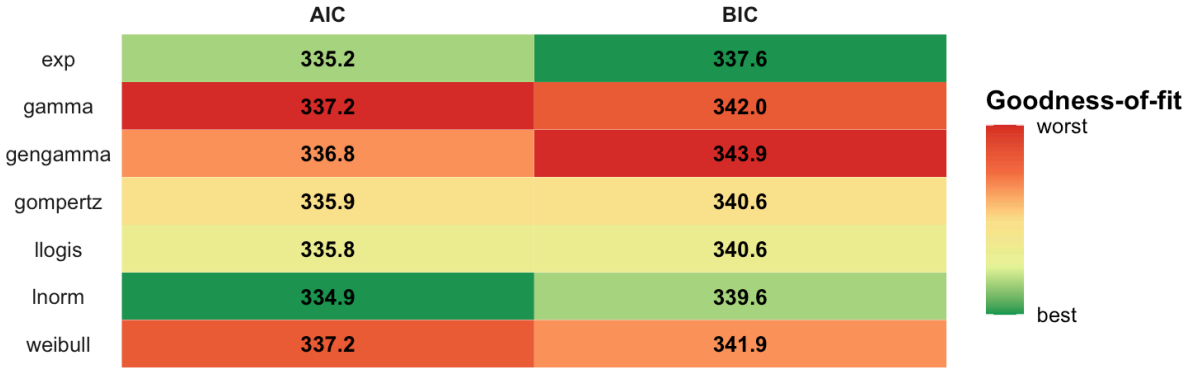
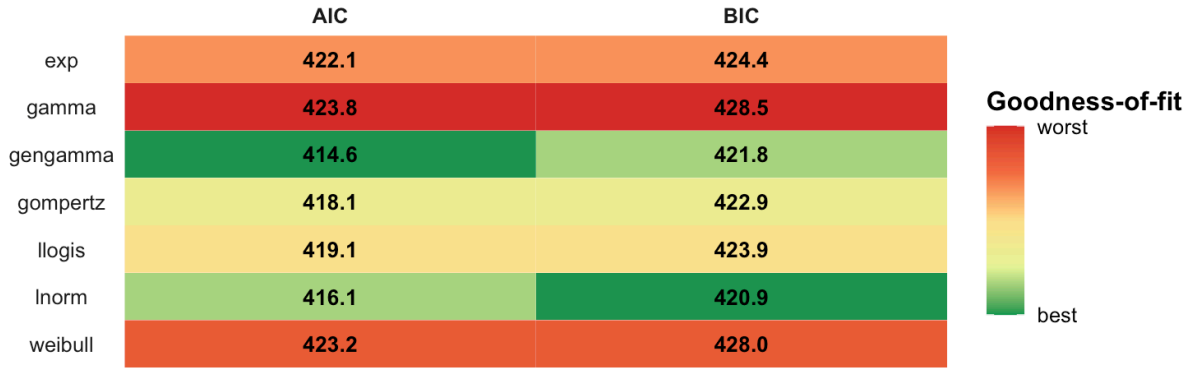


Figure 22 Statistical goodness-of-fit criteria for the fitted models of overall survival with standard of care in the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT



Plots of the empirical and smoothed hazards overlaid with the modelled instantaneous hazards for each of the independently fitted models are presented for

LFS and OS in Figure 19 and Figure 20, respectively. The figures show the sum of the AIC and BIC values for the two independent models in the facet titles.

Figure 23 Empirical, smoothed, and modelled instantaneous hazards for each independent model fitted to the LFS data in the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT

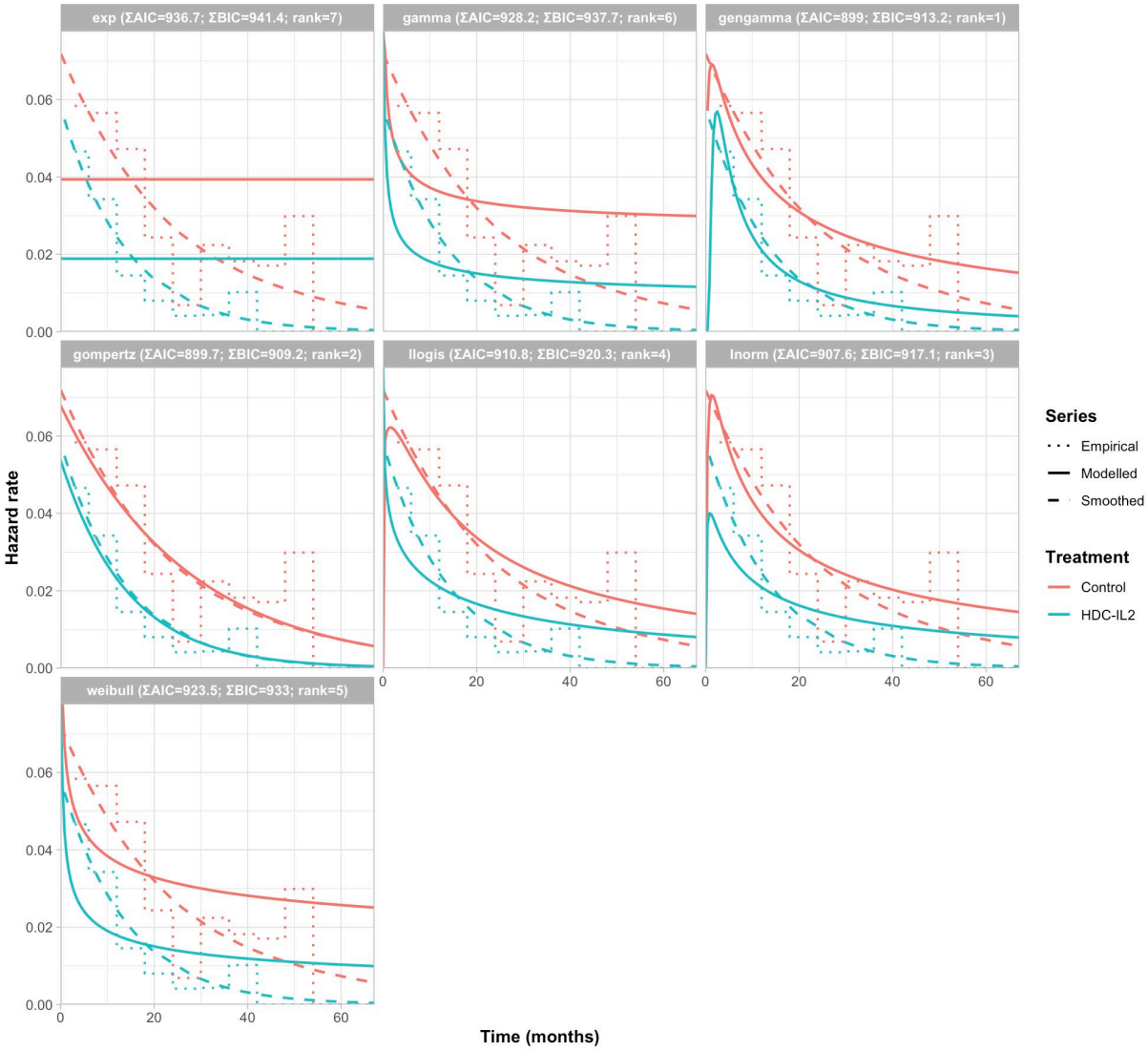
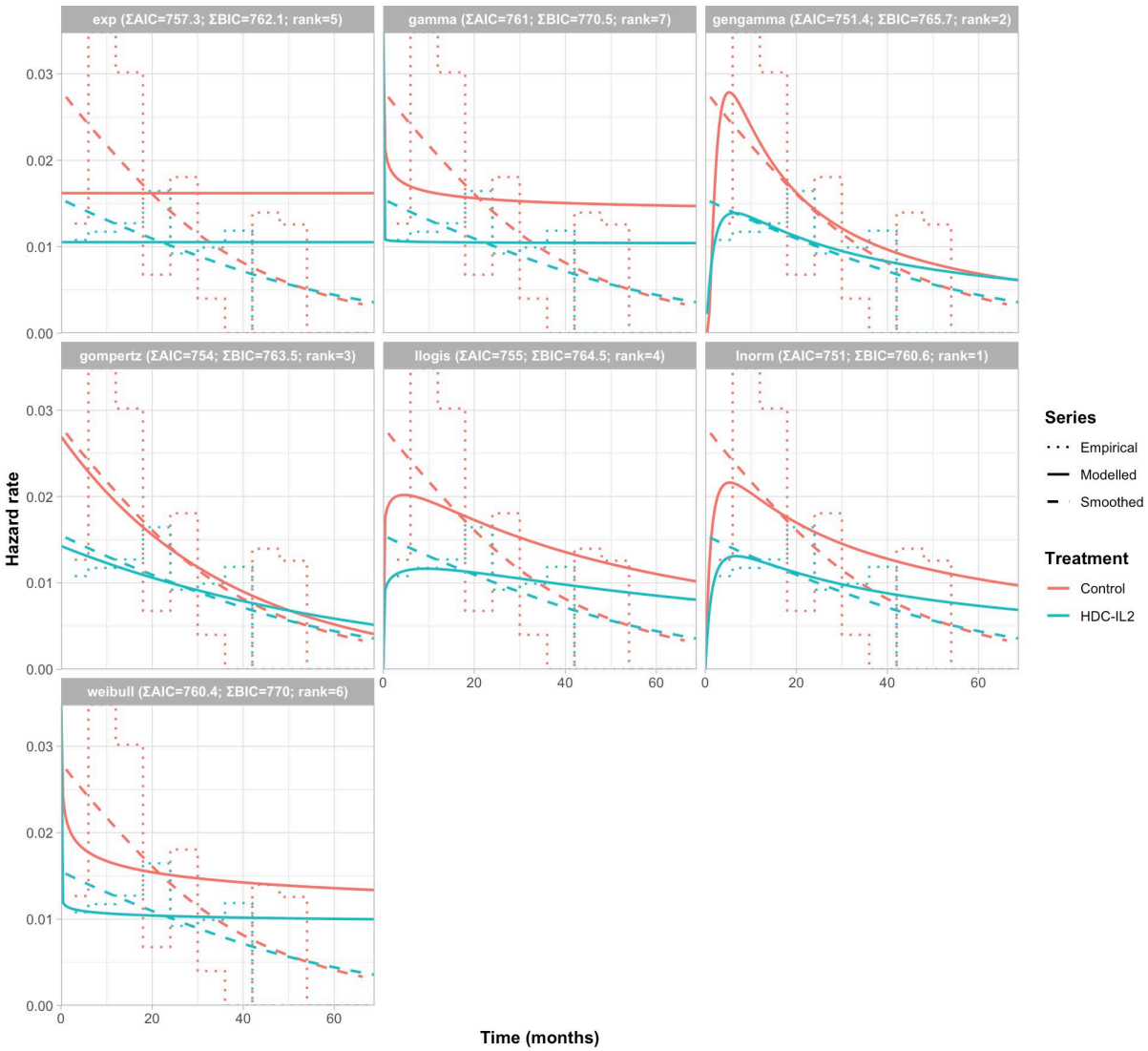


Figure 24 Empirical, smoothed, and modelled instantaneous hazards for each independent model fitted to the OS data in the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT



(b) Extrapolations over 60 years are presented in Figure 21 and Figure 22 for LFS and OS, respectively. The OS models include some that are clinically plausible with, e.g. HDC/IL-2 overall survival of <25% after 200 months. Flexible survival models may therefore not be necessary to achieve clinically plausible extrapolated outcomes, although they could enhance the ability to calibrate the model to specific long-term survival outcomes in AML.

Figure 25 Independent parametric model fits to leukaemia-free survival data and extrapolations up to 60 years (720 months) in the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT

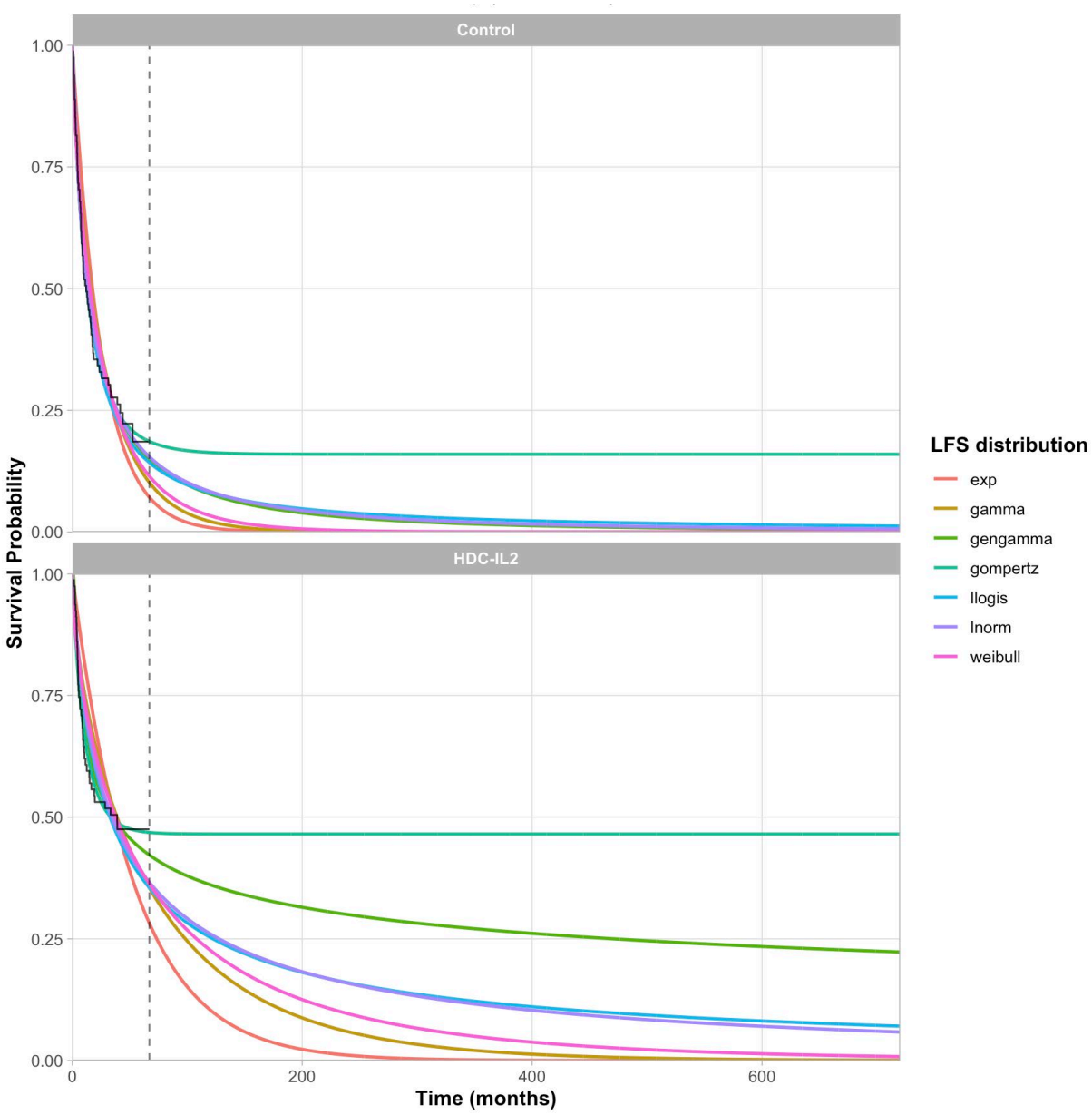
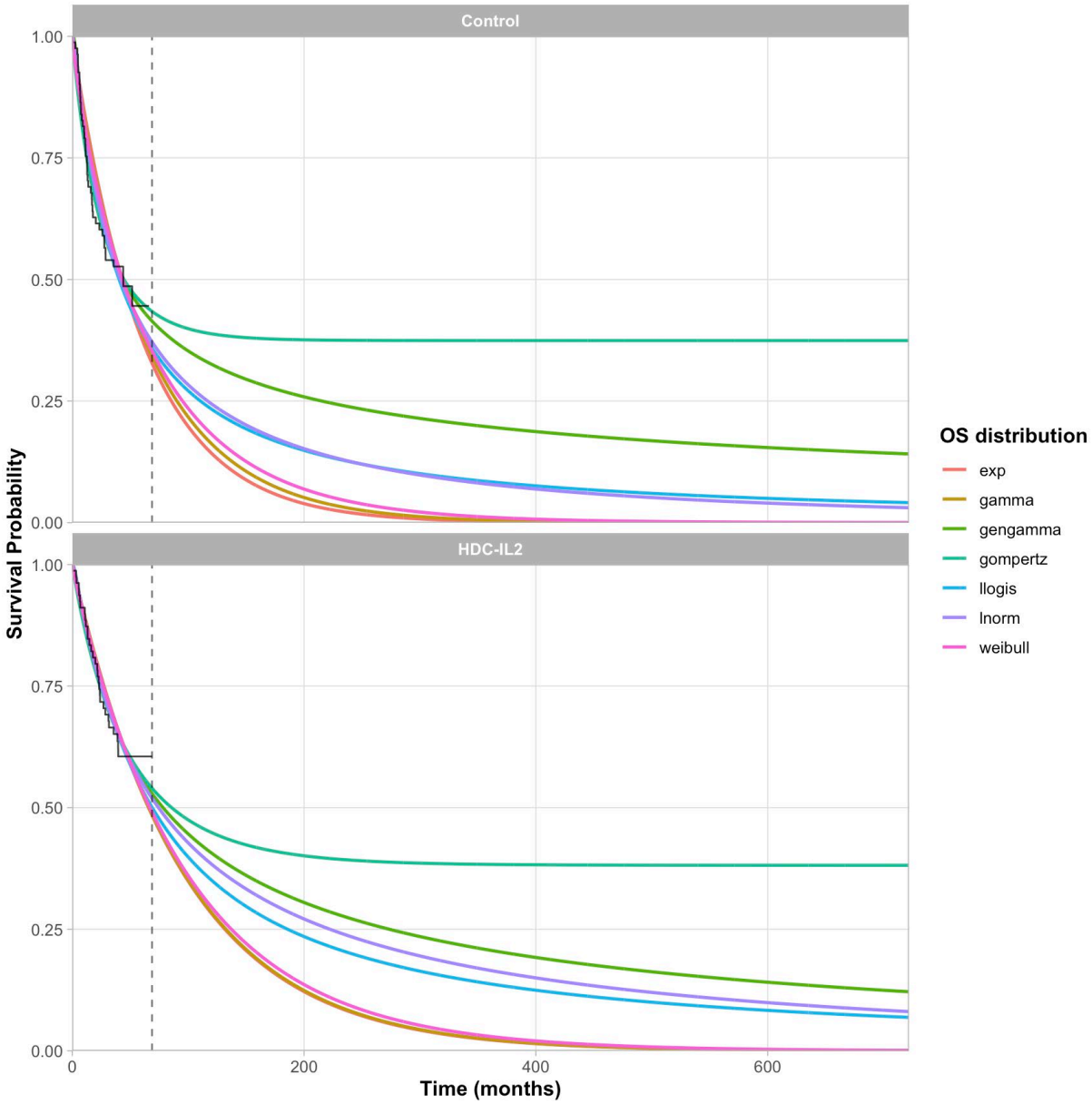


Figure 26 Independent parametric model fits to overall survival data and extrapolations up to 60 years (720 months) in the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT



(c) We have incorporated the parameters for the independent models for the subgroup of patients in first complete remission, <60 years of age, ineligible for allo-SCT into the revised health economic model.

B9. CS, Section 3.3, pages 67-80 and Model, 'OS and LFS Parameters' and 'OS and LFS Models' worksheets. For both OS and LFS extrapolations for the subgroup of patient in first complete remission and ineligible for allo-SCT, please:

(a) Fit independent standard parametric models for each treatment group for both OS and LFS, and present statistical goodness of fit and the empirical/unsmoothed and smoothed hazard functions hazard overlaying on the modelled instantaneous hazards for each of the fitted models.

(b) Provide clinical assessment of the plausibility of the survival extrapolation in the extrapolated period for both OS and LFS. If none of the standard parametric models provide plausible long-term projections, please fit the data using flexible survival models.

(c) Incorporate the results of this analysis to the economic model, ensuring the model includes the additional functionality to use its results of the independently-fitted parametric (and flexible, if applicable) OS and LFS models.

(a) Independent standard parametric models for the subgroup of patients in first complete remission and ineligible for allo-SCT have been fitted to the LFS and OS data. Goodness-of-fit criteria for these models are presented in Figure 23 and Figure 24 for the LFS model fits to the HDC/IL-2 arm and control arm, respectively, while Figure 25 and Figure 26 present goodness-of-fit criteria for the OS model fits to the HDC/IL-2 arm and control arm, respectively.

Figure 27 Statistical goodness-of-fit criteria for the fitted models of leukaemia-free survival with HDC/IL-2 in the subgroup of patients in first complete remission and ineligible for allo-SCT

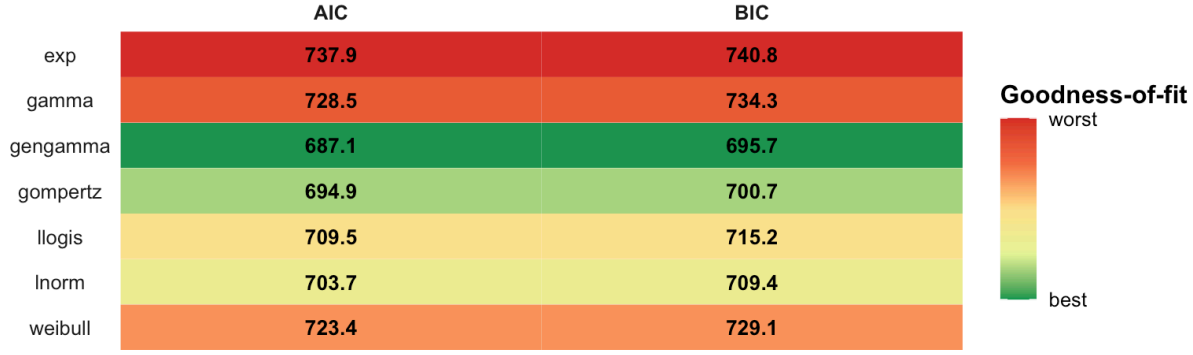


Figure 28 Statistical goodness-of-fit criteria for the fitted models of leukaemia-free survival with standard of care in the subgroup of patients in first complete remission and ineligible for allo-SCT

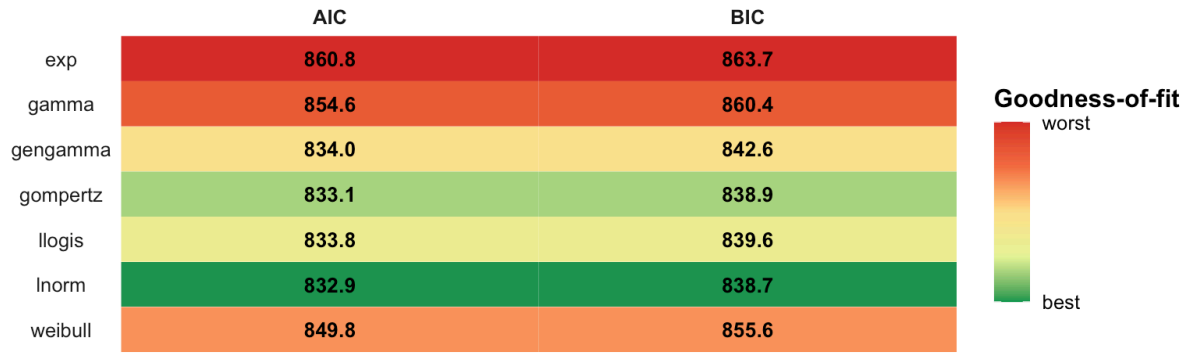


Figure 29 Statistical goodness-of-fit criteria for the fitted models of overall survival with HDC/IL-2 in the subgroup of patients in first complete remission and ineligible for allo-SCT

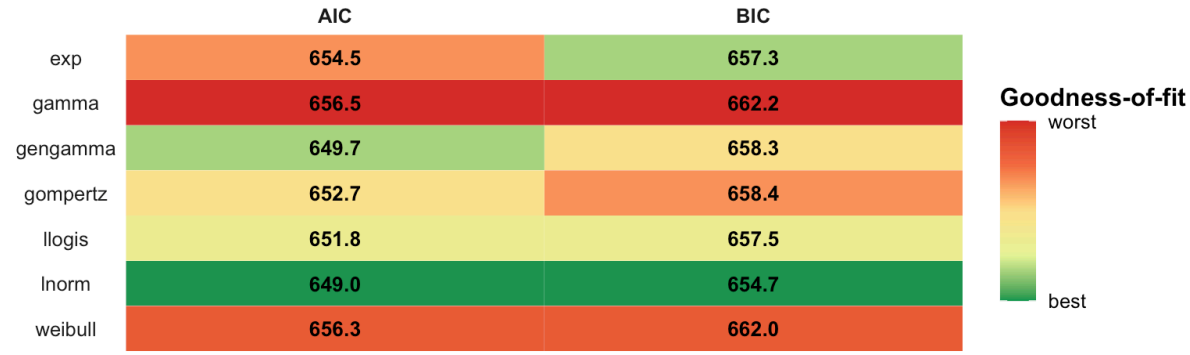
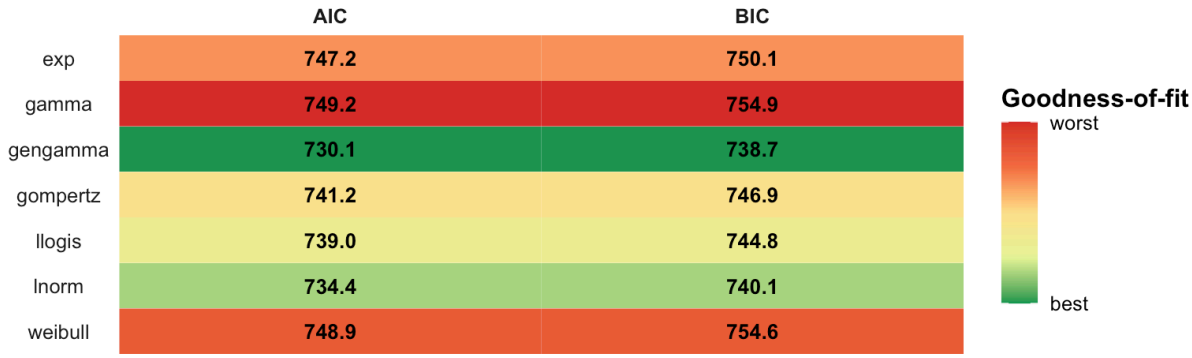


Figure 30 Statistical goodness-of-fit criteria for the fitted models of overall survival with standard of care in the subgroup of patients in first complete remission and ineligible for allo-SCT



Plots of the empirical and smoothed hazards overlaid with the modelled instantaneous hazards for each of the independently fitted models in the subgroup of patients in first complete remission and ineligible for allo-SCT are presented for LFS

and OS in Figure 27and Figure 28, respectively. The figures show the sum of the AIC and BIC values for the two independent models in the facet titles.

Figure 31 Empirical, smoothed, and modelled instantaneous hazards for each independent model fitted to the LFS data in the subgroup of patients in first complete remission and ineligible for allo-SCT

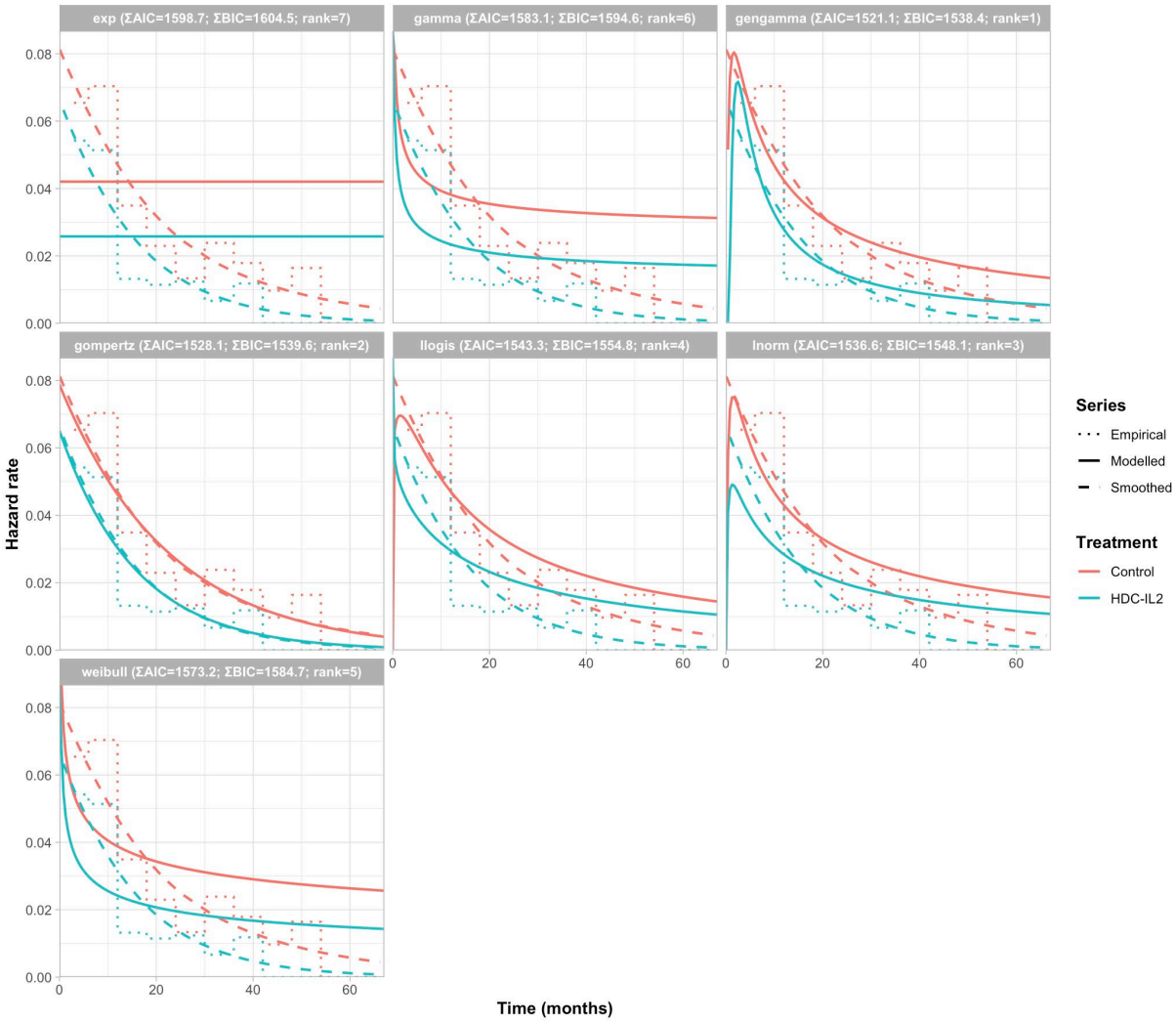
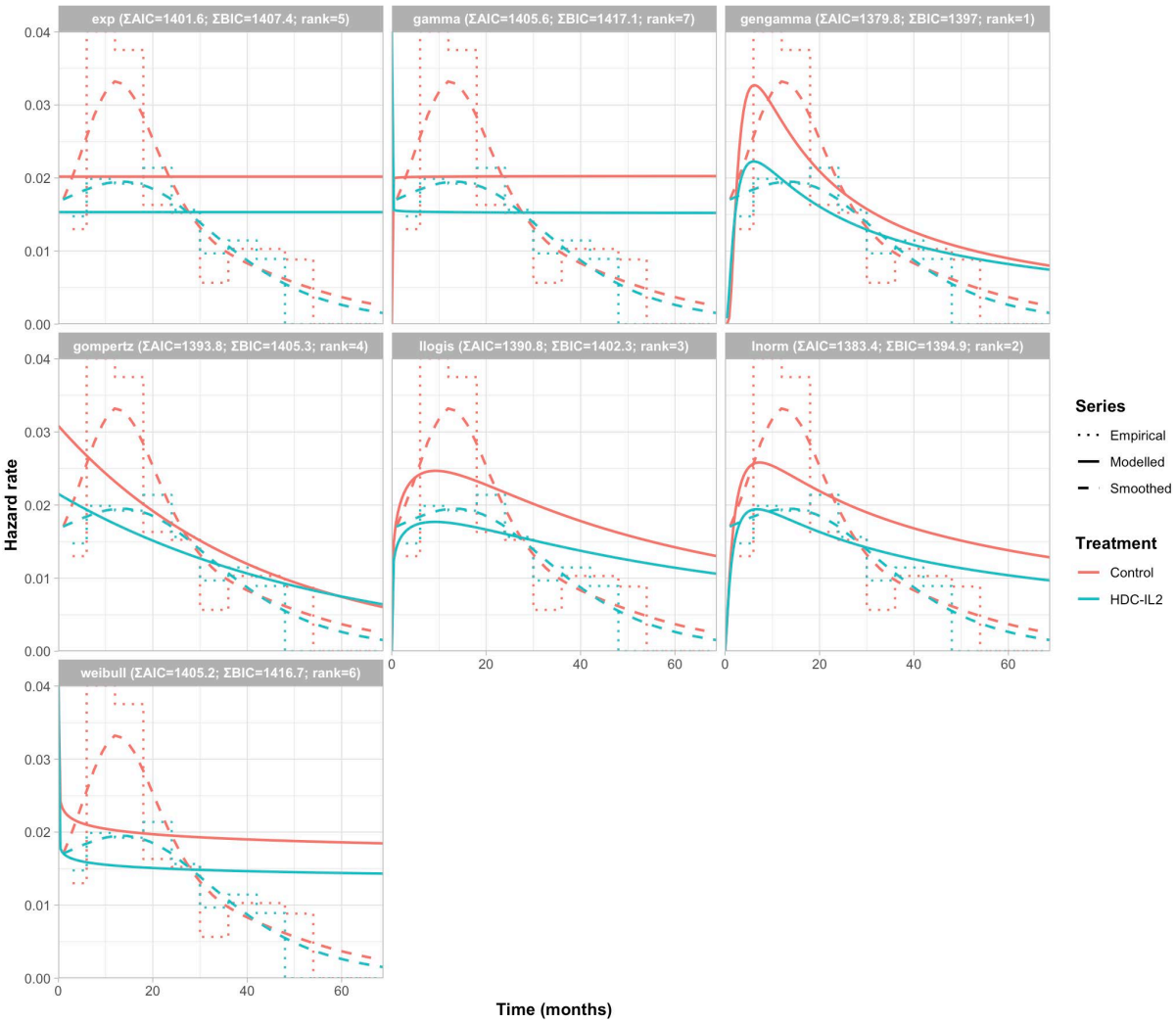


Figure 32 Empirical, smoothed, and modelled instantaneous hazards for each independent model fitted to the OS data in the subgroup of patients in first complete remission and ineligible for allo-SCT



(b) Extrapolations over 60 years are presented in Figure 29 and Figure 30 for LFS and OS, respectively. The OS models include some that are clinically plausible for the broader and older population with, e.g. HDC/IL-2 overall survival of <10% after 200 months (in the case of the exponential model). Flexible survival models may therefore not be necessary to achieve clinically plausible extrapolated outcomes, although they could enhance the ability to calibrate the model to specific long-term survival outcomes in AML.

Figure 33 Independent parametric model fits to leukaemia-free survival data and extrapolations up to 60 years (720 months) in the subgroup of patients in first complete remission and ineligible for allo-SCT

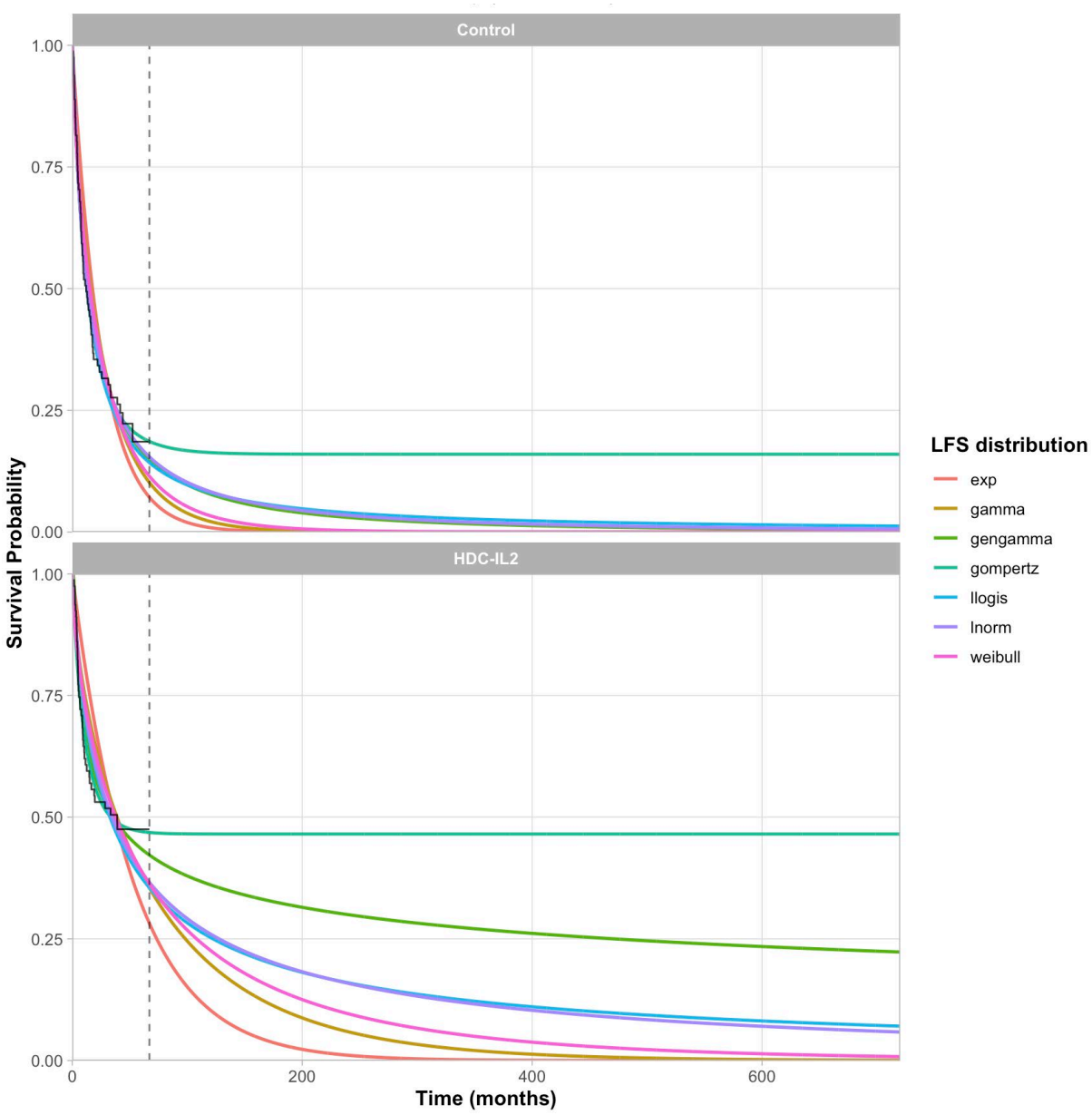
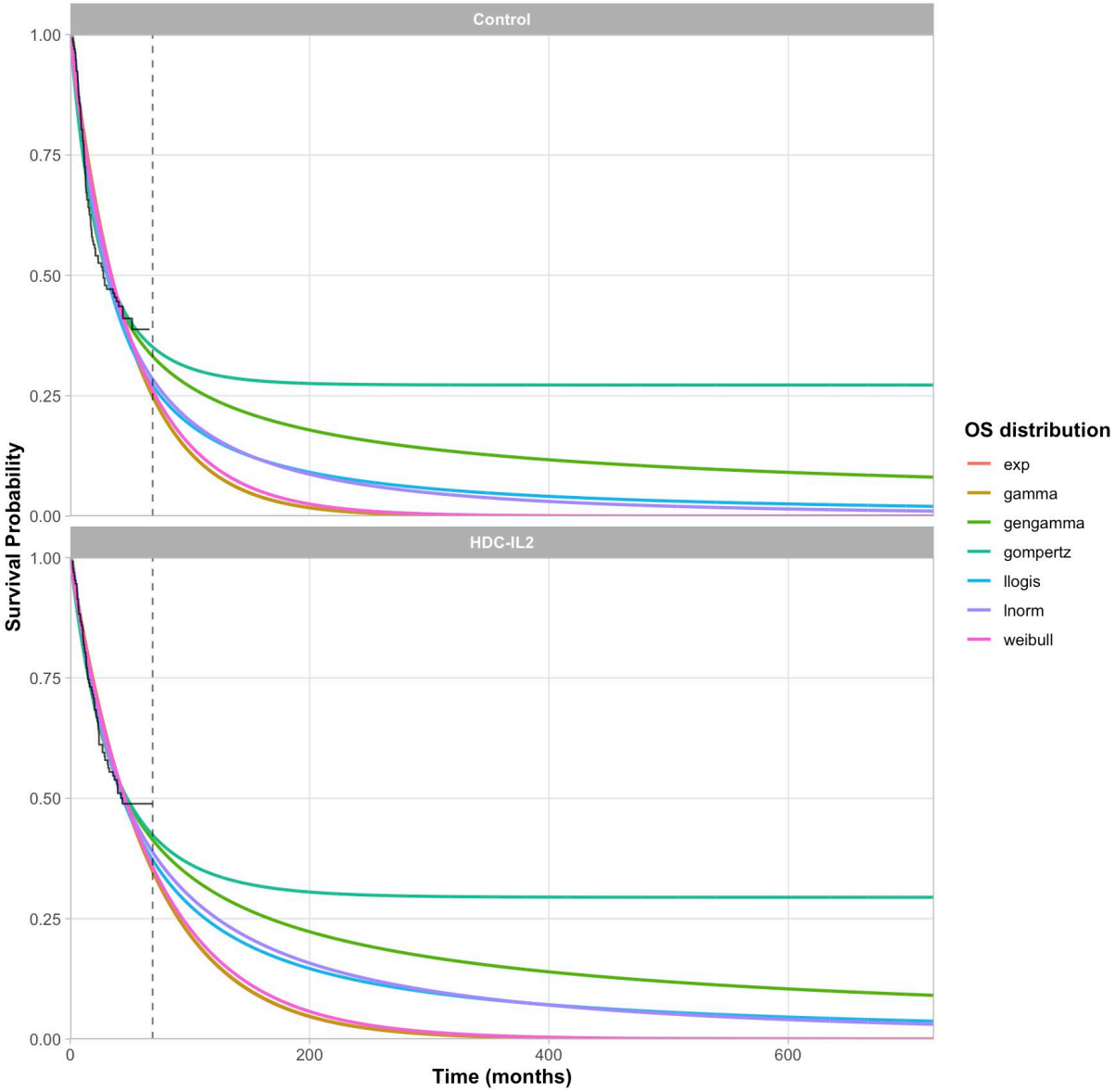


Figure 34 Independent parametric model fits to overall survival data and extrapolations up to 60 years (720 months) in the subgroup of patients in first complete remission and ineligible for allo-SCT



(c) We have incorporated the parameters for the independent models for the subgroup of patients in first complete remission ineligible for allo-SCT into the revised health economic model.

Mortality

B10. CS, Section 3.3, page 73. The model uses the lifetables for England and Wales (2021-2023). Please update the model using the lifetables for England only (2021-2023).

We have updated the model to use lifetables for England only. Lifetables for England and Wales remain as an option available from the drop-down menu on the Setup sheet. In isolation, this change reduced the deterministic base case ICER from £25,809.99 per QALY to £25,809.80 per QALY gained.

B11. CS, Section 3.3, page 80. Based on the description of the model in the CS, the model included treatment discontinuation only due to AEs not related to relapse (8.3%) at the first cycle of the model, using data from the ITT population in Brune *et al.* (2006), and due to relapse in subsequent cycles. Please comment how this approach is likely to affect drug discontinuation in the model, particularly in terms of how discontinuation in the model's targeted population is expected to differ from that in the ITT population reported in Brune *et al.* (2006).

The only information on treatment discontinuations that were available from the Brune *et al.* (2006) study was:

a) that pertaining to discontinuations related to AEs, on which the Brune *et al.* manuscript reported: *"Thirteen patients (8.3%) in the HDC/IL-2 arm discontinued treatment because of AEs not related to relapse."* and

b) the median number of treatment cycles received (6; range 1–10) and the proportion of non-relapsed patients who completed all 10 schedule treatment cycles (n=45/49 or 92%).

No further data were available on treatment discontinuations in the IPD. Based on the above descriptions, which also imply discontinuation due to relapse, the

assumption of treatment discontinuation as a result of AEs (after treatment cycle 1) or relapse (in any cycle during treatment) was therefore implemented in the model. In the absence of further treatment discontinuation information beyond that reported in the Brune et al. (2006) manuscript, the effect of this modelling approach on any differences between modelled treatment discontinuation and treatment discontinuation in the ITT population in the Brune et al. study is difficult, if not impossible, to quantify; however, we believe that the treatment discontinuation assumptions are clinically reasonable and would align with the reasons for discontinuation of HDC/IL-2 in routine clinical practice. See also the response to question B26, which documents a small change to the implementation of treatment discontinuations due to AEs or relapse.

Adverse events (AEs)

B12. CS, Section 3.5, Table 22, pages 86-87. The EAG notes that Brune *et al.* (2006) reports Grade 3 and 4 AEs with an incidence of ≥5% in either treatment arm for the following AEs: thrombocytopenia (17.3% for HDC/IL-2 and 9.4% for control); neutropenia (5.7% for HDC/IL-2 and 3.1% for control); and headache (7% for HDC/IL-2 and 0% for control). However, the model includes only Grade 3/4 AEs for fatigue, nausea, vomiting, diarrhoea and anaemia, all with incidence <5%. Please clarify the process/logic behind the selection of AEs for inclusion in the model. Please also consider including all Grade 3/4 AEs with an incidence of ≥5% in either treatment arm from Brune *et al.* (2006) in the model, and update model results accordingly.

We appreciate the suggestion and have updated the model to include thrombocytopenia, neutropenia, and headache as recommended. Updated versions of Table 22 and Table 23 from the CS are presented in Table 8 and Table 9. The previously-included AEs all showed significant differences between arms in the Brune *et al.* (2006) study and were considered to result in meaningful costs being incurred from the perspective of NHS England. The previous rationale for the exclusion of thrombocytopenia and neutropenia was based on the non-significant differences in the incidence of the adverse events across all grades as reported in

the Brune *et al.* (2006) manuscript, while the exclusion of headache was driven by challenges in identifying costs of treatment that would be widely accepted.

Table 16 [Updated CS Table 22] Grade 3/4 adverse event incidence rates from the Brune et al. randomised controlled trial

	HDC/IL-2, %	Standard of care, %
Fatigue	1.3%	1.3%
Nausea	1.3%	0.0%
Vomiting	0.6%	0.0%
Diarrhoea	1.9%	0.0%
Anaemia	1.3%	0.6%
Thrombocytopenia	17.3%	9.4%
Neutropenia	5.7%	3.1%
Headache	7.0%	0.0%

Table 17 [Updated CS Table 23] Cost and resource use assumption associated with Grade 3/4 adverse events

	Treated as outpatients, %	Non-elective short stay inpatient cost (GBP)	Day case cost (GBP)	Weighted cost (GBP)	Source
Fatigue	95.0%	864.11	515.66	533.08	2023/24 National Cost Collection Acute Sector Admitted Patient Care: SA25M AML with CC code 0-1
Nausea	100.0%	864.11	515.66	515.66	
Vomiting	95.0%	515.48	379.59	386.39	2023/24 National Cost Collection Acute Sector Admitted Patient Care: FD01J Gastrointestinal infections without interventions, with CC score 0-1
Diarrhoea	95.0%	515.48	379.59	386.39	
Anaemia	90.0%	490.98	367.81	380.13	2023/24 National Cost Collection Acute Sector Admitted Patient Care: SA04L Iron deficiency anaemia with CC score 0-1

	Treated as outpatients, %	Non-elective short stay inpatient cost (GBP)	Day case cost (GBP)	Weighted cost (GBP)	Source
Thrombocytopenia	90.0%	621.68	361.56	387.57	2023/24 National Cost Collection Acute Sector Admitted Patient Care: SA12K Thrombocytopenia with CC Score 0-1
Neutropenia	100.0%	528.81	367.21	367.21	2023/24 National Cost Collection Acute Sector Admitted Patient Care: SA35E Agranulocytosis with CC Score 0-1
Headache	100.0%	448.36	449.61	449.61	2023/24 National Cost Collection Acute Sector Admitted Patient Care: AA31E Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0-6

In isolation, the addition of thrombocytopenia, neutropenia, and headache increased the deterministic base case ICER from £25,810 per QALY to £25,832 per QALY gained.

Utilities

B13. CS, Appendix F, Table 4 (pages 7-9) and CS Section 3.4, page 82. Please clarify the rationale behind the selection of Joshi *et al.* (2019), Stein *et al.* (2018) and Tremblay *et al.* (2008) to inform the model's base case and Scenarios 1 and 2, from the 14 studies included in the SLR of health-related quality-of-life (HRQoL) studies. Please also clarify how the study by Russell-Smith *et al.* (2021), used in Scenario 3, was identified and selected.

In the absence of utility (or indeed broader patient-reported outcome) data from the pivotal Brune *et al.* (2006) RCT — despite attempts to obtain it by contacting the study authors — the base case analysis was necessarily driven by utility values obtained from the literature. The selection of utility values from Tremblay *et al.* (2018 rather than 2008 as above) in the base case analysis was driven in part by the use of the same utility values in the single technology appraisal of oral azacitidine (TA827) and the existing critiques of the utility values as presented by the EAG in TA827 and in part by the methodological proximity of the underlying studies (particularly Leunis *et al.* [2014]) to the NICE Reference Case. In brief, while the Tremblay *et al.* (2018) utility values came from disparate sources, the pre-progression off-treatment utility value of 0.83 was obtained from EQ-5D-5L responses as reported by Leunis *et al.* (2014). The relapse utility value of 0.51 from Pan *et al.* (2010), while mapped to EQ-5D utilities from the EORTC QLQ-C30 using the Kontodimopoulos *et al.* (2009) algorithm, was the relapse value preferred by the EAG in TA827. The pre-progression on-treatment utility value of 0.81 from Batty *et al.* (2014) was methodologically the furthest removed from the NICE Reference Case, but was closely aligned with the Leunis *et al.* (2014) on-treatment utility, and showed a clinically plausible difference between patients in the same disease-related health state differentiated only by their on- versus off-treatment status. Further discussion on the face validity of the Tremblay *et al.* (2018) utility values is presented in the response to question B14.

Utility values from Joshi *et al.* (2019) and Stein *et al.* (2019) were used as the basis of scenario analyses to illustrate the effects of the use of different published utility value sets on model outcomes despite methodological mis-alignment with the NICE Reference Case. Both studies served a specific purpose in demonstrating the effect of the utility value selection on the model outcomes: Joshi *et al.* (2019) widened the difference between the pre-progression and post-progression utilities to 0.38 (versus 0.3 in the base case analysis), while Stein *et al.* (2019) narrowed the difference to 0.25, thereby collectively providing evidence-based scenario analyses showing opposing effects on utility value deltas between the model partitions. Both studies were also used as the basis of analyses in the single technology appraisal of oral azacitidine (TA827), providing further motivation to run scenario analyses based on the utility sets, and allowing a comparison of the absolute and incremental modelled outcomes with similar changes to the health state utility value. The Russell-Smith *et*

al. (2021) study was identified through the economic SLR rather than the HRQoL SLR and represented the only peer-reviewed UK-specific economic evaluation in people with AML aside from the single technology appraisal of oral azacitidine (TA827 and Witlox *et al.*).

B14. CS, Section 3.4, page 81 and Table 18 (page 83). In relation of the approach adopted in the model for the health state utilities:

(a) Please comment on the face validity of the utility estimates from Trembley *et al.* (2018): 0.81 for pre-progression HDC/IL-2 on treatment, 0.83 for pre-progression HDC/IL-2 off treatment or BSC, 0.53 post-progression. The EAG notes that the utility values for the pre-progression states are very high.

(b) Please also comment on the difference of 0.02 between the utility estimates for HDC/IL-2 patients on and off therapy being intended to capture *"an average annual loss of approximately one week in perfect health in those patients receiving treatment. This was considered to be conservative from the perspective of histamine dihydrochloride and low-dose interleukin-2 given the low incidence rates of Grade 3 and 4 adverse events in the Brune et al. RCT"*, given the utility estimates were taken from a cost-effectiveness study evaluating midostaurin versus standard of care in newly diagnosed patients with AML, which may have a different adverse event (AE) profile to HDC/IL-2. Please consider including disutility values for AEs in the model, in line with the approach adopted in NICE TA827.

(a) The health state utility values used in the Tremblay *et al.* (2018) study were derived from three sources: Batty *et al.* 2014 (0.81 for the pre-progression on-treatment state), Leunis *et al.* 2014 (0.83 for the pre-progression off-treatment state), and Pan *et al.* 2010 (0.53 for the post-progression/relapse state). The pre-progression off-treatment utility value of 0.83 from Leunis *et al.* is based on data from a study that collected EQ-5D-5L values collected in 92 patients with AML and specifically reflects the utility value for patients without relapse. This value is methodologically most closely aligned with the preference for EQ-5D data in the NICE Reference Case, although we acknowledge that the study utilised the EQ-5D-5L rather than the EQ-5D-3L. Regarding face validity, in the target population

(people with AML in first complete remission, under 60 years of age, and with normal karyotype), the mean age in the Brune *et al.* (2006) RCT was 44.2 years, in whom the expected EQ-5D-3L utility value in the UK would be 0.8764 in women and 0.8943 in men (Hernández Alava *et al.* 2022). The off-treatment estimate of 0.83 for the pre-progression state utility does therefore still fall below age- and sex-matched general population norms. It is also worth noting that the target population consists exclusively of patients who are in first complete remission, which may result in (relatively) buoyant quality of life scores when compared with patients after an initial diagnosis or relapse. The pre-progression on-treatment utility estimate of 0.81 from Batty *et al*. (2014) was derived by Batty *et al.* from Goss *et al.* (2006) and Gidwani *et al.* (2012) and is closely aligned (numerically if not methodologically) with the EQ-5D utility value from Leunis *et al.* (2014), with the difference capturing effects such as the incidence of adverse events arising from treatment. Finally, the 0.53 post-progression utility was derived by Pan *et al.* by mapping to the EQ-5D utility scale from the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (Kontodimopoulos *et al.* 2009). While not the preferred approach, mapping to the EQ-5D is acknowledged as an option in the NICE Reference Case (Section 4.3.9 of the NICE Methods Guide) where EQ-5D data are not directly available.

(b) The 0.02 difference in the health state utility values was considered to present a highly conservative scenario, in which all patients “on-treatment” would experience a loss of quality-of-life equivalent to approximately one week in perfect health. The implementation of adverse-event specific utility decrements (detailed in the response to question B14 (c)) showed this to be the case, with the explicit modeling of adverse events rates from the Brune *et al.* (2006) RCT resulting in disutilities of 0.001 in the HDC/IL-2 arm versus 0.0003 in the control arm. (c) Functionality has been incorporated into the model to capture disutilities associated with each modelled adverse event. The default utility values and event durations

were informed by the single technology appraisal of oral azacitidine and are presented in **Table 10.**

Table 18 Default utility decrements in the revised health economic model

	Utility decrement	Duration of adverse event (weeks)	Utility decrement source
Fatigue	0.115	1	TA642
Nausea	0.048	1	Nafees et al. 2008
Vomiting	0.048	1	Nafees et al. 2008
Diarrhoea	0.176	1	Stein et al. 2018
Anaemia	0.119	1	TA642
Thrombocytopenia	0.09	1	TA642 (assumed same as neutropenia)
Neutropenia	0.09	1	Nafees et al. 2008 and TA642
Headache	0.34	1	Stafford et al. 2012

When combined with the additional adverse events added in response to question B12, this change increased the base case ICER from from £25,810 per QALY to £25,833 per QALY gained.

B15. CS Section 3.4, page 80. The CS refers to a paper by Wallhult *et al.* (2007), but this is not included in the reference list. Please provide the full reference and a copy of the paper.

Wallhult *et al.* 2007 refers to a conference abstract from ASH 2007. The full reference is:

> Wallhult E, Whisnant J, Rowe JM, Szer J, Bhagwat D, Hellstrand K, Nilsson BI, Brune ML. Impact on Quality of Life of Postconsolidation Immunotherapy with Histamine Dihydrochloride and Interleukin-2 in Acute Myelogenous Leukemia. Blood. 2007;110(11):4381.

The abstract is available online here: https://doi.org/10.1182/blood.V110.11.4381.4381 and has now been included in the revised reference pack.

B16. CS, Section 3.4, Table 18, page 83. In relation to the alternative sources for the health state utilities used in Scenario Analysis 1 to 3:

(a) Please justify the use of Joshi *et al.* 2019, since the utility values were not derived from EQ-5D-3L as recommended by the NICE Methods Guide.

(b) Please justify the use of Stein *et al.* 2019, since this study is based on the US population. Please also clarify the value for the post-progression utility (0.62), as this does not match the values presented in the original source.

(c) Please clarify the source of the utility values used in Scenario Analysis 3, as they do not match the reference (of Russell Smith *et al.* 2021). These values appear to correspond to the utility values reported in TA399 – the committee papers for this appraisal indicates that these values are from 'McKenzie and Van der Pol, 2009'.

(a) We acknowledge that the utility values from Joshi *et al.* (2019) were not derived from EQ-5D-3L; the study rather relied on a composite time trade-off methodology from the UK general population. The Joshi *et al.* (2019) study was not selected for use in the base case analysis for this reason, but we note its use in the single technology appraisal of oral azacitidine (TA827) and included it as a scenario analysis a) for its geographical specificity to the UK and b) to facilitate comparisons between the present analyses and those conducted as part of the single technology appraisal of oral azacitadine (TA827).

(b) We similarly acknowledge that Stein *et al.* (2019) has shortcomings, specifically pertaining to the lack of geographical specificity to the UK. The value of 0.62 was adopted to align with the values from Stein *et al.* cited in the single technology appraisal of oral azacitadine (TA827).

(c) shows the table of model parameters from Russell-Smith *et al.* (2021) that was used as the source of the utility values originally reported in Table 18 of the CS, with the values (0.74 and 0.568) highlighted in green. The table cites NICE TA399 as the original source of the utility values, with a footnote noting that the values were derived using a mapping algorithm published by McKenzie and Van der Pol (2009). The McKenzie and Van der Pol (2009) mapping algorithm mapped EORTC QLQ-C30 parameters are presented in TA399 (TA399 CS Table 40).

Figure Table 2 from Russell-Smith et al.

Variable	Value	Measurement of uncertainty (distribution)	Source
GVHD management	£26,888.92	SE = 2688.89 (normal)	Espérou et al. [39]
Hospital visits			
Inpatient attendance (per day)	£661.72	SE = 66.17 (normal)	DoH [31]
Consultant visit, first	£196.64	SE = 32.63 (normal)	DoH [31]
Consultant visit, follow-up	£162.84	SE = 22.96 (normal)	DoH [31]
Specialist nurse visit	£36.00	SE = 3.60 (normal)	Curtis and Burns [40]
Disease management[a]			
Bone marrow cytogenetics	£16.88	SE = 5.30 (normal)	DoH [31]
Bone marrow extraction	£493.90	SE = 49.39 (normal)	DoH [31]
Ultrasound examination	£611.79	SE = 61.18 (normal)	DoH [31]
Terminal care			
Last 8 weeks of life	£6658.77	SE = 697.12 (normal)	Addicott and Dewar [41]
Utility values			
Chemotherapy treatment[b]	0.6574[c]	SE = 0.07 (beta)	NICE [42]
HSCT procedure	0.6574[d]	SE = 0.07 (beta)	Assumption
GVHD (post-HSCT)	0.6700	SE = 0.02 (beta)	Kurosawa et al. [43]
CR or CRp	0.7400[c]	SE = 0.07 (beta)	NICE [42]
Relapse	0.5680[c]	SE = 0.06 (beta)	NICE [42]
Refractory	0.5680[e]	SE = 0.06 (beta)	Assumption
Functionally cured	0.8212[f]	SE = 0.08 (beta)	Ara and Brazier [26]
Dead	0	N/A	N/A

AML acute myeloid leukaemia, *BNF* British National Formulary, *BSA* body surface area, *CR* complete remission, *CRp* CR with incomplete platelet recovery, *DoH* Department of Health, *eMIT* electronic market information tool, *GO* gemtuzumab ozogamicin, *GVHD* graft-versus-host disease, *HR* hazard ratio, *HSCT* haematopoietic stem-cell transplant, *MCM* mixture cure model, *NHSBT* National Health Service Blood and Transplant, *NICE* National Institute for Health and Care Excellence, *ONS* Office for National Statistics, *OS* overall survival, *RFS* relapse-free survival, *SE* standard error, *SOC* standard of care

[a]Costs for other laboratory tests were included in the model

[b]Used for induction, consolidation, and salvage chemotherapy

[c]Values from NICE Technology Appraisal 399, using the mapping algorithm by McKenzie and Van der Pol[44]

Notes: Green highlights reflect values included in Company Submission Table 18.

Resource Use

B17. Please justify the following assumptions applied in the model related to the drug acquisition and administration costs for HDC and IL-2 regimens:

(a) Following the first doses of each treatment cycle, which is assumed to be administered in secondary care, both regimens are assumed to be given at home (after the patient learns how to administer it). Please clarify the storage time, method and stability of HDC/IL-2. In addition, how often would patients have to go to hospital to collect the drugs or would this be sent by special delivery to home? Please also clarify if any accessories would be required to allow patients to self-administer each HDC injection over 5-15 minutes (e.g., a pump). Please also comment on the potential challenges related to the regimens' adherence, compliance and implementation.

(b) The model does not include any wastage for either regimen, please justify this assumption or update the model to include it.

(c) Please clarify if the administration cost applied in the model includes training patients to self-administer the subcutaneous injections at home.

(a) HDC/IL-2 is supplied in packs of 14 0.5 mg/0.5 mL vials with a shelf life of 3 years (https://www.ema.europa.eu/en/documents/product-information/ceplene-epar-product-information_en.pdf) and does not require special storage.
IL-2 must be aseptically reconstituted, diluted and dispensed in capped polypropylene tuberculin syringes by the pharmacy based on the individual patient's weight. The chemical stability and sterility of diluted aldesleukin (dispensed in capped polypropylene tuberculin syringes) has been demonstrated for up to three weeks when prepared in a controlled aseptic environment and stored under refrigeration at 2–8°C (https://www.ema.europa.eu/en/documents/product-information/ceplene-epar-product-information_en.pdf). Patients would be expected to collect the prescription of HDC/IL-2 from the hospital once per treatment cycle and this visit

would be anticipated to coincide with the modelled haematologist visit in each treatment cycle.

Under normal circumstances, no accessories are required for the self-administration of HDC/IL-2 as both the HDC and IL-2 components are supplied in or with sterile syringes. HDC can be injected subcutaneously over a period of 5 minutes by injecting one tenth of a millilitre every minute (as it was administered in the Brune *et al.* (2006) RCT). No specific timings are recommended in the summary of product characteristics or patient information leaflets for the subcutaneous injection of IL-2 (https://mhraproducts4853.blob.core.windows.net/docs/6468b5444e3707c9f311e3012f472274fdc5a741) but general guidance suggests that subcutaneous injections can typically be administered over the course of approximately 10 seconds (e.g. https://www.gatesheadhealth.nhs.uk/resources/giving-subcutaneous-injections/ recommends "counting to 10 slowly")

(b) The submitted model implicitly captured wastage in the first cycle of HDC/IL-2 treatment in patients discontinuing due to adverse events, as the full pack costs were always incurred in all patients regardless of whether the patient discontinues treatment over the course of the cycle. Additional functionality has been incorporated to the revised model to capture the full cost of treatment in each treatment cycle based on the number of patients remaining on treatment at the end of the previous model cycle, equivalent to capturing the cost intra-cycle wastage arising from treatment discontinuation. In isolation, this change increased the deterministic base case ICER from £25,810 per QALY to £25,968 per QALY.

(c) The selection of the HRG code SB12Z "Deliver Simple Parenteral Chemotherapy at First Attendance" was deliberately chosen to reflect the possibility of providing training to patients during administration of their first dose. As reported in Annex B "Guidance on currencies" of the 2025/26 NHS Payment Scheme, HRG code SB12Z covers "Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle" (https://www.england.nhs.uk/long-read/25-26-nhsps-annex-b-guidance-on-currencies/). Given that the injection of HDC can be conducted over 5 minutes 1–3 minutes after the injection of IL-2, the

healthcare professional time covered by SB12Z at the first attendance should be sufficient to cover patient training.

B18. CS, page 84. The CS states that *"Cycles 1 to 3 comprised 3 weeks of treatment and 3 weeks off treatment, with the off-treatment periods extended to 6 weeks for cycles 4 to 10."* However, in the model, 'Clinical' worksheet, cells D55:E56 show that cycle 3 starts on week12 whilst cycle 4 starts on week 21, which suggests the off-treatment period of 6 weeks starts from cycle 3. Please clarify this discrepancy or update the model accordingly.

The treatment cycle initiation input for cycle 4 has been amended to reflect initiation of cycle 4 in week 18 rather than week 21. In isolation, this change increased the deterministic base case ICER from £25,810 per QALY to £25,913 per QALY.

B19. CS, Section 3.5, Table 20 (pages 85-86) and model, 'Costs' worksheet, cells G22:J29. In relation to the disease management unit costs included in the model, please justify:

(a) the clinical validity of the frequencies of the disease management clinical visits and tests (not reported in the CS). Advice received from the EAG's clinical experts suggests that the frequencies may be too high for both treatment groups from the third cycle of therapy onwards.

(b) using the unit cost for service code 999 ('unknown') for the costs of chemistry and liver panel and of complete blood count/lab test, instead of code 303 ('Clinical Haematology Service') which would be in line with the code chosen for the other disease management resources.

(a) The frequency of clinical visits and tests for disease management were informed by the frequencies reported in the single technology appraisal of oral azacitidine (TA827), in which it was reported that "Patients frequently visit their

haematologist and cancer clinic, often more than once per month, and may be hospitalised multiple times for treatment administration, AEs, and management of symptoms and complications of the disease" based on Bosshard *et al.* (2016) and Zeidan *et al.* (2016). The TA827 CS also noted that the resource use assumptions have been guided by UK clinical expert opinion, although we would welcome the EAG's input on this aspect of the model parameterisation.

(b) The choice of service code 999 for the cost of chemistry and liver panel was driven by the volume of tests performed under the respective service codes. IN 2023-24, there were 302,641,036 Clinical biochemistry (PATH04) tests recorded under service code 999, compared with just 106 recorded under code 303. Similarly, there were 54,740,666 Haematology (PATH05) tests recorded under code 999 compared with just 569,805 tests recoded under code 303.

These volume differences were reversed for other disease management resources, which led to the use of the specific service codes elsewhere. For instance, for consultant-led "Non-Admitted Face-to-Face Attendance, Follow-up" (WF01A), there were 814,914 attendances under service code 303 in 2023-24 versus just 18,533 under service code 999.

B20. PRIORITY. CS, Section 3.2, page 65. The CS states that *"In the absence of data on subsequent treatments after from the Brune et al. RCT and Nilsson et al. follow-up period, the only downstream treatment option captured in the model was post-progression best supportive care."* The EAG believes that patients with AML would receive other regimens currently available in the NHS after they relapse (e.g., salvage chemotherapy and allo-SCT), and not only BSC. Please reconsider the approach used in the model to include subsequent therapies currently used in the NHS for patients after progression, using external data if possible (e.g., data from QUAZAR or other external RWE data). If this is not possible, please justify.

Regarding subsequent post-relapse treatments, we would firstly reiterate that patients who have received an allogeneic SCT are explicitly contraindicated in the

marketing authorisation for HDC/IL-2 and patients are therefore ineligible for allogeneic SCT at baseline. While data on subsequent treatments were unavailable from the Brune *et al.* (2006) RCT, data on the use of subsequent allogeneic SCT were available from the QUAZAR study of oral azacitidine (despite oral azacitidine having the same allogeneic SCT ineligibility restriction in the marketing authorisation as HDC/IL-2). In QUAZAR, 6.3% of patients randomly assigned to oral azacitidine ultimately received allogeneic SCT, compared with 13.7% of patients randomly assigned to the "watch and wait plus BSC" arm. In the revised model, these proportions were conservatively applied only to the proportion of patients experiencing relapse and entering the progressed-disease partition (based simply on the per-cycle increase the size of the partition [or 0 after the partition reaches maximum size]). In isolation, this change reduced the deterministic base case ICER from £25,810 per QALY to £25,596 per QALY. Note that no adjustment was made for downstream survival, remission, or relapse in patients receiving allogeneic SCT versus those who did not receive allogeneic SCT on the grounds that no data were available on which to base such an adjustment.

B21. CS, Section 3.5, Tables 20 and 21, page 86. The unit costs for ciprofloxacin, drug included in the BSC post-progression regimen (detailed in Table 21), has a less expensive price per tablet in a different version available from the Commercial Medicines Unit's electronic market information tool ([eMIT], e.g., ciprofloxacin 500mg pack of 20) compared to the version reported in the CS. Please update the drug costs in the model using the least expensive version of this drug.

We have updated the ciprofloxacin price to reflect use of the 500 mg pack of 20 tablets at a pack price of £0.86, versus the previous 250 mg pack of 10 tablets at a pack price of £0.41. This reduced the per-cycle price of ciprofloxacin from £1.15 to £0.60 and, in isolation, this change reduced the deterministic base case ICER from £25,810 per QALY to £25,809 per QALY. Updated versions of the last section of Table 20 and the entirety of Table 21 from the CS are presented in Table 11 and Table 12, respectively.

Table 19 [Updated CS Table 20] Unit costs of disease management and best supportive care after progression

Best supportive care after progression (per cycle costs)		
Hydroxycarbamide	3.91	NICE TA827 and eMIT July 2025
Ciprofloxacin	0.60	
Posaconazole	114.75	
Fluconazole	1.95	
Tranexamic acid	2.72	

Table 20 [Updated CS Table 21] Derivation of per-cycle, post-progression best supportive care costs

	Dose, mg	Doses per cycle	mg per tablet	Pack size	Pack price (GBP)	Cost (GBP) per	
						Dose	Cycle
Hydroxycarbamide (dose is mg/kg)	40	7	500	100	8.90	0.56	3.91
Ciprofloxacin	500	14	500	20	0.86	0.04	0.60
Posaconazole	400	21	100	96	131.14	5.46	114.75
Fluconazole	200	21	200	7	0.65	0.09	1.95
Tranexamic acid	1,000	21	500	60	3.88	0.13	2.72

As of September 24, 2025 (i.e. after the CS had been submitted to NICE), the eMIT data were updated to cover the period July 1, 2024–June 30, 2025. The latest version available at the time the CS was submitted covered the period January 1, 2024–December 31, 2024. In the above table and the revised version of the model, we have continued to use the eMIT data used at the time of submission; however, for information we have also provided an updated version of Table 21 from the CS based on the values from eMIT covering the period July 1, 2024–June 30, 2025 (Table 13).

Table 21 [Updated CS Table 21 based on July 2024-June 2025 eMIT data] Derivation of per-cycle, post-progression best supportive care costs

	Dose, mg	Doses per cycle	mg per tablet	Pack size	Pack price (GBP)	Cost (GBP) per	
						Dose	Cycle
Hydroxycarbamide (dose is mg/kg)	40	7	500	100	8.55	0.54	3.76
Ciprofloxacin	500	14	500	20	0.87	0.04	0.61
Posaconazole	400	21	100	96	115.09	4.80	100.70
Fluconazole	200	21	200	7	0.62	0.09	1.86
Tranexamic acid	1,000	21	500	60	3.89	0.13	2.72

Model implementation

B22. Model, 'Calculations SoC' worksheet, cell BI8. The PF health state costs for BSC/SoC have been calculated incorrectly (£409.48 instead of £504.90). The error in the formula seems to be where it applies the frequency for the haematology visits to the unit costs of nurse visits, instead of the unit costs of haematology visits. Please correct the formula and update the model results accordingly

The equation in cell BI8 of the Calculations SoC worksheet has been amended to capture the cost haematology visits appropriately. In isolation, this change reduced the deterministic base case ICER from £25,810 per QALY to £24,977 per QALY.

B23. The EAG believes that the probabilistic sensitivity analysis (PSA) has been implemented incorrectly, as the version of the model submitted only samples the values of: OS and LFS estimates, utilities, AE incidence rates and treatment discontinuation rate. None of the resource use or cost parameters are sampled. Please update the PSA to include uncertainty around all uncertain model parameters, including costs.

The submitted version of the model included functionality to sample from all model parameters, with the inclusion of all user inputs (as distinct from parametric survival model parameters) in the sampling governed by the presence or absence of values in the SD column (column F) of the Parameters worksheet. We have reviewed this functionality and it appears to have been implemented correctly and was parameterised in line with the distributions and values described in Table 25 of the CS; however, the description above regarding the omission of uncertainty measures around resource use and costs in the submitted model is correct, with the omissions justified on the grounds of the scarcity of data on the variance around cost and resource use data.

To address this, in the revised version of the model, sampling of BSC medication costs has been implemented based on standard deviations presented in the eMIT

data. These are now sampled from gamma distributions during the PSA. The following variables have now also been included in the PSA based on assumed standard deviations of 10% of the mean: disease management costs (sampled from gamma distributions), proportion of patients utilising BSC resources (sampled from beta distributions), adverse event treatment costs (sampled from gamma distributions), and disease management resource use (covering the numbers of healthcare professional visits and laboratory tests, sampled from lognormal distributions).

B24. The EAG believes that the ICER for the PSA analysis has been calculated incorrectly, by using the mean of the ICERs of every PSA run, rather than the expectation of the mean costs and QALYs. Please update the model to resolve this error.

The ICER calculation in cell K8 of the “PSA Outputs” sheet has been amended to reflect the quotient of the mean incremental costs and QALYs rather than the average of the ICERs from every PSA run. The functionality to display a 95% credible interval around the PSA-derived ICER has been replaced with functionality to instead show the mean net monetary benefit (NMB) and 95% credible intervals around the NMB in cells O8 and O9.

B25. Model, ‘Calculations HDC’ and ‘Calculations SoC’ worksheets, column J. In the model, the formula in column J indicates that in each cycle, if LFS cumulative survival estimates are higher than OS cumulative survival estimates, then the OS estimates are pulled up (before the adjustment for age- and sex-matched general population risks of death is applied). Please justify this approach or amend the formula in column J accordingly.

The logic surrounding the LFS/OS curve adjustment has been revised in the amended model to pull the PFS curve down to meet the OS curve when the curves cross. This change in isolation had no effect on the base case analysis results.

B26. CS, Section 3.3, page 80, and model, 'Calculation HDC', column AC. The CS states that *"treatment discontinuation was modelled in line with two factors: 1) the proportion of patients remaining in the leukaemia-free partition (i.e. those free of relapse) and 2) the AE-related discontinuation rate observed in the overall Brune et al. RCT population."* and that *"the AE-related discontinuation events were assumed to be driven by treatment initiation, the discontinuation was captured in the first cycle of the model"*. However, in column AC, the proportion of patients who remain on treatment at the end of the cycle remains the same for 6 cycles, until the PFS cumulative survival estimate becomes lower than the proportion of patients who do not discontinue due to AEs. Please clarify the intended approach used to include treatment discontinuation in the model, confirm if this was an error and amend the model as necessary.

This was the intended approach to modelling treatment discontinuation, with AE-related discontinuations driving early discontinuations and relapse then driving subsequent discontinuations until the end of the treatment course; the approach was selected to present as conservative an analysis as possible by capturing the lowest HDC/IL-2 discontinuation rates (and therefore the highest treatment cost) commensurate with the data in the Brune *et al.* (2006) RCT, and to mitigate any risk of double-counting discontinuation in patients who experienced both relapse and an AE leading to discontinuation. In the revised model, we have implemented AE-related discontinuation of patients after the first cycle of treatment, *in addition* to discontinuing treatment in patients experiencing relapse, based on the per-cycle increase in the proportion of patients in the progressed disease state. In isolation, this change reduced the deterministic base case ICER from £25,810 per QALY to £24,658 per QALY.

B27. Model, ‘Calculations HDC’, columns AS, AU and AW. The HDC and IL-2 acquisition and administration costs are calculated based on column ‘AD’ (labelled as ‘Treatment required in cycle’), where the full per cycle cost is applied in the cycles where treatment is received to those patients who remain on treatment. However, in each monthly cycle patients may have different proportions of time spent receiving treatment (e.g., in the first cycle they will spend 3 of the 4.3 weeks on treatment, whilst in the second cycle they will receive treatment for approximately 2.6 of 4.3 weeks). Please review the approach to apply the drug costs in the model (in line with question B5) and update the model results accordingly.

We believe this approach is appropriate for capturing the total costs of HDC/IL-2 treatment. The values in the “Treatment required in cycle” column are Boolean values that cause the cost of the complete cycle of HDC/IL-2 treatment (including administration costs where necessary) to be incurred at the point of initiation of the treatment cycle. This is reflective of the clinical and economic reality as HDC/IL-2 covering the entire treatment cycle can be dispensed to the patient at the start of each treatment cycle. In the case where the actual duration of the treatment administration would “overflow” into a subsequent model cycle, the full cost of the treatment is correctly captured in the model cycle in which the treatment cycle is initiated; the model does not adjust costs downwards in any model cycle to adjust for the portion of the treatment administration period that occurs within cycle. The functionality can be verified to be functioning as intended in the base case analysis as the “Treatment required in cycle” results in costs being incurred in those patients still on treatment in 10 separate model cycles (Column AS of worksheet “Calculations HDC”), reflecting the 10 cycles of treatment.

B28. In line with clarification questions B13 and B14, please comment on how the utility values from Tremblay *et al.* (2008) used in the company’s base-case analysis relate to values for the UK population and to the NICE reference case (use of EQ-5D-3L).

We have included further information on how the Tremblay *et al.* (2018 rather than 2008 as above) utility values in the base case analysis align with the NICE Reference Case in the response to question B13.

B29. In addition to question B26, the EAG notes that the PFS cumulative survival estimate used in the column AC of the model 'Calculation HDC' worksheet is based on the blended PFS survival estimates (from discontinuers and non-discontinuers – column X), instead of the PFS survival estimates for non-discontinuers (column R). Please clarify if this was an error and amend the model as necessary, or justify the intended approach used.

The "Prop on treatment at end of cycle" (column AC of the Calculation HDC worksheet) has been updated in the revised model to capture the the PFS estimates for non-discontinuers rather than the blended PFS survival estimate. In isolation, this change increased the deterministic base case ICER from £25,810 per QALY to £26,004 per QALY.

Section C: Textual clarification and additional points

C1. CS, Section 3.6, page 88. The text in page 88 ends abruptly, without a conclusion from the company about if the economic analysis in the population in first complete remission, under 60 years of age, and with normal karyotype qualifies for a disease severity multiplier. Please clarify and indicate what is the position of the company regarding the severity modifier in this analysis.

The population in first complete remission, under 60 years of age, and with normal karyotype, may qualify for a disease severity modifier of 1.2 on the basis of an absolute shortfall of 14.08 QALYs (3.54 QALYs versus 17.62 QALYs in the general population) based on an exponential survival fit to the data from this subgroup from the Brune *et al.* (2006) RCT and using the adjusted, limited-dependent, variable

mixture model (ALDVMM) of 2014 HSE data from the York QALY Shortfall Calculator reference case. However, on the grounds that HDC/IL-2 already fell within a cost-effective range based on the survival assumptions in the base case analysis, the severity modifier was not applied in the base case analysis. We would, however, welcome the EAG's guidance on the appropriateness of applying the modifier. We would be open to its application in the case where the shortfall calculation is deemed to be sufficiently robust and if subsequent scenario analyses show a less favourable cost-effectiveness profile for HDC/IL-2.

C2. CS, Section 3.9, Table 25. The table with a summary of variables applied in the model does not include all the variables included in the model (e.g. it excludes the variables for drug administration, disease management, BSC, AEs and end-of-life costs). In addition, some of the distributions attributed in the table do not match with those specified in the model 'Parameters' worksheet (column J). Please provide a complete table with all the variables included in the model, their mean values and distribution used in the PSA.

A table showing all model parameters in the revised model (including, e.g. new adverse events and HSCT) is presented in Table 14.

Table 22 Base case model parameters

Parameter	Base case value	SD	Distribution
Model settings and baseline cohort characteristics			
Cost discount rate	3.50%	N/A	
Effect discount rate	3.50%	N/A	
Baseline age	44.2	N/A	
Proportion male	0.5	N/A	
Baseline weight	78.45	N/A	
Clinical			
AE discontinuations with HDC/IL-2	0.08	0.01	Beta
Treatment and acquisition costs			
HDC price	3,600.00	N/A	
IL-2 price	636	N/A	

Parameter	Base case value	SD	Distribution
IL-2 dose per kg/day (IUs)	32,800	N/A	
HDC/IL-2 administration	249.64	N/A	
SoC	0	N/A	
SoC administration	0	N/A	
Disease management: resource use			
Visits to haematologists, HDC/IL-2 (on tx)	1	0.1	Lognormal
Nurse visits, HDC/IL-2 (on tx)	2	0.2	Lognormal
Complete blood count/lab test, HDC/IL-2 (on tx)	4	0.4	Lognormal
Chemistry and liver panel, HDC/IL-2 (on tx)	1	0.1	Lognormal
RBC transfusion, HDC/IL-2 (on tx)	0	N/A	
Platelet transfusion, HDC/IL-2 (on tx)	0	N/A	
Bone marrow aspirate/biopsy, HDC/IL-2 (on tx)	0.18	N/A	
Additional procedure, HDC/IL-2 (on tx)	0	N/A	
Visits to haematologists, HDC/IL-2 (off tx)	1	0.1	Lognormal
Nurse visits, HDC/IL-2 (off tx)	1.5	0.15	Lognormal
Complete blood count/lab test, HDC/IL-2 (off tx)	1.3	0.13	Lognormal
Chemistry and liver panel, HDC/IL-2 (off tx)	1	0.1	Lognormal
RBC transfusion, HDC/IL-2 (off tx)	0.23	N/A	
Platelet transfusion, HDC/IL-2 (off tx)	0.22	N/A	
Bone marrow aspirate/biopsy, HDC/IL-2 (off tx)	0	N/A	
Additional procedure, HDC/IL-2 (off tx)	0	N/A	
Visits to haematologists, SoC	1	0.1	Lognormal
Nurse visits, SoC	1.5	0.15	Lognormal
Complete blood count/lab test, SoC	1.3	0.13	Lognormal
Chemistry and liver panel, SoC	1	0.1	Lognormal
RBC transfusion, SoC	0	N/A	
Platelet transfusion, SoC	0	N/A	
Bone marrow aspirate/biopsy, SoC	0.17	N/A	
Additional procedure, SoC	0	N/A	
Visits to haematologists, post-progression	2	N/A	
Nurse visits, post-progression	2	N/A	
Complete blood count/lab test, post-progression	8	N/A	
Chemistry and liver panel, post-progression	2	N/A	
RBC transfusion, post-progression	0.22	N/A	
Platelet transfusion, post-progression	0.22	N/A	
Bone marrow aspirate/biopsy, post-progression	0	N/A	
Additional procedure, post-progression	0	N/A	
Disease management: costs			
Haematologist visit, cost	204.32	20.43	Gamma

Parameter	Base case value	SD	Distribution
Nurse visit, cost	108.9	10.89	Gamma
Complete blood count/lab test, cost	2.98	0.3	Gamma
Chemistry and liver panel, cost	1.53	0.15	Gamma
RBC transfusion, cost	386.96	38.7	Gamma
Platelet transfusion, cost	386.96	38.7	Gamma
Bone marrow aspirate/biopsy, cost	775.46	77.55	Gamma
Additional procedure, cost	0	0	Gamma
BSC: resource use			
Hydroxycarbamide, %	0.15	0.02	Beta
Ciprofloxacin, %	0.3	0.03	Beta
Posaconazole, %	0.15	0.02	Beta
Fluconazole, %	0.15	0.02	Beta
Tranexamic acid, %	0.15	0.02	Beta
BSC: costs			
Hydroxycarbamide, dose (mg)	40	N/A	
Ciprofloxacin, dose (mg)	500	N/A	
Posaconazole, dose (mg)	400	N/A	
Fluconazole, dose (mg)	200	N/A	
Tranexamic acid, dose (mg)	1,000.00	N/A	
Hydroxycarbamide, doses per cycle	7	N/A	
Ciprofloxacin, doses per cycle	14	N/A	
Posaconazole, doses per cycle	21	N/A	
Fluconazole, doses per cycle	21	N/A	
Tranexamic acid, doses per cycle	21	N/A	
Hydroxycarbamide, mg per tablet	500	N/A	
Ciprofloxacin, mg per tablet	250	N/A	
Posaconazole, mg per tablet	100	N/A	
Fluconazole, mg per tablet	200	N/A	
Tranexamic acid, mg per tablet	500	N/A	
Hydroxycarbamide, pack size	100	N/A	
Ciprofloxacin, pack size	10	N/A	
Posaconazole, pack size	96	N/A	
Fluconazole, pack size	7	N/A	
Tranexamic acid, pack size	60	N/A	
Hydroxycarbamide, pack price	8.9	0.86	Gamma
Ciprofloxacin, pack price	0.41	0.36	Gamma
Posaconazole, pack price	131.14	174.14	Gamma
Fluconazole, pack price	0.65	0.48	Gamma
Tranexamic acid, pack price	3.88	0.46	Gamma

Parameter	Base case value	SD	Distribution
Allogeneic stem cell transplantation (SCT)			
Allogeneic SCT after progression, HDL/IL-2	0.060	N/A	
Allogeneic SCT after progression, SoC	0.137	N/A	
Allogeneic SCT, elective inpatient cost	21,658.18	N/A	
Adverse events: risks			
Fatigue, HDC/IL-2	1.30%	0.13%	Beta
Nausea, HDC/IL-2	1.30%	0.13%	Beta
Vomiting, HDC/IL-2	0.60%	0.06%	Beta
Diarrhoea, HDC/IL-2	1.90%	0.19%	Beta
Anaemia, HDC/IL-2	1.30%	0.13%	Beta
Thrombocytopenia, HDC/IL-2	17.30%	1.73%	Beta
Neutropenia, HDC/IL-2	5.70%	0.57%	Beta
Headache, HDC/IL-2	7.00%	0.70%	Beta
Fatigue, SoC	1.30%	0.13%	Beta
Nausea, SoC	0.00%	0.00%	Beta
Vomiting, SoC	0.00%	0.00%	Beta
Diarrhoea, SoC	0.00%	0.00%	Beta
Anaemia, SoC	0.60%	0.06%	Beta
Thrombocytopenia, SoC	9.40%	0.94%	Beta
Neutropenia, SoC	3.10%	0.31%	Beta
Headache, SoC	0.00%	0.00%	Beta
Adverse events: treated as outpatients			
Fatigue	0.95	N/A	
Nausea	1	N/A	
Vomiting	0.95	N/A	
Diarrhoea	0.95	N/A	
Anaemia	0.9	N/A	
Thrombocytopenia	0.9	N/A	
Neutropenia	1	N/A	
Headache	1	N/A	
Adverse events: costs			
Fatigue, inpatient cost	864.11	86.41	Gamma
Nausea, inpatient cost	864.11	86.41	Gamma
Vomiting, inpatient cost	515.48	51.55	Gamma
Diarrhoea, inpatient cost	515.48	51.55	Gamma
Anaemia, inpatient cost	490.98	49.1	Gamma
Thrombocytopenia, inpatient cost	621.68	62.17	Gamma
Neutropenia, inpatient cost	528.81	52.88	Gamma
Headache, inpatient cost	448.36	44.84	Gamma

Parameter	Base case value	SD	Distribution
Fatigue, outpatient cost	515.66	51.57	Gamma
Nausea, outpatient cost	515.66	51.57	Gamma
Vomiting, outpatient cost	379.59	37.96	Gamma
Diarrhoea, outpatient cost	379.59	37.96	Gamma
Anaemia, outpatient cost	367.81	36.78	Gamma
Thrombocytopenia, outpatient cost	361.56	36.16	Gamma
Neutropenia, outpatient cost	367.21	36.72	Gamma
Headache, outpatient cost	449.61	44.96	Gamma
Adverse events: duration (weeks)			
Fatigue duration (weeks)	1	N/A	
Nausea duration (weeks)	1	N/A	
Vomiting duration (weeks)	1	N/A	
Diarrhoea duration (weeks)	1	N/A	
Anaemia duration (weeks)	1	N/A	
Thrombocytopenia duration (weeks)	1	N/A	
Neutropenia duration (weeks)	1	N/A	
Headache duration (weeks)	1	N/A	
Mortality cost			
Cost of death	5,391	N/A	
Utilities			
Pre-progression utility, on treatment	0.81	0.08	Beta
Pre-progression utility, off treatment	0.83	0.08	Beta
Post-progression utility	0.53	0.05	Beta
Fatigue disutility	0.115	0.01	Beta
Nausea disutility	0.048	0	Beta
Vomiting disutility	0.048	0	Beta
Diarrhoea disutility	0.176	0.02	Beta
Anaemia disutility	0.119	0.01	Beta
Thrombocytopenia disutility	0.09	0.01	Beta
Neutropenia disutility	0.09	0.01	Beta
Headache disutility	0.34	0.03	Beta

References

Batty N, Yin Y, Wetzler M. Decitabine is more cost effective than cytarabine and daunorubicin in elderly acute myeloid leukemia patients. J Cancer Res Ther. 2014;2:68–73.

Bosshard R, O'Reilly K, Ralston S, Chadda S, Cork D. Systematic reviews of economic burden and health-related quality of life in patients with acute myeloid leukemia. Cancer Treat Rev. 2018;69:224-232.

Brune M, Castaigne S, Catalano J, Gehlsen K, Ho AD, Hofmann WK, Hogge DE, Nilsson B, Or R, Romero AI, Rowe JM, Simonsson B, Spearing R, Stadtmauer EA, Szer J, Wallhult E, Hellstrand K. Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. Blood. 2006;108(1):88-96.

Buyse M, Squifflet P, Lucchesi KJ, Brune ML, Castaigne S, Rowe JM. Assessment of the consistency and robustness of results from a multicenter trial of remission maintenance therapy for acute myeloid leukemia. Trials. 2011 Mar 23;12:86.

Gidwani R, Khan ZM, Fenaux P, Beach CL, Pashos CL. A cost-effectiveness analysis of using azacitidine vs. decitabine in treating patients with myelodysplastic syndromes. J Med Econ. 2012;15:145–154.

Goss TF, Szende A, Schaefer C, Totten PJ, Knight R, et al. Cost effectiveness of lenalidomide in the treatment of transfusion-dependent myelodysplastic syndromes in the United States. Cancer Control. 2005;13 Suppl:17–25.

Grimwade D, Walker H, Oliver F et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children’s Leukaemia Working Parties. Blood. 1998;92(7):2322–2333.

Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.

Joshi N, Hensen M, Patel S, Xu W, Lasch K, Stolk E. Health State Utilities for Acute Myeloid Leukaemia: A Time Trade-off Study. Pharmacoeconomics. 2019;37(1):85-92.

Juliusson G, Jadersten M, Deneberg S et al. The prognostic impact of FLT3-ITD and NPM1 mutation in adult AML is age-dependent in the population-based setting. Blood Advances. 2020;4(6):1094-1101.

Leunis A, Redekop WK, Uyl-de Groot CA, Lowenberg B. Impaired healthrelated quality of life in acute myeloid leukemia survivors: a single-center study. Eur J Haematol. 2014;93:198–206.

Liu H, Stanworth SJ, McPhail S, Bishton M, Rous B, Bacon A, Coats T. Impact of patient demographics on treatment outcomes in AML: a population-based registry in England, 2013-2020. Blood Adv. 2024;8(17):4593-4605.

McKenzie L, van der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D instrument: the potential to estimate QALYs without generic preference data. Value Health. 2009;12(1):167–71.

Nilsson MS, Hallner A, Brune M et al. Immunotherapy with HDC/IL-2 may be clinically efficacious in acute myeloid leukemia of normal karyotype. Hum Vaccines Immunother 2020;16:109–111.

Pan F, Peng S, Fleurence R, Linnehan JE, Knopf K, Kim E. Economic analysis of decitabine versus best supportive care in the treatment of intermediate- and high-risk myelodysplastic syndromes from a US payer perspective. Clin Ther. 2010;32:2444–56.

Potter N, Jovanovic J, Ivey A et al. Molecular monitoring versus standard clinical care in younger adults with acute myeloid leukaemia: results from the UK NCRI AML17 and AML19 randomised, controlled, phase 3 trials. Lancet Haematol 2025; 12: e346–56.

Russell-Smith TA, Brockbank J, Mamolo C, Knight C. Cost Effectiveness of Gemtuzumab Ozogamicin in the First-Line Treatment of Acute Myeloid Leukaemia in the UK. Pharmacoecon Open. 2021;5(4):677-691.

Schlenk RF, Döhner K, Krauter J, Fröhling S, Corbacioglu A, Bullinger L, Habdank M, Späth D, Morgan M, Benner A, Schlegelberger B, Heil G, Ganser A, Döhner H; German-Austrian Acute Myeloid Leukemia Study Group. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med. 2008 May 1;358(18):1909-18.

Stein EM, Yang M, Guerin A, Gao W, Galebach P, Xiang CQ, Bhattacharyya S, Bonifacio G, Joseph GJ. Assessing utility values for treatment-related health states of acute myeloid leukemia in the United States. Health Qual Life Outcomes. 2018;16(1):193.

Tremblay G, Dolph M, Patel S, Brandt P, Forsythe A. Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom. Cost Eff Resour Alloc. 2018;16:33.

Wallhult E, Whisnant J, Rowe JM, Szer J, Bhagwat D, Hellstrand K, Nilsson BI, Brune ML. Impact on Quality of Life of Postconsolidation Immunotherapy with Histamine Dihydrochloride and Interleukin-2 in Acute Myelogenous Leukemia. Blood. 2007;110(11):4381.

Witlox W, Grimm S, Howick J, Armstrong N, Ahmadu C, McDermott K, Otten T, Noake C, Wolff R, Joore M. Oral Azacitidine for Maintenance Treatment of Acute Myeloid Leukaemia After Induction Therapy: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics. 2023;41(8):857-867.

Zeidan AM, Mahmoud D, Kucmin-Bemelmans IT, Alleman CJ, Hensen M, Skikne B, Smith BD. Economic burden associated with acute myeloid leukemia treatment. Expert Rev Hematol. 2016;9(1):79-89.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Additional clarification questions (v2)

October 2025

File name	Version	Contains confidential information	Date
ID1627 clarification questions from EAG 3	Final	Yes	30/10/2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Questions from the EAG sent on 20th October 2025

Clarification question A23. The summary document outlining the discussion from the advisory board meeting is currently difficult to follow. For improved clarity and readability, please identify each speaker using distinct labels (e.g., Presenter 1–3, Clinician 1–7, Brancaster 1–3). These identifiers should be assigned in order of first appearance, rather than corresponding directly to the participant list at the beginning of the document, in order to maintain confidentiality.

Clarification question A27. The company has stated that it has not been possible to obtain the details of the HRQoL data collected in the Brune *et al.* study. However, the Clinical Study Report (CSR), document provided to the EAG in response to clarification question A16, refers to these data being presented in Appendix 16. As this appendix is not included in the submitted file, could you please clarify whether it is available and, if so, provide it?

The company acknowledges that in section 9.5.1.3.5 of the Clinical Study Report (CSR) on page 71 of 1042 entitled 'Quality of life' it states, *'Quality of life was assessed using the EORTC QLQ-C30 Version 2.0 instrument, as shown in Appendix 6 of the clinical study protocol (Appendix 16.1.1 of this report)* and then goes on to decare *'QLQ-C30 quality of life responses are available for 288 patients, 249 of whom filled in a baseline questionnaire.'*.

For the avoidance of doubt, Appendix 16.1.1 of the CSR describes only the study protocol and protocol amendments; and within that, Appendix 6 presents a copy of the EORTC QLQ-C30 Version 2.0 questionnaire.

Appendix 16.1.2 of the CSR contains a blank sample Case Report Form (unique pages only) that makes reference to storing completed QoL questionnaires within the CRF binder for the visit concerned.

Appendix 16.3.1 of the CSR that covers the CRFs themselves merely states "*CRFs will be forwarded upon request.*".

Therefore, unfortunately, there are no HRQoL data presented in Appendix 16 or any other part of the CSR. [redacted]

The company confirms that having contacted one of the co-authors of the Brune et al 2006 publication in order to try and obtain the HRQoL data collected during the study that it has not been possible to attain these details.

Clarification questions B7, B8 and B9. The company's response to questions B7(f), B8(f) and B9(f) state that the parameters for the independently-fitted parametric OS and LFS models were incorporated into the revised health economic model for the following groups: (i) in CR1, <60 years of age, with normal karyotype

and ineligible for allo-SCT; (ii) in CR1, <60 years of age, ineligible for allo-SCT; and (iii) in CR1 and ineligible for allo-SCT, respectively. However, the updated version of the model submitted as part of the clarification response does not seem to include any additional functionality to allow the use of the results of the independently-fitted parametric OS and LFS models for any of these groups, instead of the jointly-fitted OS and LFS models for group (i). In addition, the new parameters are not sampled, so they couldn't be varied in the PSA. Please clarify how the parameters were incorporated into the model, and please include the additional functionality to allow the use of the parameters for the independently-fitted parametric OS and LFS models in the model.

The revised version of the model now includes drop-down menus on the Clinical worksheet to select: 1) whether the “LFS and OS model type” is Joint or Independent, and 2) which data source should be used for the independent modelling, with options corresponding to the subgroup analyses requested in clarification questions B7, and B8, and B9. The standard errors, confidence intervals and Cholesky decomposition matrices for the independent model parameters are included in the “OS and LFS Ind. Parameters” worksheet, and wired into the parametric models (when PSA is active) on the “OS and LFS Models” worksheet.

Additional questions from the EAG sent on 23rd October 2025

Clarification questions B6 and B11. Please clarify if the LFS and OS IPD used to fit the parametric survival models include the 8.3% of patients receiving HDC/IL-2 who have discontinued due to AEs not related to relapse. If not, please clarify which patients were included in the data used to estimate LFS and OS model parameters for patients in the HDC/IL-2 and SoC treatment groups used in the model.

Yes the LFS and OS IPD included the 8.3% of patients in the HDC/IL-2 arm who ultimately discontinued due to AEs not related to relapse.

Clarification questions A28 and B1. Please clarify:

(a) The full source details of the quotes from the NHS provided as part of the response to question A28(a).

(b) Please justify the decision to use ITT-based HRs from the ITC rather than the ITC comparing the Brune et al. (2006) subgroup (normal karyotype, CR1, <60 years) with the QUAZAR AML-001 ITT population.

(c) The EAG notes that OS HR for oral azacitidine (0.72, CI:0.58–0.89) reported in clarification response Table 12 (clarification response v2.0) seems to correspond to the unstratified HR for OS using the QUAZAR data cut-off point of 15 July 2019, as shown in the Figure in page 67 of the clarification response and Figure 3.2 in EAG report in TA827. Please confirm the source of the data used for oral azacitidine in the Bucher ITCs of OS and LFS, and consider performing the Bucher ITC for OS of oral azacitidine versus HDC/IL-2 using the stratified HR for oral azacitidine versus SoC (0.69 [0.55–0.86]), or justify the use of the unstratified HR instead of the stratified HR.

- The quotes provided as part of the response to question A28(a) were taken directly from the Budget Impact Assessment document, which was sent to us by Nicola Cunliffe, Project Manager for Commercial Liaison at NICE, on 15th October 2025. More specifically the quotes were copied from the notes under section 2 entitled ‘Comparator treatment(s)’ and from the notes under section 3 entitled ‘‘Uptake/Market Share’ within the NHSE BI submission tab of the document.

- ITCs including both the ITT populations from Brune et al. (2006) and QUAZAR AML-001 and also the ITT population from QUAZAR AML-001 and the normal karyotype, CR1, <60 years population from Brune et al. (2006) were presented in the response to question A28. In the absence of adjustments for imbalances in patient characteristics when using the Bucher et al. approach, the ITT-based HR was then used as the basis of the economic analyses on the grounds that the ITT patient populations were more comparable than the QUAZAR AML-001 ITT population and the normal karyotype, CR1, <60 years subgroup from the Brune et al. (2006) RCT. It was considered that the assumption of transitivity would be less likely to be violated in the ITT populations than in the comparison of the QUAZAR AML-001 ITT with the Brune et al.(2006) normal karyotype, CR1, <60 years

subgroup. The resulting ITT analysis also provides an extremely conservative estimate of the HR for HDC/IL-2 versus oral azacitidine, which we considered desirable given the greater uncertainties arising from using the Bucher et al. approach rather than a matching-adjusted indirect comparison or simulated treatment comparison.

- We can confirm that the source of the data for the oral azacitidine OS HR in the ITC was the QUAZAR AML-001 Kaplan-Meier plot (and specifically the tabular overlay within the plot) presented in TA827 and reproduced in the initial clarification response. No HRs were presented in the original Wei et al. (2020) publication of the trial because the proportional hazards assumption was found to have been violated. The choice of the unstratified HR in the present ITC was driven only by the relatively small populaion in the QUAZAR AML-001; however, we appreciate that the stratified HR may be a more appropriate approach given the violation of proportional hazards and have run analyses in both the ITT/ITT population and the ITT/subgroup population (Table 1).

Table 1 Naïve indirect comparisons of overall survival with oral azacitidine versus HDC/IL-2 based on the QUAZAR AML-001 and Brune et al. (2006) randomised controlled trials

	HR	Lower 95% CI	Upper 95% CI	p
ITT populations				
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUAZAR AML-001 ITT population; Brune *et al.* (2006) normal karyotype, CR1 and <60 years				
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clarification question B1 and model, worksheet 'Clinical' cell F13. The proportion of patients receiving oral azacitidine who discontinue due to adverse events of 13.0% is referred being based on Wei *et al.* (2023). Please clarify the exact location of that data, or the calculations used to estimate this value.

The oral azacitidine discontinuation rate of 13% is mentioned in the text of the Wei *et al.* manuscript but Wei *et al.* 2020 rather than 2023 (http://dx.doi.org/10.1056/NEJMoa2004444), specifically the following:

"Adverse events led to discontinuation of the trial regimen in 13% of the patients in the CC-486 group and 4% of the patients in the placebo group (Table S8)."

This value was also reported in the NICE single technology appraisal of oral azacitidine on page 93 of the committee papers (https://www.nice.org.uk/guidance/ta827/evidence/appraisal-consultation-committee-papers-pdf-11246852557):

"Discontinuation of study treatment because of AEs was reported for 13% of patients in the oral azacitidine group and 4% of patients in the placebo group."

Clarification question B14 and model, 'Calculations HDC', 'Calculations SoC' and 'Calculations Oral Aza' worksheets, cell AS14. The updated version of the model seems to have removed the formula in cell AS14 of each worksheet, which calculated the total QALY loss related to AEs. The value in this cell feeds directly into the total QALY calculations for each treatment group in column AP. Please clarify whether this removal was intentional and, if so, provide the rationale for this change.

The formula in cells AS14 of the 'Calculations HDC', 'Calculations SoC' and 'Calculations Oral Aza' has been reinstated in the revised version of the model.

Clarification question A17(b) and model. The model uses a proportion of males of 50%, based on the estimate for the target population from Brune *et al.*, as reported in the CS page 64: *"Across both arms in the Brune et al. RCT target population, 50% were male and 50% were female (54% [20/37] male in the standard of care arm and 46% [16/35] male in the histamine dihydrochloride and low-dose interleukin-2 arm)."* However, the table with baseline characteristics provided by the company in response to question A17(b) suggests a higher proportion of males (approximately 56%). Please clarify this discrepancy.

The individual patient-level data (IPD) reports 16 males in the HDC/IL-2 arm and 19 females (total N=35); similarly, the IPD reports 20 males in the standard of care arm and 17 females (total N=37).

Clarification questions B7 and model. In addition to the question previously sent to the company on 20th October 2025, the EAG notes that some of the LFS and OS independently fitted survival models included in the model ('OS and LFS Models' worksheet, cells AN48:BT769) do not match the curves presented in the figures presented in pages 89 and 90 of the clarification response (v2.0). Please clarify and correct the formulas in the model.

We have resolved an issue with the implementation of the independently-fitted generalised gamma models in the revised model, in which one of the parameters had not been exponentiated. We have also provided overlays of the model outputs atop the figures from pages 89 and 90 of the clarification reponse (in columns DD onwards in the "OS and LFS Models" worksheet) to ease the cross-validation. Please note that the outputs from the generalised gamma models do not perfectly match the outputs from R, but these differences arise from the exponentiation of a large term in the Excel formula that causes differences in the handling of floating point numbers between Excel and R to manifest.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Wednesday 17 December 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating acute myeloid leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Andrew King
2. Name of organisation	Cambridge University Hospitals NHS Foundation Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with acute myeloid leukaemia? ☒ A specialist in the clinical evidence base for acute myeloid leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links or funding to declare.
8. What is the main aim of treatment for acute myeloid leukaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aim of treatment for people with acute myeloid leukaemia (AML) is to achieve a remission, and ultimately a cure i.e. the patient remains free from relapse.

	In people where a cure is unlikely (for example people receiving low intensity treatment), the aim is to maintain as long a remission as possible with preservation of quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant treatment response is one that demonstrates a statistically significant improvement in overall survival when compared to placebo in a phase 3 randomised control trial. Improvements in event free survival (EFS, typically used for induction treatments) or leukaemia/relapse free survival (LFS or RFS, typically used for maintenance treatments) that are statistically significant are also regarded as important. Typically, these would translate into an improvement in survival by 6-12 months, and an improvement in LFS by around 10-20%.
10. In your view, is there an unmet need for people and healthcare professionals in acute myeloid leukaemia?	Yes – there is a clear unmet need for people with AML. Despite significant advances, many people relapse, and the treatments used (intensive chemotherapy and allogeneic stem cell transplantation) are toxic and carry significant side effects.
11. How is acute myeloid leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are no current national guidelines which cover the entirety of management for AML in the NHS. Clinicians normally use local guidelines, the European LeukaemiaNet 2022 guidelines, relevant NICE guidelines, and British Society for Haematology guidelines. Treatment for AML divides into intensive chemotherapy and non-intensive chemotherapy as below depending upon the patient's age and fitness. Therapy is further refined according to the sub-type of AML (defined by genetic mutations and/or chromosomal abnormalities), whether people have received cytotoxic chemotherapy/radiotherapy, or have a preceding haematological disorder (for example myelodysplasia). The pathways are relatively well defined (explained below). However, there is centre to centre variation in terms of use of some agents depending upon

	interpretation of the evidence, and some variation in people receiving an allogeneic stem cell transplant in first complete remission (CR1). **Fit people** **Induction** People with a good performance status and few co-morbidities may receive intensive chemotherapy. There is not a hard age cut off, although many centres use 70-75 as an age threshold. The treatment pathway in the UK is based upon that developed in the UK MRC AML trials. This begins with induction (for example with Daunorubicin/Cytarabine), followed typically by a second induction (Daunorubicin/Cytarabine with lower doses). Additional agents may be added in including gemtuzumab ozogamicin or FLT3 inhibitors (midostaurin or quizartinib). For people with secondary AML, CPX351 may be used. Alternative combinations of chemotherapy (e.g. FLAG-IDA) may be used in for induction in some sub-types. **Consolidation** Consolidation normally comprises further chemotherapy (two cycles of high dose cytarabine) or an allogeneic hematopoietic stem cell transplant (HSCT). An HSCT is the most effective anti-leukaemia treatment available but carries significant upfront toxicity and is therefore reserved where there is a moderate to high risk of relapse (typically 40% or greater). **Maintenance treatments** People with a *FLT3* mutation (25-30% of patients with AML) are treated with FLT3 inhibitors and these continue as maintenance (midostaurin for 12 months; quizartinib for 36 months). Oral azacitidine is approved and used as maintenance for people not receiving an HSCT and is mutation agnostic. This

	can be continued indefinitely. These decrease the risk of relapse, although the exact benefit of FLT3 inhibitors as maintenance treatment is uncertain. People receiving an HSCT who have a *FLT3-ITD* mutation may receive sorafenib or quizartinib maintenance depending upon prior therapy. **Observation after treatment** People are normally monitored after treatment (and during maintenance) for signs of relapse (change in blood counts or symptoms). People may undergo surveillance bone marrow biopsies, particularly those people who have a measurable residual disease (MRD) marker such as an *NPM1* mutation. **Unfit or elderly people** People who are felt to be unfit for intensive chemotherapy normally receive venetoclax/azacitidine or venetoclax/cytarabine. If they have a particular mutation in *IDH1* they are eligible to receive ivosidenib/azacitidine. Some people may receive supportive care alone (transfusions, antibiotics and palliative care input). Chemotherapy treatments normally continue until progression, and there is consequently no "maintenance" treatment. The proposed technology (histamine dihydrochloride and interleukin-2) could be used as maintenance treatment in those people who either do not receive maintenance treatment or as an alternative to oral azacitidine after completing induction and consolidation. It would not be suitable for people who have undergone an HSCT.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Current care is either observation, oral azacitidine or oral FLT3 inhibitors. The proposed technology will utilise greater resource for the following reasons:

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The first dose requires observation in a healthcare facility (according to the Phase III trial), likely a chemotherapy day unit. It is a subcutaneous injection and the person, or their carers, will have to be educated on how to administer this; alternatively a chemotherapy trained nurse would have to administer. Given the treatment is twice a day for three weeks, this would entail logistical challenges. There is minimal or no experience with this treatment in the United Kingdom and there would be a requirement for training of UK haematologists, nursing staff and pharmacy teams. There would be a requirement for greater follow-up than observation to facilitate prescription and monitoring of side effects.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	If the treatment improves LFS by approximately 10-15% at 24-36 months, I would consider this a clinically meaningful result. This may translate into increased length of life when compared to the current standard of care, noting that the phase 3 trial was underpowered to demonstrate an overall survival benefit. Relapsed AML requires further induction and an HSCT to cure it, and this carries significant toxicity and potential morbidity/mortality. If an HSCT can be avoided, this would improve quality of life for people in the longer-term, noting the likely decrement in quality of life associated with treatment administration (four s/c injections a day for three weeks at a time plus associated side effects).

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The pivotal phase 3 trial only included people with a normal karyotype, people not proceeding to HSCT, and those people who had completed induction and consolidation. It also only showed a benefit in people in first remission (CR1). Post hoc analysis of the trial has shown a benefit only in people under the age of 60. Further genetic classification was not available, so it is unclear whether particular sub-groups benefit. In the phase IV Re:Mission trial which looked at people receiving this treatment, all people with *FLT3-ITD* mutations relapsed (4/4). It is possible people with a *FLT3-ITD* are therefore less likely to benefit. Registry data has suggested a possible benefit in people with an *NPM1* mutation, which is biologically plausible given this creates a neoantigen which may respond to immunotherapy. The numbers included are small and this remains somewhat speculative.
15. Will the technology be easier or more difficult to use for people or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology will be more difficult than current care due to the need for: Regular sub-cutaneous injections (storage of medicine by people, disposal of sharps and the process of injections) Need for monitoring in clinic more frequently than observation alone. This would have to be at least every treatment cycle (which is administered every 6 weeks initially – three weeks on and three weeks off, with the interval increasing to 6 weeks off from cycle 4).
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	People with a detectable measurable residual disease (MRD) marker are normally monitored every three months by bone marrow biopsies. If MRD was rising through maintenance treatment, it would be stopped. Treatment was fixed in the trial at 18 months.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I would regard this technology as providing an incremental benefit rather than a "step-change". It would offer fixed duration maintenance treatment to people and is a different option to oral azacitidine which is continued indefinitely until progression. Oral azacitidine also has side effects including cytopenias. The technology has also been used in a clinical trial in younger people in contrast to oral azacitidine (where the patient population was 55 years and older). It works via a different mechanism to standard cytotoxic therapy (it is an immunotherapy). It may therefore provide an unmet need in selected groups of patients.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects include: injection site reactions, fever, fatigue, myalgia, headaches, flushing, hypotension and GI side effects (including diarrhoea, nausea, and indigestion). About 25% of participants in the phase 3 trial required a dose reduction and 8% discontinued treatment. The trial reported minimal differences in quality-of-life assessments between beginning treatment and cessation. Comparisons of pre- vs. post-treatment QoL assessments showed transient increases in fatigue, nausea/vomiting and appetite loss in the treatment arm. By its nature, maintenance treatment requires treatment of people who may not benefit (i.e. they may already be cured).
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The phase 3 trial was published in 2006. Since this publication there have been significant advances in the understanding and treatment of acute myeloid leukaemia including: - Refinement of genetic sub-classifications and what constitutes favourable, intermediate and adverse risk leukaemia. Typically, people are now tested for 50-60 gene mutations via targeted gene panels as standard of care. - Understanding of measurable residual disease (MRD) and how this impacts upon prognosis

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	- A greater understanding of which people benefit from consolidative CR1 allogeneic stem cell transplantation - Refinement in allogenic stem cell transplantation including more effective graft vs host disease prophylaxis/treatment, infection prophylaxis/treatment and conditioning treatments. This has decreased the treatment related mortality and allows access to a greater donor pool (haploidentical donors, cord blood donors and mismatched unrelated donors). - Development of FLT3 inhibitors, gemtuzumab, IDH1 inhibitors, venetoclax and hypomethylating agents. - Approval of oral azacitidine as a maintenance treatment for people with AML not proceeding to allogeneic stem cell transplantation. It is therefore challenging to extrapolate these results to UK clinical practice in 2026. I suspect given the margin of the effect, there is likely to be a benefit in terms of LFS in the modern era for some patient groups. It would be important to collect real-world data on outcomes in the UK to confirm this should the technology be approved. The most important outcomes are overall survival, leukaemia free survival (or relapse free survival) and quality of life outcomes. These were all measured in the Phase 3 trial, which I would regard as of good quality for the era in which it was conducted. LFS or RFS is a reasonable surrogate for overall survival. I am not aware of any additional adverse events, and the treatment has been used in some European countries since 2008.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal guidance [TA827, oral azacitidine]?	A paper has examined the benefit of oral azacitidine in *NPM1* and *FLT3* mutated AML (link) shortly after the NICE appraisal and patients with detectable MRD. There are real-world studies including from the UK (presented at the American Society of Haematology in 2024) and Canada.

23. How do data on real-world experience compare with the trial data?	Registry data from 2024 has demonstrated a potential benefit in *NPM1* mutated AML, although the numbers included were small. This provides a possible sub-group of AML people who may particularly benefit from this treatment. There are no other clear real world data aside from the phase IV Re:Mission trial which contains 84 patients and when combined with the phase 3 trial, shows a benefit for normal karyotype AML in patients under the age of 60.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	People from ethnic minorities are under-represented on donor registries and this means they are less likely to receive an allogeneic stem cell transplant. Maintenance treatments which decrease the risk of leukaemia relapse are particularly important for these patients. The treatment may be more difficult for patients with disabilities to administer given it is a subcutaneous treatment.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

AML remains an unmet need with a significant risk of relapse for people undergoing treatment.

Maintenance treatments offer the opportunity to decrease the risk of relapse and are currently limited to FLT3 inhibitors (for people with a *FLT3* mutation) and oral azacitidine.

The evidence for oral azacitidine maintenance is derived from older people (55 years or above) and the evidence base in younger patients is limited; treatment is also continued indefinitely until progression.

Histamine dihydrochloride with interleukin-2 offers a fixed duration maintenance option for people not proceeding to allogeneic stem cell transplant in first remission with a demonstrated improvement in leukaemia free survival in an historical phase 3 trial.

The people most likely to benefit appear to be those under 60 with a normal karyotype AML based upon post hoc analysis; there is a small data set which suggests people with an *NPM1* mutation may particularly benefit although this remains uncertain.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Wednesday 17 December 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating acute myeloid leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Steven Knapper
2. Name of organisation	Cardiff University, Cardiff & Vale University Health Board (NHS), UK Acute Myeloid Leukaemia Research Network (UK AML RN)
3. Job title or position	Professor in Haematology, Honorary Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with acute myeloid leukaemia? ☒ A specialist in the clinical evidence base for acute myeloid leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have no links, past or present, with the tobacco industry
8. What is the main aim of treatment for acute myeloid leukaemia?	The principal aims of treatment are different in different patients.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	For younger, fitter patients, principally those who are considered suitable for an intensive treatment approach, the goals are to initially achieve disease remission and then to provide consolidation treatment (further chemotherapy or transplant) that minimises the risk of relapse and ultimately leads to cure. For the substantial number of patients who are not deemed suitable for that approach, the goals are to control the disease while maximising quality of life. The margins between these two groups have become somewhat less defined in recent years with the advent and approval of venetoclax-based low intensity schedules which are capable of achieving deeper responses than with traditional non-intensive therapy. The technology being appraised here is a maintenance therapy which is an adjunct to the intensive approach outlined above. The goal of this therapy is to extend disease remission / prevent relapse / increase rates of ultimate cure in those patients in 'group 1' above who are not deemed to be suitable for allogeneic stem cell transplant – either due to fitness or disease biology.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improved treatment response – in the context of the technology being appraised – would be considered in terms of reduced cumulative incidence of relapse (CIR), increased event free/relapse free survival (EFS/LFS/RFS) and increase in overall survival (OS). Giving precise % values for improvements in these parameters is always somewhat arbitrary, if clinical data are statistically significantly in favour, but I would generally consider a 10% improvement in any of these parameters to be clinically significant.
10. In your view, is there an unmet need for patients and healthcare professionals in acute myeloid leukaemia?	There are clearly huge unmet treatment needs for patients with AML. Across the whole spectrum of AML patients, long term survival remains <25-30% and, even in those able to receive intensive therapy (focus of this appraisal), long term survival still remains around (or slightly below) 50%. This despite major advances in supportive care, in the deployment of transplant and following the

	regulatory approval of several new drugs in recent years – those approved in the context of intensive treatment include: gemtuzumab ozogamicin (GO, Mylotarg), midostaurin, CPX-351 (Vyxeos), quizartinib and oral azacitidine. There is continuing need for well-tolerated therapies which can complement existing treatment pathways and improve longer term outcomes.
11. How is acute myeloid leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	As discussed in Q8. Patients are treated either intensively or non-intensively – the former group being the subject of this appraisal. Intensive chemotherapy is usually given over 3-4 cycles, over 4-6 months. 1-2 cycles of induction therapy consisting (usually) of daunorubicin and cytarabine (AraC), followed by consolidation therapy with high dose AraC (2 cycles). Patients deemed to be at substantial risk of relapse (usually >25-30%) will usually receive allogeneic stem cell transplant in first remission (after 2-4 cycles of chemotherapy). New drug approvals mean that some patients (secondary AML / therapy-related AML / MDS-related AML) may be offered CPX-351 induction therapy. Others with additionally receive GO or a FLT3 inhibitor (midostaurin, quizartinib if FLT3+). Patients in first remission who are not proceeding to allograft – either due to frailty / physical unsuitability or a lower than 25% perceived risk of relapse – may be offered oral azacitidine (Onureg) as maintenance therapy as per previous NICE approval. This treatment can be given for an indefinite number of cycles up until the patient relapses (if that happens) – so is 'open ended'. Although the QUASAR trial (oral aza vs placebo) only included patients with non-favourable risk cytogenetics who were aged >55 years, the NICE approval of this agent did not limit its access along these lines, so any patient who is in first remission post chemotherapy and is not headed to transplant can currently access this drug. There is relatively little variation in these pathways through the NHS. Some patients at some sites may be treated on clinical trial pathways, eg Optimise-

	FLT3. I work in Wales where all recently NICE-approved agents have been incorporated into treatment pathways, so there is very little difference with NHS England. We don't currently have up to date BCSH guidelines for intensive treatment of AML. The most relevant guideline is probably the most recent ELN Guideline. Diagnosis and management of AML in adults: **2022** recommendations from an international expert panel on behalf of the **ELN**. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, Ebert BL, Fenaux P, Godley LA, Hasserjian RP, Larson RA, Levine RL, Miyazaki Y, Niederwieser D, Ossenkoppele G, Röllig C, Sierra J, Stein EM, Tallman MS, Tien HF, Wang J, Wierzbowska A, Löwenberg B.Blood. 2022 Sep 22;140(12):1345-1377. doi: 10.1182/blood.2022016867. If this technology were incorporated, it would impact the care of *some* intensively treated patients who achieve first remission but are not going to allograft. At present these patients either receive 1) oral azacitidine maintenance, 2) FLT3 inhibitor maintenance – midostaurin for 12 months or quizartinib for up to 36 months – this applies to the 25-30% of patients with FLT3 mutations (although a significant proportion of those will go to transplant in first CR) or 3) no maintenance therapy – ie. watchful waiting, sometimes involving serial bone marrow biopsy surveillance for 2-3 years if there is a suitable genetic lesion to monitor. The technology *may* be used in some of these non-transplant patients, though it is difficult to precisely determine which ones because the principal clinical evidence comes from a trial published in 2006 at which point some of the gene mutations that now determine treatment choice had not been discovered and others were certainly not part of routine testing. The general conclusions from the evidence accumulated on histamine / IL-2 to date is that it is likely to benefit patients in 1st remission, aged<60yrs who have normal karyotype AML –

	perhaps especially those with NPM1-mutated disease. NPM1+ cases comprise approximately 30-35% of those with intensively treated AML, but half of these cases are FLT3+ and would generally receive FLT3-inhibitory therapy as maintenance (or go to transplant in 1st CR). So, in my opinion, this treatment would mainly be deployed in NPM1+ (FLT3 negative) patients in 1st CR – approximately 15% of intensively treated patients, where it would compete with oral azacitidine (although the clinical evidence for oral azacitdine was only in patients aged >55yrs, it was approved on an 'age agnostic' basis by NICE).
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology is not currently used in the NHS. In my opinion, in the patients receiving it it would generally be additional to existing 'watchful waiting' (ie. no active therapy) or would replace oral azacitidine therapy (that is given as a daily oral medication for 14 days in every 28 days). The technology is given in 10 cycles which each includes 3 weeks of subcutaneous injections (four injections per day: 2 IL-2, 2 histamine) – this equates to 840 self-administered injections over an 18-month period. Each takes 5-15 minutes to administer. Only the first dose requires in-hospital observation, so the vast majority of the treatment takes place at home. The technology will be supervised, prescribed via specialist hospital clinics generally specialising in the treatment of AML – combination of secondary and tertiary care hospital centres. There will be some requirement for training of nurses in administration, and a training package then required for individual patients.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It is difficult to precisely answer this question because the principal clinical evidence supporting the technology was published in 2006 and treatment pathways have evolved substantially since then. As detailed above, several new drugs have been approved in recent years and rates of 1st CR and OS have

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	improved over the ensuing period. It is generally accepted that more patients now go to transplant in 1st CR than was the case 20 years ago. There have also been major advances in genetic evaluation / prognostication of patients at the point of diagnosis. In the Brune et al study (2006) there was an appreciable improvement in 3-yr EFS from 26% to 40% in those patients receiving treatment in 1st CR but this did not translate into statistically significant improvements in OS (although there was a strong trend which reached p=0.07). Patients <60yrs with normal karyotype saw an improvement in 3yr LFS from 31% to 66%. My overall feeling is that I *would* expect the technology to increase survival length in a significant sub-group of AML patients but it very difficult to define exactly which patients these are by 2025 disease classifications. They are likely to be adults aged <60yrs with normal karyotype AML – 40-50% of normal karyotype AML patients have NPM1 mutations (so would apply to those who are FLT3-ITD negative) and might also extend to others with CEBPA, IDH1, IDH2 and DNMT3A mutations. In terms of quality of life (QoL) there is likely to be a balance of pros and cons. Clearly having 840 injections over 18 months isn't great in terms of QoL although the study evidence suggests this is fairly well tolerated and that compliance is generally good – that is in comparison to taking no therapy or a daily tablet. The potential pros are that preventing relapse certainly improves QoL over having relapsed AML, and that, unlike oral azacitidine, this treatment is given over a finite period and stops after 18 months.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As above. The effective population is likely to be under-60s, in first remission following intensive therapy but not planned for allogeneic stem cell transplant. Normal disease karyotype and possibly especially those with *NPM1*+/*FLT3*-ITD negative disease.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Unquestionably more difficult given that current care comprises nothing (watchful waiting) or a daily tablet (oral azacitidine). There will be additional training (patients and staff) required. Additional hospital pharmacy activities and costs. There is likely to be some increase in the frequency of outpatient clinic visits and blood test monitoring over the 18 months of treatment.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Probably no additional tests to current standard of care. The genetic tests at diagnosis (cytogenetics and molecular genetics) will likely determine whether a patient is in a subgroup that is likely to benefit from the technology. One additional complexity is the impact of current technologies of measurable disease monitoring (MRD) on the implementation of the technology. For NPM1 patients in particular, certain aspects of management are determined by levels of mutation in blood / bone marrow at different timepoints during treatment and in the post-treatment surveillance / monitoring phase. The clinical evidence for the technology pre-dates the advent of these processes. That does not, however, mean additional testing will be needed compared to standard of care.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No issues identified

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, if the technology is deployed correctly and the right set of AML patients it will potentially significantly reduce the rates of disease relapse and substantially improve LFS. At present, there is no maintenance treatment option currently used for significant proportions of intensively treated AML patients so represents a 'step change' for those patients. The proposed technology also represents a mechanistically innovative therapeutic approach which is very different to anything used in current pathways.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The technology was well tolerated in the main published clinical trial (Brune et al) in which 90% of patients completed the prescribed 18-month schedule. The events that were most prominent included relatively minor infusion reactions, fever, fatigue and myalgia – in the trial, 26% of patients required dose reductions, the commonest reason for this being local inflammatory reactions at the injection sites (7%) or fever (5%). In comparison, with oral azacitidine, 50% of patients experience drug-related diarrhoea and substantial numbers of patients require dose reduction due to drug-related neutropenia or thrombocytopenia.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	The clinical trials really reflect UK practice 15-20 years ago – as discussed in answers above. Far more patients are now transplanted in 1st CR, thus reducing the proportion of likely recipients and very few patients receive just anthracycline plus cytarabine as intensive chemotherapy – so it is difficult to extrapolate the results to the era of GO, CPX-351 and FLT3 inhibitors.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	In my opinion the most important outcomes – CIR, LFS, OS were measured in the trials. As discussed above, MRD status was not measured at trial entry – knowing whether patients who are MRD+ or MRD- stand to benefit from this technology would potentially further sub-stratify likely responders and sub-responders. There is some limited evidence that NPM1+ MRD positive patients may achieve MRD negativity while on treatment, but that is also the case with NPM1 MRD+ patients who entered the QUASAR trial and received oral azacitidine maintenance. I'm not aware of any adverse effects that have come to light since the original trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal guidance [TA827, oral azacitidine]?	No
23. How do data on real-world experience compare with the trial data?	I am not personally aware of data on real world experience of the IL-2/HDC combination
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	There are certainly some equality issues impacting access to AML therapies. Some geographical issues may impact access, with patients living in more remote areas, away from major tertiary centres sometimes being less able to access new drugs. I would have concerns that this may particularly impact access to a fairly involved / complex drug administration schedule such as the 18 months of cyclical IL-2/HDC where smaller hospitals will require significant educational support to be able to correctly prescribe, deliver and monitor this treatment and ensure patient compliance.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Despite significant improvements in treatment options for AML patients, more than half continue to die of their disease and there is a pressing need for new therapies that can reduce the risk of relapse
- Histamine dichloride/IL-2 maintenance therapy significantly improved leukaemia free survival (LFS) in patients in first complete remission following intensive chemotherapy in a phase 3 non-placebo controlled trial; improvements were particularly evident in patients aged <60yrs with normal disease karyotype
- The treatment is generally very well tolerated but the schedule includes 840 separate subcutaneous injections, most of which are self-adminstered by the patient over an 18-month period
- The clinical results are historical in that the principal trial enrolled patients between 1998-2000 and was published in 2006; there are some challenges in extrapolating these data into the modern treatment setting given the incorporation of additional drugs into standard treatment schedules and substantial changes in genetic diagnostics, patient subgroupings and disease monitoring
- There are potential advantages over the principal comparator drug oral azacitidine given that the comparator doesn't really have supporting clinical evidence for use in patients <55yrs or with favourable risk disease, has greater toxicity and is prescribed on an ongoing (indefinite?) basis for patients who remain in remission

Thank you for your time.

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with acute myeloid leukaemia or caring for a patient with acute myeloid leukaemia. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Monday 2 March 2026.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with acute myeloid leukaemia

Table 1 About you, acute myeloid leukaemia, current treatments and equality

1. Your name	Adam Claxton
2. Are you (please tick all that apply)	☒ A patient with acute myeloid leukaemia? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with acute myeloid leukaemia? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Blood Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with acute myeloid leukaemia? **If you are a carer (for someone with acute myeloid leukaemia) please share your experience of caring for them**	I was diagnosed with Acute Myeloid Leukaemia in September 2024. I was treated in Worcester Royal for induction chemotherapy including midostaurin as the genetic was FLT3. After 2 rounds of treatment and being back in remission I was put under the team at Birmingham Clinical Centre of Haemotology where I first met with Professor Craddock. I was then fortunate enough to receive a stem cell transplant on 24/12/24 courtesy of my brother who was a 12/12 match. Recovery was excellent until the summer of 2025 when I found out that I had relapsed. I received more treatment including a round of Venetoclax and Azacitidine. Once back in remission I received 2 rounds of DLI. As it stands today I am remission, progressing well with regular bloods and managing chronic GVHD. I am so blessed and grateful.
7a. What do you think of the current treatments and care available for acute myeloid leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I feel that my treatment and care on the NHS has been excellent. I am here to tell my story and fully trusted Professor Craddocks judgement of treatment plans. I am aware of many treatment options that are available and how unique certain treatments are depending on the patients condition, genetics, health, strength etc. We are all individuals so I understand that treatments may differ for better outcomes of patients and that is something we wont have control over so I just focused on my own journey.
8. If there are disadvantages for patients of current NHS treatments for acute myeloid leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I have witnessed many things whilst going through treatment and have remained positive, upbeat and focused on my own individual treatment to give me the best possible outcome. I experienced side effects but also how to adapt and overcome some of the situations that I found myself in.
9a. If there are advantages of histamine dihydrochloride with interleukin-2 over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	I didn't receive the mentioned treatment but experienced the effects that AML has on the quality of life, being able to work, self care and care for others. It has a massive impact on all aspects of life. For me not being able to work and run my business has a huge financial strain but we found a way to get by, life definitely takes a pause as whilst you may have many problems, when one is your health you only have one. My biggest advantage was

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does histamine dihydrochloride with interleukin-2 help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	being able to focus on my mindset and continue with my daily practices that help me and my wellbeing. I truly believe that integrating science/medication with mindset and a belief system of being able to survive have been pinnacle in my recovery.
10. If there are disadvantages of histamine dihydrochloride with interleukin-2 over current treatments on the NHS please describe these. For example, are there any risks with histamine dihydrochloride with interleukin-2? If you are concerned about any potential side effects you have heard about, please describe them and explain why	N/A
11. Are there any groups of patients who might benefit more from histamine dihydrochloride with interleukin-2 or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	N/A
12. Are there any potential equality issues that should be taken into account when considering acute myeloid leukaemia and histamine dihydrochloride with interleukin-2? Please explain if you think any groups of people with this condition are particularly disadvantage	N/A

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	The review of care once treatment has finished and how to find life again. Identity is a big part of recovery and how to heal from a terrifying near death experience.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Mindset and gratitude is key
- Doing more for our wellbeing whilst undergoing treatment helps our survival
- Every patients journey is different, making it hard to compare
- Treatment options are incredible but also unique as we are all unique
- Transparency with your consultant helps so we are fully aware of positive and negative outcomes

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]. A Single Technology Appraisal External Assessment Group report

Produced by	Sheffield Centre for Health and Related Research (SCHARR), Division of Population Health, University of Sheffield
Authors	Aline Navega Biz, Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK Abdullah Pandor, Senior Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK Shije (Kate) Ren, Professor of Statistical Health Technology Assessment, SCHARR, Division of Population Health, University of Sheffield, UK Jen-Yu (Amy) Chang, Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK Andrew Rawdin, Research Assistant, SCHARR, Division of Population Health, University of Sheffield, UK Mark Clowes, Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK
Correspondence Author	Aline Navega Biz, Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK
Date completed	17th November 2025

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR177228.

Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

Acknowledgements

We would like to thank Gail Jones, Newcastle upon Tyne Hospitals NHS Foundation Trust, and Anjum Khan, Leeds Teaching Hospitals NHS Trust, for clinical advice relating to this project. We would also like to thank Matt Stevenson, SCHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, SCHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Navega Biz, A.; Pandor, A.; Ren, K.; Chang, JY.; Rawdin, A.; Clowes, M. Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]: A Single Technology Appraisal. Sheffield Centre for Health and Related Research (SCHARR), Division of Population Health, University of Sheffield 2025.

Contributions of authors

Aline Navega Biz led the assessment. Mark Clowes critiqued the company's search strategy. Abdullah Pandor summarised and critiqued the clinical effectiveness data reported within the company's submission. Kate Ren critiqued the statistical aspects of the submission. Aline Navega Biz, Jen-Yu Amy Chang and Andrew Rawdin critiqued the health economic analysis submitted by the company and conducted additional exploratory analyses. All authors were involved in drafting and commenting on the final report.

CONTENTS

TABLES

FIGURES

BOX

Abbreviations

AE	Adverse event
AFT	Accelerated failure time
Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
Allo-SCT	Allogeneic stem cell transplant
AIC	Akaike Information Criterion
AML	Acute myeloid leukaemia
AML-MR	AML-MR
Auto-HSCT	Autologous hematopoietic stem cell transplantation
Auto-SCT	Autologous stem cell transplant
AS	Absolute shortfall
ASA	Additional sensitivity analysis
BIC	Bayesian Information Criterion
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CBC	Complete blood count
CD33	Cluster of Differentiation 33
CDA/AMC	Canada's Drug Agency
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CML	Chronic myeloid leukaemia
CMML	Chronic myelomonocytic leukaemia
CR	Complete response
CR1	First complete remission
CR>1	Subsequent complete remission
CRp	Incomplete platelet recovery
CRUK	Cancer Research UK
CS	Company's submission
CSR	Clinical Study Report
cTTO	Composite time trade off
DALY	Disability-adjusted life year
DCE	discrete choice experiment
DM	Decision modifier
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire
EQ-5D-3L	EQ-5D 3-Level

EQ-5D-5L	EQ-5D 5-Level
EQ-VAS	EQ Visual Analogue Scale
FAB	French-American-British
FLAG-IDA	Fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin
FLT3	FMS-like tyrosine kinase 3
FLT3-ITD	FLT3-internal tandem duplication
FMS	Feline McDonough Sarcoma
GVHD	Graft-versus-host disease
HCRU	Health care resource use
HDC	Histamine hydrochloride
HDC/IL-2	Histamine hydrochloride with interleukin-2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HTAi	Health Technology Assessment International
ICC	International Consensus Classification
ICER	Incremental cost-effectiveness ratio
IDH1	Isocitrate dehydrogenase 1
IL-2	Interleukin-2
IPD	Individual patient data
ISPOR	The Professional Society for Health Economics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
LF	Leukeamia-free
LFS	Leukaemia-free survival or leukeamia free state
LYG	Life year gained
MCM	Mixture-cure model
MDS	Myelodysplastic syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
N/a	Not applicable
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NK	Natural killer
NPM1	Nucleophosmin 1
OS	Overall survival
PastSA	Partition survival analysis
PAS	Patient Access Scheme
PCV	Polycythaemia rubra vera
PD	Progressed disease
PFS	Progression-free survival
PH	Proportional hazards
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PS	Performance status *or* proportional shortfall
PSA	Probabilistic sensitivity analysis

PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Qualiy of life
Q-Q	Quantile-quantile
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RDI	Relative dose intensity
RoB 2	Risk of Bias version 2
ROS	Reactive oxygen species
SD	Standard deviation
SAE	Serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
STM	State transition model
TA	Technology appraisal
TSD	Technical Support Document
TTD	Tine-to-treament discontinuation
Tx	Treatment
UK	United Kingdom
VOD	Veno-occlusive disease
WBC	White blood cells
WHO	World Health Organization
WTP	Willingness-to-pay
YLD	Year lived with disability
YLL	Year of life lost

1 Executive summary

This report assesses histamine hydrochloride with interleukin-2 (HDC/IL-2) for the maintenance treatment of patients with acute myeloid leukaemia (AML). This executive summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 outlines the key model outcomes and the modelling assumptions that have the greatest impact on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail, any secondary issues and modelling errors identified by the EAG, respectively. The results of the EAG's preferred analyses and additional sensitivity analyses are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are presented in the main EAG report.

The results presented in the EAG report include list prices for HDC/IL-2, comparator technologies and other technologies given as subsequent treatments. The company has not proposed a Patient Access Scheme (PAS) for HDC/IL-2. Results including confidential prices for oral azacitidine are presented in the confidential appendix to this report.

All issues identified represent the EAG's view, not necessarily the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of EAG's key issues

The company's proposed positioning of HDC/IL-2 presented in the company's submission (CS) is for adults with AML who have a normal karyotype, are in first remission (CR1), are not considered suitable for allogeneic hematopoietic stem cell transplantation (allo-HSCT) and are under 60 years of age. The key studies informing the CS are Brune *et al.*, which compares HDC/IL-2 versus standard of care (SoC), and Nilson *et al.*, a *post-hoc* subgroup analysis of data from the Brune *et al.* study. The company's economic analysis compares HDC/IL-2 with SoC against SoC alone and against oral azacitidine. The comparison against oral azacitidine was also informed by an indirect treatment comparison (ITC) between oral azacitidine and HDC/IL-2 using a Bucher approach based on the evidence from the Brune *et al*. study and the QUAZAR AML-001 trial. The economic analysis is also informed by Tremblay *et al.* for health state utilities, summary of product characteristics (SmPCs), a previous NICE technology appraisal (TA827), additional studies, standard costing sources and assumptions. The key issues identified by the EAG are summarised in Table 1.

Table 1: Summary of the EAG's key issues

ID6405	Summary of issue	Impact on results	Report sections
Issue 1	Uncertainty regarding the generalisability of the results from Brune *et al*. and Nilsson *et al*. to the current patients with AML who would currently be eligible for AML maintenance treatment in the NHS	Unknown but potentially very important	3.2.1.3 and 4.3.5 (critical appraisal point 2)
Issue 2	Use of *post-hoc* subgroup analysis to inform the treatment effects for HDC/IL-2 and SoC	Unknown but potentially very important	3.2.1.3 and 3.6
Issue 3	Uncertainty around the estimated treatment effect between HDC/IL-2 and oral azacitidine from the company's ITC	Large	3.4.1 and 4.3.5 (critical appraisal point 3)
Issue 4	Uncertainty in the long-term extrapolation of LFS and OS for HDC/IL-2 and SoC	Varies by analysis and comparison* (greater impact vs SoC)	4.3.5 (critical appraisal point 4)
Issue 5	Uncertainty around the utility values used in the company's model	Small/Moderate (varies by analysis and comparison)	4.3.5 (critical appraisal points 6 (a) and (b))
Issue 6	Inappropriate inclusion of treatment discontinuation approach for modelling survival estimates for HDC/IL-2 and oral azacitidine groups	Small/Large (varies by comparison)	4.3.5 (critical appraisal point 5)
Issue 7	Uncertainty around the costs of subsequent therapies	Small	4.3.5 (critical appraisal point 8 (e))
Issue 8	Uncertainty around modelled drug costs for HDC/IL-2, oral azacitidine and SoC	Small/moderate (varies by analysis and comparison)	4.3.5 (critical appraisal point 8 (a)(b)(c)(d))
Issue 9	Weak characterisation of uncertainty	Unknown	4.3.5 (critical appraisal point 9)

AML - EAG - External Assessment Group; HDC/IL-2 – Histamine hydrochloride with interleukin-2; ITC - Indirect treatment comparison; LFS – leukaemia-free survival; OS - overall survival; SoC – standard of care; vs – versus.
**The survival models chosen for HDC/IL-2 also influence the outcomes for oral azacitidine (see issue 3 and Section 4.2.4.1 of the main report)*

The key differences between the company's updated base case model and the EAG's preferred analysis are as follows:

- Use of alternative models for LFS and OS in HDC/IL-2 and SoC groups: The company's model applies jointly fitted exponential models for LFS and OS in the HDC/IL-2 and SoC groups. The

EAG's preferred analysis applies the following models for each endpoint and treatment group: independently fitted exponential (LFS, HDC/IL-2 group), independently fitted log-normal (LFS, SoC), independently fitted Weibull (OS, both HDC/IL-2 and SoC groups).

- Modelling the effects of HDC/IL-2 versus oral azacitidine: The company's model applies hazard ratios (HRs) for OS and LFS for HDC/IL-2 versus oral azacitidine from the ITC of QUAZAR AML-001 intention-to-treat (ITT) population vs Brune *et al.* ITT population based on the unstratified HR for OS from QUAZAR AML-001. The EAG's preferred analysis applies the stratified HR for OS from the oral azacitidine trial.
- Oral azacitidine costs: The company's model applies only the drug acquisition costs for oral azacitidine and assumes a relative dose intensity (RDI) of 100%, whilst the EAG's preferred analysis also includes additional cost elements for oral azacitidine, such as the RDI estimate, costs of premedication and administration costs, all sourced from TA827 and standard costing sources.
- HDC/IL-2 acquisition and administration costs: The company's model estimated the acquisition costs for IL-2 based on the patients' mean weight for the general population in England, whilst the EAG's preferred analysis uses the methods of moments based on patients' mean weight and distributions from Brune *et al.* The EAG model also assumed a higher administration cost, based on the assumption that patients would have to collect their prescribed medication at least twice per 3-week treatment cycle (instead of once), in line with the dispensing instructions for IL-2.
- Removal of blended approach to health outcomes: The company's model applies a blended survival approach to account for treatment discontinuation in the HDC/IL-2 and oral azacitidine groups. The EAG's preferred analysis applies only the LFS and OS survival models from the corresponding treatment groups to inform the health outcomes.
- Impact of HDC/IL-2 injections to health-related quality of life (HRQoL): The company's model did not model the impact of HDC/IL-2 injections to HRQoL. The EAG's preferred analysis applies an additional utility decrement related to the high frequency of injections required for the treatment of patients with HDC/IL-2, based on data from Boye *et al.*

The EAG's model also includes other minor amendments including the correction of model errors and alternative assumptions regarding the SoC drugs (with removal of fluconazole as part of the SoC drug regimens).

1.2 Overview of key model outcomes

NICE TAs compare how much a new technology improves length of life (OS) and HRQoL in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

For the comparison against SoC, the company's model indicates that HDC/IL-2 impacts on QALYs by:

- Extending LFS relative to SoC, with additional time spent in the LFS health state is associated with a higher HRQoL compared to the post-progression state. However, this is partially offset by additional time spent in LFS on treatment state for HDC/IL-2 which is associated with slightly lower HRQoL compared to LFS in the SoC group.
- Extending OS relative to SoC.
- Slightly increasing QALY losses associated with adverse events (AEs) compared to SoC.

For the comparison against SoC, the company's model suggests that HDC/IL-2 impacts on costs by:

- Increasing drug costs compared to SoC, due to the higher acquisition and administration costs associated with the HDC/IL-2 regimen.
- Increasing health state costs compared to SoC as a consequence of extended LFS and OS.
- Increasing the expected costs of managing AEs compared to SoC.
- Reducing costs for allo-HSCT as a subsequent treatment to patients who have relapsed, compared to the SoC treatment group.

For the comparison against oral azacitidine, the company's model indicates that HDC/IL-2 impacts on QALYs by:

- Reducing LFS relative to oral azacitidine, with less time spent in the LFS health state which is associated with higher HRQoL.
- Reducing OS compared to oral azacitidine.

For the comparison against oral azacitidine, the company's model suggests that HDC/IL-2 impacts on costs by:

- Reducing drug costs compared to oral azacitidine, due to lower acquisition costs associated with the HDC/IL-2 regimen, which is partially offset by higher administration costs.
- Reduced health state costs compared to oral azacitidine as a consequence of decreased LFS and OS.

The modelling assumptions that have the greatest effect on the ICER are:

- The choice of survival extrapolation approach (jointly fitted or independent) and parametric survival model fitted to the LFS and OS data for the HDC/IL-2 and SoC groups.
- The approach used to model the relative effects of HDC/IL-2 versus oral azacitidine.
- The source choice for health state utility values.

- The removal of the impact of the blended approach to health outcomes (in particular versus oral azacitidine).

1.3 EAG's key issues

The key issues identified during the EAG's critical appraisal, related to the decision problem, clinical effectiveness and cost-effectiveness of HDC/IL-2 with SoC versus SoC alone and versus oral azacitidine are summarised below as issues 1 to 6.

Issue 1: Uncertainty regarding the generalisability of the results from Brune *et al.* and Nilsson *et al.* to the current patients with AML who would currently be eligible for AML maintenance treatment in the NHS

Report section	3.2.1.3 and 4.3.5 (critical appraisal point 2)
Description of issue and why the EAG has identified it as important	The company's proposed positioning of HDC/IL-2 is for patients with AML with normal karyotype, in CR1, ≤60 years old and ineligible for allo-SCT, and it also excludes patients with a Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3 (FLT3) mutation. Patients enrolled into the Brune *et al.* study with a normal karyotype were within the intermediate karyotype classification, based on the European LeukemiaNet (ELN) 2022 classification. Molecular testing for genetic subtypes was not routine practice at the time of patient recruitment for the study, and therefore it is unclear how many FLT3-positive patients have contributed to the efficacy data used to inform the clinical effectiveness and economic analysis in the CS. In addition, given the significant advances in the AML management in the UK since the Brune *et al.* study was conducted, the population included in the Brune *et al.* subgroup of patients with normal karyotype, in CR1, ≤60 years old and ineligible for allo-SCT may not entirely reflect the current population of patients with AML who would be eligible for maintenance therapy with HDC/IL-2 in the NHS clinical practice in England. As such, the EAG considers that there is considerable uncertainty regarding the applicability of the study outcomes to current UK clinical practice, affecting both the clinical evidence and the economic analyses for this appraisal.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	The impact of this issue on the relative clinical effectiveness and cost-effectiveness of HDC/IL-2 versus SoC and versus oral azacitidine is unclear. The EAG cautions the interpretation of the results from the clinical evidence and the economic analyses informing this appraisal.
What additional evidence or analyses might help to resolve this key issue?	The absence of additional clinical data for the target population in a more contemporary setting precludes further analyses by the EAG regarding this issue. Additional clinical studies are required to determine outcomes for patients receiving HDC/IL-2 in a more contemporary setting.

Issue 2: Use of *post-hoc* subgroup analysis to inform the treatment effects for HDC/IL-2 and SoC

Report section	3.2.1.3 and 3.6
Description of issue and why the EAG has identified it as important	The pivotal evidence for HDC/IL-2 is derived from a single international, multicentre, open-label, randomised phase III trial (NCT0000399137, Brune *et al*., and Nilsson *et al*.). The results presented in Nilsson *et al*. are from a *post-hoc* analysis of the subgroup of patients in CR1, with normal karyotype and aged ≤60 years, which was used to inform the CS. The *post-hoc* analysis of the HDC/IL-2 regimen (n=35) in the target population demonstrated a statistically significant improvement in LFS compared with the control (n=37) group (HR: 0.40; 95% CI: 0.20–0.79; p=0.006), and an improvement in OS (HR: 0.43; 95% CI: 0.18–1.01; p=0.04), although the statistical significance for OS remains uncertain because the CI includes 1. However, the EAG notes that the lack of pre-specification for the *post-hoc* analysis introduces the potential for a high risk of bias (e.g., from selective reporting or data-driven identification of subgroup effects). Both the EAG and the authors of Nilsson *et al.* caution against interpreting these results as confirmatory; instead, they should be treated as exploratory.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Further clinical studies in the specific group of patients with AML in CR1, aged ≤60 years and with normal karyotype (or which would be included as a pre-specified subgroup) in a more recent setting are required to determine outcomes for patients receiving HDC/IL-2 in the target population of this appraisal. The absence of additional clinical data precludes any further analyses by the EAG regarding this issue.

Issue 3: Uncertainty around the estimated treatment effect between HDC/IL-2 and oral azacitidine from the company's ITC

Report section	3.4.1 and 4.3.5 (critical appraisal point 3)
Description of issue and why the EAG has identified it as important	The company conducted Bucher ITCs between oral azacitidine and HDC/IL-2, which included the QUAZAR AML-001 trial for oral azacitidine and the Brune *et al.* study for HDC/IL-2, and using the control arm in these studies as the common comparator. The results of the ITC using the ITT populations in both studies informed the relative efficacy of oral azacitidine versus HDC/IL-2 in the model. The EAG considers that the estimated treatment effect between HDC/IL-2 and oral azacitidine is highly uncertain for the target population of this appraisal. The EAG concerns relate to: (i) the limited population overlap between QUAZAR AML-001 and Brune *et al.* populations and the targeted subgroup in Brune *et al.* (CR1, ≤60 years, normal karyotype), with age being a potential treatment effect modifier of HDC/IL-2. Without adjusting for population differences in the ITC, a more favourable estimated treatment effect of HDC/IL-2 versus oral azacitidine would be expected due to age differences between the populations.

	(ii) potential differences in SoC between QUAZAR AML-001 and Brune *et al*. trials, due to significant changes in the treatment landscape for AML between the periods when the studies were conducted. Treating the SoC from the two trials as the common comparator could introduce bias into the ITC, but the exact impact on the estimates of relative effect is uncertain. (iii) absence of subgroup results from QUAZAR AML-001 for patients with AML in CR1, aged ≤60 years, with normal karyotype, necessitating reliance on Bucher ITC results based on the ITT populations of QUAZAR AML-001 and Brune et al., which are not representative of the company's proposed population. (iv) the estimates of HR for OS and LFS that the company used to inform the economic model were derived from a mixture of stratified and unstratified HRs from the two studies used to inform the ITC. The company's current approach is more in favour of HDC/IL-2.
What alternative approach has the EAG suggested?	The EAG has conducted scenario analyses to explore the potential impact of this uncertainty from the ITC on the ICER, where: (i) the inconsistency between the different approaches from the company regarding HRs from the studies used to inform the ITC was fixed, with all the HRs used being based on the stratified HRs from the studies (exploratory analysis 2 [EA2]); (ii) alternative estimates for OS and LFS HRs were applied in the model: (a) the lower range of the 95% CI from the ITC of oral azacitidine versus HDC/IL-2 (more in favour of oral azacitidine – additional sensitivity analysis 2 [ASA2]), and (b) assuming no treatment difference between HDC/IL-2 and oral azacitidine (HR=1.0 for both OS and LFS, ASA3)
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's analysis which includes error corrections (EA1), the use of stratified HRs for LFS and OS inform the relative effect of HDC/IL-2 versus oral azacitidine (EA2) decreases the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted]. Relative to the EAG's preferred analysis (EA10) of [redacted], the use of the estimates from the lower range of the 95% CI from the ITC (ASA2) decreases the ICER for HDC/IL-2 versus oral azacitidine to [redacted], whilst assuming equivalent clinical effect between the two groups (ASA3) increases the ICER to [redacted]. These analyses do not affect the results for the comparison of HDC/IL-2 versus SoC.
What additional evidence or analyses might help to resolve this key issue?	The EAG believes that the alternative approaches used in the exploratory analyses explore the uncertainty in the model-predicted outcomes for the oral azacitidine group, provided the evidence available from the submission. IPD from the Brune *et al.* study, if available, would allow the use of alternative approaches for the ITC which employ population adjustments (even though the EAG notes the inherent uncertainty associated with the small numbers included in the Nilsson *et al*. analyses, if this subgroup is chosen to inform the ITC). However, given this data was not available to the company, further clinical input may be useful to determine the most plausible outcomes for patients receiving oral azacitidine.

Issue 4: Uncertainty in the long-term extrapolation of LFS and OS for HDC/IL-2 and SoC

Report section	4.3.5 (critical appraisal point 4)
Description of issue and why the EAG has identified it as important	The company's base case model uses exponential models jointly fitted to OS and LFS data for HDC/IL-2 and SoC treatment groups from the *post-hoc* subgroup of patients with AML in CR1, ≤60 years old, and normal karyotype reported by Nilsson *et al.* The EAG has the following key concerns regarding the company's survival analysis: (i) The EAG considers the company's survival modelling to be subject to substantial uncertainty, particularly due to the very small sample size and high degree of censoring in the data, limited follow-up, which may prevent reliable extrapolated long-term hazard. (ii) The company's use of the jointly fitted exponential model as the base case implicitly assumes a lifetime treatment effect on LFS and OS, based on Schoenfeld residuals tests not showing a statistically significant violation of the proportional hazards (PH) assumption. However, the EAG notes that based on the visual observation of complementary log-log plots for both LFS and OS and smoothed Schoenfeld residuals, the PH assumption might not necessarily hold. Additionally, there is no clinical evidence to suggest that treatment effect remains constant over time. Therefore, the EAG considered fitting models independently to be a more appropriate approach. (iii) The visual assessment of both jointly and independently fitted models indicated that several models, particularly the Gompertz and generalised gamma distributions, produced highly optimistic long-term survival estimates, which were deemed clinically unplausible. (iv) For LFS, the jointly fitted standard parametric models showed a suboptimal fit based on visual assessment, particularly for the HDC/IL-2 group, with the independently fitted models offering only marginal improvement. For OS, both jointly and independently fitted standard parametric models provided similar visual fits, though none achieved a satisfactory overall fit. However, these should be interpreted with caution due to (i). (v) The EAG notes that consideration of smoothed and unsmoothed empirical hazards, along with the modelled hazards should be interpreted with caution due to (i), and as a consequence, the later portion of the modelled hazard within the follow-up period may not reflect the long-term hazard pattern expected in clinical practice. (vi) Clinicians declared expected survival estimates could potentially be reflecting current treatment pathways for AML, which may not have been available at the time of the Brune *et al.* study.
What alternative approach has the EAG suggested?	The EAG explored the use of alternative LFS and OS models for HDC/IL-2 and SoC groups (EA3): - LFS, HDC/IL-2: independently fitted exponential - LFS, SoC: independently fitted log-normal - OS, HDC/IL-2: independently fitted Weibull - OS, SoC: independently fitted Weibull The EAG also included the reinstatement of the company's preferred models for LFS and OS as part of an additional sensitivity analysis (ASA5). No further alternative approaches for the long-term extrapolation of LFS and OS are suggested. This is because the Brune *et al.* study concluded several years ago (first published in 2006), and no additional follow-ups are expected. Had additional follow-up data been available, it would have helped to better characterise long-term outcomes and improve the reliability of LFS and OS extrapolations for the three

	treatment groups (given that LFS and OS estimates for oral azacitidine in the model were dependent on the selected HDC/IL-2 models).
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's analysis which includes error corrections (EA1), the use of alternative LFS and OS models for HDC/IL-2 and SoC (EA3) increases the ICER for HDC/IL-2 versus SoC from £20,915 per QALY gained (including a DM of 1.2) to £27,357 per QALY gained, and decreases the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted]. Relative to the EAG's preferred analysis (EA10), reintroducing the company's preferred OS and LFS models (ASA5) decreases the ICER for HDC/IL-2 versus SoC from £28,918 to £21,647 per QALY gained (DM=1.2), and increases the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Further clinical opinion may be useful to determine the most plausible outcomes for patients receiving HDC/IL-2 or SoC.

Issue 5: Uncertainty around the utility values used in the company's model

Report section	4.3.5 (critical appraisal points 6 (a) and (b))
Description of issue and why the EAG has identified it as important	The health state utility values used in the company's model have been informed by external data (Tremblay *et al.*), an economic evaluation study which in turn based their utility estimates from different literature sources. In the CS, the company also presented scenario analyses exploring alternative sources from Joshi *et al.*, Stein *et al.* and Russell-Smith *et al.*; however, results for these scenarios were not presented by the company using the updated version of the model. The EAG notes that some of the sources used by the company have limitations, related to their valuation methods: Joshi *et al.* used a composite time trade off (cTTO) methodology instead of EQ-5D, Stein *et al.* used a discrete choice experiment (DCE) methodology with participants from the general population in the US, whilst some of the estimates from Tremblay *et al.* were based on studies using EQ-5D-5L data or conducted in patients with myelodysplastic syndromes in US settings. The EAG considers that, due to the limitations in most sources presented by the company and in the absence of HRQoL data from the clinical study that reflects the specific target population, it is unclear which would be the best source of utilities for this population. In addition, the company does not include any evidence regarding the impact to HRQoL of the number of injections required for the treatment with HDC/IL-2 in patients with AML. The EAG has concerns around the high number of injections required for patients receiving treatment with HDC/IL-2, which has also been commented by [redacted] The impact of the number of injections to patients' HRQoL and how they may influence patients' preferences regarding therapy, however, is unclear.
What alternative approach has the EAG suggested?	The EAG's preferred analysis retains the company's base case utility values from Tremblay *et al.* (LFS on treatment=0.81, LFS off treatment=0.81, post-progression=0.53); however, the EAG has conducted additional sensitivity

	analyses (ASA1-3) to explore the impact of using health state utility values from the three alternative sources. The EAG also considered the impact of daily injections to patients' HRQoL as part of exploratory analysis (EA9), by including an additional utility decrement of 0.124, related to the high frequency of injections required for patients receiving HDC/IL-2, which was calculated by the EAG based on estimates for patients with type 2 diabetes from Boye *et al.* This decrement is applied in the model in cycles where patients are assumed to receive treatment with HDC/IL-2 to patients who remain on treatment (in LFS on treatment state).
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's analysis which includes error corrections (EA1), the inclusion of a disutility related to the high number of injections for patients receiving HDC/IL-2 (EA9) increases the ICER for HDC/IL-2 versus SoC from £20,915 per QALY gained to £21,520 per QALY gained (DM=1.2), and decreases the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted]. Relative to the EAG's preferred analysis (EA10), the use of alternative health state utility values from Joshi *et al.* (LFS on and off treatment=0.89, post-progression= 0.51) has a moderate impact on the ICER for HDC/IL-2 versus SoC, which decreases from £28,918 to £25,746 per QALY gained (DM=1.2), whilst having only a minor impact on the ICER for HDC/IL-2 versus oral azacitidine, which decreases from [redacted] to [redacted]. The use of estimates from Stein *et al.* (LFS on and off treatment=0.87, post-progression= 0.62) has a small impact on the results for both comparisons, with the ICER for HDC/IL-2 versus SoC decreasing from £28,918 to £28,143 per QALY gained (DM=1.2), and the ICER for HDC/IL-2 versus oral azacitidine decreasing from [redacted] to [redacted]. The use of values from Russell-Smith *et al.* (LFS on and off treatment=0.74, post-progression= 0.57), conversely, led to increases on the ICERs for both comparisons, for HDC/IL-2 versus SoC from £28,918 to £34,276 per QALY gained (DM=1.2), and for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted]
What additional evidence or analyses might help to resolve this key issue?	Further clinical input may be useful in determining the plausibility of the utility values applied in the company's base case model. This should include consideration of the impact on HRQoL of the high number of injections required for treatment with HDC/IL-2.

Issue 6: Inappropriate inclusion of treatment discontinuation approach for modelling survival estimates for HDC/IL-2 and oral azacitidine groups

Report section	4.3.5 (critical appraisal point 5)
Description of issue and why the EAG has identified it as important	In the model, the overall LFS and OS cumulative probabilities for the HDC/IL-2 and oral azacitidine treatment groups is based on weighted mean estimates of LFS and OS for discontinuers and non-discontinuers (i.e., a 'blended' model), with weights based on the proportion of patients who discontinued due to AEs not related to relapse. Patients who discontinue treatment at the first cycle due to AEs in the HDC/IL-2 and oral azacitidine groups follow the same survival (LFS and OS) cumulative probabilities as for the SoC group, and those who do not discontinue treatment with these therapies, or discontinue in subsequent cycles due to relapse, follow the LFS and OS cumulative probabilities for the respective groups.

	The EAG has concerns regarding this approach, given that the data used to inform the LFS and OS standard parametric models for HDC/IL-2 included patients who had discontinued treatment, which has been confirmed by the company during the clarification stage. As such, applying the blended survival approach effectively double counts the impact of treatment discontinuation into the health outcomes of the model.
What alternative approach has the EAG suggested?	The EAG considered that LFS and OS for the HDC/IL-2 (and as a consequence, for oral azacitidine – see issue 3) groups should be modelled based directly on standard parametric survival estimates for each respective group (i.e., using a non-blended approach). The EAG notes that the removal of the company's approach improves estimated survival for HDC/IL-2 and oral azacitidine groups.
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's analysis which includes error corrections (EA1), the removal of the company's blended approach (EA8) decreases the ICER for HDC/IL-2 versus SoC from £20,915 to £19,806 per QALY gained (DM=1.2), and the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The EAG does not believe that further analyses are required to resolve this issue.

1.4 Secondary issues identified by the EAG

The EAG identified three additional secondary issues, which are described below as issues 7 to 9.

Issue 7: Uncertainty around the costs of subsequent therapies

Report section	4.3.5 (critical appraisal point 8(e))
Description of issue and why the EAG has identified it as important	The original model submitted by the company only included the costs of SoC drugs after patients' progression (relapse), due to the lack of information on subsequent therapies from Brune *et al.* The costs of the allo-SCT procedure were included at the clarification stage, based on estimates for the proportion of patients receiving the transplant obtained from TA827 and based on the QUAZAR AML-001 trial. This cost is applied in the model as a one-off cost at the point of relapse, and the transplant is assumed to have no impact on health outcomes and on downstream costs of treatment for AML. The EAG has a few concerns regarding the approach adopted by the company. The lack of data on subsequent therapies received in the Brune *et al.* study limits the reproducibility of costs which also would reflect the outcomes for the patients in the trial. However, given this limitation, data from previous TAs in similar populations (e.g., TA827) could be used, or these could be based on clinical opinion in the absence of suitable data. By including only the costs of all-SCT without either adjusting the health outcomes for patients who receive the transplant, or the impact of this procedure on subsequent management costs, the company's approach disfavours the SoC group in comparison to HDC/IL-2 and oral azacitidine, given the higher incidence of transplants in this group in QUAZAR AML-001. The EAG also considers that the costs of other post-relapse therapies were omitted, when the costs of regimens such as cytarabine, injectable azacitidine, and salvage chemotherapy were also available from TA827.

What alternative approach has the EAG suggested?	The EAG explored the impact of the costs of subsequent therapies as part of additional sensitivity analysis (ASA4a and 4b), where the costs of allo-SCT were removed (ASA4a) and costs of the other regimens from TA827 were also included (ASA4b). The EAG notes that these analyses do not incorporate any adjustments to OS related to patients receiving allo-SCT or other subsequent therapies.
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's preferred analysis (EA10), the exclusion of the costs of allo-SCT has only a minor impact on the ICERs, increasing the ICERs for HDC/IL-2 versus SoC from £28,918 to £29,247 per QALY gained (DM=1.2) and decreasing the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted]. Including the costs of other subsequent treatment regimens from TA827 has also a minor impact on results, decreasing the ICERs for HDC/IL-2 versus SoC from £28,918 to £28,620 per QALY gained (DM=1.2) and increasing the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The absence of additional clinical data for the target population in a more recent setting which includes data on subsequent therapies received after relapse precludes any further analyses by the EAG regarding this issue.

Issue 8: Uncertainty around modelled drug costs for HDC/IL-2, oral azacitidine and SoC

Report section	4.3.5 (critical appraisal point 8 (a)(b)(c)(d))
Description of issue and why the EAG has identified it as important	The EAG has a few concerns regarding the company's approach to modelling drug acquisition and administration costs for HDC/IL-2, oral azacitidine and SoC: (i) *Patients' mean weight used to derive drug costs for IL-2 and hydroxycarbamide (part of SoC)*: the company's model uses the mean weight reported for the general population in England, which is not specific for patients with AML. The EAG notes that mean weight estimates were available from the Brune *et al.* clinical study report for [redacted]. (ii) Exclusion of RDI, wastage and concomitant drugs from drug cost calculations: the company's model does not include any considerations regarding RDI, adherence or compliance, and the approach regarding wastage included at the clarification stage is unclear on how it addressed wastage within the model, in addition to the original approach whereby the full 3-week treatment costs of HDC/IL-2 is applied regardless if patients discontinue therapy due to AE or relapse. The model also assumes vial sharing for IL-2, which may not be feasible due to a number of factors. Although estimates of RDI were not available for HDC and IL-2 from Brune *et al.,* an estimate of mean RDI was available from TA827 for oral azacitidine. Equally, the costs of concomitant drugs (ondansetron) given alongside oral azacitidine, available from TA827, were not included in the model. The inclusion of the RDI and concomitant costs for oral azacitidine would better reflect the modelled drug costs for this regimen and increase comparability with TA827. (iii) Issues regarding modelled drug administration costs for HDC/IL-2 and oral azacitidine: the company's model includes the costs of administering HDC/IL-2 injections from NHS Cost Collection for 2023/24 assuming that patients would be expected to collect the prescription of HDC/IL-2 from the hospital once per treatment cycle, and that this cost includes patient training in self-administering the injections from home at the application of the first dose. However, the SmPC for HDC/IL-2 states that only up to two

	weeks supply of pre-filled syringes may be provided to patients for home administration, and therefore patients would have to collect their prescriptions at least twice in each 3-week treatment cycle. Conversely, the model assumes that no administration costs are incurred by patients receiving oral azacitidine since it corresponds to an oral therapy; however, the EAG considers that administration costs, equivalent to the 'Deliver Exclusively Oral Chemotherapy' should be applied to this treatment group. (iv) Concerns regarding potential HDC/IL-2 accessories' costs regarding the delivery of the HDC/IL-2 at home not included in the model: the company's model considers that all patients are able to self-administer the HDC/IL-2 regimen at home, and no accessories are required. However, the EAG notes that SmPC for HDC/IL-2 specifically mentions that *"Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection can be administered via an ambulatory infusion syringe pump or by controlled manual subcutaneous injection by syringe with a timer."* It is unclear if the use of any accessories to ensure the HDC injection is delivered within the intended timeframe of 5-15 minutes was allowed or implemented in Brune *et al.*, and clinical advisors for the EAG have noted that some patients may not be able to self-administer at home. Data regarding the acceptability of the regimen and what would happen to patients in clinical practice who are unable to self-administer at home were not provided by the company, and therefore this remains an area of uncertainty regarding the implementation of HDC/IL-2 if this regimen is recommended for use in the NHS.
What alternative approach has the EAG suggested?	The EAG's preferred analysis applies the following changes regarding the modelled costs for: (a) HDC/IL-2: - Use of mean weight and distributions from the CR1 population in the Brune *et al.* study to inform the costs of IL-2 (EA1f) - Inclusion of wastage-based costs for IL-2 (EA5) (b) oral azacitidine: - Adjustment of the costs of oral azacitidine to the model monthly cycles (EA1d) - Inclusion of additional cost elements to oral azacitidine: mean RDI estimate, costs of premedication and administration costs from TA827 (EA4) (c) SoC drugs (which impacts the three treatment groups): - Use of mean weight and distributions from the CR1 population in the Brune *et al.* study to inform the costs of hydroxycarbamide (EA1f) - Fluconazole was removed from the pool of SoC drug regimens, based on opinion from clinical advisor, with the proportion of patients receiving the remaining drugs being reweighted by the EAG to maintain the overall proportion of patients who receive SoC drugs (EA7) In addition, as part of additional sensitivity analyses aiming to explore the impact of uncertainty on costs of HDC/IL-2, hypothetical RDIs for HDC and IL-2 were applied using two different assumptions: same RDI as oral azacitidine (86.9%, ASA6a), and 95% for both HDC and IL-2 (assumption from the EAG, ASA6b).
What is the expected effect on the cost-effectiveness estimates?	Based on the updated version of the company's base-case, applying the two corrections of the model (EA1d and EA1f) have limited impact on the ICERs. EA1d does not impact the ICER for HDC/IL-2 versus SoC, and increased the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted]. EA1f reduces the ICER for HDC/IL-2 versus SoC from £20,153 to £20,019 (DM=1.2), and increased the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted].

	Based on the EAG's analysis which includes error corrections (EA1), the inclusion of additional elements for oral azacitidine costs (EA4) only affects the ICER for HDC/IL-2 versus oral azacitidine, whereby it decreases from [redacted] to [redacted]. The inclusion of wastage-based costs for IL-2 (EA5) and the use of an alternative assumption for HDC/IL-2 administration costs (EA6) have only a minor impact on the ICERs, increasing the ICERs for HDC/IL-2 versus SoC from £20,915 to £21,646 and to £21,578 per QALY gained (DM=1.2), respectively. These analyses lead to decreases in the ICER for HDC/IL-2 versus oral azacitidine, from [redacted] to [redacted] and [redacted], respectively. Applying different assumptions to the SoC drugs (EA7) had a negligible impact on ICERs. Based on the EAG's preferred analysis (EA10), applying the same RDI for HDC/IL-2 as oral azacitidine (ASA6a) decreased the ICER for HDC/IL-2 versus SoC from £28,918 to £25,991 per QALY gained (DM=1.2), whilst increased the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted]. Applying an assumed RDI of 95% for HDC/IL-2 decreased the ICER for HDC/IL-2 versus SoC from £28,918 to £27,800 per QALY gained (DM=1.2), whilst increased the ICER for HDC/IL-2 versus oral azacitidine from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Further clinical input may be useful in determining the plausibility of the self-administration proposed by the company, and any potential challenges regarding the logistics, training and delivery of the regimen to patients eligible for HDC/IL-2.

Issue 9: Weak characterisation of uncertainty

Report section	4.3.5 (critical appraisal point 9)
Description of issue and why the EAG has identified it as important	The EAG has concerns regarding characterisation of parameter uncertainty presented in the CS and company's model. Uncertainty surrounding some parameters is still not modelled in the updated version of the model submitted by the company at the clarification stage, although the company has included the functionality to also sample some aspects related to the SoC drug costs, disease management resource use and costs and AE treatment costs. However, the EAG is still unclear about the criteria used for the exclusion of some of the parameters still maintained fixed in the probabilistic sensitivity analysis (PSA), given that upon inspection of the model, the EAG noted some inconsistency in the choice of parameters to sample or hold fixed within these categories. The EAG also observes that the HR values for OS and LFS on the comparison against oral azacitidine are assumed fixed, when they could be varied based on the results from the ITC. In addition, the EAG noted that the approach used to sample health state utility values in the PSA ignores the logical ordering of the parameters, allowing that in the same probabilistic model run, sampled utility value for the leukaemia-free on treatment to be higher than the value for LF off treatment, and the utility for post-progression disease (PD) to be higher than the values for LF states. Overall, the EAG believes that the company's PSA provides a weak characterisation of parameter uncertainty, and for this reason the results of the

	deterministic model are considered to be more reliable than those obtained from the probabilistic model.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	A revised version of the model which addresses the inconsistencies regarding the characterisation of parameter uncertainty in the company's model could help to reduce parameter uncertainty in the model. The issue around sampling health state utility values could be resolved by using the method described by Ren *et al.*

1.5 Company's modelling errors identified by the EAG

The EAG identified a few programming errors in the original model submitted at the CS, which were partially resolved by the company during the clarification process. Additional modelling errors identified by the EAG after the clarification stage are described in Section 4.3.5 (issue 1). In summary, the errors relate to the use of life tables for the England and Wales population rather than England only, programming error on the formulae for the independently fitted log-logistic OS model for the HDC/IL-2 group, programming error in the implementation of the application of the OS HR of oral azacitidine vs HDC/IL (after the inclusion of the general population mortality risk constraint instead of before), lack of adjustment of the oral azacitidine drug acquisition costs to the monthly cycles (treatment cycles of 28 days vs monthly cycles in the model), minor programming error in the mortality risks per monthly cycle from OS models, and exclusion of age-adjustment of utility values. The corrections to these errors applied in the EAG's exploratory analyses are described in Section 5.2.1.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The results of the EAG's preferred model and additional sensitivity analyses are summarised in Table 2. EA10 reflects the EAG's preferred model. Owing to unresolvable problems with the company's probabilistic sensitivity analysis (PSA, issue 9), results are presented only using the deterministic versions of the model. All results presented here include the list prices for HDC/IL-2 and other drugs. The results of the analyses including confidential price discounts for comparators are available in a separate appendix to this EAG report.

Modelling errors identified by the EAG are described in Section 4.3.5. For further details of the exploratory analyses undertaken by the EAG, see Section 5.2.

Table 2: Summary of EAG's preferred model results (deterministic), HDC/IL-2 versus oral azacitidine and versus SoC

Scenario	HDC/IL-2 vs oral azacitidine				HDC/IL-2 vs SoC			
	Inc. QALYs	Inc. costs	ICER (SWQ)	DM	Inc. QALYs	Inc. costs	ICER	DM
Company's updated model	[redacted]	[redacted]	[redacted]	[redacted]	3.20	£77,317	**£20,153**	1.2
EA1: Correction of errors	[redacted]	[redacted]	[redacted]	[redacted]	3.06	£76,809	**£20,915**	1.2
EA2: Use of stratified HR for OS from QUAZAR AML-001 to estimate outcomes for oral azacitidine group	[redacted]	[redacted]	[redacted]	[redacted]	3.06	£76,809	**£20,915**	1.2
EA3: Use of alternative LFS and OS models for HDC/IL-2 and SoC	[redacted]	[redacted]	[redacted]	[redacted]	1.74	£57,046	**£27,357**	1.2
EA4: Inclusion of additional elements for oral azacitidine costs	[redacted]	[redacted]	[redacted]	[redacted]	3.06	£76,809	**£20,915**	1.2
EA5: Inclusion of wastage-based costs for IL-2	[redacted]	[redacted]	[redacted]	[redacted]	3.06	£79,494	**£21,646**	1.2
EA6: Alternative assumption regarding administration costs for HDC/IL-2	[redacted]	[redacted]	[redacted]	[redacted]	3.06	£79,244	**£21,578**	1.2
EA7: Alternative assumptions regarding the SoC drugs	[redacted]	[redacted]	[redacted]	[redacted]	3.06	£76,835	**£20,922**	1.2
EA8: Removal of the impact of the discontinuation approach to health outcomes	[redacted]	[redacted]	[redacted]	[redacted]	3.34	£79,370	**£19,806**	1.2
EA9: Inclusion of disutility related to HDC/IL-2 injections	[redacted]	[redacted]	[redacted]	[redacted]	2.97	£76,809	**£21,520**	1.2
EA10: EAG preferred analysis	[redacted]	[redacted]	[redacted]	[redacted]	1.81	£62,851	**£28,918**	1.2
ASA1a: Use of Joshi *et al*.	[redacted]	[redacted]	[redacted]	[redacted]	2.03	£62,851	**£25,746**	1.2
ASA1b: Use of Stein *et al*.	[redacted]	[redacted]	[redacted]	[redacted]	1.86	£62,851	**£28,143**	1.2
ASA1c: Use of Russell-Smith *et al*.	[redacted]	[redacted]	[redacted]	[redacted]	1.53	£62,851	**£34,276**	1.2
ASA2: Use of alternative HRs for LFS and OS to estimate the outcomes for oral azacitine (based on lower range of estimates from ITC)	[redacted]	[redacted]	[redacted]	[redacted]	1.81	£62,851	**£28,918**	1.2
ASA3: Oral azacitidine's treatment effect assumed equivalent to HDC/IL-2	[redacted]	[redacted]	[redacted]	[redacted]	1.81	£62,851	**£28,918**	1.2
ASA4a: Costs of allo-SCT excluded	[redacted]	[redacted]	[redacted]	[redacted]	1.81	£63,567	**£29,247**	1.2
ASA4b: Costs of subsequent treatments included (based on TA827)	[redacted]	[redacted]	[redacted]	[redacted]	1.81	£62,204	**£28,620**	1.2
ASA5: Company's preferred LFS and OS models included (jointly fitted exponential models)	[redacted]	[redacted]	[redacted]	[redacted]	3.25	£84,517	**£21,647**	1.2
ASA6a: Alternative RDI assumption for HDC/IL-2 (RDI=68.9%)	[redacted]	[redacted]	[redacted]	[redacted]	1.81	£56,490	**£25,991**	1.2
ASA6b: Alternative RDI assumption for HDC/IL-2 (RDI=95.0%)	[redacted]	[redacted]	[redacted]	[redacted]	1.81	£60,423	**£27,800**	1.2

AE - adverse event; ASA - additional sensitivity analysis; DM - decision modifier; EA - exploratory analysis; EAG - External Assessment Group; HR - hazard ratio; HRQoL - Health-related quality of life; ICER - incremental cost-effectiveness ratio; Inc. - incremental.; N/a - not applicable; QALY - quality-adjusted life year; SoC – standard of care

2 Background

This chapter presents a brief summary and critique of the company's description of acute myeloid leukaemia (AML), the company's overview of the current treatment pathway and its intended positioning of histamine dihydrochloride in combination with interleukin-2 (HDC/IL-2), and a summary and critique of the decision problem addressed in the company's submission (CS).[1]

2.1 Description of the underlying health problem

2.1.1 Disease overview

The CS[1] contains a brief overview of AML, which is a type of haematologic (blood) cancer, characterised by the uncontrolled proliferation of early myeloid blood cells in the bone marrow.[2] The CS also mentions that AML starts in the bone marrow but can also be detected in the blood or other tissues (e.g. lymph nodes, liver, spleen, and central nervous system).[1] AML can develop in the form of *de novo* AML, where there is no prior history of myelodysplastic syndrome (MDS), myeloproliferative disorder, or exposure to potentially leukaemogenic therapies or agents,[3] whilst secondary AML may arise in patients who have been exposed to therapies for other malignancies, or have previous clinical history of haematological disorders.[4]

The CS highlights that AML accounts for less than 1% of all new cancer cases in the UK in 2017-2019, and is less frequent in younger patients (<45 years old) and women. Estimates reported by Cancer Research UK (CRUK) indicate that around 2,900 people are diagnosed with AML in the UK every year, with more than 40% of new cases being in people aged 75 and over, and approximately 44% of new cases being in females.[5] The Global Burden of Disease study estimated that in 2021 there were approximately 145,000 new AML cases globally and 3,580 in the UK.[6] Data also reported by CRUK indicate that in 2017-2019 the age-standardised incidence rate for AML was 4.6 per 100,000 people in the UK, and 4.7 per 100,000 people in England. There were around 2,700 annual deaths related to AML in the UK in 2017-2019, which accounts for 2% of all cancer deaths in the country. Mortality rates in the same period were highest in people aged 85 to 89, and have increased by 55% since the 1970s but have remained stable over the last decade in the UK.[5] More recent data from the Global Burden of Disease study suggest 130,189 deaths globally in 2021 related to AML.[6]

The classification of AML has evolved since the development of the French-American-British (FAB) classification of AML in the 1970s, with the identification of cytogenetic and molecular abnormalities which have implications for prognosis and treatment.[1] The World Health Organization (WHO) classification system is based on molecular genetics and cytogenetic abnormalities; major categories include: AML with recurrent genetic abnormalities, AML myelodysplasia-related (AML-MR), AML defined by differentiation, and myeloid sarcoma.[7] Recommendations for diagnosis and management of

AML in adults published by the European LeukemiaNet (ELN) includes a revised classification system by the International Consensus Classification (ICC), based on genetic risk classification at diagnosis: favourable risk, intermediate risk and adverse risk.[8, 9] People in the adverse risk group have a greater risk of relapsing or not responding to treatment.[10]

Risk factors for AML include age, smoking status, ionising radiation, some types of blood disorders (e.g., MDS, myeloproliferative neoplasms such as polycythaemia rubra vera [PCV] and chronic myeloid leukaemia [CML], and chronic myelomonocytic leukaemia [CMML]), particular autoimmune conditions (e.g., rheumatoid arthritis, autoimmune haemolytic anaemia, and ulcerative colitis), previous chemotherapy treatments (e.g., for Hodgkin lymphoma or breast cancer), exposure to benzene or petrol at the workplace, and certain rare inherited conditions (e.g., Fanconi anaemia, Bloom syndrome, and Li Fraumeni syndrome).[11]

Patients are usually diagnosed with symptoms or signs of AML, which might include one or more of the following: general weakness or fatigue, fever, frequent infections, easily bruised skin, ecchymoses and unusual bleeding, dyspnoea, unexplained weight loss, swollen lymph nodes, pain in bones or joints, pale skin, and abdominal discomfort or feelings of fullness and early satiety.[12, 13] Diagnostic tests and procedures may include tests to establish the diagnosis (complete blood count [CBC], bone marrow aspiration, bone marrow trephine biopsy, and immunophenotyping by flow cytometry), genetic analyses (cytogenetics and screening for gene mutations and for gene rearrangements), evaluation of medical history (demographics and medical history, including bleeding history, analysis of comorbidities, and detailed family history), and additional tests and procedures (e.g., physical examination, lumbar puncture, biochemistry, coagulation tests, tests to check for infections such as human immunodeficiency virus, hepatitis A, B and C herpes simplex, varicella-zoster, Epstein-Barr viruses, and cytomegalovirus, and others).[8]

The primary objective of treatment for AML is to achieve disease control and, ideally, eradication of the disease. AML treatment is generally divided into intensive or non-intensive treatment. The non-intensive treatments include chemotherapy as the main treatment.[14] Intensive therapy usually involves an initial treatment phase aiming to induce a complete response (CR), followed by consolidation and/or maintenance therapy phases designed to deepen the achieved remission and maximise the duration of the response.[8] Other treatment options may include allogenic hematopoietic stem cell transplant (allo-HSCT), radiotherapy or leukapheresis.[14]

Patients considered fit for intensive therapy may receive anthracyclines and cytarabine, or alternative options such as fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-

IDA), with consolidation therapies involving regimens which include intermediate or high-dose cytarabine.[8] In the UK, the National Institute for Health and Care Excellence (NICE) has recommended liposomal cytarabine–daunorubicin (TA552, for therapy-related AML or AML with MDS-related changes in adults)[15] and gemtuzumab ozogamicin with daunorubicin and cytarabine (TA545, for Cluster of Differentiation 33 [CD33]-positive patients)[16] for both induction and consolidation phases in certain groups. Patients with Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3 (FLT3)-mutations may receive FLT3 inhibitors, such as midostaurin (TA523)[17] or quizartinib (TA1013)[18] in combination with intensive therapy in both phases.

Döhner *et al.* [8] describes the main objective of maintenance therapy as being to deliver a minimally toxic therapy capable of reducing the risk of relapse, and mentions azacitidine administered subcutaneously, orally administered azacitidine and midostaurin (for FLT3 mutation positive patients) as therapy options for the maintenance phase. Current NICE recommendations for maintenance therapy include oral azacitidine for patients who are ineligible for haematopoietic stem cell transplant (HSCT, TA827),[19] and patients with FLT3 mutations who received midostaurin or quizartinib during induction and consolidation may continue these agents as monotherapy during maintenance (TA523 and TA1013).[17, 18] Off-label use of sorafenib in patients with FLT3-internal tandem duplication (FLT3-ITD) AML after allo-HSCT has been also recommended by the NHS England Clinical Priorities Advisory Group committee.[20]

Patients considered not suitable for intensive therapy may receive azacitidine in combination with venetoclax, low dose cytarabine with venetoclax, azacitidine with ivosidenib if isocitrate dehydrogenase 1 (IDH1) mutation positive, or best supportive care.[8] Non-intensive chemotherapies recommended by NICE include azacitidine (TA218),[21] venetoclax with low dose cytarabine (TA787),[22] venetoclax with azacitidine (TA765),[23] and ivosidenib with azacitidine for patients with IDH1 R132 mutation (TA979).[24] Patients unable to tolerate active intensive or non-intensive treatment options may receive blood and/or platelet transfusions and other supportive care measures with the objective of optimising quality of life and decrease the incidence of cytopenia-related complications.[8]

The CS highlights age, presence of comorbidities, general health status (functional status), genetic alterations and response to treatment as prognostic factors for AML,[1] with younger patients, with good functional status and without some genetic alterations (e.g., FLT3 negative patients, non-adverse karyotype, no adverse molecular mutations) having a more favourable prognosis, whilst typical survival prognosis for older, with impaired functional status, concomitant diseases, secondary AML and certain genetic alterations is generally poor.[1] Data reported by CRUK suggest that survival is strongly influenced by age, with survival rates of around 60% at 5 years for patients younger than 40 years old,

which declines to around 35% for those aged between 50 and 59, 15% for those aged between 60 and 69, and only 1% for those aged 80 and over.[25]

2.1.2 Disease burden

The CS[1] does not include any considerations about the burden of AML on patient's health-related quality of life (HRQoL). The CS highlights in Section 3.13 the HRQoL burden for caregivers and family of hematologic cancer patients, whereby the caregiver quality of life (QoL) follows patients' symptom burden and social well-being, with worse outcomes being associated to phases of uncontrolled disease or uncertainty. Grover *et al.,*[26] in a study with 30 family caregivers of adolescent and adult patients with AML in a tertiary hospital in India, reported a high level of caregiver burden in caregivers of patients with AML, with families from middle or low socio-economic status reporting more financial burden, and caregivers who have lower social support experiencing higher level of burden. Nielsen *et al.*[27] investigated the QoL and the impact of caregiving in family caregivers of haematological cancer patients in 375 patients and 140 caregivers in Denmark and its association with patient symptom burden. The study reported a high symptom burden in patients with haematological cancers, which was significantly associated with caregiver QoL, including sleep, psychological well-being, and emotional health.

The CS[1] also highlights that any reduction in relapse risk and expanded periods of controlled disease as a result of HDC/IL-2 therapy would be expected to reduce caregiver burden during 'no-treatment' phases, and that not including the impact on HRQoL in the economic analysis submitted for the current Technology Appraisal (TA) likely biases the QALY results by omitting material family and caregiver QoL benefits.

The Global Burden of Disease study report estimated that approximately 4.14 million total disability-adjusted life years (DALYs) and 130,189 deaths were attributed to AML globally in 2021, with 3,430 deaths and 69,914 DALYs attributed to the disease in the UK. In the same year, 69,056.42 years of life lost (YLL) and 857.58 years lived with disability (YLDs) were estimated to be associated with AML in the UK.[6]

2.1.3 Description of the technology

The CS (Section 1.2)[1] describes histamine dihydrochloride (HDC) as an immunotherapy, with mechanism of action which involves the modulation of the immune response to effectively target residual leukaemic cells, particularly by enhancing the cytotoxic activity of natural killer (NK) cells and T cells. The Summary of Product Characteristics (SmPC) for HDC describes its function as *"to protect lymphocytes, in particular NK cells and T cells, which are responsible for the immune-mediated*

destruction of residual leukaemic cells", whilst interleukin-2 (IL-2) would be responsible for promoting *"the functions of NK cells and T cells by activating the anti-leukaemic properties of these cells and by expanding these cell populations by inducing cell cycle proliferation."*[28] The SmPC also describes the mechanism by which HDC improves the anti-leukaemic function of lymphocytes not to be completely established. Martner *et al.*[29] describes it as reducing the production of immunosuppressive reactive oxygen species (ROS) from myeloid cells and avoiding ROS-induced inactivation and apoptosis of NK cells, whilst the IL-2 component aims at promoting antitumor functions of NK cells.

The HDC/IL-2 regimen is described by the company[1] as being composed of 2 subcutaneous injections twice daily, administered in treatment cycles of 21 days followed by a non-treatment period with the duration defined by which cycle treatment the patient is on (three weeks in cycles 1-3 and six weeks in cycles 4-10). The full treatment with HDC/IL-2 ideally starts 6 to 8 weeks after the patient's last chemotherapy and has a maximum duration of 10 cycles, or approximately 18 months.

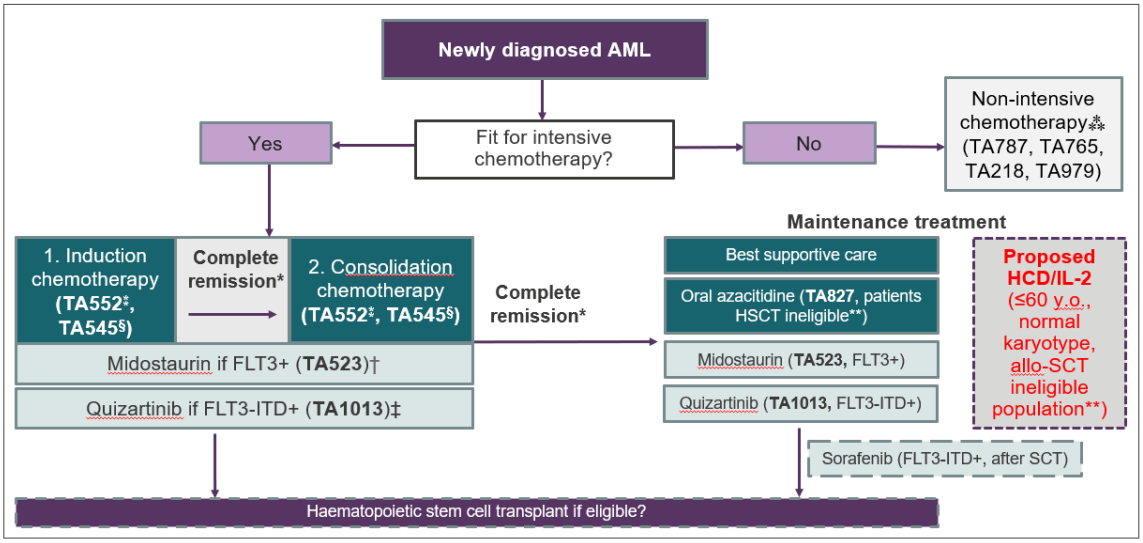
The company obtained a marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) in August 2025. The SmPC for HDC/IL-2 states that *"Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection maintenance therapy is indicated for adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60."* At the clarification stage (clarification response question A1),[30] the company clarified that the wording in the approved SmPC should be considered an exclusion of the group over 60 years of age from the group of patients who would be considered eligible for treatment with HDC/IL-2. The company stated that although not explicitly contraindicated, the use of HDC/IL-2 in this group is not supported and, therefore, it *"would be considered "off-label" use and the decision and responsibility to prescribe in this manner would therefore lie with the prescribing healthcare professional on a case-by-case basis."*

2.2 Company's overview of current service provision

2.2.1 Current treatment pathway and proposed positioning of HDC/IL-2

Section 1.3 of the CS[1] outlines the company's view of the current treatment pathway for adult patients with AML. The company's view of the current treatment pathway, together with the proposed positioning of HDC/IL-2, is reproduced in Figure 1 (clarification response, question A7).[30]

Figure 1: Current treatment pathway for AML and proposed positioning for HDC/IL-2 (adapted by the EAG from TA827 committee meeting slides)



*Complete remission or complete remission with incomplete blood count recovery.
‡ Liposomal cytarabine–daunorubicin for therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
§Gemtuzumab ozogamicin, with daunorubicin and cytarabine, for untreated de novo CD33+ AML patients, except acute promyelocytic leukaemia, in people ≥15 years
** Includes people eligible for HSCT but who choose not to undergo the procedure.
† Midostaurin given with standard daunorubicin plus cytarabine during induction therapy and high-dose cytarabine during consolidation therapy.
‡ Quizartinib given with standard cytarabine and anthracycline chemotherapy during induction therapy and standard cytarabine during consolidation therapy
⁂Venetoclax with low dose cytarabine (TA787), venetoclax with azacitidine (TA765), ivosidenib with azacitidine (IDH1 R132+ patients, TA979), azacitidine (HSCT ineligible patients, TA218)

The CS describes the proposed positioning of HDC/IL-2 as *"a maintenance immunotherapy after consolidation therapy to AML patients with normal karyotype who are in first complete remission and 60 years old or less and who are not considered suitable for allogeneic stem cell transplant."* The company also stated that the proposed positioning of HDC/IL-2 aligns with its approved marketing authorisation, but in fact corresponds to a narrower subgroup of patients, of those with normal karyotype (clarification response, question A1).[30] The company's target population in this appraisal, therefore, corresponds to patients in first complete remission (CR1), ≤60 years-old, with normal karyotype and considered ineligible for allogeneic stem cell transplant (allo-SCT), which corresponds to the subgroup of patients in the Brune *et al.*[31] study which were included in the *post-hoc* analysis reported by Nilsson *et al*.[32] Whilst not shown in the diagram, HDC/IL-2 is expected to be given alongside standard of care (SoC).

The relevant part of the treatment pathway for this appraisal relates to the lower right portion of the figure (maintenance treatments for patients in first remission, after receiving induction with or without consolidation therapies). The company's intended positioning of HDC/IL-2 is as an alternative to SoC or oral azacitidine (clarification response, question A1),[30] since patients with FLT3 mutations would be expected to receive FLT3 inhibitors, such as midostaurin, quizartinib and sorafenib, in addition to patients eligible for sorafenib having received SCT, and therefore would not be eligible to receive HDC/IL-2. The company estimates that annually 50 to 100 people with AML in England would be eligible for treatment with HDC/IL-2, excluding patients with a FLT3 mutation.

2.2.2 EAG's critique of the company's treatment pathway and positioning of HDC/IL-2

The clinical advisors to the External Assessment Group (EAG) considered that the company's description of the current treatment pathway is a generally reasonable representation of the current treatment pathway for patients with AML. The company's proposed positioning of HDC/IL-2 within the pathway is consistent with the final NICE scope[33] and the marketing authorisation for HDC.[28]

The EAG notes that the indication for HDC/IL-2 within this appraisal relates to AML patients in CR1, less than 60 years old, have a normal karyotype and are considered ineligible for allo-SCT at the start of maintenance treatment. However, the CS does not specifically exclude any groups of patients based on genetic mutations, with the company only mentioning that patients with FLT3-positive mutations will likely receive a targeted therapy (FLT3 inhibitor) instead of HDC/IL-2. The EAG's clinical advisors agreed that patients with FLT-3 mutations would preferably receive targeted therapies. As part of the clarification response company (question A2[c]), the company clarified that its intended positioning of HDC/IL-2 is specifically in patients who do not have a FLT3 mutation. Issues related to the population, intervention and comparators are discussed in Sections 2.3.1, 2.3.2 and 2.3.3 of the report, respectively.

2.3 Critique of the company's definition of decision problem

This section presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final scope issued by NICE[33] and addressed in the CS is presented in Table 3. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 3: Summary of decision problem (adapted from CS, Table 1, with amendments made by the EAG for brevity)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with AML who are in first remission.	Adult AML patients who have undergone intensive therapy with induction and consolidation treatment, who are not considered suitable for allogeneic stem cell transplant, who are in CR1 and 60 years old or younger.	*"The eligibility criteria for patients in the pivotal Phase III RCT published by Brune, 2006 included patients who had undergone treatment with both induction and consolidation treatment and who were not considered suitable for allogeneic stem cell transplant. For this reason, we believe that the same patients should be considered for this technology appraisal."*	The company's target population aligns with the subgroup of patients from the Brune *et al.* study reported in Nilsson *et al.*,[32] however it is narrower than the population eligible for HDC/IL-2 in the marketing authorisation (SmPC).[28] The company explicitly excluded patients with FLT3 mutations from the targeted population in clarification response A1.[30]
Intervention	Histamine dihydrochloride with interleukin-2 as maintenance therapy.	Histamine dihydrochloride with interleukin-2 as maintenance therapy.	*"Not applicable – no difference to final scope."*	Aligned with the HDC/IL-2 SmPC[28] and NICE final scope.[33]
Comparator(s)	Established clinical management without histamine dihydrochloride with interleukin-2 including but not limited to: • oral azacitidine for people who cannot have or do not want a HSCT • midostaurin for people with an FLT3-mutation • sorafenib, after a stem cell transplant, for people with an FLT3-ITD mutation • quizartinib for people with	Best supportive care	*Section edited by the EAG, with paragraphs curtailed or amended for brevity:* *"The comparator used in the pivotal Phase III RCT published by Brune, 2006 was best supportive care and hence we believe that this should be considered as the main comparator within this appraisal.* *The full licensed indication for HDC/IL-2 in section 4.1 ("Therapeutic indications") of the*	The CS only included SoC as a comparator;[1] oral azacitidine was included as a comparator in the updated version of the economic analysis submitted at clarification.[30] The company did not include the remaining comparators listed in the final NICE scope (midostaurin, quizartinib, sorafenib and cytarabine) based on either one of the following arguments: (i) being a FLT3 target therapy, for which patients with FLT3 mutations

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	an FLT3-ITD mutation • cytarabine alone or in combination with other antineoplastic agents • best supportive care		*approved SmPC includes the qualifying statement: 'The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.' (...)* *The qualifying statement about age is based on the univariate analysis of Cox proportional hazards modelling of prognostic factors for LFS in the Brune, 2006 study population which revealed that no clinical benefit was seen in patients aged older than 60 years. In addition, post-hoc sub-group analyses by Nilsson, 2020 showed no benefit with HDC/IL-2 for patients with normal karyotype in CR1 who are 60 years or older.* *The clinical evidence supporting the patients who are 60 years old or less should therefore be evaluated within the context of this appraisal for HDC/IL-2.* *Interpretation of results from clinical trials of AML maintenance therapy should account for significant variability in the study populations with respect to age and disease*	would have already received during induction and consolidation treatment, and therefore would not switch to HDC/IL-2; (ii) being used in patients who had received allo-HSCT (in addition to (i)); or (iii) not being used in clinical practice in the UK in patients eligible for intensive induction and consolidation treatment, and therefore in patients who reach maintenance phase. The EAG's clinical advisors agree with the view that patients with FLT3 mutations would remain with FLT3 targeted therapies during maintenance treatment where possible. The EAG also agrees that given the information on genetic subtypes of patients recruited in the Brune *et al.* study is unavailable, the level of uncertainty in the results of indirect treatment comparisons (ITCs) between HDC/IL-2 versus midostaurin, sorafenib and quizartinib is likely to be high. The EAG also notes that the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			features. Cross-trial comparisons should not be made where the study populations are dissimilar (Patel, 2021). *Oral azacitidine* *It is acknowledged that oral azacitidine is recommended by NICE (TA827) for the maintenance treatment of AML patients who are in complete remission and cannot have or do not want a HSCT. On this basis, it would seem a relevant comparator to HDC/IL-2.* *However, interviews with 17 UK haematologists specialising in the treatment of AML patients, 15 of them mentioned that the evidence from the pivotal QUAZAR randomised controlled study included only older AML patients who were ≥55 years and they were curious why this was not reflected in the NICE recommendation. They also stated that there was limited use of oral azacitidine in the UK. This is supported by NHS Business Services Authority (NHSBSA) Secondary Care Medicines Data (SCMD): in March 2024 and March 2025, treatment*	marketing authorisation and NICE recommendation for oral azacitidine do not restrict its use in adults by age groups, therefore patients under 55 years may receive oral azacitidine. The EAG's clinical advisors also agreed with the exclusion of cytarabine as a comparator, given it is not routinely used in clinical practice in the UK in the target population of this appraisal.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			courses were prescribed for approximately 60 and 65 patients, respectively. (…) *Considering the approved indication for HDC/IL-2 immunotherapy is limited to AML patients in first remission who are 60 years or younger, our feasibility assessment concluded that there is likely to be very little data available on the use of oral azacitidine in a similar group of patients where HDC/IL-2 is specifically indicated (patients 55-60 years of age).* *If we used the data from the QUAZAR study for an indirect treatment comparison, then this is at best likely to produce high levels of uncertainty and at worst possibly even be misleading due to the differing ages and prognoses of the eligible patients. (…)* *Midostaurin, Sorafenib and Quizartinib* *NICE has previously approved these therapies as a maintenance treatment for AML patients with FLT3 mutations (TA523) and quizartinib*	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			for AML patients with FLT3-ITD mutations (TA1013). *There are no comparative data published on the efficacy of HDC/IL-2 versus these therapies as maintenance treatment in people with FLT3-mutation-positive AML or sorafenib/quizartinib for FLT3-ITD mutations.* *The clinical experts involved with the oral azacitidine appraisal (TA827) explained that most people with FLT3- mutation positive AML would have targeted treatment with midostaurin during induction, consolidation and maintenance treatment and would be unlikely to switch to oral azacitidine.* *We believe that it would be a similar situation with HDC/IL-2, where few patients would switch from midostaurin to HDC/IL-2 during maintenance.* *We note that midostaurin was considered a relevant comparator for people with FLT3-mutation positive AML in the oral azacitidine appraisal*	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			and an indirect treatment comparison was conducted. *We note that the EAG* [in TA827] *also considered that survival analyses for this population are likely to be biased because of limitations associated with the indirect treatment comparison.* *The committee concluded that the results of the indirect treatment comparison comparing oral azacitidine with midostaurin were highly uncertain and considered this in its decision making.* *There are no data from the pivotal Phase III RCT published by Brune, 2006 on the genetic subtypes of patients recruited to the study and hence there are very limited data on the efficacy of HDC/IL-2 in AML patients with FLT3 mutations and FLT3-ITD mutations.* *For this reason, we have not attempted an indirect treatment comparison. As indicated above, without further data on the efficacy of HDC/IL-2 in genetic subtypes, the*	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			level of uncertainty in an indirect treatment comparison versus midostaurin is likely to be very high. *HDC/IL-2 would therefore likely be of most benefit to patients whose AML does not have an FLT3-mutation or FLT3-ITD mutation.* *Cytarabine* *In TA827, the NICE committee concluded that low dose cytarabine and subcutaneous azacitidine are not used routinely after induction and consolidation chemotherapy, being more commonly used when intensive chemotherapy is unsuitable, and therefore very few people had maintenance treatment with low dose cytarabine and subcutaneous azacitidine. The same rationale applies for the comparison with HDC/IL-2."*	
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Minimal residual disease • Remission rate • Adverse effects (AEs) of treatment • Health-related quality of	• Leukaemia-free survival (LFS) • OS • Remission rate • AEs of treatment • HRQoL	*"Not applicable – no difference from final scope."*	The EAG notes that neither the CS nor the company's clarification response[1, 30] report clinical results for minimal residual disease, remission rate or HRQoL. The company presents the results for LFS which is used as equivalent to PFS. The

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	life (HRQoL)			company justify the absence of results for HRQoL due to the unavailability of data for this outcome from Brune *et al.*, despite the company's attempts to obtain it from the study's authors.[1, 30]
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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. The availability and cost of biosimilar products of should be taken into account. The availability of any commercial arrangements for the intervention, comparator and	Cost-utility analysis using a three-state partitioned survival model based on leukaemia-free survival and overall survival.	N/R	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	subsequent treatment technologies will be taken into account.			
Subgroups	If the evidence allows the following subgroups will be considered: • people who are eligible or ineligible for allogeneic stem cell transplant • people with or without an FLT3 mutation • people with or without an FLT3-ITD mutation	Adult AML patients who have undergone intensive therapy with induction and consolidation treatment, are not suitable for allogeneic stem cell transplant, have normal karyotype, are in CR1 and are less than 60 years old.	*"The pivotal Phase III RCT published by Brune, 2006 excluded patients who had prior allogeneic stem cell transplant (allo-SCT) and hence enrolled only patients who were considered ineligible for the therapy. Consequently, the main evidence supporting maintenance immunotherapy with HDC/IL-2 is in AML patients who are not considered suitable for allo-SCT.* *The pivotal Phase III RCT published by Brune, 2006 was conducted prior to routine genetic subtype testing and hence there are limited data on the efficacy of HDC/IL-2 within those patients with FLT3 mutations and FLT3-ITD mutations.* *There are post-hoc analyses data however on the efficacy of HDC/IL-2 in AML patients with normal karyotype in CR1 and less than 60 years old which indicate improved efficacy.* *For this reason, this population has*	The CS and the company's clarification response[1, 30] report LFS and OS outcomes for the following subgroups of the Brune *et al.* study: ITT population, CR1, CR1 and ≤ 60 years old, CR1, ≤ 60 years old and normal karyotype. Results are not presented for any of the subgroups listed in the scope. The EAG notes that Burne *et al.* study did not present data for these subgroups. The evidence presented for the ITT, CR1, CR1 and ≤ 60 years old is not directly used to inform the results of the economic analysis presented by the company, with exception of AE incidence rates.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			been presented as the base case in the economic analysis."	
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The full licensed indication for HDC/IL-2 in section 4.1 ("Therapeutic indications") of the approved SmPC includes the qualifying statement: 'The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.'	"*It is noted that NICE guidance will only be issued in accordance with the marketing authorisation.* *The full licensed indication for HDC/IL-2 in section 4.1 ("Therapeutic indications") of the approved SMPC includes the qualifying statement: 'The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.'* *The approved indication clearly states that the evidence for the therapy is best supported in patients who are 60 years old or less and hence should exclude those who are older than 60 years.* *The qualifying statement about age is based on the univariate analysis of Cox proportional hazards modelling of prognostic factors for leukaemia free survival (LFS) in the Brune, 2006 study population which revealed that no clinical benefit was seen in patients aged older than 60 years.*	The company, in response to EAG's clarification question A1,[30] clarified that the use of HDC/IL-2 in patients over 60 years is not supported and the wording in therapeutic indication's section of the HDC/IL-2 SmPC should be considered an exclusion of this group.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			In addition, post-hoc sub-group analyses by Nilsson, 2020 showed no LFS or OS benefit with HDC/IL-2 for patients with normal karyotype in CR1 who are 60 years or older. Since the indication clearly states that the efficacy of HDC has not been fully demonstrated in patients older than age 60, then this population should be excluded from the evaluation, in accordance with NICE guidelines."	

allo-HSCT - allogeneic hematopoietic stem cell transplantation; AE - adverse event; AML - acute myeloid leukaemia; CR1 - first complete remission; CS - company's submission; EAG - External Assessment Group; FLT3 - FMS-like tyrosine kinase 3; FLT3-ITD - FLT3- internal tandem duplication; HDC/IL-2 - histamine dihydrochloride with interleukin-2; HSCT - haematopoietic stem cell transplant; HRQoL - Health-related quality of life; ITC - indirect treatment comparisons; ITT - intention -to-treat; LFS - leukaemia-free survival; N/a – not applicable; OS - overall survival; PFS - progression free survival; RCT - randomised controlled trial; SmPC - Summary of products characteristics; SoC - standard of care.

2.3.1 Population

The patient population in the CS relates to adults with AML "*who have a normal karyotype, have completed induction and consolidation treatment, are in first remission (CR1), are not considered suitable for allogeneic hematopoietic stem cell transplantation (allo-HSCT) and are 60 years old or younger"*.[1] This population is narrower than the population defined in the final NICE scope,[33] which defined the population as people with AML who are in first remission, and broadly in line with the SmPC for HDC (CS Appendix A), with the only difference being that the marketing authorisation does not restrict eligibility to HDC only to patients with normal karyotype.[28]

This indication is also in line with a *post-hoc* subgroup analysis of data from the Brune *et al.*[31] study presented in Nilsson *et al.*,[32] which corresponds to the main source of clinical evidence included in the CS. The Brune *et al.* study (NCT00003991) was conducted between June 1998 and October 2004 across 100 sites in Australia, Canada, Europe, Israel, New Zealand and the USA. There were no UK-based dedicated centres, but 3 patients from the UK were recruited in the trial.[34] The EAG notes that this clinical study was not conducted by the company from this current appraisal; the Brune *et al.* publication lists Maxim Pharmaceuticals as the study sponsor. The EAG's clinical advisors suggested that the population recruited into this trial broadly reflects a population with AML who would be treated in England, based on their baseline characteristics. However, patients currently eligible for maintenance would have received a different range of previous therapies, since the therapeutic landscape for AML has changed significantly since the study was conducted.

HDC/IL-2 has received an UK marketing authorisation in August 2025. The SmPC states that HDC/IL-2 is indicated for adult patients with AML in first remission, and that the efficacy of HDC/IL-2 has not been fully demonstrated in patients aged above 60 years.[28] In response to EAG's clarification question A1,[30] the company clarified that the wording in the SmPC regarding the efficacy of HDC/IL-2 in patients over 60 years old leads to an outright exclusion of this group of patients in terms of eligibility for treatment with HDC/IL-2 by clinicians, and that its use in patients over 60 years is not supported.

As part of clarification response to questions A2(a) and (b),[30] the company also explained that the target population includes only patients with a normal karyotype, and that this definition in AML refers to leukaemic cells which appear to have a normal set of chromosomes when viewed under a microscope, with absence of large-scale chromosomal abnormalities, such as translocations, inversions, deletions, or gains. The company also clarified that a correlation between karyotypes and genetic subtypes is not exact, with the latter being used in the 2022 ELN recommendations for risk classification at initial diagnosis, which corresponds to a more recent classification system. The company also mentioned that some genetic subtypes (such as nucleophosmin 1 [NPM1]) are predominantly normal karyotype, but a

smaller percentage can also be abnormal karyotype (clarification response, question A2[c]), and commented that the assessment of the karyotype status is still routinely conducted as part of protocols for initial diagnostic of AML in the UK (clarification response, question A2[b] and [d]).

Patients who do have a FLT3 mutation are not excluded from eligibility to treatment with HDC/IL-2 in England according to the SmPC wording, but the company believes that HDC/IL-2 would likely be of most benefit to patients whose AML does not have an FLT3-mutation or FLT3-ITD mutation, given that these patients are likely to be given FLT3 inhibitors, and few, if any, patients would switch from these targeted therapies to HDC/IL-2 during maintenance, based on clinical expert opinion in NICE TA827.[19] Therefore, the company clarified that its intended positioning of HDC/IL-2 is in patients who do not have a FLT3 mutation (clarification response question A2[c]).[30] The company also stated that data from Brune *et al.*[31] on the efficacy of HDC/IL-2 are not available by genetic subtypes, due to molecular testing for genetic subtypes not being routine practice at the time of the study patients' recruitment. The company, based on Schlenk *et al.*,[35] also reported that within the group of normal karyotype AML, NPM1 mutations account for approximately 40–50% of cases, whilst FLT3-ITD accounts for approximately 30–40% of cases, and both mutations together account for >75% of all normal karyotype AML (clarification response, question A26).[30] The EAG notes that it is unclear whether the majority of patients who would receive HDC/IL-2 would correspond to patients with NPM1 mutations, if HDC/IL-2 would be recommended.

2.3.2 Intervention

The intervention considered in the CS[1] is HDC which is manufactured by Brancaster Pharma Ltd. Each vial of HDC with 0.5ml solution for injection contains 0.5mg of HDC. HDC is administered via subcutaneous injections at a dosage of 0.5mg twice daily, in combination with IL-2 (aldesleukin). The recommended dose for IL-2 is 16,400 IU/kg, also administered twice daily as a subcutaneous injection, 1 to 3 minutes prior to the administration of HDC. The SmPC recommends the HDC administration to be given slowly, over 5 to 15 minutes, under the supervision of a physician experienced in the management of AML.[28]

Both regimens are administered for 10 treatment cycles, which consists of a treatment period of 21 days followed by either three (cycles 1 to 3) or six (cycles 4 to 10) weeks without receiving the therapy. The SmPC also recommends the monitoring of patients for expected adverse events (AEs) and laboratory changes associated with treatment.[28] The SmPC mentions that the first therapy dose should be administered under direct supervision of a physician, but subsequent doses may be self-administered at home if the patient demonstrates adequate injection skills and a good understanding of necessary precautions, but preferably these doses should be supervised by *"an adult family member, friend, or*

other care provider who is capable of responding appropriately should signs or symptoms of hypotension occur". Patients who experience significant change in vital signs at the first dose should be monitored during subsequent treatments,[28] however, it is unclear in which setting the subsequent doses would be administered for the entire 10 treatment cycles in these cases.

HDC was first granted a licence with the European Medicines Agency (EMA) on 7th October 2008 (under the brand name Ceplene®), and has received an UK marketing authorisation on 1st August 2025. The current MHRA license indication is for the treatment of adult patients with AML in first remission, concomitantly with IL-2. Section 4.1 of the SmPC also states that the efficacy of HDC *"has not been fully demonstrated in patients older than age 60."*[28]

The anticipated list price per pack of 14 vials for injections (7 days' supply) is £1,200. The company has not proposed a Patient Access Scheme (PAS).

The SmPC states that treatment with HDC is contraindicated in patients with significantly compromised cardiac function, receiving systemic steroid therapy, clonidine and H2 blocking agents, or hypersensitivity to the active substance or to any of the excipients, and who have received an allogenic stem cell transplant, are pregnant or breast feeding.[28] The SmPC mentions temporary or permanent treatment discontinuation for patients experiencing grade 1-3 neurologic toxicity, grade 3-4 generalised toxic dermatitis, grade 2 (including cardiac function, renal, hepatic) toxicity, grade 3 and 4 (including hypotension, arrhythmia) toxicities, fever (when IL-2 should be discontinued for 24 hours), and localised toxic dermatitis. Within the Brune *et al.* study, the criteria for discontinuing treatment with HDC/IL-2 included [redacted].[34]

In response to clarification question A3(a),[30] the company stated that the HDC/IL-2 regimen is feasible and acceptable to patients in routine clinical practice, citing the incidence of AEs that led to dose reductions or treatment interruption in 26% of patients in Brune *et al.,*[31] with the most common reasons being local inflammatory reactions at the injection sites (7.1%) or fever (5.1%). The company also stated that the experience from a clinical centre in Sweden reports that those AEs were more likely to occur during the first three treatment cycles, and that after the patient is trained to self-administer the HDC/IL-2 regimen in the hospital setting during the first day of the first treatment cycle, haematology nurse specialists would routinely contact the patient on day 4 of each cycle to discuss any issues or concerns related to treatment administration or AEs. Patients unable to self-administer at home, described by the company as exceptional cases, would be able to be assisted with the procedure by a partner and/or carer (clarification response, question A3[b]).[30]

2.3.3 Comparators

The final NICE scope[33] lists six comparators: (i) oral azacitidine (for people who cannot have or do not want a HSCT); (ii) midostaurin (for people with FLT3-mutation); (iii) sorafenib (after SCT in people with FLT3-ITD mutation); (iv) quizartinib (for people with FLT3-ITD mutation); (v) cytarabine (alone or in combination with other antineoplastic agents); and (vi) best supportive care (BSC).

The comparators considered by the company within the company's health economic model correspond to SoC and oral azacitidine, with oral azacitidine being included at the clarification stage. Clinical outcomes are presented for SoC at the clinical section of the of the CS,[1] whilst these are presented for oral azacitidine in clarification response question A28.[30] The company still maintained its view that the main evidence case for oral azacitidine is in patients who are 55 or older, and an indirect treatment comparison (ITC) between HDC/IL-2 and oral azacitidine is likely to produce high levels of uncertainty, given the differences between the populations from Wei *et al.*[36] and Brune *et al.*,[31] in particular related to age and prognosis (clarification response, question A5[a]).[30] Quantitative evidence that the use of oral azacitidine in clinical practice in England is restricted only to patients aged 55 years and older was not provided (i.e., no age-stratified real-world usage data of patients currently receiving treatment was presented, such as clinical audit or patient registry data), although the company provided qualitative clinician feedback suggesting uptake in patients aged 55 years and older may be limited as the QUAZAR AML-001 trial only included patients aged 55 years and older.. The company suggested that the potential overlap between the populations with AML who would be eligible for both HDC/IL-2 and oral azacitidine would be very small, based on the likely number of patients who specifically are between 55 and 60 years old (clarification response, question A5[c] and [c]).[30] The EAG highlights that there is no formal age restriction for oral azacitidine stated in the marketing authorisation or in the NICE recommendation (NICE TA827),[19] and therefore the size of the population with AML who would be eligible for both drugs is unclear, but could be bigger than this age group suggested by the company.

The CS (Section 1.1)[1] and clarification response (question A6)[30] state the following arguments for excluding the remaining comparators:

(a) midostaurin: (i) no comparative data published on the efficacy of HDC/IL-2 versus midostaurin as maintenance treatment in people with FLT3-mutation-positive AML; (ii) most patients with FLT3-mutated AML would have received targeted therapy with midostaurin during induction, and consolidation stages, and would be unlikely to switch to non-targeted therapies on maintenance treatment (based on clinical expert statements in TA827, which would also happen for HDC/IL-2); (iii) a survival analyses conducted based on an ITC between midostaurin and oral azacitidine in the FLT3+ population was considered highly uncertain by the committee in TA827,[19] and given the lack of data on the efficacy of HDC/IL-2 in genetic subtypes in Brune

et al., the results of an ITC for HDC/IL-2 versus midostaurin would also be considered highly uncertain;

(b) sorafenib: similar arguments to (a) would apply to a comparison against sorafenib, with the difference of data for sorafenib being related to FLT3-ITD-mutated patients; the EAG notes that patients who would be eligible for sorafenib (after SCT) would not be eligible for HDC/IL-2;

(c) quizartinib: similar arguments to (a) would apply to a comparison against quizartinib, with the difference of data for sorafenib being related to FLT3-ITD-mutated patients;

(d) cytarabine: the committee in TA827[19] considered that this drug is not routinely used in patients in the UK as part of maintenance therapy, this therapy is used instead in patients for whom intensive chemotherapy is considered unsuitable.

2.3.4 Outcomes

Outcomes specified in the final NICE scope[33] include:

- Overall survival (OS)
- Progression-free survival (PFS)
- Minimal residual disease
- Remission rate
- AEs of treatment
- HRQoL

The CS[1] reports clinical results for OS, leukaemia-free survival (LFS) and AEs. In clarification response question A27,[30] the company explained that HRQoL data were not available from the Brune *et al.* study, despite the company's attempts to obtain it by contacting the study's authors. The company's model includes data relating to OS, LFS and AEs from the clinical study, and HRQoL from external sources (see Section 4.2.4.3).

2.3.5 Other relevant factors

The final NICE scope does not identify any special considerations related to equity or equality.[33] The CS[1] does not include any discussions regarding issues of equality relevant to this appraisal, or related to quality-adjusted life year (QALY) weighting for disease severity. This is discussed further in Section 5.3.

3 Clinical effectiveness

This section presents a summary and critique of the clinical-effectiveness evidence included in the CS. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a summary and critique of the included studies and clinical-effectiveness analyses. Sections 3.4 critiques any ITCs presented by the company. Section 3.5 covers additional work done by the EAG, and Section 3.6 presents the conclusions of the clinical-effectiveness section.

3.1 Critique of the methods of review

The clinical evidence submitted by the company for HDC/IL-2 in the maintenance treatment of AML is comprised of:

- A systematic literature review (SLR).
- A summary and results of an open label, randomised, multicentre, phase III trial (Brune *et al.*,[31] NCT00003991[37]) and *post-hoc* analyses (Nilsson *et al.*[32])
- A summary and results of ITCs comparing HDC/IL-2 with oral azacitidine, as a part of a response to clarification question A28.[30]

Full details of the company's SLR are presented in Section 2 of the CS[1] and CS Appendix B and C. In general, the EAG noted that appropriate methods were used in the conduct of the clinical effectiveness review, while also identifying some concerns regarding certain aspects of the review process. Further details are provided below.

3.1.1 Searches

The CS[1] describes an unconventional approach for the clinical SLR, where searches largely omitted the term 'histamine dihydrochloride' (except for its brand name, Ceplene) and focused instead on the companion intervention, interleukin-2, with which the agent is delivered. When the EAG questioned this strategy at the clarification stage (see clarification response, question A8),[30] the company defended its approach stating that it was sufficient because it successfully identified known studies and reports. Although this defence clearly undermines the core objective of a systematic review, the EAG is unaware of any relevant studies that may have been missed.

Search filters were drawn from various well-known sources (including Canada's Drug Agency [CDA/AMC], Scottish Intercollegiate Guidelines Network [SIGN] and the Cochrane handbook) though in some cases the original syntax was modified in order to be compatible with the company's choice of platforms (PubMed and Embase.com). Searches are presented in long strings making them difficult to parse. For example, line 7 of the EMBASE search string presented in Table 3 (CS appendix B, page 4)[1] is an unbroken string of 279 words containing terms for RCTs but also double negatives excluding

RCTs. This may be a result of the company recycling strings created for different purposes, or a result of automated query expansion of the Embase.com interface, but it prevented the EAG from replicating the company's search on the more traditional command-line interface of the Ovid platform.

No separate searches of grey literature were conducted, with the company arguing that clinical trials and conference abstracts would be picked up in the searches of Cochrane Central Register of Controlled Trials (CENTRAL) and Embase, respectively (clarification response, A10).[30] While the EAG does not dispute this point, it is conventional in STA submissions to search the platforms where these records originate rather than only the sites that aggregate them, thereby capturing the very latest results in case of any delay in their harvest by the larger databases.

As part of the clarification process, the company ran additional searches for a comparator treatment, oral azacitidine (clarification response, question A28),[30] this time using Ovid to run a simultaneous search of MEDLINE and Embase. While multi-file searching is not optimal for reproducibility, the EAG acknowledges that it can save time and may therefore be justifiable in rapid contexts. However, there appears to be a logic error in search reported in Table 6 of the clarification response: in line 51 at the end of the search, line 9 is included rather than line 10 – meaning that lines 7 and 8 are orphaned. Moreover, by searching exclusively for RCTs, the company may miss data on AEs reported in other study types. Nonetheless, the EAG thanks the company for this additional work and for reporting the methods by which evidence was identified.

Despite the noted limitations above, the EAG considers the company's approach to meet the minimum required standards for an SLR of this type.

3.1.2 Inclusion criteria and study selection

The CS[1] describes an adequate method of identifying and screening references for inclusion in the SLR of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria to citations identified by the searches. Any disagreements were resolved through discussion (see CS Appendix B.3.3 and clarification response, question A12).[1, 30] The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. However, as noted in the company's response to clarification question A12, the company applied *post-hoc* changes to the SLR inclusion/exclusion criteria. These changes included: (i) re-running searches and omitting the English-language filter; (ii) including further information on using PFS as a key broader outcome measure covering LFS; and (iii) exclusion of observational or single-arm studies due to the availability of RCT-based evidence (CS, Appendix B1.1). The EAG notes that it remains a fundamental prerequisite for a SLR to clearly pre-specify unambiguous inclusion and exclusion criteria as this approach minimises

bias and enhances transparency and reproducibility of the review process. As required, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart detailed the results of the study selection process (CS Appendix B, Figure 1).

3.1.3 Data extraction

Data extracted from the included study are presented in the CS,[1] Sections 2.2 to 2.11. Details of the data extraction process were provided by the company following a clarification request (question A12),[30] which indicated that data extraction was conducted by a single reviewer, with 20% of the data independently checked by a second reviewer. According to guidance from the Cochrane Handbook,[38] data extraction should be performed independently by at least two people to minimise errors and reduce the risk of bias. Relying on a partial (20%) check for critical data represents a methodological limitation and increases the risk of extraction errors compared with full dual, independent data extraction[38, 39] with disagreements resolved through discussion or arbitration by a third reviewer, if necessary.

3.1.4 Quality assessment

Quality assessment was conducted using an appropriate critical appraisal tool. The CS (Appendix B. Section 1.3)[1] used the revised Cochrane risk of bias tool (RoB 2)[40] to assess the included RCT. As stated in the company's clarification response to question A12,[30] '*...quality assessment were conducted in full by one reviewer with 20% of extracted values being checked by a second reviewer'*. This approach falls short of best practice in systematic reviewing,[41] as reliance on a single reviewer increases the risk of errors and subjective bias. Furthermore, the CS does not clearly specify how any disagreements between reviewers were resolved. According to guidance from the Cochrane Handbook,[41] risk of bias/quality assessments should be conducted independently by at least two reviewers, with discrepancies resolved through discussion or by consulting a third reviewer, where necessary.

3.1.5 Evidence synthesis

The company conducted a narrative synthesis of the evidence for HDC/IL-2; however, the CS[1] did not provide sufficient methodological detail on how this approach was undertaken. Ideally, the narrative synthesis approach should be justified, transparent, and conducted in a way that avoids selective reporting or undue emphasis on particular findings to minimise potential bias.[42, 43]

The EAG agrees with the company (CS section 2.9)[1] that a meta-analysis of comparing HDC/IL-2 and SoC is not appropriate given only a single relevant trial was identified (Brune *et al.*[31]) and no other relevant trial has been missed. Moreover, the CS argues that an ITC between HDC/IL-2 and several potential comparators were considered inappropriate. The comparators included:

- oral azacitidine for people who cannot have or do not want a HSCT;

- midostaurin for people with an FLT3-mutation;
- sorafenib, after a stem cell transplant, for people with an FLT3-ITD mutation;
- quizartinib for people with an FLT3-ITD mutation; and
- cytarabine alone or in combination with other antineoplastic agents.

While the EAG agrees with the exclusion of midostaurin, sorafenib, quizartinib, and cytarabine as potential comparators in this appraisal (see Section 2.3.3), the company conducted an ITC between oral azacitidine (only a single relevant trial was identified - pivotal QUAZAR AML-001) and HDC/IL-2, as a part of its response to clarification question A28. Further details (see CS,[1] Section 2.10 and the clarification response[30] to questions A28 to A30), along with a critique of the methods and results of the ITC conducted following an EAG request, are provided in Section 3.4.

3.2 Summary and critique of the methods of the trials of the technology of interest

The clinical effectiveness review presented in the CS[1] identified only one single RCT (NCT00003991,[37] Brune *et al.*,[31] and Nilsson *et al.*[32]) which was reported across 12 citations (CS, Appendix B, Figure 1 and Table 5). The EAG and its clinical advisors are not aware of any additional relevant completed studies of HDC/IL-2 that fall within the defined scope of this appraisal. Furthermore, the CS (Section 2.12) does not cite any ongoing studies that will provide additional evidence for HDC/IL-2 in the indication being appraised in the next 12 months.

3.2.1 Main supporting evidence – Brune et al.

3.2.1.1 Study design

The company's SLR of HDC/IL-2 in the maintenance treatment of AML identified and included one pivotal study: Brune *et al*.[31] A summary of this study is provided in Table 4.

Table 4: Summary of the trial design - Brune *et al.*[31] (adapted from CS, Section 2.2, and Table 4)

Study details	Interleukin-2 Plus Histamine Dihydrochloride in Treating Patients With AML (NCT00003991,[37] Brune *et al*.,[31] and Nilsson *et al*.[32])
Role in this evaluation	This trial is the key source of clinical effectiveness evidence for HDC/IL-2 maintenance therapy following CR in AML. It is used to inform both clinical efficacy assumptions and health economic evaluations - specifically improvement in LFS and OS post-consolidation compared with SoC. The study does not directly contribute to some of the other parameters used in the health economic evaluation, including the utility values, but underpins the model's assumptions on relapse risk and treatment effect.
Study type	Phase 3, open-label, randomised controlled trial.
Setting and location	Multicentre international trial conducted at 100 centres in Australia, Canada, Israel, New Zealand, the USA and several European countries

	(with 3 patients from the UK, although no dedicated UK centres).
Patient group	Adult AML patients not considered suitable for allo-HSCT) who are in complete remission (CR1 or subsequent remissions [CR>1]) after induction and consolidation treatment with an ECOG performance status of 0 or 1.
Subgroups	*Pre-planned subgroups*: Patients stratified by remission status - CR1 and CR>1 *Post-hoc analyses[a] - Company's target population in CS:* Adult AML patients who have undergone intensive therapy with induction and consolidation treatment, are not suitable for allo-SCT, have normal karyotype, are in CR1 and are less than 60 years old.
Exclusion criteria	Prior allo-HSCT; active peptic ulcer disease; recent asthma or hypersensitivity reactions; ECOG >1; poor renal, cardiac, or pulmonary function; time >6 months from CR or >3 months from consolidation completion.
Intervention	HDC in combination with IL-2 • HDC: administered by subcutaneous injection twice daily 1 to 3 minutes after an injection of IL-2. Each 0.5 ml dose of HDC is administered slowly, over a period of 5 to 15 minutes. • IL-2: administered by subcutaneous injection twice daily, 1 to 3 minutes prior to HDC injection. Each dose of IL-2 (aldesleukin) is 16,400 IU/kg (1 µg/kg). Investigators supervised the administration of the first dose; all subsequent doses were taken by the patients at home. The rate of administration of HDC was 0.1 mg/min., extended by 7-10 minutes if the patients experienced AEs. If the adverse events failed to be resolved, the dosage was reduced by 20%; similar to that for IL-2 administration. Schedule: 10 cycles (cycles 1–3 included 3 weeks treatment, then 3 weeks rest; cycles 4–10 included 3 weeks treatment, then 6 weeks rest)
Comparator	SoC (no treatment)
Primary outcomes	• LFS (defined as the time from randomisation to relapse or death from any cause)
Other outcomes	• OS • Remission rate • Adverse effects of treatment • Health-related quality of life
Duration of study	Duration: up to 18 months of HDC/IL-2 therapy, followed by at least 18 months of follow-up post-treatment. Median total follow-up approx. 47 months.

Allo-HSCT - allogeneic haematopoietic stem cell transplant; AML - acute myeloid leukaemia; CR - complete remission status; ECOG - Eastern Cooperative Oncology Group; HDC - histamine dihydrochloride; IL-2 - interleukin-2; LFS - leukaemia free survival; OS - overall survival; SoC - standard of care.
a Numerous potential subgroups were explored post-hoc according to CS, Nilsson et al.32 and Nilsson et al.[44]

The Brune *et al*.[31] study published in 2006, was an international, multicentre, open-label, randomised, phase III trial designed to assess the efficacy of HDC in combination with IL-2 compared with SoC

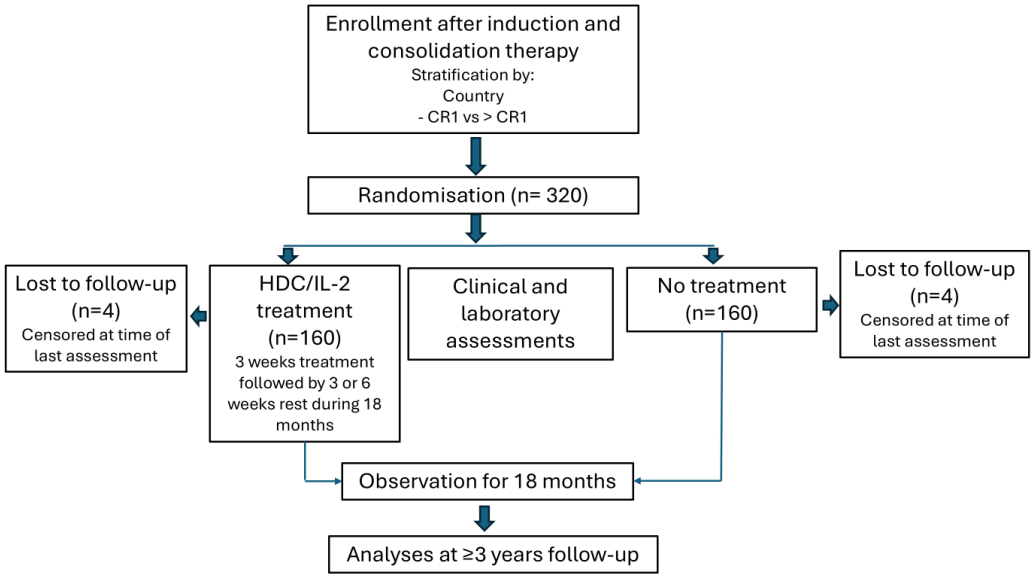
(defined as no treatment) in adults aged 18 years or older with *de novo* or secondary AML. Eligible patients were those who had achieved a first (CR1) or subsequent complete remission (CR>1) following standard induction or consolidation therapy, which could include autologous haematopoietic stem cell transplantation (auto-HSCT) but not allo-HSCT. Participants were required to have a life expectancy greater than three months and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Key exclusion criteria included patients with active peptic ulcer disease, recent asthma or known hypersensitivity reactions.

Randomisation was performed centrally and stratified by country and remission status. Between June 1998 and October 2000, 320 patients were enrolled and randomised to either the treatment arm (HDC/IL-2; n=160) or the no treatment (SoC; n=160) arm across 100 centres in Australia, Canada, Israel, New Zealand, the USA, and Europe (including 3 patients from the UK [company's clarification response to question A19][30] but no dedicated UK centres [CS, p32]).[1]

Participants allocated to the treatment arm received subcutaneous IL-2 at 16,400 IU per kg twice daily, followed by HDC at 0.5 mg per dose administered twice daily at a maximum rate of 0.1 mg per minute. Each treatment cycle comprised dosing on days 1–21 for a total of ten cycles. Cycles 1–3 were followed by a 3-week rest interval, and cycles 4–10 were followed by a 6-week rest interval. The treatment phase lasted 18 months, after which patients entered an additional follow-up period of at least 18-months.

The pre-specified primary endpoint was LFS, defined as the time from randomisation to relapse (defined as ≥ 5% marrow blasts or presence of extramedullary disease) or death from any cause. Initially, two co- primary endpoints were proposed for the CR1 and CR>1 groups. Sample size calculations required recruitment of 96 participants per arm in CR1 and 51 per arm in CR>1 to detect respective LFS improvements of 50% and 75% at 80% power. After 320 individuals had enrolled (261 in CR1 and 59 in CR>1), further recruitment for CR>1 was deemed unfeasible. Consequently, further recruitment was terminated in October 2000 and a protocol amendment redefined LFS for the entire cohort as the single primary outcome. The primary analysis was conducted after all patients had completed a minimum of 36 months of follow-up for haematological relapse or death following randomisation. The median follow-up of living patients was and 46.7 months (range, 1-66 months) in the HDC/IL-2 arm and 47.3 months (range, 1-68 months) in the control arm. All efficacy analyses were conducted using the intention-to-treat (ITT) principle. A diagram summarising the study design of the Brune *et al*.[31] study is reproduced in Figure 2.

Figure 2: Summary diagram of the Brune *et al.*[31] study (reproduced from CS, Section 2.3, and Appendix B, Figure 2)



3.2.1.2 Baseline and disease characteristics

The baseline demographic and clinical characteristics of the overall study population in Brune *et al.*[31] are presented in Table 5. The two arms were generally well balanced at baseline across key demographic and clinical variables, including prognostic factors such as age, sex, karyotype, ECOG performance status, and prior treatment history. The mean age was 55 years (range 18–81 years) in the HDC/IL-2 group and 54 years (range 18–84 years) in the control group. Most patients were in CR1, comprising 81% and 82% of the HDC/IL-2 and control groups, respectively. The distribution of cytogenetic risk was similar across groups, with favourable karyotypes observed in 9% and 8% of patients, intermediate in 59% and 59%, adverse in 6% and 4%, and unknown in 26% and 28%, respectively. The sex distribution was comparable between arms, with approximately 60% male participants. Overall, no meaningful differences were observed between treatment groups at baseline. However, the EAG notes that approximately 12.2% of patients in the ITT population of the study (22 patients in the HDC/IL-2 and 17 patients in the control group) received previous treatment with auto-HSCT. Clinicians consulted by the EAG mentioned that auto-HSCT has not been used in the UK in patients with AML for several years. In addition, due to missing (unknown) information, reliable risk classification based on cytogenetics could only be determined in approximately 73% of patients, which may have contributed to an imbalance between the groups.

Table 5: Baseline characteristics of the overall study population (reproduced with minor corrections from CS Section 2.3, Table 6)

Baseline characteristic	HDC/IL-2 N=160	Control N=160
Sex, n (%)		
Men	86[a] (54)	86 (54)
Women	74 (46)	74 (46)
Age, years		
Global, median (range)	55 (18-81)	54 (18-84)
Patients older than 60 years, n (%)	66 (41)	59 (37)
CR, n (%)		
CR1	129 (81)	132 (82)
CR>1	31 (19)	28 (18)
FAB classification, n (%)		
M0[b]/M1/M5/M6	60 (38)	56 (35)
M2/M3/M4	87 (54)	93 (58)
Functional status, n (%) [c]		
0	125(78)	114(71)
1	35(22)	46(29)
WBC count at diagnosis, x10^9 L, n (%)		
<20	97 (61)	111 (69)
20-100	51 (32)	36 (23)
>100	12 (7)	13 (8)
Karyotype, n (%) [d]		
Favourable	14 (9)	13 (8)
Intermediate	95 (59)	95 (59)
Adverse	10 (6)	7 (4)
Unknown	41 (26)	45 (28)
≤15% blastocysts after first induction	147 (92)	144 (90)
History of hematologic cancer [e]	15 (9)	14 (9)
Pretreatment with high-dose cytarabine [f]	105 (66)	108 (68)
Pretreatment with autologous HSCT	22 (14)	17 (11)
Time from CR to randomisation, days		
Global, median (range)	147 (6-727)	135 (4-553)
≤6 months, n (%)	117 (73)	125 (78)
>6 months, n (%)	43 (27)	35 (22)
Time from consolidation to randomisation, days		
Global, median (range)	63 (20-545)	64 (14-468)
≤3 months, n (%)	125 (78)	122 (76)
>3 months, n (%)	34 (21)	35 (22)

AML - acute myeloid leukaemia; HSCT - hematopoietic stem cell transplantation; HDC - histamine dihydrochloride; IL-2 - interleukin-2; CR1 - first remission; CR>1 - subsequent remissions; WBC - white blood cells.
[a] Data corrected by EAG- originally reported as 84.
[b] Data corrected by EAG - originally reported as M1.
[c] Evaluated at the time of randomisation.
[d] Classified according to the criteria of the Medical Research Council (Grimwade, 1998).[45]
[e] 12 patients (control) and 13 (HDC/IL-2) had myelodysplastic syndrome prior to AML. Two patients in each group had other previous hematologic malignancies.
[f] At least 2 g/m2 per day for 3 or more days during induction or consolidation.

Following a clarification request (question A17),[30] the company provided additional details on the baseline characteristics of the target population described in the CS, as represented in the Brune *et al*.[31] study. This population corresponded to adults with AML in CR1, aged under 60 years, with normal karyotype, and not eligible for allo-SCT. Further details are presented in Table 6. In general, the mean baseline age of the target population was 45.4 years in the HDC/IL-2 group (n=35) and 43.0 years in the control group (n=37). The sex distribution was comparable between arms, with approximately 50% male participants (additional clarification questions v2, page 9).[46] Overall, no meaningful differences were observed between treatment groups at baseline. However, as noted earlier, the prior use of auto-HSCT in the study (approximately 18% in the target population) remains a key difference from current UK practice. The company suggests (clarification response, question A18)[30] that despite major advances in modern AML management (specifically the widespread use of molecular genetic testing, the introduction of targeted therapies such as FLT3 inhibitors and increased reliance on allogeneic transplants), the study population remains relevant to UK practice. The company contends that these changes have narrowed the current pool of UK patients eligible for HDC/IL-2, ensuring that this remaining group has a comparable risk profile to the population studied in Brune *et al*.[31]

However, the EAG's clinical advisors note that the target population and the one studied in Brune *et al.* may not be fully comparable. One of the clinicians also notes that the risk profile of the target population may differ, as outcomes in younger patients have substantially improved due to major advances in modern AML management.[47, 48]

Table 6: Baseline characteristics of the target population (adapted from company's clarification response, A17 and additional clarification questions v2, page 9)

Baseline characteristic	HDC/IL-2 (n=35)	Control (n=37)
Age (mean, median)	45.4, 46.0	43.0, 44.5
Female/male (%)	19/16 (54%/46%)	17/20 (46%/54%)
ECOG performance status (0/1)	30/5 (86%/14%)	31/6 (84%/16%)
Prior auto-SCT (yes/no)	8/27 (23%/77%)	5/32 (14%/86%)
Prior high-dose cytarabine (yes/no)	32/3 (91%/9%)	33/4 (89%/11%)

Auto-SCT - Autologous stem cell transplant; ECOG - Eastern Cooperative Oncology Group; HDC - histamine dihydrochloride; IL-2 - interleukin-2

3.2.1.3 Summary and critique of the company's quality assessment

The company's (and the EAG's) assessment of the design, conduct, and internal validity of the Brune *et al*.[31] study is summarised in Appendix 1. This appraisal was conducted using a recognised methodological instrument - the Cochrane RoB 2 tool. Although the tool was not completed correctly by the company, neither section of the CS (Appendix B.1.3)[1] and the company's clarification response to question A15[30] provide a narrative assessment of trial quality to aid interpretation of the results. The EAG considers it important to highlight that the target population in the CS aligns with a subgroup of patients with AML (i.e., in CR1, aged under 60 years of age, with normal karyotype, and who were not eligible for allo-SCT). In addition, the study was not statistically powered for subgroups to detect differences in any of the measured outcomes.

In general, based on the full trial population and the *post-hoc* subgroup analyses from Nilsson *et al.,*[32] the EAG broadly agreed with the company's judgements of 'low risk of bias' for the management of missing data (including the application of an appropriate ITT analysis), and outcome measurement. However, the company's assessment of the randomisation process and bias due to deviations from intended interventions appear inaccurate. The randomisation process in the Brune *et al*.[31] study should be considered low risk (the CS rated this as 'some concerns'), as the allocation sequence was random, baseline characteristics were balanced across key variables, and allocation was adequately concealed through a centralised process. In contrast, bias due to deviations from the intended interventions is a potential concern (the company rated this as 'low risk'), primarily because the study was open-label and participants and carers were aware of treatment allocation. Although no actual deviations affecting outcomes were observed and appropriate analyses were conducted, the lack of blinding introduces the theoretical possibility that knowledge of the intervention could have influenced behaviour or adherence. Importantly, the study outcomes were largely objective, which mitigates the practical impact of this potential bias. There is potential for selective reporting bias, as the company relied on *post-hoc* subgroup analyses from Nilsson *et al.*[32] to inform the treatment effect in their proposed target population. The EAG cautions against the interpretation of the results from these analyses, as the subgroup analyses were not pre-specified and were conducted *post-hoc*, making them exploratory rather than confirmatory in nature. The lack of pre-specification introduces a high risk of bias arising from selective reporting and data-driven identification of apparent subgroup effects. The authors of Nilsson *et al.*[32] also acknowledged this limitation stating that "*The exploratory nature of these results should be emphasized, and controlled trials are warranted to determine the potential benefit of HDC/IL-2 in defined genetic subgroups of normal karyotype AML*." Consequently, although most domains, including the randomisation process, missing data and outcome measurement, were considered at low risk, the EAG judged the study to have a high overall risk of bias, primarily due to the potential for selective reporting of results.

The generalisability of the results from Brune *et al*.[31] and Nilsson *et al.*[32] (subgroup analysis) to current UK clinical practice is uncertain. Only three patients from the UK were included, and no UK centres participated in the trial, which limits the direct applicability of the findings to the UK AML population. Differences in healthcare systems, patient demographics and clinical management approaches (including administration techniques and patient support infrastructure) may further affect the relevance and optimal delivery of HDC/IL-2 in the UK context. Moreover, since the trial's recruitment ended over two decades ago, substantial advances have since transformed AML management in the UK. These include the widespread adoption of molecular risk stratification, the introduction of personalised and targeted therapies such as FLT3 and IDH inhibitors, and improvements in supportive care. Collectively, these developments have significantly altered SoC, treatment pathways and patient outcomes.[49] In addition, as noted in the CS (section 2.7)[1] and clarification response (question B20),[30] no data are available on the treatments patients received after relapse in the study by Brune *et al*. Therefore, caution is urged when extrapolating the trial's findings to current UK clinical practice.

3.3 Critique of the results of the trials of the technology of interest

Based on information reported in the CS (Section 2.6)[1] and the company's clarification response to question A1,[30] this section briefly summarises the key findings of a *post-hoc* analysis from Nilsson *et al.*[32]. This analysis focuses on the specific subgroup of AML patients in CR1 who are ≤60 years of age, have a normal karyotype, and are ineligible for allo-SCT following induction and consolidation chemotherapy. As this subgroup is expected to benefit most from HDC/IL-2 therapy, it represents the target population in the CS and serves as the base case for the economic model. Further details and results pertaining to the full study (ITT) population and relevant subgroups (e.g., patients in CR1 and those in CR1 aged ≤60 years at randomisation) are provided in brief for completeness. Full details of all reported results can be found in Section 2.6 of the CS.

3.3.1 Primary endpoint – Duration of LFS in the CS target population

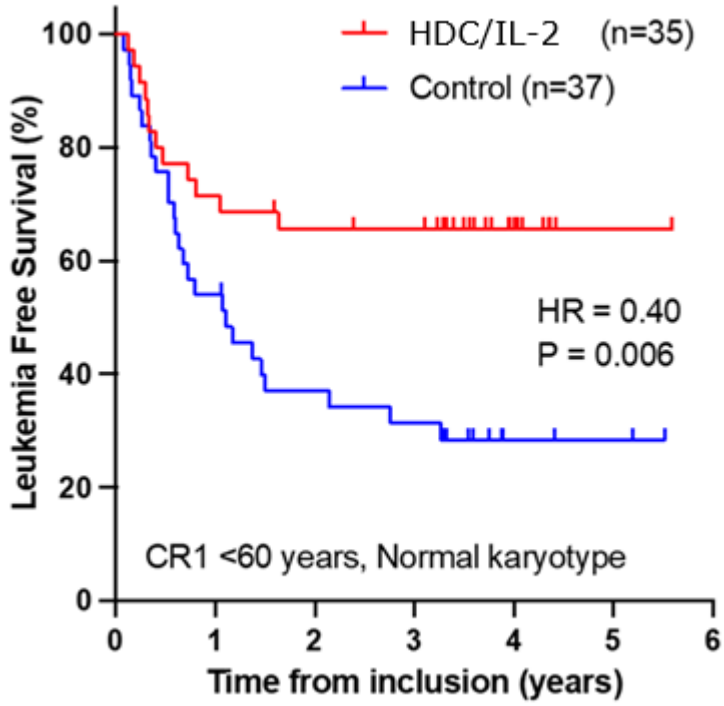
A summary of the LFS results is presented in Table 7 and the corresponding Kaplan-Meier estimates are shown in Figure 3. The *post-hoc* analysis of the HDC/IL-2 regimen in the target population demonstrated a statistically significant improvement in LFS compared to the control group (hazard ratio [HR], 0.40; 95% CI: 0.20–0.79; p=0.006). At 36-months after randomisation 65.6% of patients were leukaemia free in the HDC/IL-2 arm compared with 31.3% in the control arm.

Table 7: LFS in patients with normal karyotype, CR1 and ≤ 60 years (n=72) (adapted from CS, Table 12)

	HDC/IL-2 N=35	Control N=37
HR (95%CI); p-value	0.40 (0.20-0.79) p=0.006	
Percentage of patients alive and leukaemia-free at 12 months	71.4	54.1
Percentage of patients alive and leukaemia-free at 24 months	65.6	37.0
Percentage of patients alive and leukaemia-free at 36 months	65.6	31.3
Percentage of patients alive and leukaemia-free at 48 months	65.6	28.4
Percentage of patients alive and leukaemia-free at 60 months	65.6	28.4

HDC - histamine dihydrochloride; CI - confidence interval; HR - hazard ratio; IL-2 - interleukin-2; OS - overall survival.
Source: Nilsson, 2025; Data on file

Figure 3: Kaplan-Meier curves of LFS in normal karyotype, CR1, ≤ 60 years (n=72) (reproduced from CS, Figure 10)



LFS - leukaemia-free survival.: CR1 - complete remission; HDC - histamine dihydrochloride; IL-2 - interleukin-2.
Source: Nilsson, 2020, Data on file

For completeness, Table 8 briefly summarises the LFS results for the ITT population as well as relevant subgroups of interest (e.g., patients in CR1 and those in CR1 aged ≤60 years at randomisation).

Table 8: Duration of LFS in AML patient groups (adapted from CS, Tables 7, 8, 10 and company's clarification response, question A24)

AML patient group	LFS		
	Median (95%CI), days	HR (95%CI)	p-value
All patients (ITT) Population, (n=320)			
HDC/IL-2, n=160	324 (266, 550)	[redacted]	[redacted]
Control, n=160	264 (231, 341)		
CR1 (n=261)			
HDC/IL-2, n=129[b]	450 (293, 974)	0.69 (0.51-0.93)	0.01[a]
Control, n=132[b]	291 (232, 406)		
CR1 and ≤60 years (n=165)			
HDC/IL-2, n=80	1015 (351, 2120)	0.58 (0.40-0.86)	0.01[a]
Control, n=85	341 (232, 534)		

CR1 - first complete remission; HDC - histamine dihydrochloride; HR - hazard ratio; IL-2 - interleukin-2; ITT - intention to treat; LFS - leukaemia-free survival
[a] Statistical analysis using the Mantel-Cox test (log-rank test), stratified by country and, if applicable, CR stratum
[b] Data corrected by EAG

3.3.2 Secondary endpoints – OS in the CS target population

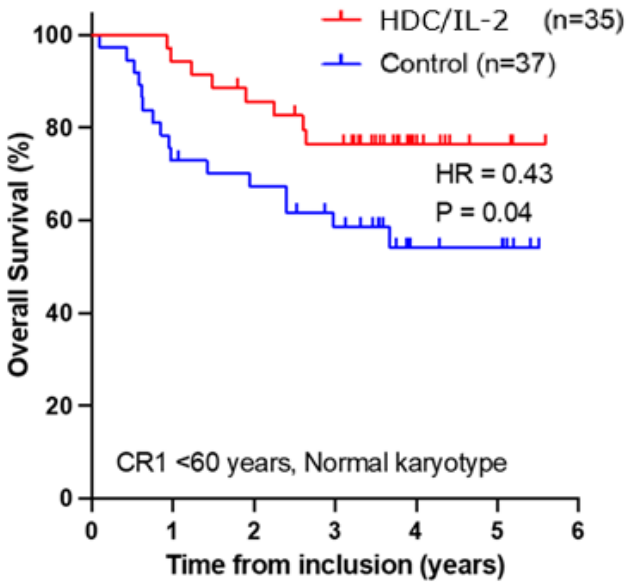
A summary of the OS results is presented in Table 9 and the corresponding Kaplan-Meier estimates are shown in Figure 4. The *post-hoc* analysis of the HDC/IL-2 regimen in the target population demonstrated an improvement in OS compared with the control group (HR, 0.43; 95% CI: 0.18–1.01; p=0.04). The EAG notes a discrepancy between the conclusion based on the 95% confidence interval and the p-value, whereby the confidence interval crossed 1, yet the p-value indicated statistical significance. At 36-months after randomisation, 76.5% were alive in the HDC/IL-2 arm compared with 58.7% in the control arm.

Table 9: OS in patients with normal karyotype, CR1 and ≤60 years (n=72) (adapted from CS, Table 13)

	HDC/IL-2 (N=35)	Control (N=37)
HR (95%CI); p-value	[redacted][a]	
Percentage of patients alive at 12 months	94.3	73.0
Percentage of patients alive at 24 months	85.6	67.4
Percentage of patients alive at 36 months	76.5	58.7
Percentage of patients alive at 48 months	76.5	54.1
Percentage of patients alive at 60 months	76.5	54.1

HDC - histamine dihydrochloride; HR - hazard ratio; IL-2 - interleukin-2; CR1 - first complete remission; OS - overall survival.
Source: Nilsson, 2025, Data on file.
[a] EAG notes data discrepancy between the 95% confidence interval and the p-value, whereby the confidence interval crossed 1, yet the p-value indicated statistical significance

Figure 4: Kaplan-Meier curves of OS in normal karyotype, CR1, ≤60 yrs (n=72) (reproduced from CS, Figure 11)



CR1 - first complete remission; HDC - histamine dihydrochloride; HR - hazard ratio; IL-2 - interleukin-2; OS - overall survival.
Source: Nilsson, 2020, Data on file

For completeness, Table 10 briefly summarises the OS results for the ITT population as well as relevant subgroups of interest (e.g., patients in CR1 and those in CR1 aged ≤60 years at randomisation).

Table 10: OS in AML patient groups (adapted from CS, Table 11 and company's clarification response, A24)

AML patient group	OS	
	HR (95%CI)	p-value
All patients (ITT Population, n=320)		
HDC/IL-2, n=160	[redacted]	[redacted]
Control, n=160		
CR1 (n=261)		
HDC/IL-2, n=129 [b]	0.78 (0.56-1.09)	p=0.16 [a]
Control, n=132 [b]		
CR1 and ≤60 years (n=165)		
HDC/IL-2, n=80	0.71 (0.45-1.13)	p=0.149 [a]
Control, n=85		

CR1 - first remission; HDC - histamine dihydrochloride; HR - hazard ratio; IL-2 - interleukin-2; ITT - intention to treat; OS - overall survival.
[a] Statistical analysis using the Mantel-Cox test (log-rank test), stratified by country and, if applicable, CR stratum
[b] Data corrected by EAG

3.3.3 Safety and tolerability

This section presents the main safety evidence from the Brune *et al.*[31] study, based on the safety population of the study, comprising all patients who received at least one dose of study medication, along with all randomised patients in the control group who completed the baseline visit. Consequently, 317 patients were included in the safety population: 157 in the HDC/IL-2 treatment arm and 160 in the control arm.

Patients in the treatment arm received a median of 6 (range: 1–10) 3-week cycles of HDC/IL-2, and among 49 non-relapsed patients, 45 (92%) completed all 10 scheduled cycles. AEs leading to dose reduction or treatment interruption occurred in 26% of patients, most commonly due to local inflammatory injection site reactions (7.1%) and fever (5.1%). Thirteen patients (8.3%) discontinued treatment because of AEs unrelated to relapse. Reasons for discontinuation or early termination included neutropenia (n=3), asthenia, polyarthritis, acute congestive heart failure, bronchospasm, venous thrombosis or renal-cell cancer, hepatobiliary disorder, hypersensitivity with local reaction/flush, gastrointestinal haemorrhage, nausea/vomiting, and thrombocytopenia.

All patients in the treatment arm and 95% in the control arm experienced AEs (Table 11). Most AEs with HDC/IL-2 were mild to moderate in severity, predominantly involving IL-2–related side effects such as injection site reactions, fever, fatigue, and myalgia, along with HDC-related effects like palpitations, flushing, and headache. As noted in the SmPC,[28] the most common adverse reactions experienced by 30% or more of patients HDC/IL-2 (listed in descending order of frequency) were: flushing, headache, fatigue, injection site granuloma, pyrexia and injection site erythema.

Table 11: Adverse events[31] (reproduced with minor changes from CS, Table 14)

Adverse Event	Control * (n =160)			HDC/IL-2 * (n = 157)			P†
	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4	
Blood							
Thrombocytopenia	13.8	9.4	0	13	16	1.3	0.16
Eosinophilia	0	0	0	18	1.9	0	< 0.001
Neutropenia	5.0	3.1	0	6.4	5.7	0	0.27
Leukopenia NOS	11	1.9	0	7.0	0.6	0.6	0.20
Anaemia	5.0	0.6	0	5.7	1.3	0	> 0.5
Cardiac							
Tachycardia NOS	1.3	0	0	14	0	0	< 0.001
Palpitations	1.9	0	0	8.3	0	0	0.01
Gastrointestinal							

Adverse Event	Control * (n =160)			HDC/IL-2 * (n = 157)			P†
	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4	
Nausea	9.4	0	0	31	1.3	0	< 0.001
Dyspepsia	3.8	0	0	15	0.6	0	< 0.001
Vomiting	5	0	0	15	0.6	0	0.003
Diarrhoea	10	0	0	18	1.9	0	0.02
Abdominal pain	3.8	0	0	6.4	0	0	0.32
General							
Fatigue	16	1.3	0	42	1.3	0	< 0.001
Pyrexia	16	1.3	0	41	2.5	0	< 0.001
Pain NOS	2.5	0	0	7.7	0	0	0.04
Weakness	6.9	0	0	7.6	0	0	> 0.5
Chest pain	5.7	0.6	0	8.9	0	0	0.40
Injection sites							
Erythema	NA	NA	NA	38	0	0	NA
Granuloma	NA	NA	NA	44	0	0	NA
Rigors	NA	NA	NA	18	0	0	NA
Pruritus	NA	NA	NA	22	0.6	0	NA
Infections							
Upper respiratory	14	0	0	18	0	0	0.36
Sinusitis	5.7	0	0	5.8	0	0	> 0.5
Metabolic and nutrition							
Anorexia	3.1	0	0	8.3	0.6	0	0.03
Musculoskeletal							
Myalgia	1.9	0	0	19	0	0	< 0.001
Arthralgia	14	0	0	23	1.3	0	0.02
Back pain	12	0	0	13	0.6	0	> 0.5
Pain in limb	6.9	0	0	12	0	0	0.13
Nervous system							
Headache	14	0	0	51	7	0	< 0.001
Dizziness	8.8	0	0	23	0.6	0	< 0.001
Dysgeusia	0	0	0	13	1.3	0	< 0.001
Psychiatric							
Insomnia	6.2	0	0	7.0	0.6	0	>0.5
Depression	3.1	0.6	0	7.7	0.6	0	0.10
Anxiety	8.8	0.6	0	5.1	0	0	0.19
Respiratory							
Cough	14	0	0	27	0.6	0	0.003
Pharyngitis	15	0	0	15	0.6	0	> .5

Adverse Event	Control * (n =160)			HDC/IL-2 * (n = 157)			P†
	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4	
Nasal congestion	1.3	0	0	12	0	0	< 0.001
Dyspnoea NOS	3.2	0	0	16	0.6	0	< 0.001
Rhinitis	1.9	0	0	5.7	0	0	0.08
Rhinorrhoea	2.5	0	0	6.3	0	0	0.11
Epistaxis	2.5	0	0	5.7	0	0	0.17
Sinus congestion	0.6	0	0	5.8	0	0	0.01
Skin							
Rash NOS	4.4	0	0	12	0.6	0	0.01
Sweating	1.3	0	0	9.5	0	0	< 0.001
Urticaria	0	0	0	5.1	0	0	0.003
Vascular							
Flushing	0	0	0	87	1.3	0	< 0.001
Hypotension NOS	2.5	0	0	13	0	0	< 0.001

HDC- Histamine hydrochloride; IL-2 - interleukin-2; NOS - not otherwise specified; NA - not applicable.
**Data are presented as the percentage of the safety population reported by at least 5% of patients in any of the control or HDC/IL-2 arms.*
†Statistical analysis using Fisher exact test.

Serious adverse events (SAEs) were similarly frequent in both groups (17.8% HDC/IL-2 *vs* 18.8% control), mostly associated with relapse. Notably, severe IL-2 related toxicities, such as capillary leakage syndrome or renal insufficiency, were not observed, likely due to the substantially lower IL-2 dose used. In the HDC/IL-2 group, nine SAEs in seven patients (4.5%) were deemed treatment-related, including fever, congestive heart failure, dehydration, endocarditis, grand mal convulsion, polyarthritis, and aspergillosis. The most common grade 3 or 4 adverse events in the HDC/IL-2 group were thrombocytopenia (17.3%), headache (7.0%), neutropenia (5.7%), and pyrexia (2.5%) (see clarification response to question B12).[30] There were no treatment-related deaths.

Overall, the safety profile suggests that although AEs were common, HDC/IL-2 treatment was mostly tolerable and manageable for patients with AML in remission.[28, 31]

3.4 Summary and critique of the indirect treatment comparison

The company did not perform ITCs comparing HDC/IL-2 to any of the comparators listed in the final NICE scope[33] (oral azacitidine, midostaurin, sorafenib, quizartinib and cytarabine) in the original CS. As a part of the clarification response, the company has conducted an ITC between oral azacitidine and HDC/IL-2 (question A28), but not for the other comparators (questions A29 and A30).[30] The company's justifications and the EAG's critique are summarised below.

3.4.1 Oral azacitidine

The company has conducted an ITC between oral azacitidine and HDC/IL-2 as a part of the response to clarification question A28.[30] The EAG highlights that there is an overlap between the population in the QUAZAR AML-001 trial for oral azacitidine and the company's proposed target population for this appraisal. The company also emphasised that HDC/IL-2 would be used for younger patients and oral azacitidine for older patients and quoted NHS England, which stated that "*the majority of use for the two interventions will be in non-overlapping populations.*" The company clarified the quote was from the Budget Impact Assessment document, which was not shared with the EAG as part of the CS.[46] At the factual accuracy check stage, the company further clarified that this document was received by the company after the CS and it is not usually shared with any stakeholders other than the company and NHSE.

The summary and critique of the searches used to retrieve clinical evidence related to oral azacitidine can be found in Section 3.1.1. Studies used to inform the ITC included the QUAZAR AML-001 trial for oral azacitidine and Brune *et al*. for HDC/IL-2. The company conducted a Bucher ITC (i.e., without population adjustment to the Brune *et al*. study) treating the control arm in the QUAZAR AML-001 trial and Brune *et al*. as the common comparator.

The comparison of baseline characteristics between the two trials is presented in Table 12. The results for OS and LFS from the QUAZAR AML-001 trial are presented in Figure 5 and Figure 6, respectively.[19] The safety results for oral azacitidine are reported in clarification response (question A28).[30]

Table 12: Baseline characteristics comparisons between the populations in QUAZAR AML-001 trial and Brune *et al*.

Patient Characteristics	**QUAZAR AML-001 (N=472)‡**	**Brune *et al*. ITT (N=320) ⁂**	**CS targeted population* (≤60 years old, CR1 and normal karyotype) (N=72)**
Mean age (SD)	67.9 (5.66)	[redacted]	44.2
Median age (Range)	68 (55-86)	55 (18-81) intervention, 54 (18-84) control	46.0 intervention, 44.5 control
Proportion males, % (n/N)	52% (245/472)	53.13% (170/320)	50%
Mean weight, kg (SD)	redacted	N/A	N/A
Mean height, cm (SD)	redacted	N/A	N/A
ECOG performance – N (%) (or mean if not split)			

0	227 (48%)	239(74.7%)	61 (84.7%)
1	207 (44%)	81(25.3%)	11 (15.3%)
2 or 3	38 (8%)	0	0
Cytogenetic risk at diagnosis			
Favourable	0	27(8.4%)	0
Intermediate	406 (86%)	190(59.4%)	72 (100%)
Poor	66 (14%)	17(5.3%)	0
Unknown	0	86(26.9%)	0

CI - confidence interval; CR1- first complete remission; CS - company's submission; ECOG - Eastern Cooperative Oncology Group; ITT - intention-to-treat; SD - Standard deviation; SoC - standard of care
‡ Using information from the CS, and TA827 EAG report.
⁂ Using information from the CS, Brune et al. and study CSR.
**Subgroup from Brune et al. reported in Nilsson et al., using information from CS and clarification response.*

Figure 5: Kaplan-Meier analysis of overall survival (data cut-off date, 15 July 2019) in the intention-to-treat population in the QUAZAR AML-001 randomised controlled trial (reproduced from TA827)

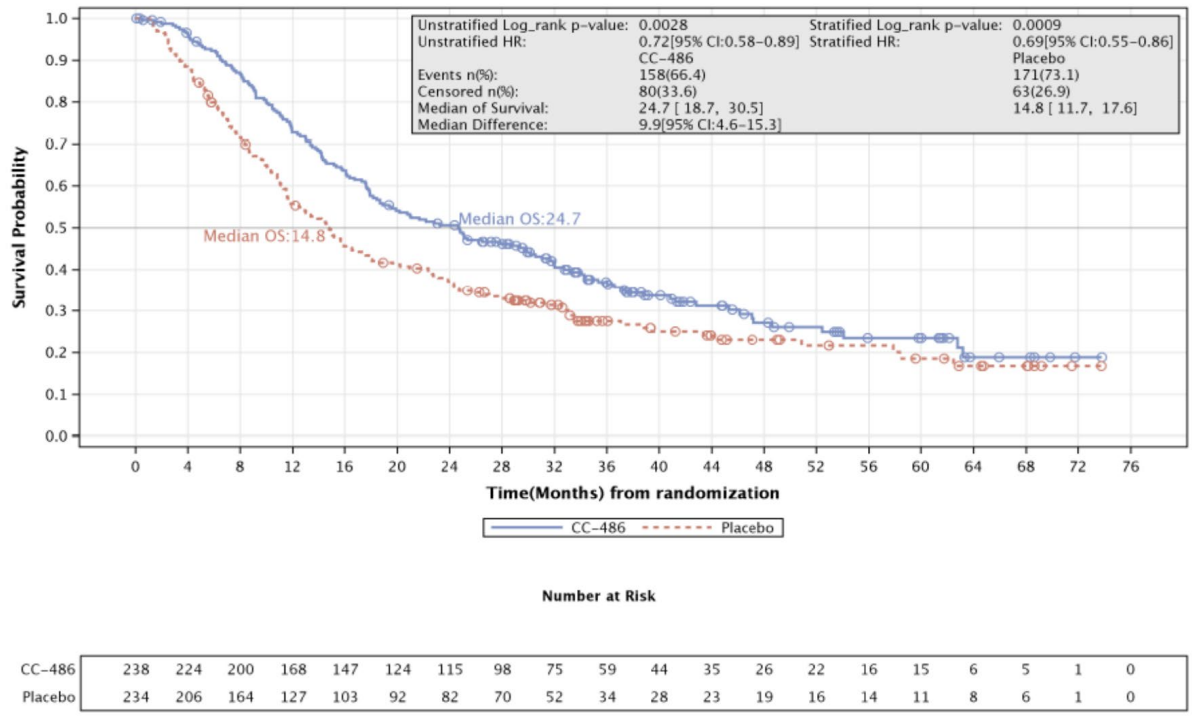
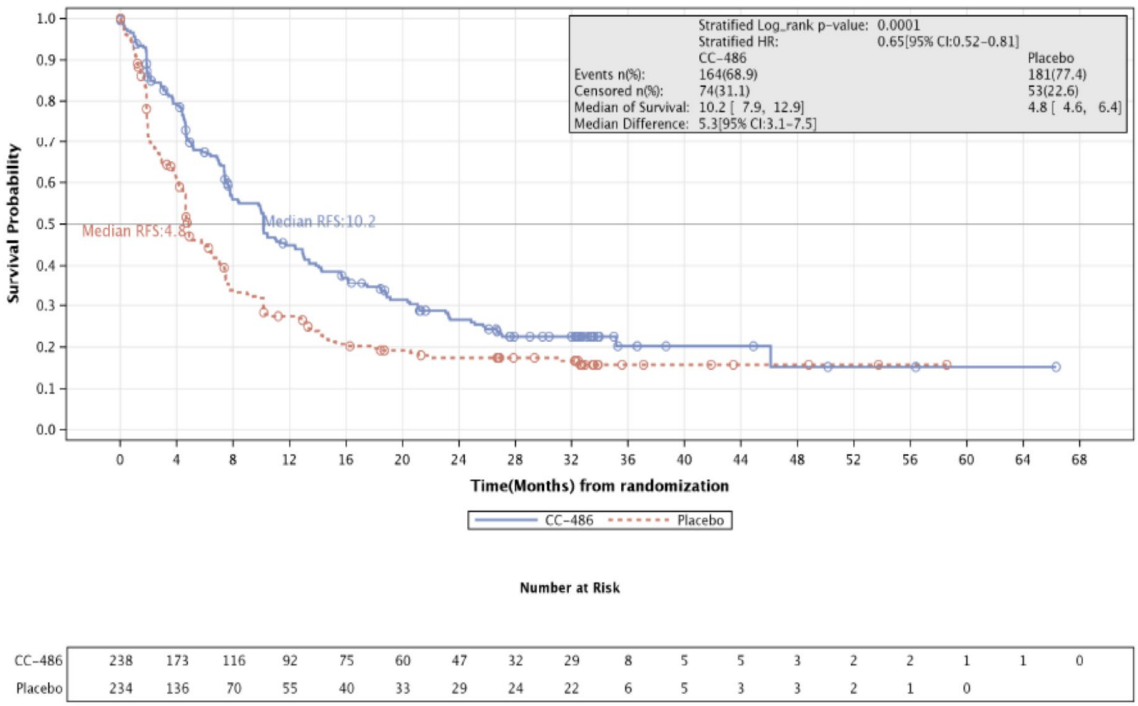


Figure 6: Kaplan-Meier analysis of relapse-free survival (data cut-off date, 15 July 2019) in the intention-to-treat population in the QUAZAR AML-001 randomised controlled trial (reproduced from TA827)



The ITC results for OS and LFS are presented in Table 13 and Table 14, respectively. The EAG notes that the ITC results based on the ITT populations were used in the economic model to inform the relative efficacy of oral azacitidine versus HDC/IL-2. The ITC results based on the QUAZAR AML-001 ITT population and Brune *et al.* subgroup were not used in the company's updated model.

Table 13: ITC results for OS with oral azacitidine versus HDC/IL-2 (adapted from response to clarification question A28)

	HR	Lower 95% CI	Upper 95% CI	p
ITT populations				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUAZAR AML-001 ITT and Brune *et al.* normal karyotype, CR1 and <60 years populations				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI - confidence interval; CR1 - first complete remission; HDC/IL-2 - Histamine hydrochloride with interleukin-2; HR - hazard ratio; ITT - intention-to-treat; SoC - standard of care
** The company's original response used unstratified HR of [redacted] and presented results using stratified HR in response to additional questions during the clarification stage.*
*** The estimated HR was [redacted] with 95% CI ([redacted]) when unstratified HR was applied for oral azacitidine vs SoC. The HR of [redacted] was still used in the economic model.*

Table 14: ITC results for LFS with oral azacitidine versus HDC/IL-2 (adapted from response to clarification question A28)

	HR	Lower 95% CI	Upper 95% CI	p
ITT populations				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUAZAR AML-001 ITT and Brune *et al.* normal karyotype, CR1 and <60 years populations				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI - confidence interval; CR1 - first complete remission; HDC/IL-2 - Histamine hydrochloride with interleukin-2; HR - hazard ratio; ITT - intention-to-treat; SoC - standard of care

The EAG acknowledges the challenges in conducting an ITC between oral azacitidine and HDC/IL-2 and highlights its concerns regarding the company's ITC analysis, as outlined below. The concerns include the use of a Bucher ITC and the assumption that the SoC was the same regimen in both clinical studies.

- The Brune *et al*. ITT population and the subpopulation used as the target population for this appraisal (≤60 years old, CR1 and normal karyotype) are a much younger and healthier population than the QUAZAR ITT population (see Table 12). Findings from Nilsson *et al.*[32] implies that age may be a potential treatment effect modifier of HDC/IL-2. A study of azacitidine suggests that age may potentially also be a treatment effect modifier for azacitidine.[50] Therefore, the Bucher ITC without population adjustments would be expected to result in a more favourable estimated treatment effect of HDC/IL-2 versus oral azacitidine due to age differences, compared with a population adjusted ITC.
- Given that Brune *et al*. was conducted much earlier than the QUAZAR AML-001 trial and the treatment landscape has evolved dramatically in the past 20 years, the EAG questions the validity of treating the SoC from the two trials as the common comparator and notes the impact on the relative effect is uncertain.

The EAG also notes that estimates of HR for OS and LFS that the company used to inform the economic model were derived from a mixture of stratified and unstratified HRs: the stratified HR for both OS and LFS from the Brune *et al*., the reported stratified HR for LFS from the QUAZAR AML-001 trial, but the unstratified HR for OS from the QUAZAR AML-001 trial. The EAG notes that the unstratified HR for OS from the QUAZAR AML-001 trial is less favourable to oral azacitidine compared to the stratified HR.

Overall, the EAG concludes that the estimated treatment effect between HDC/IL-2 and oral azacitidine is highly uncertain for the company's proposed target population in this appraisal. The EAG has conducted scenario analysis to illustrate the potential impact of this on the ICER (see Section 5.2).

3.4.2 Midostaurin, sorafenib, quizartinib, cytarabine

The EAG agrees with the company on the exclusion of midostaurin, sorafenib, quizartinib and cytarabine as comparators in this appraisal. The summary and critique of these comparators can be found in Section 2.3.3.

3.5 Additional work on clinical effectiveness done by the EAG

No additional work was conducted by the EAG.

3.6 Conclusions of the clinical-effectiveness section

The pivotal evidence for HDC/IL-2 is derived from a single international, multicentre, open-label, randomised phase III trial (NCT00003991[37], Brune *et al*.,[31] and Nilsson *et al*.[32]). This study compared HDC/IL-2 with SoC (defined as no treatment) in adults (≥18 years) with de novo or secondary AML in first or subsequent complete remission (CR1/CR>1) following standard induction or consolidation therapy (excluding allo-SCT). Between June 1998 and October 2000, 320 patients were enrolled and randomised 1:1 across 100 centres in Australia, Canada, Europe, Israel, New Zealand and the USA. Although there were no dedicated UK centres, 3 UK patients were included in the study. The trial endpoints, particularly LFS and OS, were aligned with the NICE final scope and the safety data were comprehensively detailed.

The EAG notes that the CS[1] focuses on a narrower population than that evaluated in Brune *et al*.[31] study, corresponding to a subset of the marketing authorisation. Specifically, the submission is restricted to adult AML patients who have a normal karyotype, have completed induction and consolidation treatment and are in CR1, with 60 years old or younger and are not considered suitable for allo-HSCT. This population serves as the base case in the company's economic model. The Brune *et al*.[31] study was critically appraised using the Cochrane RoB 2 tool and judged by the company and EAG to be at an overall low risk of bias. No additional phase III trials or real-world evidence were identified.

The *post-hoc* analysis[32] of the HDC/IL-2 regimen (n=35) in the target population demonstrated a statistically significant improvement in LFS compared with the control (n=37) group (HR: 0.40; 95% CI: 0.20–0.79; p=0.006). At 36-months after randomisation 65.6% of patients were leukaemia free in the HDC/IL-2 arm compared with 31.3% on the control arm. Although an improvement in OS was observed compared with the control group (HR: 0.43; 95% CI: 0.18–1.01; p=0.04), the statistical

significance remains uncertain because the CI includes 1, despite the p-value being below the conventional 0.05 threshold. At 36-months after randomisation, 76.5% of patients were alive on the HDC/IL-2 arm compared with 58.7% in the control arm. Although AE data were not reported for the target population, nearly all patients in the safety population (n=317) experienced mild-to-moderate AEs, which were generally considered manageable and well-tolerated by Brune *et al*.,[31] and the EMA.[51] In the HDC/IL-2 arm, patients received a median of 6 (range 1–10) 3-week treatment cycles. Dose reductions or treatment interruptions occurred in 26% of patients, mainly due to injection site reactions (7.1%) and fever (5.1%), while 13 patients (8.3%) discontinued for non-relapse related AEs. SAEs were similar between HDC/IL-2 and control groups (17.8% vs 18.8%), mostly associated with relapse. Severe IL-2 related toxicities such as capillary leakage syndrome, or renal insufficiency, were not observed and the most common grade 3 or 4 AEs in the HDC/IL-2 group were thrombocytopenia (17.3%), headache (7.0%), neutropenia (5.7%), and pyrexia (2.5%). No treatment-related deaths occurred.

In general, the EAG's key concern regarding the clinical evidence relates to the limited applicability and generalisability of the pivotal Brune *et al*.[31] study to current UK practice. Only three UK patients were included, and no dedicated UK centres participated, restricting the direct relevance of the findings to the UK AML population. Differences in healthcare systems, patient demographics and clinical management approaches (including administration techniques and patient support infrastructure) may further affect the applicability and optimal delivery of HDC/IL-2 in the UK context. Moreover, recruitment in the Brune *et al*.[31] study concluded more than two decades ago, and since then substantial advances have transformed AML management in the UK. These include the widespread adoption of molecular risk stratification, the introduction of personalised and targeted therapies, and improvements in supportive care. Collectively, these developments have significantly altered standard care, treatment pathways and patient outcomes. In addition, cytogenetic characterisation was incomplete (with >25% missing data in the ITT population, potentially undermining subgroup analyses) and information on post relapse treatments was unavailable. Therefore, these limitations introduce uncertainty and warrant caution when extrapolating the trial's findings to current UK clinical practice. In addition, the EAG also cautions the interpretation of the results from the *post-hoc* subgroup analysis from Nilsson *et al*.[32] to inform the treatment effect in the company's proposed target population. The lack of pre-specification introduces a high risk of bias arising from selective reporting and data-driven identification of apparent subgroup effects. The results should be treated as exploratory rather than confirmatory.

Following an EAG request the company conducted a Bucher ITC based on the ITT population from the QUAZAR AML-001 trial and Brune *et al*.[31] study, with the SoC arm from both studies as the common comparator. The estimated HR for OS with oral azacitidine versus HDC/IL-2 was [redacted]

[redacted]). The estimated HR for LFS with oral azacitidine versus HDC/IL-2 was [redacted]. The company also presented a sensitivity analysis based on the QUAZAR AML-001 trial ITT population and Brune *et al*.,[31] study subpopulation (normal karyotype, CR1 and <60 years). The estimate HRs were more in favour of HDC/IL-2 [redacted].

The estimated treatment effect between HDC/IL-2 and oral azacitidine is highly uncertainty for the company's proposed target population in this appraisal because (i) of the limited population overlap between the QUAZAR AML-001 and Brune *et al*.[31] study, and the Bucher ITC was conducted without adjusting for population differences in the presence of potential treatment effect modifiers; and (ii) treating SoC from the two studies as a common comparator may introduce bias into ITC as Brune *et al*.[31] was conducted much earlier than the QUAZAR AML-001 trial and the treatment landscape has evolved dramatically in the past 20 years and the impact on the relative effect is uncertain.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the CS[1] and clarification response.[30] As part of its clarification response, the company submitted three updated versions model which addresses some of the errors identified by the EAG during the clarification process. For brevity, the description in this chapter focuses on the latest version of the model and revised submission submitted by the company at clarification stage.

Section 4.1 focuses on the company's review of the cost-effectiveness evidence and Section 4.2 covers the company's economic evaluation. Section 4.3 presents the EAG's critical appraisal of the company's economic model. The results of the company's post-clarification version of the model and the EAG's exploratory analyses are presented in Section 5.

4.1 Critique of the review of cost-effectiveness evidence

4.1.1 Summary and critique of company's searches

Search strategies for the SLRs undertaken to identify literature for published cost-effectiveness studies are presented in CS Appendix E, HRQoL studies in CS Appendix F, and cost and health care resource use (HCRU) studies in CS Appendix G.[1]

For the three SLRs, the company conducted a common set of searches for published literature (reported in Appendix E of the CS) using the core databases as required by NICE. As with the clinical effectiveness SLR, the company conducted no additional searches for conference proceedings, with the Justification that these are included in EMBASE (clarification response, question A10).[30] The EAG acknowledges that EMBASE has adequate coverage of clinical congresses, and also includes abstracts of health economics conferences from The Professional Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Health Technology Assessment international (HTAi) following their publication in supplements to Value In Health and International Journal of Technology Assessment in Health Care (IJTAHC), respectively.

The company also mentions that individual international HTA websites were only searched outside the SLRs as part of model conceptualisation, and NICE website was searched for previous technology appraisals in AML, but not the international HTA literature other than that published in major journals indexed by the mainstream databases like MEDLINE and EMBASE. However, details about these additional searches were not provided, nor any results were presented by the company.

Overall, the EAG considers the company's approach to meet the minimum required standards for an SLR of this type.

4.1.2 Summary and critique of company's review of existing economic evaluations

The inclusion criteria for the company's review of published economic evaluations are reported in Table 1 of CS Appendix E.[1] Studies were eligible for inclusion in the review if the population included in the economic analysis related to people with AML who are in first remission. No restrictions were applied to the interventions or comparators assessed within the studies. Relevant study types included cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses and budget impact analyses. The inclusion criteria also specified that studies must have reported incremental cost-effectiveness ratios (ICERs), QALY, resource use, direct or indirect costs of treatment and illness, drivers of cost/resource use, or cost-minimisation or cost-benefit results (without specifying which outcomes would be expected from those). Editorials, reviews, comments, letters, case reports, and clinical, epidemiological, adherence or qualitative studies were excluded from the review. Studies were restricted to those published in the English language since 2015. The company noted that the same inclusion and exclusion criteria were used for the review of HCRU studies. The CS does not mention any quality assessment being carried out for the included studies as part of the SLR.

The company's initial and updated bibliographic searches identified a total of 1,983 studies after deduplication, of which 13 unique studies were included in the review. CS Appendix E (Table 4) presents a summary of the studies included in the review. Two of the identified studies were model-based cost-effectiveness/cost-utility analyses, 10 were healthcare costs and/or resource use analyses, and one was a systematic review. None of the studies were budget impact analyses. The company mentions that even though these studies met the inclusion criteria, particularly the criterion regarding the population including patients in first remission, none of them were UK-based economic evaluation studies. The company stated that, as a result of this, they have reassessed all the retrieved studies to identify UK studies in broader AML populations, which led to three studies being identified through this process. The identified subset of UK economic evaluation studies are summarised in Table 15, based on further examination of each included study by the EAG.

Table 15: Summary of studies included in the company's review of existing economic evaluations

Study	Population	Population characteristics	Intervention / Comparators	Model type	Health states included	Time horizon	Cycle length	Modelled cure?	Utility values (sources)	Subsequent costs included	Cost perspective and year
Witlox *et al.* 2023[52] (TA827[19])*	Adults with AML who reached complete disease remission after induction therapy (+- consolidation treatment) and are not eligible for (or choose not to receive) HSCT	Mean starting age: 67.9 Proportion of males: 51.9%	Intervention: • Oral azacitidine Comparators: • Watch and wait + BSC • Midostaurin (FLT-3+ subgroup)	PartSA	Relapse-free (on Tx and Off Tx), relapse and death	Lifetime (30 years)	28 days	Base- case: No Scenario analysis: 5-year cure point (SMR=2.0 applied)	• Relapse-free (on and Off Tx): N/R[19] • Relapse: N/R (based on utility difference of 0.28 between RFS and relapse in Tremblay 2018§)[53] • HSCT: one-off 28-day disutility of 0.21[54] • One-off disutility due to AEs included[55-57]	• Cytarabine • Injectable azacitidine • salvage chemotherapy (daunorubicin and cytarabine) • HSCT** • BSC	NHS and PSS perspective, 2019/2020 prices (except drug prices, valued at 2021 prices)
Russell-Smith *et al.*[58] (2021)	Adult patients with previously untreated de novo CD33+ AML who were eligible to receive intensive chemotherapy	Mean starting age: 61.2 Proportion of females: 50.9%	Intervention: • Gemtuzumab ozogamicin + SoC Comparator: • SoC	STM (Markov)	Induction, CR/CRp (on/off consolidation therapy), relapse (salvage/ non-curative therapies), refractory (salvage/non-curative therapies), HSCT, post-HSCT (with/without GVHD), functionally cured, death	Lifetime (40 years)	1 month	Yes, cure fraction estimated from different MCM functions; SMR=1.36 applied after 5 years to cured patients	• Chemotherapy: 0.6574[59] • HSCT: 0.6574 • Post-HSCT GVHD: 0.6700[60] • CR or CRp: 0.7400[59] • Relapse: 0.5680[59] • Refractory: 0.5680 • Functionally cured: 0.8212[61] • One-off disutility of 0.0207 for each	N/A (treatments after treatment initiation were modelled as separate states, and costs were included)	NHS and PSS perspective, 2017 prices

Study	Population	Population characteristics	Intervention / Comparators	Model type	Health states included	Time horizon	Cycle length	Modelled cure?	Utility values (sources)	Subsequent costs included	Cost perspective and year
									AE included except VOD[59] • One-off disutility of 0.208 for VOD[62]		
Tremblay *et al.* (2018)[53]	Untreated adult patients with FLT3-mutated AML who were eligible to receive standard induction and consolidation chemotherapy	Median starting age: 47.9, Proportion of females: 55.5%*	Intervention: • Midostaurin + standard chemotherapy (SoC) Comparator: • Standard chemotherapy (SoC)	PartSA	Induction, CR, relapse, SCT (including SCT treatment, SCT recovery, and post-SCT recovery) and death	Lifetime (specific duration not specified)	28 days	Yes, structural cure assumption applied at the end of the trial period (approximately 6.8 years)	• Induction Tx: 0.648[63] • Consolidation Tx: 0.710[64] • Monotherapy Tx: 0.810[64] • Complete remission: 0.830[65] • Relapse: 0.530[66] • SCT treatment: 0.613[67] • SCT recovery 0.810[67] • Post-SCT recovery: 0.826[67]	• Secondary therapy (fludarabine, cytarabine, idarubin, filgrastim, FLAG-IDA • SCT	NHS and PSS perspective, 2017 prices

AE – adverse event; BSC – best supportive care; CR – complete remission; CRp – incomplete platelet recovery; HSCT - haematopoietic stem-cell transplantation; PartSA - partition survival analysis; SMR - standardised mortality ratio; SoC – standard of care; PF - progression-free; PD - progressed disease; PSS - Personal Social Services; OS - overall survival; SCT – stem cell transplant; Tx – treatment; VOD - veno-occlusive disease.

‡ *With additional information from TA827 committee papers[19].*

§ *Based on EAG's and committee's preferred analysis.*

* *from CS Table 15 and Stone et al. 2017[68]*

⁂ *For 6.3% of patients receiving oral azacitidine, 5.8% of patients receiving midostaurin and 13.7% of patients receiving BSC.*

Amongst the three economic evaluations included in the company's SLR, all studies corresponded to full-text publications which describe cost-utility analyses. The EAG notes that Witlox *et al.*[52] corresponds to a summary of the NICE TA827, which compared oral azacitidine against watch and wait plus BSC in the overall population with AML who reached remission and were ineligible for HSCT, and against midostaurin in the subgroup of patients who were FLT3-positive.[52] One study compared gemtuzumab ozogamicin plus SoC versus SoC in previously untreated de novo CD33-positive AML patients,[58] and one study compared midostaurin plus SoC versus SoC in previously untreated patients with FLT3-mutated AML.[53]

All three analyses adopted the perspective of the NHS and Personal Social Services (PSS) and adopted a lifetime horizon (which varied between 30 and 40 years – one study did not specify the duration). Both Witlox *et al*[52]. and Tremblay *et al.*[53] describe the adopted modelling approach as a partition survival (PartSA), whilst Russell-Smith *et al.*[58] describes the use of a Markov approach. The models included in the three analyses adopted different structures, in line with the point of the pathway that was evaluated in the study. Russell-Smith *et al.* and Tremblay *et al.* included health states related to induction, CR, relapse, transplant (HSCT treatment and post-HSCT) and death. Russell-Smith *et al.* also included states related to partial remission (on and off treatment), relapse and refractory states subdivided by the therapy received, a functional cure, and subdivided the post-HSCT state based on whether graft-versus-host disease (GVHD) is present. The SCT state in Tremblay *et al.* was also subdivided into 3 states which included SCT treatment, recovery, and post recovery. Conversely, Witlox *et al.* models the AML pathway from the starting point of remission being achieved, and therefore only includes health states related to relapse-free (on and off treatment), relapse and death.

The survival modelling approaches applied in the models varied: Russell-Smith *et al.* modelled cure using mixture-cure models (MCMs);[58] Tremblay *et al.*[53] implicitly model cure through the use of a structural cure assumption whereby general population mortality risks are assumed to take over at the end of the observed trial period; and Witlox *et al.*[52] did not include any cure as part of their base case, but explored the use of a structural cure assumption at 5 years as part of a scenario analysis. Standardised mortality ratios (SMRs) reflecting excess mortality risks were included in Russell-Smith *et al.* (SMR=1.36) and Witlox *et al.* (SMR=2.0).

Only Witlox *et al.*[52] included health state utility values from EQ-5D 3-Level (EQ-5D-3L) data collected in the study's pivotal trial (QUAZAR AML-001 trial), which were combined with external sources (Tremblay *et al.*[53] for relapse state, and various sources for HSCT[54] and AE disutilities).[55-57] The other studies included various sources from the published literature,[60, 61, 63-67] previous NICE TAs[59, 62] and assumptions to inform the utility values used for the health states in their models.

The CS[1] provides limited information about how these three existing modelling studies were used to inform the design of the current economic model of HDC/IL-2 for AML, and in particular, the reasons behind the choice of the parameters from these sources. In response to clarification question B3(b),[30] the company clarified that these three existing modelling studies guided the choice of model structure (in particular Tremblay *et al.*[53] and Witlox *et al.*),[52] whilst the health state utility estimates were informed by Tremblay *et al.*[53] in the base case and Russell-Smith *et al.*[58] in one of the scenario analyses, whilst Witlox *et al.*[52] was also used to identify resource utilisation estimates for best supportive care.

The EAG also considers that other models related to previous NICE TAs relevant to AML may have been missed by the review carried out by the company, possibly in part due to additional searches not being conducted in relevant HTA websites (as mentioned in Section 4.1.1). One particular analysis that was missed relates to the assessment of HDC/IL-2 undertaken by the Scottish Medicines Consortium (SMC) published in 2011 (SMC N. 666/10 document).[69] The company stated in response to clarification question B3(b)[30] that this analysis was not identified as part of their SLR; however, it was identified by targeted searches to inform the model conceptualisation and excluded from the SLR due to the documentation of the model being sparse. Another analysis potentially missed corresponds to Tikhonova *et al.*,[70] which corresponds to a summary of the NICE TA399, which evaluated azacitidine for treating AML in patients with more than 30 % bone marrow blasts. This study is included in the list of excluded references in the SLR of economic evaluations provided in response to clarification question A14,[30] but the reasons for its exclusion after the reassessment to identify UK studies in broader AML populations remain unclear. Nonetheless, the EAG considers that the impact of the potential missing studies to the results of the current assessment is likely to be small.

4.2 Summary of the company's submitted economic evaluation

4.2.1 Scope of the company's economic analyses

As part of their submission to NICE,[1] the company submitted an executable health economic model programmed in Microsoft Excel. The company's updated base case analysis compares HDC/IL-2 and SoC versus SoC alone and versus oral azacitidine, for adult patients with AML who are ≤60 years of age, in CR1, and have a normal karyotype. The scope of the company's economic analysis is summarised in Table 16.

Table 16: Scope of the company's economic analysis

Population	Patients with AML, in CR1, aged under 60 years, with normal karyotype, and who were not eligible for allo-SCT
Time horizon	60 years (lifetime)
Intervention	HDC/IL-2 plus SoC
Comparator	• SoC alone • Oral azacitidine
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum
Price year	2023/2024 (except for drug costs which reflect current prices)

Allo-SCT - allogeneic stem cell transplantation; AML - acute myeloid leukaemia; HDC - histamine dihydrochloride; IL-2 - interleukin-2; NHS - National Health Service; PSS - Personal Social Services; QALY - quality-adjusted life year; SoC - standard of care.

The company's economic model assesses the cost-effectiveness of HDC/IL-2 plus SoC versus SoC and versus oral azacitidine in terms of the incremental cost per QALY gained from the perspective of the NHS and Personal Social Services (PSS) over a 60-year (lifetime) horizon. Unit costs are valued at 2023/2024 prices, except for drug acquisition costs which are valued at current prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

4.2.2 Population

The company's economic analysis is intended to reflect the population of patients with AML who have received induction and consolidation chemotherapy, are in CR1, have a normal karyotype, are aged ≤60 years and are not considered suitable for allo-SCT. This population reflects a subgroup of the population enrolled in the Brune *et al.* study who were selected in a *post-hoc* analysis reported by Nilsson *et al.*[32]. At model entry, patients are assumed to be 44.2 years of age and 50.0% of patients are assumed to be male. Patients are assumed to have a mean weight of 78.5kg, based on the mean weight reported for the general population in England from the NHS Health Survey for England (NHS HSE) 2021[71] (clarification response, question B4).[30] The EAG notes that the estimate for mean weight does not reflect the values reported for the target population in the Brune *et al*. study; this issue is discussed in Section 4.3, critical appraisal point 8(a).

4.2.3 Intervention and comparators

The intervention included in the company's economic analyses is HDC/IL-2. HDC and IL-2 are assumed to be administered separately, both via subcutaneous injections twice a day. HDC is assumed to be administered at a dose of 0.5 mg/0.5ml, over a period of 5 to 15 minutes, and 1 to 3 minutes after an injection of IL-2. IL-2 (aldesleukin) is assumed to be administered at a dose of 16,400 IU/kg. Treatment schedule includes a maximum of 10 treatment cycles (approximately 18 months) which

consists of 3-week treatment periods followed by 3-week periods without treatment (cycles 1 to 3) or 6-week periods without treatment (cycles 4 to 10).

The original version of the company's model submitted at CS included only SoC as a comparator. At the clarification stage, the company submitted an updated version of the model which included both SoC and oral azacitidine as comparators as part of the base case analysis (clarification response, question B1).[30]

Oral azacitidine is assumed to be administered orally at a dosage of 300mg once daily, for 14 consecutive days in each 28-day treatment cycle (clarification response, question B1).[30] The CS does not specifically define SoC, but the model assumes that it includes monitoring and disease management for patients whilst remaining in remission (pre-progression), whilst it also includes medications such as a chemotherapy and antifungals for patients who relapse. The EAG's clinical advisors agreed that in the target population for this appraisal, patients in the SoC treatment group would not receive any active therapies whilst on remission, but after relapse they would likely receive different therapies to the ones modelled by the company, including allo-SCT, FLAG-IDA or other chemotherapy regimens. The company has included the costs of allo-SCT as a subsequent therapy for a proportion of patients who relapse in the updated version of the model (clarification response question B20, see Section 4.2.4.4).

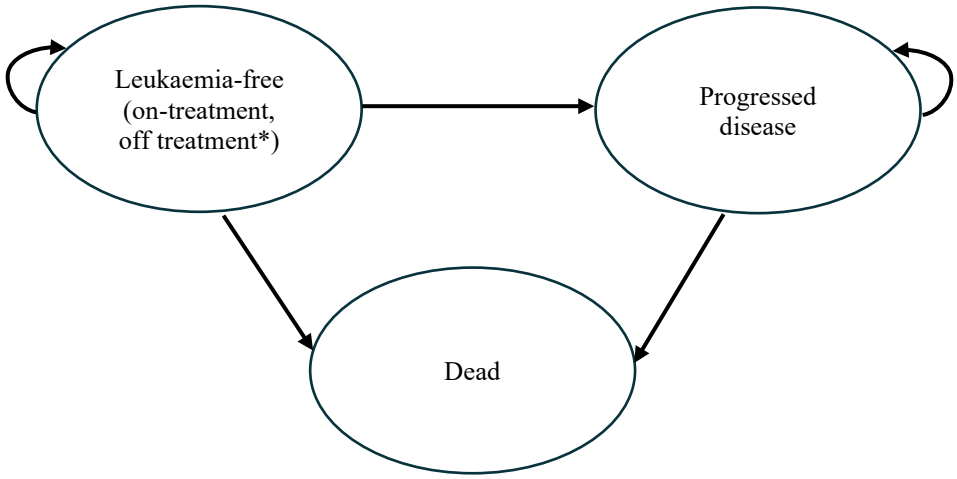
As previously discussed in Section 2.3.3, the NICE final scope also included the following comparators: midostaurin (for patients with FLT-3 mutation); sorafenib (for patients with FLT-ITD mutation); quizartinib (for patients with FLT-ITD mutation); and cytarabine (monotherapy or in combination with other antineoplastic agents). The company justified the exclusion of these comparators from the analysis based on the lack of comparative data on the efficacy of HDC/IL-2 versus midostaurin (for FLT3 mutated patients), sorafenib and quizartinib (for FLT3-ITD mutated patients), and that clinical experts in TA827 have stated that it is unlikely that patients with these mutations using targeted therapy during induction and consolidation treatment would switch to non-targeted treatment (oral azacitidine) during maintenance, and the company would expect a similar situation for HDC/IL-2. The company also excluded cytarabine based on the committee's understanding in TA827 that this regimen would not be used routinely as maintenance treatment in patients with AML who are in complete remission. The EAG's clinical advisors have agreed with these views.

4.2.4 Model structure

The structure of the company's model is described in Section 3.2. of the CS.[1] The economic model submitted by the company adopts a partitioned survival model (PSM) approach, which includes three health states: (i) leukaemia-free (which is further sub-divided into on-treatment and off-treatment for

patients receiving HDC/IL-2 or oral azacitidine), (ii) progressed disease (PD), and (iii) dead (see Figure 7).

Figure 7: Company's model structure (drawn by the EAG)



** Nested sub-states for the HDC/IL-2 and oral azacitidine groups*

All patients enter the model in the leukaemia-free state and receive either HDC/IL-2 (with SoC), oral azacitidine (with SoC), or SoC alone. At any given time t, health-state occupancy is defined by the cumulative probabilities of LFS and OS, as follows:

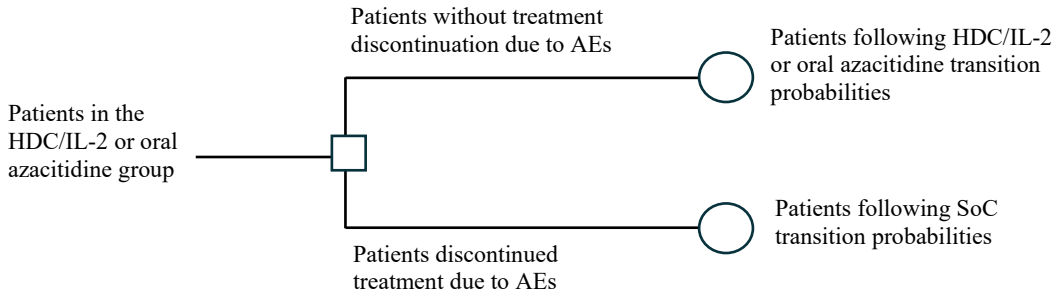
- The probability of being alive and leukaemia-free is given by the cumulative probability of LFS.
- The probability of being alive after disease progression is derived as the cumulative probability of OS minus the cumulative probability of LFS.
- The probability of being dead is calculated as one minus the cumulative probability of OS.

The cumulative probabilities of OS and LFS for patients receiving HDC/IL-2 or SoC were modelled using parametric survival distributions fitted to time-to-event data from a subgroup of patients in the Brune *et al.* study (see Section 4.2.4.1). The cumulative probabilities of OS and PFS for patients receiving oral azacitidine were modelled by applying the HRs estimated from the ITC conducted by the company (see Section 3.4) to the extrapolated models for the HDC/IL-2 group. Patients in the HDC/IL-2 and oral azacitidine groups are assumed to receive treatment until they discontinue due to AEs or relapse, for a maximum duration of 10 treatment cycles (up to approximately 18 months) and 12 months, respectively.

The EAG notes that, although not described in the CS, the company's model implicitly applies an underlying decision tree for the HDC/IL-2 and oral azacitidine treatment groups, whereby the proportion of patients who discontinue treatment at the first cycle due to AEs not related to relapse follow the same survival (LFS and OS) cumulative probabilities as for the SoC group (Figure 8).

Patients who do not discontinue treatment with HDC/IL-2 and oral azacitidine or discontinue in subsequent cycles due to relapse follow the LFS and OS cumulative probabilities for the respective groups. The overall LFS and OS cumulative probabilities for each of these treatment groups is based on weighted mean estimates of LFS and OS for discontinuers and non-discontinuers (i.e., a blended model), with weights based on the proportion of patients who discontinued due to AEs.

Figure 8: Company's implicit decision tree for active treatment (drawn by the EAG)



Patients in the leukaemia-free (LF) state within the HDC/IL-2 and oral azacitidine groups were further subdivided into on-treatment and off-treatment sub-states (i.e., LFS_{on} and LFS_{off}) to capture differential HRQoL outcomes and costs, respective to their current treatment status. Patients in all treatment groups are assumed to receive SoC therapies after disease progression; these therapies are assumed to be given for a fixed and initial treatment-independent proportion of patients (see Section 4.2.4.4 for more details on the components included). In the updated version of the model submitted at clarification, a proportion of patients in each treatment group are assumed to receive allo-SCT after disease progression (clarification response, question B20[30]). These post-progression treatments were assumed to have no impact on OS. The company's model includes half-cycle correction.

Several structural constraints were applied in the model:

- If the per-cycle risk of death from the parametric survival model was lower than that of the age- and sex-matched general population in any given cycle, the general population mortality risk was used; otherwise, the unadjusted OS probability was applied.
- LFS was constrained not to exceed OS at any time point.

HRQoL is determined by the disease status (leukaemia-free/progressed disease) and whether patients are receiving treatment with HDC/IL-2 or oral azacitidine whilst leukaemia-free. Utility values for the LFS and progressive disease (PD) states were based on external data from Tremblay *et al.*[53] No adjustments to utility due to increasing age were applied. The updated version of the model also

accounts for short-term QALY losses associated with Grade 3/4 adverse events, which are assumed to have a duration of one week (see Section 4.2.4.3).

The model includes costs associated with: (i) drug acquisition and administration (HDC/IL-2 and oral azacitidine), (ii) health state management (clinical visits, tests and transfusions), (iii) SoC therapies during post-progression, (iv) AE management, and (v) end-of-life care. Drug acquisition and administration costs for HDC/IL-2 and oral azacitidine were modelled based on: (a) the probability of patients remaining leukaemia-free and on treatment (based on the approach to treatment discontinuation – see Section 4.2.4.3), (b) treatment schedule, and (c) the maximum treatment duration. No relative dose intensity (RDI) information was included in the model. SoC treatment costs are applied in every cycle to patients in all treatment groups after they progress. Health state management costs are applied in every model cycle and are based on disease status and treatment status by treatment group, with health-state-specific frequencies or incidence rates for each intervention. AE and end-of-life costs are applied once only at model entry or at the point of death, respectively.

The incremental health gains, costs and cost-effectiveness for HDC/IL-2 versus SoC are estimated over a 60-year time horizon using a monthly cycle duration. The EAG notes that the company did not specify the model cycle length in the CS, and that the chosen cycle length does not match the treatment regimen cycle (approximately 4.3 weeks versus 3 weeks, with 3 or 6 weeks off-treatment periods). No economic subgroup analyses are presented in the CS.[1]

4.2.5 Key assumptions employed in the company's base case model

The company's base case model employs the following key assumptions:

- The modelled population is assumed to be 44.2 years of age,[31] 50% male, and to have a mean weight of 78.45kg at model entry, based on the mean weight reported for the general population in England.[71]
- The model assumes that patients in the HDC/IL-2 treatment group may receive up to 10 treatment cycles of HDC/IL-2 regimen (approximately 18 months) whilst in the LF state, and that these patients may discontinue therapy either due to AEs in the first treatment cycle, or upon disease progression (relapse) or death in any remaining cycle. Patients are assumed to discontinue both components of the combination therapy simultaneously.
- Patients in the oral azacitidine treatment group receive up to 12 months of treatment with oral azacitidine whilst leukaemia-free, and that these patients may also discontinue therapy either due to AEs, or disease progression (relapse) or death.
- Patients who discontinued HDC/IL-2 or oral azacitidine on the first cycle due to AEs are assumed to follow the LFS and OS cumulative probabilities for the SoC group rather than that for their

respective therapy groups. Patients who have not discontinued therapy or discontinued due to disease relapse are assumed to follow OS and LFS probabilities from their respective groups. The final modelled OS and LFS cumulative probabilities for the HDC/IL-2 and oral azacitidine treatment groups are based on weighted OS and LFS survival probabilities from the discontinued and non-discontinued groups.

- Both LFS and OS for HDC/IL-2 and SoC are modelled using standard parametric survival models fitted to individual patient-level data (IPD) data from Nilsson *et al.* (clarification response, question B6).[30] For these treatment groups, LFS and OS are both modelled using jointly-fitted exponential models (i.e., with treatment as a covariate), implying constant hazards in both groups and a constant HR between treatments over time.
- For the comparison of HDC/IL-2 versus oral azacitidine, the model applies HRs for OS and LFS derived from the ITC conducted by the company (see Section 3.4), applied to the OS and LFS cumulative probabilities for the HDC/IL-2 group.
- The model applies a structural constraint to ensure that the mortality risk in AML patients is never lower than that of the age- and sex-matched general population. It also assumes that cumulative LFS cannot exceed cumulative OS at any time point. Under the partitioned survival approach, progression and death risks remain structurally unrelated.
- No treatment waning assumption is applied in the model.
- No structural cure assumption is applied in the model.
- HRQoL is determined by disease status (LFS/PD), and by treatment group. For patients receiving HDC/IL-2 or oral azacitidine, it also varies by treatment status (on/off) in the LF state. A higher utility value is applied to patients who are leukaemia-free compared with those who have progressed disease, and a lower utility value is applied to patients receiving treatment with HDC/IL-2 or oral azacitidine compared to patients who have discontinued or receiving SoC. Utility values are not adjusted for increasing age.
- AEs result in additional costs and QALY losses, and all AEs are assumed to occur in the first model cycle and persist for one week.
- Patients receiving oral azacitidine are assumed to have the same HRQoL and AEs, and the same proportion of patients to receive allo-SCT after relapse, as patients receiving HDC-IL-2.
- The model assumes that in each model monthly cycle which includes a treatment initiation week (of each 3-week or 28-day treatment cycle), patients receiving HDC/IL-2 or oral azacitidine who have not discontinued in the previous cycle incur the whole treatment cycle drug acquisition and administration costs.
- The model assumes that patients in the three treatment groups receive SoC therapy only after relapse, and the cost of these therapies are the same for all treatment groups.
- The model assumes that a proportion of patients will receive allo-SCT after relapse (clarification

response, question B20),[30] with a higher proportion of patients on the SoC group being assumed to receive allo-SCT compared to HDC/IL-2 and oral azacitidine. Patients receiving allo-SCT are assumed to only incur the costs of the procedure; its impact on survival, HRQoL, AEs or further costs was not included in the model.

- The model includes the costs of follow-up for all patients. Disease management costs are assumed to be higher for HDC/IL-2 and oral azacitidine patients on treatment compared to those off treatment, and to those receiving SoC. Patients are assumed to incur higher costs disease management costs after relapse, due to more frequent clinical visits and tests; these are assumed to be the same regardless of treatment group.
- The company's model does not apply a disease severity modifier for any of the comparisons of HDC/IL-2 versus SoC and versus oral azacitidine (see Section 5.3).

4.2.6 Evidence used to inform the company's model parameters

Table 17 summarises the evidence sources used to inform the base case model parameters. The derivation of the model parameter values is discussed in detail in the subsequent sections.

Table 17: Summary of evidence used to inform the company's updated base case analysis

Parameter / group	HDC/IL-2	SoC	Oral azacitidine
Patient characteristics (age, sex, weight)	Baseline characteristics of patients in CR1, ≤60 years and normal karyotype group of Brune *et al.* study.[31, 32] Mean patient bodyweight was based on estimate for the general population in England from the NHS HSE 2021[71] (clarification response, question B4)[30]		
LFS	Exponential models jointly fitted to LFS data from the HDC/IL-2 and SoC arms for the CR1, ≤60 years and normal karyotype subgroup from the *post-hoc* analysis published by Nilsson *et al.*[32]		LFS HR from company's ITC (see Section 3.4), applied to LFS probabilities for HDC/IL-2 group.
OS	Exponential models jointly fitted to OS data from HDC/IL-2 and SoC groups for the CR1, ≤60 years and normal karyotype subgroup from the *post-hoc* analysis published by Nilsson *et al.* [32]		OS HR from company's ITC (see Section 3.4), applied to OS probabilities for HDC/IL-2 group.
General population mortality	ONS life tables for the England and Wales (2021-2023).[72]		
Discontinuation rate	Discontinuation rate based on the incidence of discontinuation due to AEs not related to relapse from the ITT population in Brune *et al.*, [31] applied in the first cycle of treatment.	N/a	Discontinuation rate based on the incidence of discontinuation due to AEs from TA827, applied in the first cycle of treatment.
Health state utility values	Utility values for leukaemia-free (pre-progression, on and off treatment) and post-progression (relapse) states were sourced from Trembley *et al.* 2018.[53] Utilities for LFS on and off treatment for oral azacitidine assumed the same as HDC/IL-2.		
AE frequencies	Selected Grade 3/4 AEs arising in the ITT population from Brune *et al.* study.[31] AE incidences for oral azacitidine assumed the same as HDC/IL-2.		
AEs disutilities	TA642,[57] Nafees *et al.,*[55] Stein *et al*.[56] and Stafford *et al.*[73]		
AE duration	TA827[19] (implicit assumption of duration of 1 week)		
Drug acquisition costs	List price for HDC informed by the company and for IL-2 was taken from the BNF.[74] Treatment schedule and dosage were based on the drug's SmPC.[28] RDI was not included in the model.	N/a	List price from BNF,[74] treatment schedule and dosage from TA827,[19] and assumption. RDI was not included in the model.
Drug administration costs	National Cost Collection for the NHS 2023/24[75]	N/a	Not included.
SoC post-progression drug costs	Drug usage and information on dosing were taken from TA827.[19] Drug acquisition costs were taken from eMIT.[76]		

Parameter / group	HDC/IL-2	SoC	Oral azacitidine
Allo-SCT costs	Procedure usage from Wei *et al.*[36] and assumption. Unit costs from the National Cost Collection for the NHS 2023/24.[75]		
Health state costs	Resource use was based on TA827.[19] Unit costs were taken from the National Cost Collection for the NHS 2023/24.[75]		
AE management costs	Unit costs from NHS Cost Collection 2023/24.[75]		
End-of-life care costs	The cost of death was taken from Round *et al.*,[77] which was uplifted to current prices using HCHS/NHSCII indices.[78]		

AE - adverse event; Allo-SCT – allogeneic stem cell transplant; BNF - British National Formulary; EQ-5D-5L - Euroqol 5-Dimensions 5-Level; 3L - 3-level; HCHS - Hospital and Community Health Services; LFS - leukaemia-free survival; N/a - not applicable; NHSCII - NHS Cost Inflation Index; ONS - Office for National Statistics; OS - overall survival; SoC – standard of care; TA - Technology Appraisal; TTD - time to treatment discontinuation.

4.2.6.1 Time-to-event parameters

Summary of company's parametric survival model fitting for HDC/IL-2 and SoC treatment groups

In the model, LFS and OS cumulative probabilities were estimated for HDC/IL-2 and SoC treatment groups based on standard parametric survival models jointly fitted by the company to LFS and OS data from a *post-hoc* subgroup analysis of patients with AML in CR1, ≤60 years old, and normal karyotype from the Brune *et al.* study, as reported by Nilsson *et al.*[32] These included the exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull distributions.

The CS[1] also reports Kaplan-Meier estimates for other subgroups of patients from Brune *et al.* study: ITT, CR1, and CR1 and ≤60 years old. In clarification response to questions B7, B8 and B9,[30] the company provided additional analyses for LFS and OS, including independent models for these same subgroups, in addition to the target population (patients in CR1, aged ≤60 years and with normal karyotype). The EAG notes that estimates using flexible survival models were also requested by the EAG in case the standard parametric models did not provide plausible long-term projections, however, these were not provided by the company. The EAG also notes that the LFS and OS estimates for these additional subgroups were not used to inform the results of the model.

The selection and results of the model fitting process undertaken by the company are discussed separately for OS and LFS in the subsequent subsections.

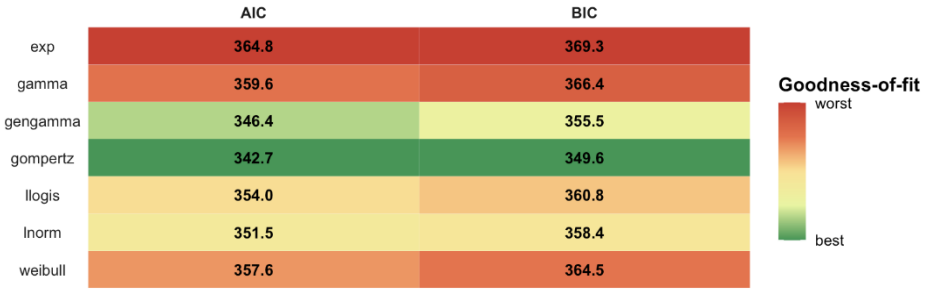
Leukaemia-free survival (LFS) – selection process

The company assessed the proportional hazards (PH) assumption for LFS using the clog-log plot, Cox–Snell residuals, and Schoenfeld residuals (CS Section 3.3).[1] The EAG notes that the non-parallel pattern in the clog-log plot suggests a potential violation of the PH assumption, whereas the company interpreted it as parallel. Schoenfeld residuals from the Cox model for LFS did not show statistically significant evidence to reject the null hypothesis that the PH assumption holds ($p = 0.076$). On this basis, the company considered the PH assumption holds and fitted seven jointly fitted (i.e., with treatment as a covariate) standard parametric models to the LFS data for the subgroup of patients with AML under 60 years, in CR1 and with normal karyotype.

Akaike Information Criterion (AIC) and Bayesian information Criterion (BIC) statistics for the fitted models are summarised in Figure 9. These statistics indicate that the jointly fitted Gompertz and generalised gamma models provided the best statistical goodness-of-fit among those tested. The company presented modelled survival curves against the observed Kaplan-Meier curve for visual assessment (Figure 10). The company provided empirical, smoothed, and modelled hazard plots for these models as part of the clarification response question B7 (Figure 11), which showed that the hazard

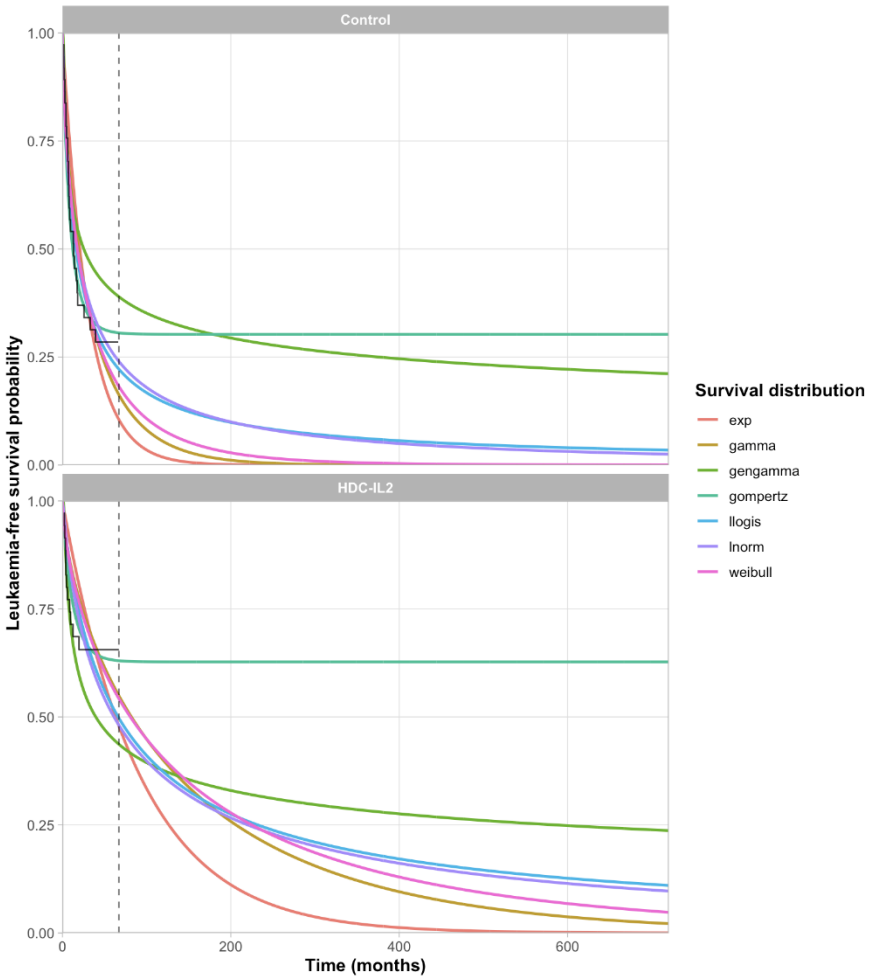
was not constant.[30] The company selected the jointly fitted exponential model as the base case for LFS, as it offered the most pessimistic long-term estimates for HDC/IL-2. The EAG notes that the company did not provide any justification for their base case model choice based on clinical plausibility of the models in the CS or in the clarification response. The jointly fitted exponential model implies a constant hazard over time for each treatment group (sustained treatment effect between the two treatment arms) throughout the lifetime horizon. The model includes a structural assumption where LFS cannot not exceed OS.

Figure 9: Statistical goodness-of-fit criteria for the jointly fitted parametric models of LFS (reproduced from CS Figure 26)



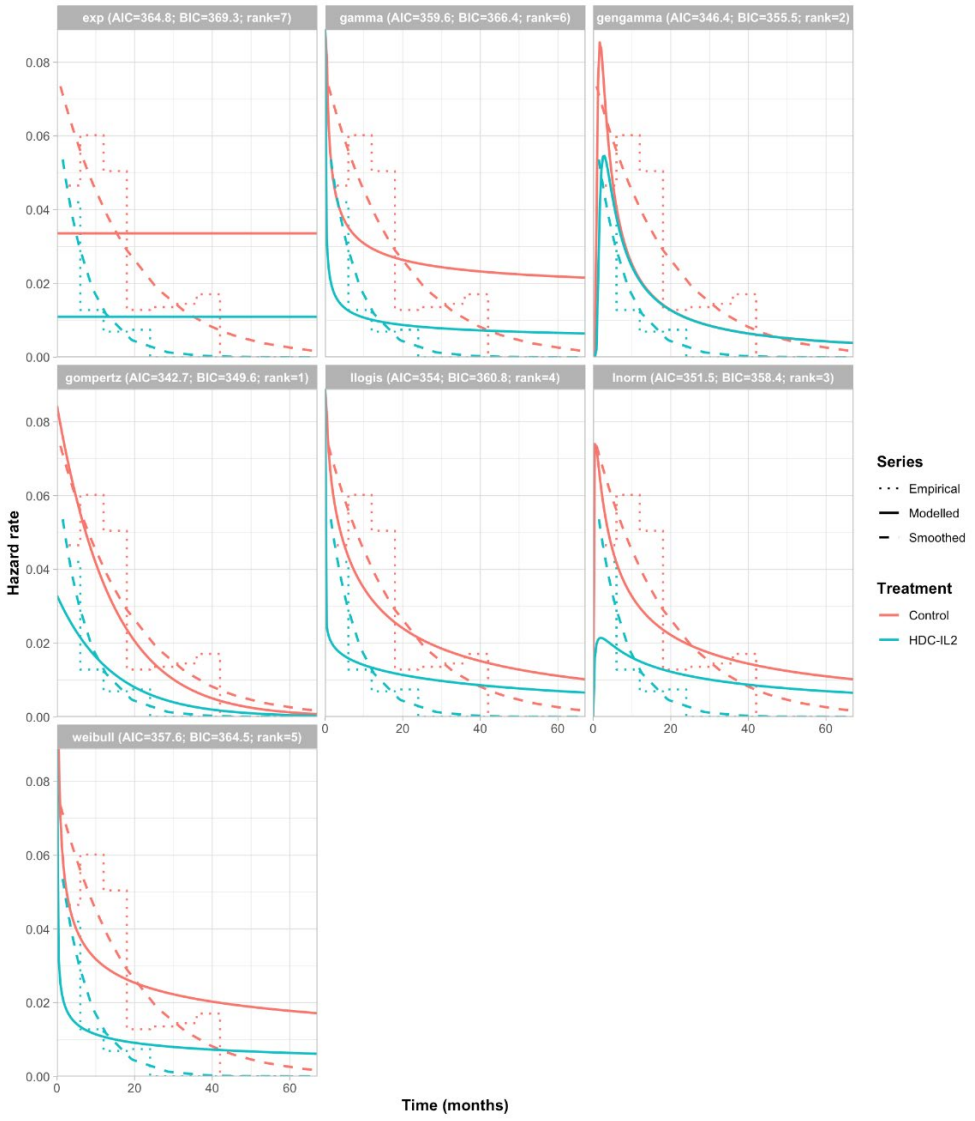
AIC - Akaike information criterion; BIC - Bayesian information criterion.

Figure 10: Observed versus predicted LFS (60 years) from jointly fitted models for adults with AML in CR1, ≤60 years old and with normal karyotype (reproduced from CS Figure 25)



Note: Dashed line marks end of observed follow-up (67.1 months).

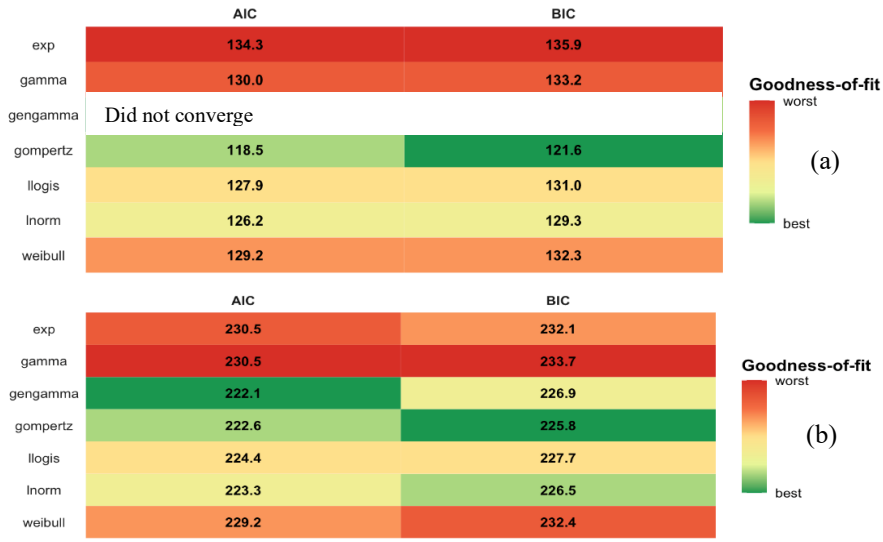
Figure 11: Empirical, smoothed, and modelled instantaneous hazards for each of the jointly fitted LFS parametric model (reproduced from CS Figure 27)



In the company's updated model submitted at the clarification stage,[30] LFS estimates from independent models were included in the model for HDC/IL-2 and SoC treatment groups for the CR1, ≤60 years, and with normal karyotype population. The corresponding AIC/BIC statistics, modelled versus observed Kaplan-Meier curves, and hazard plots are shown in Figure 12, Figure 13, and Figure 14, respectively. The independent generalised gamma model for HDC/IL-2 LFS showed an abrupt drop in survival to zero, which appeared visually unusual (Figure 13). Therefore, the EAG digitised the company's LFS curves from the CS Figure 23[1] and replicated the independent model fitting. Results indicated that the independent generalised gamma model for the HDC/IL-2 group did not converge. The company also repeated the independent parametric LFS modelling analyses for other subgroups (i.e., patients in CR1, and patients in CR1 and aged ≤60 years); the results for these analyses are presented in the response to clarification question B8 and B9. The EAG notes that, although the updated

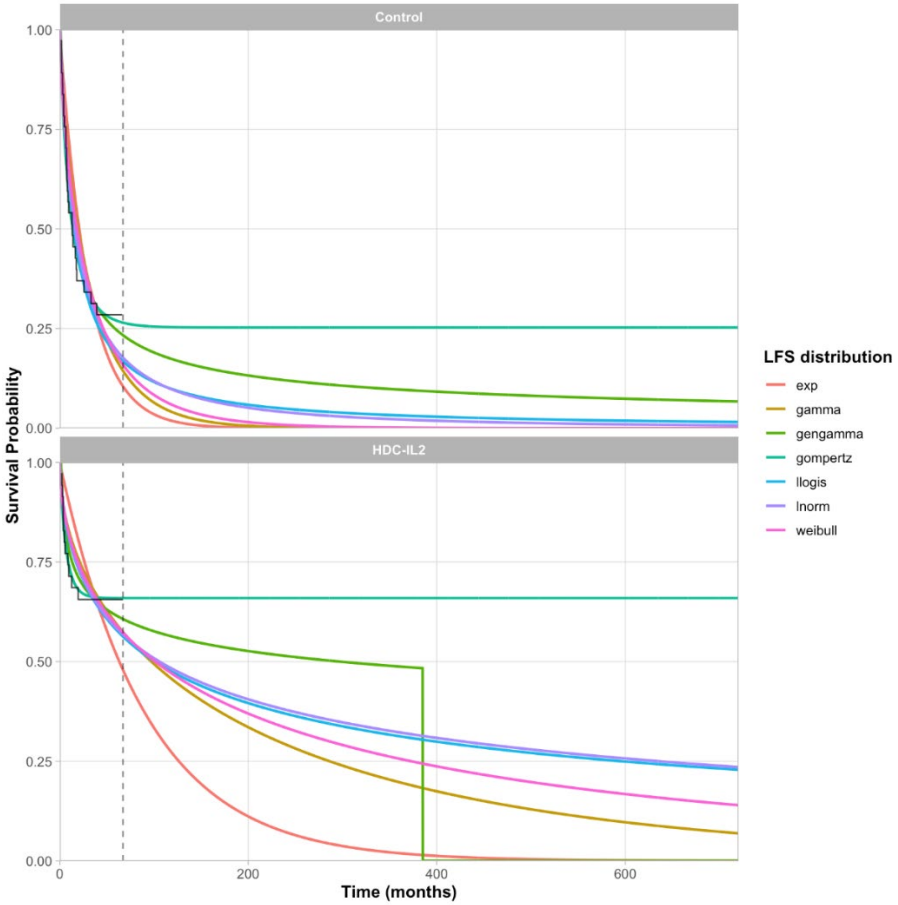
version of the model submitted at clarification includes the functionality to use these additional models, they were not used to in the company's updated base case or scenario analyses.

Figure 12: Statistical goodness-of-fit criteria for the independent parametric models of LFS (a) HDC/IL-2 group (b) standard of care group (adapted from clarification response, page 91)



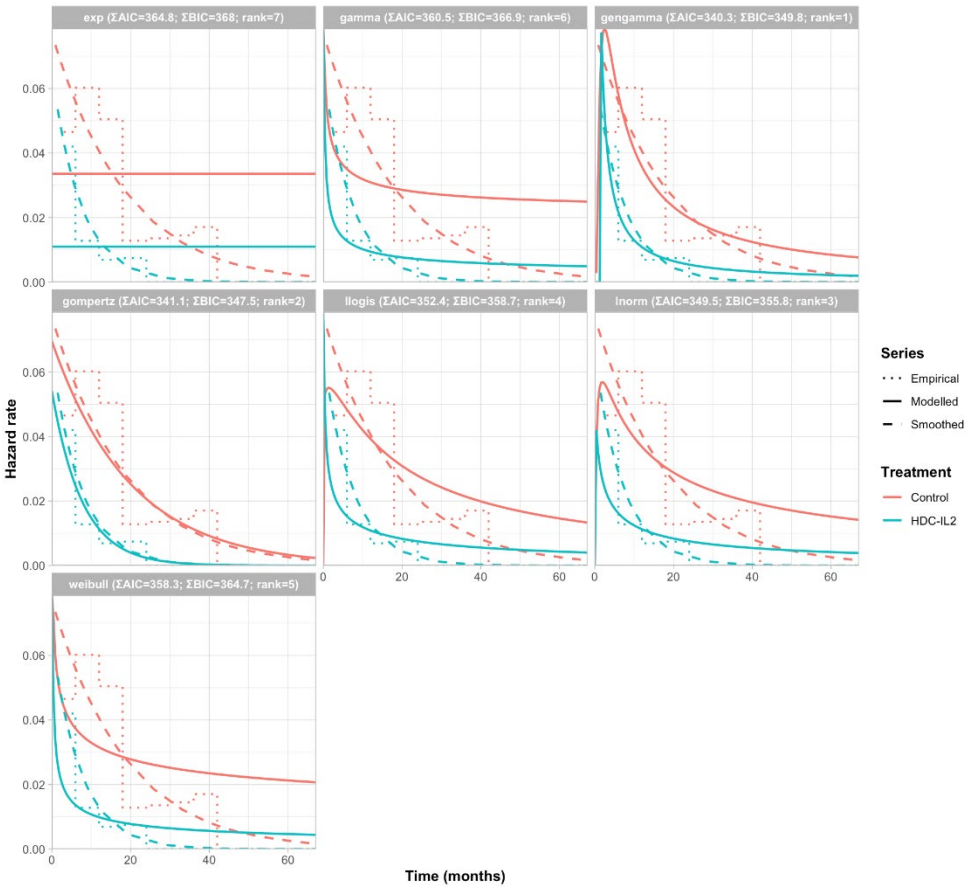
AIC - Akaike information criterion; BIC - Bayesian information criterion.

Figure 13: Observed versus predicted LFS from independent models (60 years) for adults with AML in CR1, ≤60 years old and with normal karyotype (reproduced the clarification response, page 89)



Notes: Dashed line marks end of observed follow-up (67.1 months).

Figure 14: Empirical, smoothed, and modelled instantaneous hazards for each of the independently fitted LFS parametric model (reproduced the clarification response, page 93)



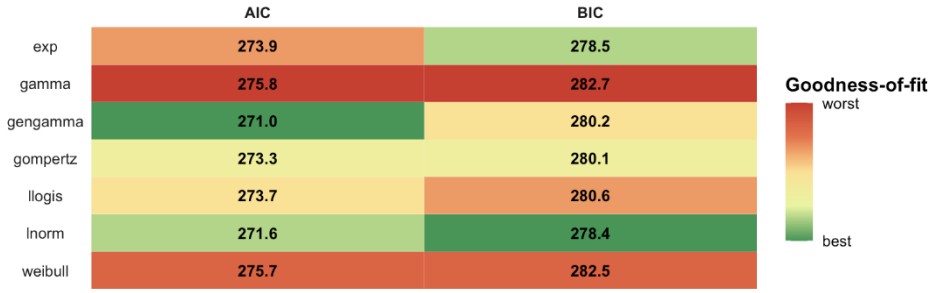
In the updated model, LFS estimates for the oral azacitidine treatment group were added. The extrapolation of LFS for the oral azacitidine treatment group was obtained by applying the HR of [redacted] (oral azacitidine vs HDC/IL-2) estimated from the ITC using the ITT population (clarification response, question A28,[30] see Section 3.4) to the cycle-specific risk of leukaemia progression of the chosen HDC/IL-2 LFS model. The estimated LFS for oral azacitidine is contingent on the specific LFS model chosen for HDC/IL-2.

Overall survival (OS)

Similarly to LFS, the company assessed the PH assumption for OS using the clog-log plot, Cox–Snell residuals, and Schoenfeld residuals. The company noted that although the smoothed Schoenfeld residuals was not entirely horizontal, the Schoenfeld residual test was not statistically significant (p = 0.15), so the PH assumption could not be rejected. On this basis, the company fitted seven jointly fitted standard parametric models to the OS subgroup data.

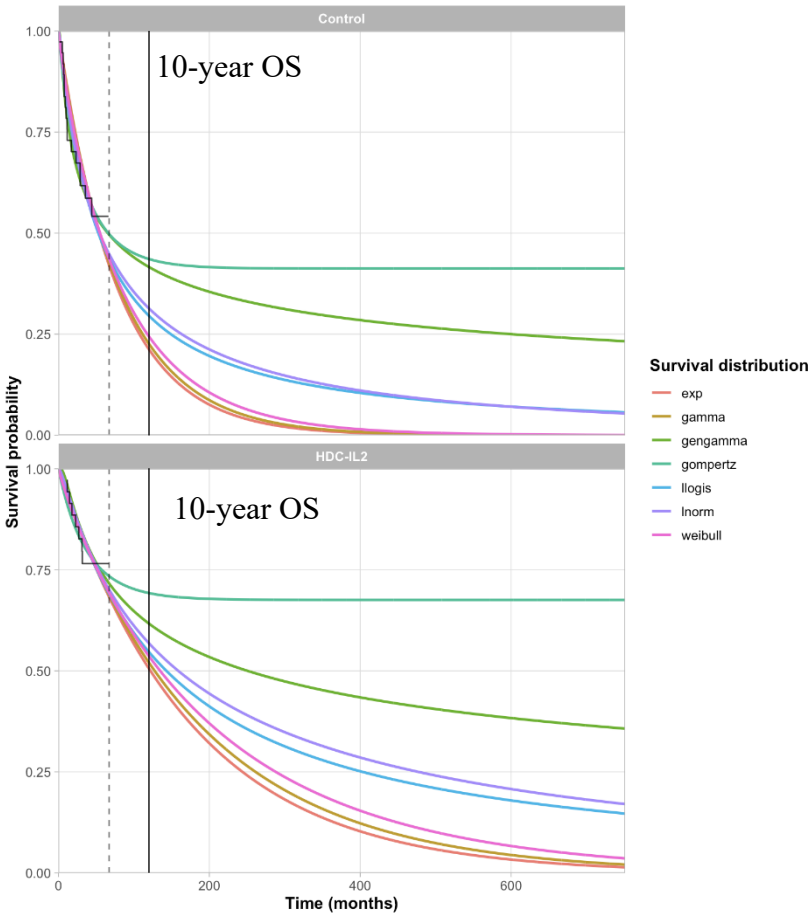
AIC and BIC statistics indicated that the jointly fitted log-normal and generalised gamma models provided the best statistical goodness-of-fit among those tested (Figure 15). The company presented modelled survival curves against the observed Kaplan-Meier curve for visual assessment (Figure 16). The company also provided empirical, smoothed, and modelled hazard plots for these models in its clarification response (Figure 17), which shows that the hazard was not constant. The company considered the Gompertz, generalised gamma, log-logistic, and log-normal models produced clinically implausible survival estimates over the extrapolation period. Among the remaining options (Weibull, gamma, and exponential), the gamma and Weibull models were ranked as the worst fits by AIC and BIC; therefore, the company selected the jointly fitted exponential model as the base case for OS. The company commented on the clinical plausibility of the OS for HDC/IL-2 in their response to clarification question B7,[30] noting that an OS of less than 25% at 200 months (i.e., 16.7 years) may be clinically plausible for HDC/IL-2.

Figure 15: Statistical goodness-of-fit criteria for the jointly fitted models of overall survival (reproduced from CS Figure 18)



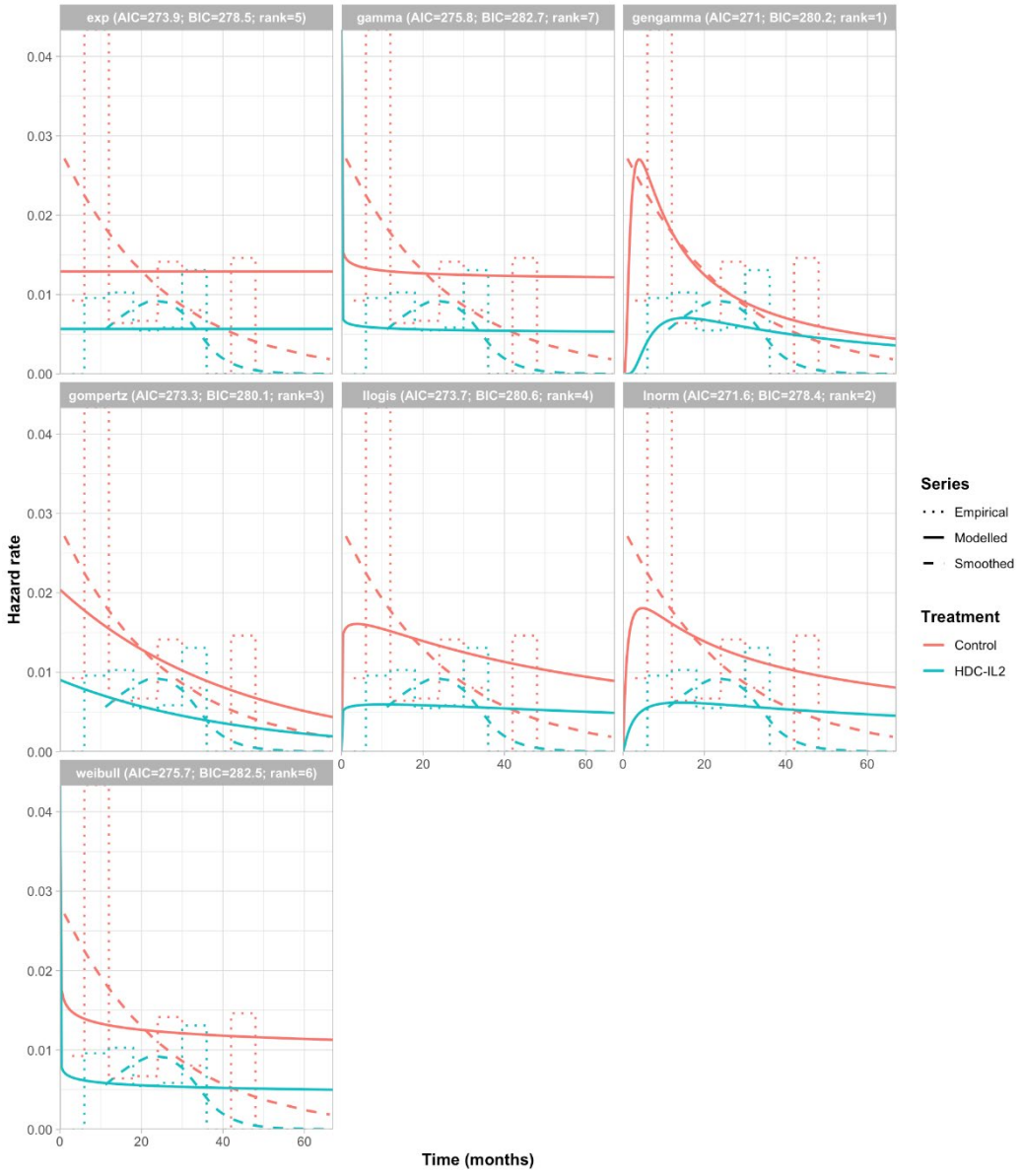
AIC - Akaike information criterion; BIC - Bayesian information criterion.

Figure 16: Observed versus predicted OS (60 years) from jointly fitted models for adults under 60 with acute myeloid leukaemia in first complete remission and normal karyotype (adapted from CS Figure 17)



Note: Dashed line marks end of observed follow-up (67.1 months), and the solid black vertical line marks 10 years (120 months).

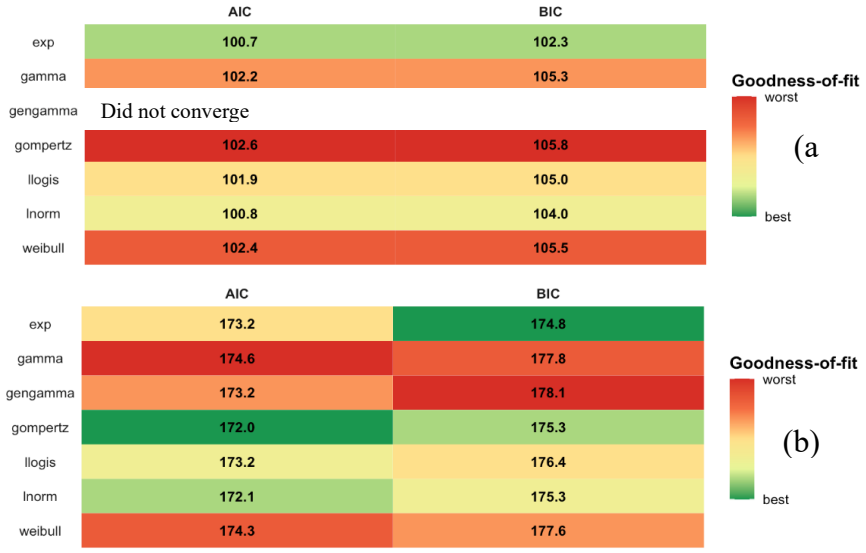
Figure 17: Empirical, smoothed, and modelled instantaneous hazards for each of the jointly fitted overall survival parametric models (reproduced from CS Figure 19)



In the company's updated model submitted at the clarification stage (response to clarification question B7),[30] OS estimates from independent models were included for the HDC/IL-2 and SoC treatment groups for the CR1, ≤60 years, and with normal karyotype population. The corresponding AIC/BIC statistics, modelled versus observed Kaplan-Meier curves, and hazard plots are shown in Figure 18, Figure 19 and Figure 20, respectively. The independent generalised gamma model for HDC/IL-2 OS showed an abrupt drop in survival to zero, which appeared visually unusual (Figure 19). Therefore, the EAG digitised the company's OS curves from CS Figure 15 and replicated the independent model fitting. Results indicated that the independent generalised gamma model for the HDC/IL-2 group did not converge. The company also repeated the independent parametric OS modelling analyses for other

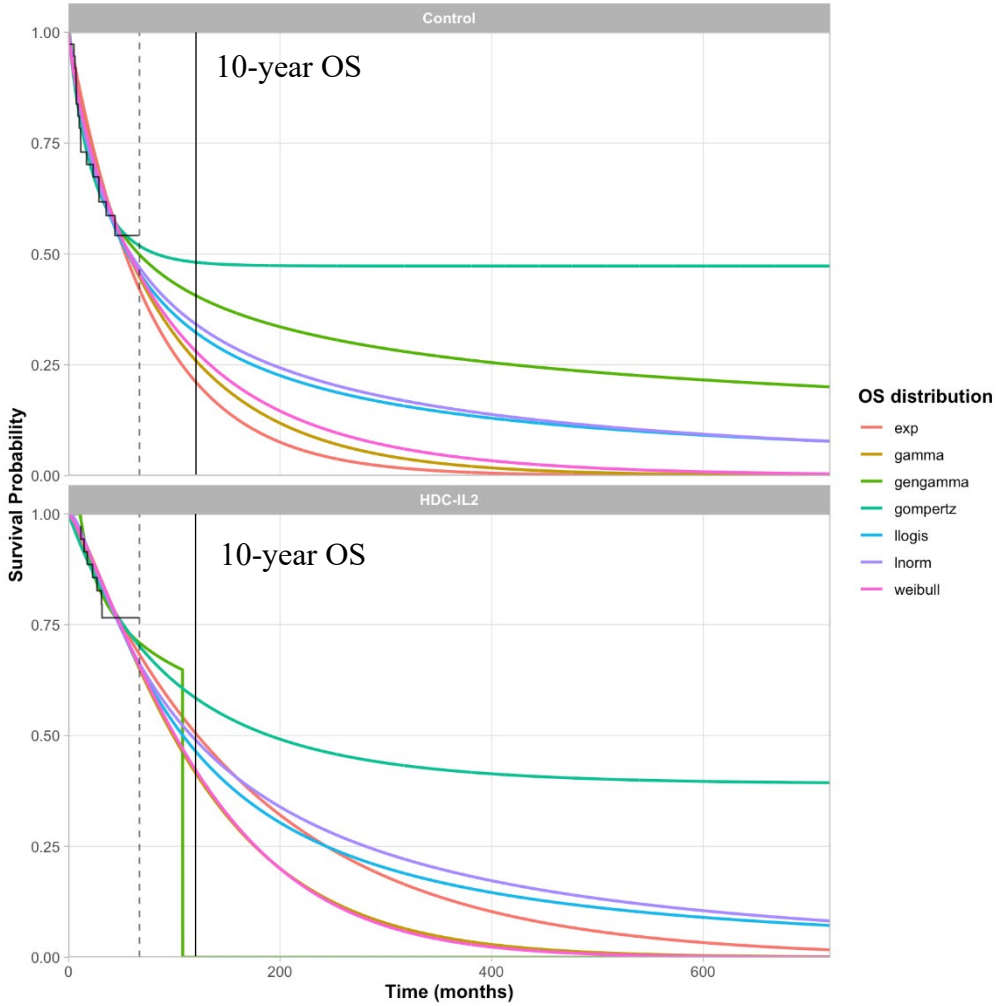
subgroups (i.e., patients in CR1, and patients in CR1 aged ≤60 years); these results can be found in the response to clarification question B7.[30]

Figure 18: Statistical goodness-of-fit criteria for the independent parametric models of OS (a) HDC/IL-2 group (b) standard of care group (adapted from the clarification response, page 91)



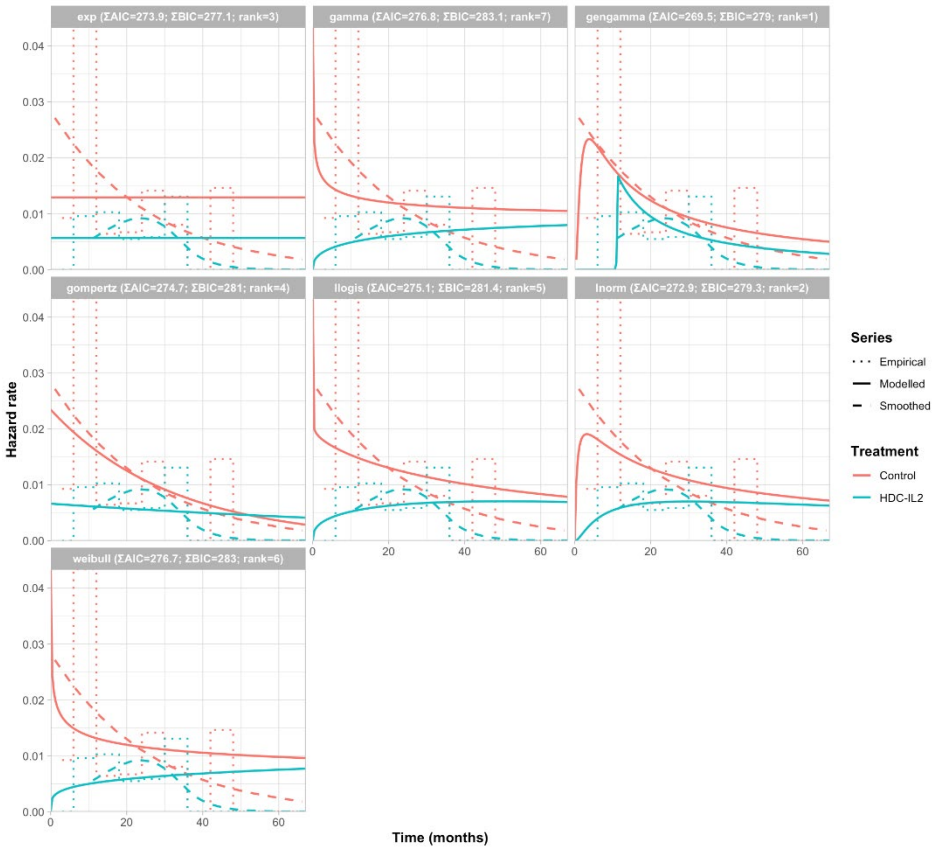
AIC - Akaike information criterion; BIC - Bayesian information criterion.

Figure 19: Observed versus predicted OS from independent models (60 years) adults with AML in CR1, ≤60 years old and with normal karyotype (adapted the clarification response, page 90)



Note: Dashed line marks end of observed follow-up (67.1 months), and the solid black vertical line marks 10 years (120 months).

Figure 20: Empirical, smoothed, and modelled instantaneous hazards for each of the independently fitted OS parametric model (reproduced the clarification response, page 93)



OS estimates for the oral azacitidine treatment group were included in the updated version of the model. The extrapolation of OS for the oral azacitidine treatment group was obtained by applying the HR of [redacted] (oral azacitidine vs HDC/IL-2) estimated from the ITC using the ITT population (clarification response, question A28,[30] see Section 3.4) to the cycle-specific risk of death of the chosen HDC/IL-2 OS model. The estimated OS for oral azacitidine is contingent on the specific HDC/IL-2 model chosen for OS. The EAG notes that the HR of [redacted] was based on the unstratified HR for overall OS from QUAZAR AML-001. During the clarification stage, the company provided the stratified HR for OS from QUAZAR AML-001 ([redacted]); however, this was not used as the base case. This issue is discussed in Section 4.3.5.

In addition to the OS estimates based on parametric survival models, and in the ITC estimates in the case of oral azacitidine, the company applied a structural constraint ensuring that, in any cycle, the mortality hazard did not exceed that of the age- and sex-matched general population, based on life tables for England and Wales (2021-2023).[72]

Summary of the LFS and OS parametric models

Table 18 summarises the parametric models selected by the company. The company selected a jointly fitted exponential model for both LFS and OS of HDC/IL-2 and SoC in patients in CR1, aged ≤60 years, and with normal karyotype. For oral azacitidine, the LFS and OS were derived by applying the corresponding HRs from the ITC (azacitidine vs HDC/IL-2, based on the Brune *et al.* and QUAZAR AML-001 trials ITT populations) to the selected LFS and OS parametric models for the HDC/IL-2 group.

In scenario analyses, the company explored alternative model specifications, including other jointly fitted parametric models. In each scenario, the same alternative distribution was applied to both treatment groups (as the models were jointly fitted) within LFS and OS. Only one outcome (LFS or OS) was varied at a time. In the company's updated model submitted at the clarification stage, the company provided independently fitted standard parametric models for each of the following additional patient subgroups: patients in CR1 and patients in CR1 and aged ≤60 years. However, scenario analyses were not presented for alternative combinations of LFS and OS models beyond those reported in the original submission.

Table 18: Summary of parametric models selected by the company

	Base case			Scenario analyses		
	HDC/IL-2	**SoC**	**Oral azacitidine**	**HDC/IL-2**	**SoC**	**Oral azacitidine**
LFS	Exponential, jointly fitted†		HR ([redacted]) from ITC applied to the selected HDC/IL-2 curve¶	Other jointly fitted models*		HR ([redacted]) from ITC applied to the selected HDC/IL-2 curve¶
OS	Exponential, jointly fitted†		HR ([redacted]) from ITC applied to the selected HDC/IL-2 curve¶	Other jointly fitted models*		HR ([redacted]) from ITC applied to the selected HDC/IL-2 curve¶

HDC/IL-2 - histamine dihydrochloride with interleukin-2; HR - hazard ratio; ITC - indirect treatment comparison; LFS - leukaemia-free survival; OS - overall survival; SoC - standard of care.
† Jointly fitted for the patients in CR1, aged ≤60 years, and with normal karyotype.
¶ HR applied to the risk of leukaemia relapse or of death of HDC/IL-2 at each cycle.
** Jointly fitted gamma, generalised gamma, Gompertz, log-logistic, lognormal, Weibull for the patients in CR1, aged ≤60 years, and with normal karyotype.*

Model-predicted LFS and OS

The company's base case model predictions of LFS and OS for HDC/Il-2 and both comparators are shown in Figure 21. These predictions incorporate the 'blended model' in which the company's obtained the resulting LFS and OS estimates from a weighted mean for discontinued and non-discontinued patients (see Section 4.2.2), and the constraints for LFS and OS (the latter by the general population mortality risks). The EAG noted that for both LFS and OS, oral azacitidine predicted higher

survival than HDC/IL-2, and HDC/IL-2 higher than SoC. In addition, LFS for HDC/IL-2 also exceeded OS for SoC.

Figure 22 summarises the effect of applying the 'blended model' model approach, by showing the company's modelled LFS and OS estimates for the HDC/IL-2 group with and without weighting the LFS and OS estimates for discontinued and non-discontinued patients. The non-weighted model uses the company's estimates considering only the data for the HDC/IL-2 group in Nilsson *et al.* and includes the structural constraints for LFS and OS.

Figure 21: Model predictions of LFS and OS for HDC/IL-2 versus SoC and oral azacitidine, company's base case (generated using the company's model, includes blended approach)

BC - base case; HDC/IL-2 - histamine dihydrochloride with interleukin-2; HR - hazard ratio; LFS - leukaemia-free survival; OS - overall survival; SoC - standard of care.

Figure 22: Model predictions of LFS and OS for HDC/IL-2, company's base case, blended approach vs fitted parametric chosen distributions only (generated using the company's model)

BC - base case; HDC/IL-2 - histamine dihydrochloride with interleukin-2; LFS - leukaemia-free survival; OS - overall survival.

4.2.6.2 Treatment discontinuation

The company reports in CS Section 3.3[1] that time-to-treatment discontinuation (TTD) data were not available from the Brune *et al.* study. As part of the clarification response (question B11)[30] the company stated that the only information on treatment discontinuations available from the Brune *et al.*[31] related to the number of patients who discontinued treatment with HDC/IL-2 due to AEs not related to relapse (8.3%), the median number of treatment cycles received (6; range 1–10) and the proportion of non-relapsed patients who completed all 10 schedule treatment cycles (n=45/49 or 92%). The company also stated that differences in discontinuation patterns between ITT population in Brune *et al.* and the target population, and the impact of these differences in the model results are difficult to quantify, but the assumptions adopted in the model *"are clinically reasonable and would align with the reasons for discontinuation of HDC/IL-2 in routine clinical practice"*.

In the absence of further information from the study, discontinuation in the HDC/IL-2 and oral azacitidine treatment groups is modelled using two components: (i) the proportion of patients who discontinued the HDC/IL-2 regimens due to AEs, as reported in the Brune *et al.*[31] and TA827[19] (8.3%

for HDC/Il-2 and 13.0% for oral azacitidine, respectively), which are assumed to have occurred at treatment initiation (and therefore applied only at the first model cycle), and (ii) discontinuation due to relapse, based on patients leaving the LF state, and which is applied in every model cycle. Patients in the SoC treatment group are assumed not to receive any therapies whilst on LF state, and to remain on SoC treatment until death.

The EAG notes that this approach affects not only the costs and HRQoL incurred by patients receiving these therapies or after treatment discontinuation, but also the survival outcomes for those patients who discontinue early in the model. The EAG has concerns related to the approach adopted for treatment discontinuation in the model, which are discussed in Section 4.3.5.

4.2.6.3 Health-related quality of life

The model includes HRQoL parameters related to health state utility values, based on progression status (LFS and PD), and on treatment status (on/off treatment) for patients receiving HDC/IL-2 or oral azacitidine. Table 19 summarises the HRQoL data included in the company's base case and scenario analyses; the derivation of these parameters is described in further detail below.

Table 19: HRQoL parameters used in the company model's

Health State	Mean utility			Source
	HDC/ IL-2	Oral azacitidine	SoC	
Base Case				
Pre-progression, on treatment	0.81		N/A	Tremblay *et al.*[53]
Pre-progression, off treatment and SoC	0.83			
Post Progression, all groups	0.53			
Utility decrement related to AEs	0.000996	0.000996	0.000259	See 'QALY losses due to AEs' section below
Scenario Analysis 1*				
Pre-progression, HDC/IL-2 on treatment	0.89			Joshi *et al.*[79]
Pre-progression, HDC/IL-2 off treatment and SoC	0.89			
Post Progression, both groups	0.51			
Scenario Analysis 2*				
Pre-progression, HDC/IL-2 on treatment	0.87			Stein *et al.*[56]
Pre-progression, HDC/IL-2 off treatment and SoC	0.87			
Post Progression, both groups	0.62			
Scenario Analysis 3*				

Pre-progression, HDC/IL-2 on treatment	0.74	Russell-Smith *et al.*[58]
Pre-progression, HDC/IL-2 off treatment and SoC	0.74	
Post Progression, both groups	0.57	

HDC - histamine dihydrochloride; IL-2 - interleukin-2; N/A – not applicable; NICE - National Institute of Health and Care Excellence; SoC – standard of care.
**The scenario analyses were not presented by the company using the updated version of the model at clarification stage.*

Health state utility values

Section 3.4 of the CS[1] states that Brune *et al.* study included HRQoL data collection using the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30). The study CSR reported that the version 2.0 of the questionnaire was administered at specific patients' visit points (at randomisation, visits 6, 7, 10, 11, 16, 17, 22, and at early termination), and that responses were available for 288 patients (249 patients had responses at baseline, and 'the majority of these patients' had responses through cycle 5, at study completion or termination).[34] The company also stated in the CS that aggregate data regarding the quality-of-life in these patients had previously been published in Wallhult *et al.*;[80] however, patient level data from the study were not available despite the attempt from the company to obtain it from the authors. The company used this justification as the basis for using health state utility values from published estimates to inform the utility values in the model.[1]

The EAG notes that Wallhult *et al.*[80] only reports the number of patients who had completed at least one questionnaire (n=285, 89%), and results in a qualitative way (increase or maintenance of QoL status in certain dimensions), without providing estimates that could be used in any mapping models, and that the copy of the CSR shared by the company does not include any results regarding the QoL outcomes collected in the Brune *et al.* study.[34]

The company undertook a SLR in July 2025 to identify published HRQoL studies which are relevant to the decision problem. The methods and results of the SLR are presented in CS Appendix F.[1] The EAG's critique of the searches performed by the company is reported in Section 4.1 of this report. The company reports that 14 studies were included in the review of HRQoL studies; however, the company selected three studies within these to inform their model base case and scenario analysis: Tremblay *et al.*,[53] Joshi *et al.*[79] and Stein *et al.*[56] The company's justification for the selection of these studies was based on the fact that they were extensively discussed by the company and EAG in NICE TA827.[19] The company also included an additional scenario analysis using values reported by Russell-Smith *et al.,*[58] identified from the company's SLR of economic evaluations (rather than the SLR for HRQoL studies – see Section 4.1.2), as clarified by the company in clarification response (question B13).[30]

In the base case analysis, utility values for all health states were taken from Tremblay *et al.*,[53] a cost-effectiveness analysis of midostaurin versus SoC for patients with AML in the UK. For the leukaemia-free state (pre-progression) in patients receiving HDC/IL-2 whilst on treatment, the utility value of 0.81 applied in the model corresponds to the utility value for the monotherapy treatment, which in turn was based on the unweighted mean of values for patients with active AML and in remission from Batty *et al.*[64] The resulting utility value is assumed to incorporate disutility *'related to toxicity and adverse events resulting from treatment'*,[53] for which the company assumes to correspond to the loss of approximately one week of perfect health in those patients receiving treatment with HDC/IL-2. The company also assumed that patients receiving oral azacitidine whilst on treatment would incur the same utility value as patients receiving HDC/IL-2; the EAG notes that the reasons behind this approach are unclear.

The utility value for leukaemia-free patients in HDC/IL-2 or oral azacitidine treatment groups who are off treatment, or patients receiving SoC (0.83) was based on the utility value for 'complete remission' state in Tremblay *et al.*,[53] which in turn was based in the EQ-5D utility value for patients with no relapse from Leunis *et al.*,[65] a study which evaluated HRQoL in 103 patients diagnosed with AML who had participated in clinical trials between 1999 and 2011 using the QLQ-C30, EQ-5D-5L and EQ Visual Analogue Scale (EQ-VAS) instruments.

The utility applied by the company for the post-progression state of 0.53 corresponds to the value for 'relapse' in Tremblay *et al.*,[53] which in turn corresponds to the utility value for patients with MDS who have progressed to AML in Pan *et al.*,[66] using EORTC QLQ-C30 mapped to EQ-5D using a published algorithm.[81]

The CS[1] also includes 3 scenario analyses which apply health state utility values from Joshi *et al.,*[79] Stein *et al.*[56] and Russell-Smith *et al.*[58] (Table 15). The EAG notes that:

- Joshi *et al*.[79] elicited health state utilities associated with AML from 210 participants from the general public in the UK using a composite time trade off (cTTO) methodology. The utilities selected by the company for LFS (on/off treatment and SoC) and PD states correspond to the mean utilities for patients on maintenance treatment or at long term (>1 year) follow-up, and following treatment failure/relapse/refractory, respectively.
- Stein *et al.*[56] used a discrete choice experiment (DCE) methodology and included 300 participants from the general population in the US to estimate utilities for treatment-related health states in AML. The utilities selected for LFS and PD states correspond to, respectively, the utility value for 'complete remission' and the difference between this utility and the utility for 'relapse'.

- Russell-Smith *et al.*[58] corresponds to a cost-effectiveness analysis of gemtuzumab ozogamicin versus SoC as first line therapy for AML in the UK. The utilities selected by the company for LFS and PD states correspond to the utility values used in the study for complete remission or complete remission with incomplete platelet recovery (CR or CRp) and for relapse, respectively. Both values are referred as being from a previous NICE STA for azacitidine for treating AML (TA399),[59] and mapped to EQ-5D from EORTC QLQ-C30 data using a published algorithm.[82]

In response to clarification question B16,[30] the company acknowledged the limitations of Joshi *et al.*[79] and Stein *et al.*[56] and justified the inclusion of these sources as scenario analyses to provide comparability to TA827, which also used both studies as scenario analyses. The results for these scenarios were not presented by the company as part of their clarification response.[30] Health state utility values are not adjusted for increasing age in the model.

QALY losses due to AEs

The updated version of the model submitted during the clarification stage (question B14[a])[30] includes short-term QALY losses associated with Grade 3/4 AEs. Disutility values were taken from previous NICE TA827[19] (which in turn has taken them from TA627[57], Nafees *et al.*,[55] and Stein *et al.*[56]), Stafford *et al.*[73] and assumptions (see Table 20). Overall utility decrements attributable to AEs were estimated to be 0.052 for HDC/IL-2 and oral azacitidine, and 0.013 for SoC, which are applied in the first model cycle as QALY losses of 0.0010 and 0.0003, respectively, based on the assumption that all AEs last for one week.

Table 20: AE utility decrements applied in the company's updated base case model, by treatment group

Adverse event	AE incidence		Utility decrement	Total utility decrement		Sources of decrements
	HDC/IL-2 or oral azacitidine	SoC		HDC/IL-2 or oral azacitidine	SoC	
Fatigue	0.013	0.013	0.115	0.001	0.001	TA827[19] (TA642)[57]
Nausea	0.013	0.000	0.048	0.001	0.000	TA827[19] (Nafees *et al.*)[55]
Vomiting	0.006	0.000	0.048	0.000	0.000	
Diarrhoea	0.019	0.000	0.176	0.003	0.000	TA827[19] (Stein *et al.*)[56]
Anaemia	0.013	0.006	0.119	0.002	0.001	TA827[19] (TA642)[57]
Thrombocytopenia	0.173	0.094	0.090	0.016	0.008	
Neutropenia	0.057	0.031	0.090	0.005	0.003	TA827[19] (Nafees *et al.*[55] and TA642)
Headache	0.070	0.000	0.340	0.024	0.000	Stafford *et al.*[73]
Total (utility decrements)	-	-	-	**0.052**	**0.013**	-

Total (QALY losses)	**-**	**-**	**-**	**0.0010**	**0.0003**	**-**

4.2.6.4 Resources and costs

The model includes costs associated with: (i) drug acquisition and administration; (ii) disease management; (iii)costs of subsequent therapies (allo-SCT procedure); (iv) management of AEs and (v) end of life (terminal care). Table 21 summarises the costs applied within the model.

Table 21: Summary of costs applied in the company's base case analysis by treatment group

Cost parameter	HDC/IL-2	SoC	Oral azacitidine
Drug acquisition costs (per monthly cycle)*	List price: £5,509.28	£0.00	List price: £11,734.00
Drug administration costs (per monthly cycle)	£249.64	£0.00	£0.00
SoC medication - post-progression only (per monthly cycle)	£18.68		
Disease management – progression-free, on treatment (per monthly cycle)	£571.28	£504.90	£571.28
Disease management – progression-free, off treatment (per monthly cycle)	£545.27		£545.27
Disease management – post-progression (per monthly cycle)	£822.05		
Subsequent treatment (allo-SCT, once-only at point of relapse)‡	£1,364.47	£2,967.17	£1,364.47
AE management (once-only at first cycle) ⁂	£147.69	£57.03	£147.69
End-of-life care (once-only at point of death)	£5,391.47		

AE: adverse event; N/A – not applicable; SoC: standard of care.
** Drug acquisition costs assume no wastage and 100% RDI.*
‡*Includes the proportion of patients in each group which are assumed to receive allo-SCT after relapse.*
⁂*Includes the incidence of AEs by treatment group.*

Drug acquisition and administration costs

The drug acquisition and administration costs are applied in the model are summarised in Table 22. The company's model includes a per three-week treatment cycle cost for HDC of £3,600, based on the list price informed by the company.[1] No patient access scheme has been proposed by the company for HDC. In line with the SmPC,[28] HDC is assumed to be administered at a fixed dose of 0.5 mg/0.5ml twice daily via subcutaneous injections, to be given 1 to 3 minutes after the administration of IL-2. The costs for

IL-2 therapy given before HDC include the administration of aldesleukin at a dosage of 16,400IU/kg twice per day on the same days that HDC is given, and based on an assumed baseline patient weight of 78.45 kg, estimate taken from the NHS Health Survey for England.[71] Unit costs of £636 per pack of 18 million IUs were obtained from the BNF,[74] which leads to a total cost of £1,909.28 per three-week treatment cycle.

The model applies the full 3-week treatment costs for HDC and IL-2 at specific model cycles, which are assumed to reflect the treatment schedule which alternates 3 weeks on treatment with 3 weeks off therapy for the first 3 treatment cycles and 6 weeks off therapy for the remainder 3 treatment cycles. The EAG notes that the company's approach does not include RDI estimates from the Brune *et al.* study.[31]. As part of the clarification response to question A3(c),[30] the company stated that treatment compliance was measured in the Brune *et al.* study[31] though the investigator's assessment of the patient taking at least 80% of the required dose of IL-2 and HDC, and that between 95% and 100% of patients met this requirement in each of the treatment cycles. The study CSR reported similar data, based [redacted].[34]

As part of their updated model submitted at clarification, the company intended including wastage for patients who received HDC/IL-2 and oral azacitidine (clarification response, question B17[b]).[30] The company also considers the wastage for patients who discontinue at the first cycle due to AEs by applying the full 3-cycle treatment costs to all patients starting treatment. Nonetheless, the EAG has concerns regarding the approach adopted by the company and the implementation of this approach was found to contain errors; these issues are discussed in Section 4.3.5.

The costs of administering the HDC/IL-2 injections include one simple parenteral chemotherapy delivery at first attendance (currency code SB12Z for outpatient care), taken from the NHS Cost Collection for 2023/24.[75] The administration cost of £249.64 is applied once per cycle on the same model cycles as the treatment costs. The company, in clarification response to question B17(c), states that the administration costs chosen reflects '*the possibility of providing training to patients during administration of their first dose'*, and since the code SB12Z includes 30 minutes of nurse time and 30 to 60 minutes of chair time, it should be sufficient to include the first cycle delivery of IL-2 and HDC over 6-18 minutes in total and the patient training.[30] The company does not include the costs of any accessories that might be required to allow patients to self-administer each HDC injection over 5-15 minutes (e.g., a pump). In clarification response (question B17), the company clarified that patients would be expected to collect the prescription of HDC/IL-2 from the hospital once per treatment cycle,

and that *"under normal circumstances, no accessories are required for the self-administration of HDC/IL-2 as both the HDC and IL-2 components are supplied in or with sterile syringes."*[30] The EAG notes, however, that the SmPC for HDC/IL-2 specifically mentions that *"Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection can be administered via an ambulatory infusion syringe pump or by controlled manual subcutaneous injection by syringe with a timer."*[28]

Drug acquisition costs for oral azacitidine were based on a list price cost of £5,867.00 from BNF.[74] Oral azacitidine is assumed to be administered at a fixed dose of 300mg daily, to be given orally for 14 days in each 28-day treatment cycle. A total per cycle cost of £11,734.00 is applied in every model cycle for 12 cycles, based on the median treatment duration of 11.4 months from TA827 (clarification response, question B11).[30] The model assumes that no administration costs are incurred by patients receiving oral azacitidine since it corresponds to an oral therapy. The EAG believes that the calculations of the per cycle drug costs for oral azacitidine to contain an error; this issue is detailed in Section 4.3.5. The EAG also notes that there is a confidential comparator Patient Access Scheme (cPAS) price available for oral azacitidine (see Section 5.4). The results of the economic analyses presented in the EAG report include list or Electronic Market Information Tool (eMIT) prices for all drugs; results including comparator PAS discounts are available in a separate confidential appendix.

Table 22: Costs associated with drug acquisition and administration

Description	Price per pack (list price)	Pack size and strength	Dosage schedule	Total costs per treatment cycle	Sources
Drug acquisition					
HDC	£1,200.00	14 vials with 0.5 ml each	One injection with 0.5 ml twice daily for 21 consecutive days in every treatment cycle	£3,600.00*	Unit costs informed by the company; dosage and schedule from HDC SmPC[28]
IL-2	£636.00	1 vial with 18 million units	One injection with 16,400 units twice daily for 21 consecutive days in every treatment cycle	£1,909.28*	BNF;[74] dosage and schedule from HDC SmPC[28]
Oral azacitidine	£5,867.00‡	7 tablets with 300mg each	One tablet daily for 14 days in the first 12 model cycles	£11,734.00‡	BNF;[74] TA827[19]
Drug administration					
Delivery of chemotherapy (HDC/IL-2 only)	-	-	Only applied once per treatment cycle	£249.64	NHS NCC 2023/24[75] (outpatient care,

					currency code SB12Z)

BNF - British National Formulary; HDC - histamine dihydrochloride; IL-2 - interleukin-2; NCC - National Cost Collection.
** Applied in the model at cycles, 1, 2, 3, 5, 7, 9, 11, 13, 15 and 17.*
‡ Based on list price for oral azacitidine. A comparator Patient Access Scheme (cPAS) price is available for this drug (see Section 5.4).

SoC drug costs (post progression health state only)

The company's model assumes that patients do not receive any active therapy as part of standard of care whilst they are still in the leukaemia-free state. The EAG's clinical advisors noted that this approach is in line with clinical practice, since patients still in remission would not receive any additional therapy if receiving HDC/IL-2 or oral azacitidine, or any active therapy if in SoC treatment group. Post-progression patients are assumed to incur the costs related to the drug therapies presented in Table 23. The proportions of patients receiving each drug, dosage schedule and number of administrations per treatment regimen were sourced from NICE TA827,[19] which in turn were informed by clinical opinion, and each drug's respective SmPCs. Unit costs were obtained from eMIT.[76] The total acquisition costs of £18.68 is applied in every cycle of the model to all patients in the progressed disease state, regardless of initial treatment group.

Table 23: SoC drug costs included in the company's model

Drug	Price per pack	Pack size (mg)	Total dose per administration (mg)	Number of administrations per cycle	Proportion of patients receiving resource use	Total costs per model cycle
Hydroxycarbamide	£8.90	50,000	3,138*	7	0.15	£0.59
Ciprofloxacin	£0.86	1,000	500	14	0.30	£0.18
Posaconazole	£131.14	9,600	400	21	0.15	£17.21
Fluconazole	£0.65	1,400	200	21	0.15	£0.29
Tranexamic acid	£3.88	30,000	1,000	21	0.15	£0.41
Total	-	-	-	-	-	**£18.68**

SoC: Standard of care; mg: milligram.
**Based on a dose of 40mg per kg and an assumed patient weight of 78.45 kg.*

Subsequent treatment costs

The company's original model submitted at CS did not include any further costs related to subsequent-line treatments after patients' relapse, based on the unavailability of data[1] on subsequent treatments patients received after relapse in the Brune *et al.* study,[31] despite attempts from the company to obtain these data. The version of the model submitted at clarification stage (clarification response, question B20)[30] includes the cost of allo-SCT as a subsequent treatment for a proportion of patients who relapse in each model cycle, based on NICE TA827[19] (6.3% for HDC/IL-2 and oral azacitidine, and 13.7% for

SoC). Unit costs were taken from NHS Cost Collection 2023/24[75] (£21,658, currency SA26A: Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over). Patients receiving allo-SCT are assumed to only incur the costs of the procedure; its impact on survival, HRQoL, AEs or further costs as a consequence of the procedure were not included in the model. The company noted that no data were available that would allow an adjustment "*for downstream survival, remission, or relapse in patients receiving allogeneic SCT versus those who did not receive allogeneic SCT*". A cost per patient of £1,364.47 is applied in the model at the point of relapse for patients in the HDC/IL-2 and oral azacitidine treatment groups, and of £2,967.17 for patients in the SoC group.

The EAG notes that in TA287 the costs of subsequent therapies also included treatment with cytarabine, injectable azacitidine, and salvage chemotherapy (daunorubicin and cytarabine), and these costs were estimated based on data from the QUAZAR trial, and therefore the outcomes from that study reflect the subsequent therapies received by the patients in this trial.[19] One of the EAG's clinical advisor noted that patients may become eligible for transplant at relapse, and that 30-40% of patients might get allo-SCT in CR2. Issues related to the implementation of subsequent treatment costs are further discussed in Section 4.3.5.

Disease management costs

Health care resource use related to disease management includes the costs associated with medical visits (haematologists and specialist cancer nurses), blood tests (complete blood counts and blood chemistry with liver panel testing), red blood cell and platelet transfusions, and bone marrow aspiration. These costs are assumed to be dependent on treatment group and treatment status (on and off treatment for HDC/IL-2 and oral azacitidine patients), with per-cycle costs associated with ongoing disease management being assumed to increase after disease progression. The costs per cycle for each disease management category are summarised in Table 24. The frequencies of each visit, test or intervention per monthly cycle were taken from NICE TA827, which in turn were informed by clinical opinion and QUAZAR AML-001 trial.[19] Unit costs were obtained from NHS Cost Collection 2023/24.[75] A total per cycle costs of £571.28 is applied for patients progression-free whilst receiving HDC/IL-2 or oral azacitidine, £545.27 for patients who remain progression-free after they stop treatment with these therapies, £504.90 for patients in the SoC treatment group, and £822.05 for patients in all treatment groups after progression. These per cycle costs are applied to each corresponding health state occupancy in every model cycle.

Table 24: Summary of health state resource use and costs per cycle used in the model for disease management costs

Resource	Resource use frequency (per cycle)				Unit cost	Total costs				Sources
	HDC/IL-2 or oral aza on Tx	HDC/IL-2 or oral aza off Tx	SoC	Post-progression		HDC/IL-2 or oral aza on Tx	HDC/IL-2 or oral aza off Tx	SoC	Post-progression	
Haematology	1.00	1.00	1.00	2.00	£204.32	£204.32	£204.32	£204.32	£408.64	TA827;[19] NHS NCC 2023/24[75] (outpatient care; currency WF01A; 303 service)
Nurse visit	2.00	1.50	1.50	2.00	£108.90	£217.80	£163.35	£163.35	£217.80	TA827;[19] NHS NCC 2023/24[75] (community health services; currency N10AF; 03 service)
Complete blood count	4.00	1.30	1.30	8.00	£2.98	£11.92	£3.87	£3.87	£23.84	TA827;[19] NHS NCC 2023/24[75] (directly accessed pathology services; currency PATH05; ; 999 service)
Blood chemistry and liver panel	1.00	1.00	1.00	2.00	£1.53	£1.53	£1.53	£1.53	£3.06	TA827;[19] NHS NCC 2023/24[75] (directly accessed pathology services; currency PATH04; 999 service)
RBC transfusion	0.000	0.227	0.000	0.218	£386.96	£0.00	£87.84	£0.00	£84.36	TA827;[19] NHS NCC 2023/24[75] (outpatient procedures; currency SA44A; 303 service)
Platelet transfusion	0.000	0.218	0.000	0.218	£386.96	£0.00	£84.36	£0.00	£84.36	
Bone marrow aspiration	0.175	0.000	0.170	0.000	£775.46	£135.71	£0.00	£131.83	£0.00	TA827;[19] NHS NCC 2023/24[75] (daycase; currency SA33Z)
Total costs	-	-	-	-	-	**£571.28**	**£545.27**	**£504.90**	**£822.05**	-

Aza – azacitidine; RBC: red blood cell; HDC: histamine dihydrochloride; IL-2: low dose interleukin-2; NCC: National Cost Collection 2023/24; SoC – standard of care; Tx - treatment.

AE management costs

The model includes the costs of managing grade 3/4 AEs which are applied as a lump sum cost in the first cycle of the model. Incidence rates were taken from the ITT population in Brune *et al.*[31] In the original version of the model, the company had only included Grade 3/4 AEs for fatigue, nausea, vomiting, diarrhoea and anaemia, all with incidence <5%. As part of the clarification response to question B12,[30] the company updated the model to also include thrombocytopenia, neutropenia, and headache, which an incidence of ≥5% in either treatment arm in the study. The company clarified the original approach being based on the selection of AEs which had significant differences in incidence across all grades between the treatment arms in the study, and which resulted in significant costs being incurred from the perspective of NHS England. The company also mentioned having originally excluded headache due to challenges in identifying widely accepted costs of treatment for this AE. The EAG notes that the criteria used by the company in the updated version of the model to select the AEs for inclusion in the model is still unconventional, since the criteria for selection of AEs is usually based on incidence (≥5% or 10% of Grade 3/4 AEs) instead of the impact on costs.

The model assumes that patients receiving oral azacitidine experience the same AEs as patients receiving HDC/IL-2; the reason behind this approach is unclear since TA827 reports the AE incidence from QUAZAR study (clarifications response, questions A28 and B1).[30] However, one of the clinical advisors to the EAG noted that given the different periods when the studies were conducted, and Brune *et al.* having recruited patients more than 20 years ago, the AEs in this study might have been to be under-estimated compared to more recent QUAZAR data, given improvements over time in clinical trial reporting standards and technology.

Unit costs associated with treatment emergent AEs were taken from the NHS cost collection 2023/24,[75] with the company assuming different proportions of patients receiving each AE management as outpatient care (costed as daycare) versus inpatient care (costed as non-elective short stay admission) based on TA827.[19] The AE incidences, proportions of patients treated in outpatient setting, unit costs and resulting total AE costs per treatment group used in the updated version of the model are presented in Table 25.

Table 25: Summary of adverse event costs included in the company's base case analysis

Adverse event	AE incidence		Proportion treated as outpatient	Inpatient unit cost*	Outpatient (day case) unit cost*	Unit cost (weighted)	Total AE costs		Source of unit costs
	HDC/IL-2	SOC					HDC/IL-2	SOC	
Fatigue	0.013	0.013	0.95	£864.11	£515.66	£533.08	£6.93	£6.93	NHS NCC 2023/24[75] (currency SA25M: Acute Myeloid Leukaemia CC Score 0-1)
Nausea	0.013	0.000	1.00	£864.11	£515.66	£515.66	£6.70	£0.00	
Vomiting	0.006	0.000	0.95	£515.48	£379.59	£386.39	£2.32	£0.00	NHS NCC 2023/24[75] (currency FD01J: Gastrointestinal Infections without Interventions CC Score 0-1)
Diarrhoea	0.019	0.000	0.95	£515.48	£379.59	£386.39	£7.34	£0.00	
Anaemia	0.013	0.006	0.90	£490.98	£367.81	£380.13	£4.94	£2.28	NHS NCC 2023/24[75] (currency SA04L: Iron Deficiency Anaemia CC Score 0-1)
Thrombocytopenia	0.173	0.094	0.90	£621.68	£361.56	£387.57	£67.05	£36.43	NHS NCC 2023/24[75] (currency SA12K: Thrombocytopenia CC Score 0-1)
Neutropenia	0.057	0.031	1.00	£528.81	£367.21	£367.21	£20.93	£11.38	NHS NCC 2023/24[75] (currency SA35E: Agranulocytosis CC Score 0-1)
Headache	0.070	0.000	1.00	£448.36	£449.61	£449.61	£31.47	£0.00	NHS NCC 2023/24[75] (currency AA31E: Headache, Migraine or Cerebrospinal Fluid Leak CC Score 0-6)
Total	**-**	**-**	**-**	**-**	**-**	**-**	**£147.69**	**£57.03**	**-**

HDC - histamine dihydrochloride; IL-2 - low dose interleukin-2; NCC - National cost collection 2023/24
**All inpatient costs relate to non-elective short stay costs and outpatient costs relate to daycase costs.*

End of life costs

The model includes a cost of end-of-life care, which was estimated to be £5,391 per patient. This cost is applied once-only at the point of patient's death, and was based on the value reported in Round *et al.*[77] for the costs associated with health care for four cancers (breast, colorectal, lung and prostate) in the UK. The cost estimate reported at 2015 prices (£4,254) was uplifted by the company to 2023/24 prices using the NHS Cost Inflation Index (NHSCII) published by the Personal Social Services Research Unit (PSSRU) 2023.[78] The EAG notes that only the cost associated with health care has been included in the estimates used by the company, although Round *et al.* reports costs associated with health, social, charity and informal care.

4.3 Critical appraisal of the company's submitted economic evaluation

This section presents the EAG's critical appraisal of the company's economic model, as presented in the updated version submitted at clarification stage. Section 4.3.1 summarises the EAG's methods for the critical appraisal of the company's model. Section 4.3.2 describes the EAG's verification of the company's model. Section 4.3.3 describes the correspondence between the CS, the model inputs and their original sources. Section 4.3.4 describes the extent to which the company's economic analysis adheres to the NICE Reference Case.[83] Section 4.3.5 presents the main issues identified during the EAG's critical appraisal of the company's model.

4.3.1 Critical appraisal methods

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying model upon which this is based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Double-programming of the deterministic version of the company's original model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS[1] and clarification response[30] and the company's executable model.
- Where possible, checking parameter values used in the company's model against their original data sources.
- Replication of the base case results, probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSAs) and scenario analyses reported in the CS, and the base case results reported in the clarification response using the company's executable model.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

4.3.2 Model verification by the EAG

The EAG rebuilt the deterministic version of the company's original and updated base case model in order to verify its implementation. During the process of rebuilding the original version of the model, the EAG identified a few programming errors which were partially resolved by the company during the clarification process.[30] Additional programming errors were identified by the EAG after the clarification stage; remaining errors are described in Section 4.3.5. The EAG believes the company's updated version of the model to be generally well programmed despite these errors, and that the version of the model used by the EAG after correcting these errors are appropriate for the decision problem.

4.3.3 Correspondence between the model, the CS and original sources of parameter values

Where possible, the EAG checked the company's model input values against their original sources, including published sources and additional sources provided by the company such as the Brune *et al.* study CSR.[34] The original version of the company's model included a few discrepancies, which were either clarified or resolved by the company during the clarification process.[30] The other model parameters appear to be consistent with their original sources.

4.3.4 Adherence to the NICE Reference Case

Table 26 summarises the extent to which the company's economic model adheres to the NICE Reference Case.[84] The EAG does not believe that the company's model is subject to any major deviations from the Reference Case.

Table 26: Adherence to the NICE Reference Case

Element of HTA	Reference Case	EAG comments
Defining the decision problem	The scope developed by NICE	The population included in the company's analysis is narrower than the population in HDC/IL-2 marketing authorisation and is in line with the subgroup of patients from the Brune *et al.* study included in the *post-hoc* analysis of data presented in Nilsson *et al.*[32] The EAG notes that given the period the study was conducted (1998-2004) and the changes in the treatment landscape in AML in the last two decades, it is unclear how the outcomes of the comparator arm in Brune *et al.* would be comparable to current practice for patients with AML eligible for maintenance therapy in the UK.
Comparator(s)	As listed in the scope developed by NICE	The NICE scope[33] specifies six comparators: (a) oral azacitidine (for people who cannot have or do not want a HSCT) (b) midostaurin (for people with an FLT3-mutation) (c) sorafenib, after a stem cell transplant (for people with an FLT3-ITD mutation) (d) quizartinib for people with an FLT3-ITD mutation (e) cytarabine alone or in combination with other antineoplastic agents

Element of HTA	Reference Case	EAG comments
		(f) best supportive care The original model submitted at CS[1] compared only HDC/IL-2 (plus SoC) versus SoC alone. The updated version of the model submitted at the clarification stage[30] also included the comparison against oral azacitidine. No comparison has been presented between HDC/IL-2 versus the comparators listed in the final NICE scope which are recommended for FLT-3 and FLT3-ITD mutation positive patients (midostautrin, sorafenib and quizartinib), and versus cytarabine. As noted in Section 2.3.3, the EAG's clinical advisors commented that FLT-3 and FLT3-ITD mutation positive patients, during induction and consolidation phases, will likely receive targeted therapies and will unlikely switch to other types of therapies during maintenance treatment. The advisors also noted that cytarabine is not commonly used in this population in the UK. The EAG notes that the CS states that *"there are very limited data on the efficacy of HDC/IL-2 in AML patients with FLT3 mutations and FLT3-ITD mutations"*, and therefore sufficient data are unlikely to be available to inform an ITC for this subgroup.
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The model includes health outcomes accrued by patients. Health impacts on caregivers are not included.
Perspective on costs	NHS and PSS	The model includes costs borne by the NHS and PSS.
Types of economic evaluation	Cost-utility analysis with fully incremental analysis	The model is evaluated using a cost-utility approach.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model includes a 60-year (lifetime) horizon. At the end of the time horizon, only 0.03% of patients in the HDC/IL-2 group, 0.07% of patients in the oral azacitidine group, and no patients in the SoC group are still alive.
Synthesis of evidence on health effects	Based on systematic review	Health outcomes are modelled using data from Brune *et al.* (2006),[31] the pivotal Phase 3 trial of HDC/IL-2 for AML (NCT00003991), and *post-hoc* analysis from this study presented in Nilsson *et al.* (2020).[32] Both studies were identified within the company's SLR of clinical effectiveness studies. Health outcomes for oral azacitidine are modelled using the results of an ITC conducted by the company between oral azacitidine and HDC/IL-2 which applied the Bucher method using data for the ITT populations in Brune *et al.* and QUAZAR AML-001.[19] Studies related to the QUAZAR AML-001 trial were identified within the additional

Element of HTA	Reference Case	EAG comments
		review undertaken by the company in response to clarification question A28.[30]
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Health state utility values are based on external data from Tremblay *et al.* (2018).[53] This study corresponds to an economic evaluation of midostaurin plus standard chemotherapy versus standard chemotherapy for patients with FLT3-mutated AML who were eligible to receive standard induction and consolidation chemotherapy. The utility values in this study were derived from different sources, where the majority of them use EQ-5D-3L. The study was identified within the company's SLR of HRQoL outcomes studies, and it was also used in TA827[19] to inform the utility for the relapse state. The updated version of the model includes disutilities associated with AEs, based on incidence rates from Brune *et al.,*[31] utility values and event durations from NICE TA827,[19] and assumptions (clarification response, question B14[b]).[30]
Source of data for measurement of HRQoL	Reported directly by patients or carers, or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	The economic analyses presented by the company at the CS and clarification response do not apply any decision modifier weights. However, this is not consistent with estimates of absolute and proportional QALY shortfall generated using the York QALY Shortfall calculator,[85] which suggests a decision modifier of 1.2 would be applicable for the targeted population of patients (in CR1, ≤60 years old, and with normal karyotype) in the comparison against SoC, but not against oral azacitidine. In the clarification response (question C1),[30] the company suggests that the analysis for the target population may qualify for a disease severity modifier of 1.2.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be values using the prices relevant to the NHS and PSS	Unit costs are taken from the NHS Cost Collection,[75] the BNF[74] and relevant literature.[77]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5% per annum.

AE - adverse event; BNF - British National Formulary; EAG - External Assessment Group; HDC - histamine dihydrochloride; IL-2 - interleukin-2; ITC - indirect treatment comparison; NICE - National Institute for Health and Care Excellence; NHS - National Health Service; PSS - Personal Social Services; SLR - systematic literature review; QALY - quality-adjusted life year.

4.3.5 Main issues identified from the EAG's critical appraisal

Box 1 summarises the main issues identified within the EAG's critical appraisal of the company's economic analyses. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified from the EAG's critical appraisal

(1) Model errors
(2) Concerns regarding the generalisability of the efficacy results from the Brune *et al.* study to current patients in NHS practice
(3) Concerns regarding the ITC conducted by the company to estimate the relative treatment effect of oral azacitidine versus HDC/IL-2
(4) Concerns regarding the survival extrapolation for HDC/IL-2 and SoC
(5) Concerns regarding the treatment discontinuation approach and impact on survival estimates
(6) Concerns regarding the utility values used in the model
(7) Uncertainty around the impact of AEs to costs and HRQoL
(8) Issues related to model costs
(9) Weak characterisation of uncertainty

(1) Model errors

The EAG's double-programming exercise identified a number of minor errors in the original version of the company's executable model, which have been resolved at the corrected version of the model submitted at clarification stage (see clarification response,[30] questions B18, B21 to B26, and B29). The EAG notes the following remaining concerns regarding the updated model:

(a) The model uses life tables for the England and Wales population[72] rather than England. Following the clarification stage (clarification response, question B10),[30] the updated economic model submitted by the company included the option to use the life tables for the England population; however, the company's updated base case still uses the life tables for England and Wales.
(b) Programming error in implementation of the LFS and OS independently fitted survival models for HDC/IL-2 and SoC included in the model. Some of the LFS and OS independently fitted survival models included in the updated version of the model did not match the curves presented in the figures presented in the clarification response (question B7[d])—specifically, the independently fitted generalised gamma models of both LFS and OS for HDC/IL-2 and SoC, as well as the independently fitted log-logistic OS model for HDC/IL-2.[30] The company provided an updated version of the model as part of additional clarification request from the EAG which included these corrections. However, the EAG notes that the formulae for the independently fitted log-logistic OS model for the HDC/IL-2 group still remained incorrect. Furthermore, the EAG replicated the company's analysis and noted that the independently fitted generalised gamma models did not

converge for either LFS or OS (see Figure 12 and Figure 18). Consequently, the EAG noted that the independently fitted generalised gamma models for HDC/IL-2 were not suitable for inclusion.

(c) The OS HR of oral azacitidine vs HDC/IL-2 is applied to the OS estimates for HDC/IL-2 after the general population mortality risk constraint is included, instead of before. The EAG believes this is an error.

(d) The costs of oral azacitidine are calculated based on the drug being received for 14 days in each 28-day treatment cycle. The EAG believes this cost should be adjusted to the monthly cycles (approximately 30.4 days) employed in the model.

(e) The model does not include age-adjustment of utility values. However, the EAG believes that adjustments for sex and age-matched general population HRQoL using Hernandez Alava *et al.*[86] should have been included in the model to reflect the pattern of decreasing HRQoL with increasing age.

(f) Within the company's model, mortality risks per monthly cycle calculated from OS models are one cycle out. The EAG believes this is a minor programming error which produces an inconsistency in the model traces.

(g) The approach used to sample health state utility values in the PSA ignores the logical ordering of the parameters (e.g., the sampled utility value for the LFS off treatment state may be lower than the sampled utility value for the LFS on treatment state, or the sampled utility value for the PD state may be higher than the sampled values for one the LF states, in the same probabilistic model run). This issue could be resolved by sampling from difference distributions using the method described by Ren *et al.*[87]

The EAG's exploratory analyses include scenarios which correct some of these issues, which are described in Section 5.2.

(2) Concerns regarding the generalisability of the efficacy results from the Brune *et al.* study to current patients in NHS practice

The EAG has concerns regarding the generalisability of data from the Brune *et al.* study to the population who would currently be eligible for AML maintenance treatment in the UK. The targeted population in the current appraisal is restricted to patients with AML with normal karyotype, in CR1, ≤60 years old and ineligible for allo-SCT. The company also confirmed in the clarification response to question A2(c)[30] that the company's intended positioning for HDC/IL-2 excludes patients with a FLT3 mutation. In the Brune *et al.* study, all normal karyotype patients were within the intermediate karyotype classification (clarification response, question A22).[30] The EAG also notes that based on the ELN 2022 risk classification by genetics at initial diagnosis (CS Table 3), patients in the intermediate risk category may include patients with FLT3-ITD mutations. The company stated that at the time of patient

recruitment for the Brune *et al.* study,[31] molecular testing for genetic subtypes was not routine practice, and therefore efficacy data for HDC/IL-2 by different genetic subtypes such as FLT3 mutations are unavailable from the study. Although the marketing authorisation for HDC/IL-2 does not exclude these patients from eligibility criteria to receive HDC/IL-2, the company considers that patients with FLT3 mutations would have received FLT3-targeted therapies during the induction and consolidation phases of treatment and would not switch to a non-targeted therapy such as HDC/IL-2 or oral azacitidine, and therefore excludes this group from the population of interest for this appraisal. This opinion was shared by experts in TA827,[19] and the clinical advisors to the EAG also agreed with this view. Nonetheless, it is unclear how many FLT3-positive patients have contributed to the efficacy data and other parameters used to inform the economic analysis presented by the company.

The EAG also has concerns regarding the generalisability of the Brune *et al.*[31] study results to patients who would currently be eligible to receive HDC/IL-2, given the change in the AML treatment landscape since the period the study was conducted (patients enrolled between 1998-2000). The clinical advisors to the EAG consider that given the advances in the AML landscape since the study period (e.g., the introduction of personalised and targeted therapies, molecular risk stratification, and improvements in supportive care), it is unclear how different outcomes for patients in current clinical practice would be from the patients receiving standard/best supportive care included in the trial. The EAG considers that it is likely that these changes in the AML treatment may have an impact on outcomes of patients who currently reach the maintenance stage of their treatment. This issue was highlighted by the Scottish Medicines Consortium (SMC) in its decision in 2011 to not recommend HDC/IL-2 for use in NHS Scotland (SMC 666/10),[69] which stated that it *"also had concerns that the outcomes for patients treated with standard care were poorer than might be expected with current practice and that adjustment for this would worsen the cost-effectiveness ratios."*

The company acknowledged in the CS that it is possible that the induction and consolidation therapies used in the trial differ from those used in a more contemporary setting, and that these differences might have an impact in the relative outcomes.[1] In response to clarification question A4,[30] the company stated that *"there is a high level of uncertainty in attempting to compare the outcomes of patients who have different baseline characteristics between different trials."* Nonetheless, the company presented in the CS naïve comparisons between the survival outcomes from the Brune *et al.* study with patients with AML in other studies, suggesting that patients in the population of interest (normal karyotype subgroup reported in Nilsson *et al.* 2020) have similar overall survival outcomes to other more contemporary populations (CS Section 2.5).[1] For example, the company suggests that patients with a normal karyotype, who reached CR1 and are less than 60 years old in the control group in Nilsson *et al.*[32] showed a similar 3-year survival rate to: (a) non-monitored patients with NPM1 and FLT3 mutations who were 60 years

old or younger (N=140) in two UK randomised controlled trials (UK AML 17 & 19, with enrolment periods between 2012-2014 and 2015-2018, respectively) reported by Potter *et al.*[88] (58.7%. vs 58%); and (b) patients with an NPM1 mutation who were 60 years old or younger and diagnosed with AML between 2007-2019 (N=198) from a Swedish registry of AML patients reported by Juliusson *et al.* (58.7%. vs 59.4%).[89]

Nonetheless, the EAG notes that there is uncertainty around the absolute and relative treatment effects of HDC/IL-2 and SoC in the targeted population of patients with AML who would be currently eligible for maintenance therapy in the UK, given concerns regarding the generalisability of data from the Brune *et al.* study. and subsequent *post-hoc* analyses. The absence of additional clinical data for the target population in a more recent setting precludes any further analyses by the EAG regarding this issue.

(3) Concerns regarding the ITC conducted by the company to estimate the relative treatment effect of oral azacitidine versus HDC/IL-2

The EAG provided a detailed critique of the company's ITC in Section 3.4 and concluded that the estimated treatment effect between HDC/IL-2 and oral azacitidine is highly uncertain for the target population. This uncertainty arises from: (i) limited population overlap between QUAZAR AML-001,[36] Brune *et al.,*[31] as well as the targeted subgroup in Brune *et al.* (CR1, ≤60 years, normal karyotype), without adjusting for population differences in the conducted ITC; (ii) inconsistency in selecting the stratified HR and the unstratified HR from the two studies to inform the ITC, with the company's currently approach more in favour of HDC/IL-2; and (iii) potential differences in SoC between QUAZAR AML-001 and Brune *et al*., potentially introducing bias into the ITC by treating SoC from the two studies as a common comparator.

To illustrate the potential impact of this uncertainty on the ICER, the EAG conducted two additional scenario analyses using the following assumptions (summarised in Table 27): (i) HR = 1 (no treatment difference between HDC/IL-2 and oral azacitidine), and (ii) the lower bound of the 95% CI from the HR estimate derived from the QUAZAR AML-001 ITT population *vs* the Brune *et al*. ITT population (more in favour of oral azacitidine). The results of these scenarios are presented in Section 5.2.2.

Table 27: Summary of EAG's preferred HR for ITC

Scenario	HR for oral azacitidine versus HDC/IL-2		Justification for EAG scenario analysis
	LFS	OS	
Company's updated base case	[redacted]‡	[redacted]*	Company's base case without any corrections
EAG's preferred analyses	[redacted]‡	[redacted] (updated point estimate**‡)	Company's base case for LFS and use of the HR for OS from the ITC which used stratified hazard ratio for OS from QUAZAR AML-001
EAG's additional analysis 1	[redacted]‡	[redacted]**‡	These scenario analyses aimed to assess the uncertainty around the HR estimates for LFS and OS and their impact on the ICER. One of the scenarios uses LFS and OS HRs more favourable to oral azacitidine (the lower bound of the 95% CIs). The other scenario, rather than using the upper bound of the 95% CIs, assumes equal effectiveness between the two therapies (HR=1.0), as there is no strong clinical evidence and experience that oral azacitidine is more effective than HDC/IL-2.
EAG's additional analysis 2	1.00	1.00	

EAG - External Assessment Group; LFS – leukaemia-free survival; OS – overall survival; HDC/IL-2 - HDC - histamine dihydrochloride with interleukin-2; SoC – standard of care.
** Based on unstratified hazard ratio for OS from QUAZAR AML-001 used in the ITC of QUAZAR AML-001 ITT population vs Brune et al. ITT population*
*** Based on stratified hazard ratio for OS from QUAZAR AML-001 used in the ITC of QUAZAR AML-001 ITT population vs Brune et al. ITT population*
‡HR estimate of the QUAZAR AML-001 ITT population vs Brune et al. ITT population

(4) Concerns regarding the survival extrapolation for HDC/IL-2 and SoC

Overall, the EAG considers the company's survival modelling to be subject to substantial uncertainty particularly due to: (i) the very small sample size and high degree of censoring in the data; (ii) limited follow-up, which prevents reliable extrapolated long-term hazard; (iii) the implicit assumption of a lifetime treatment effect on LFS and OS through the use of the jointly fitted exponential model as the base case; (iv) clinicians' expected survival estimates potentially reflecting current SoC and subsequent treatment options not available at the time of the trial; and (v) uncertainty surrounding the estimated hazard ratio between oral azacitidine and HDC/IL-2 from the Bucher ITC based on the ITT population. These concerns are discussed below in details in line with the recommendation from NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 21.[90, 91] Specifically, the EAG's critique of these issues is organised into the following aspects (a)–(f). These cover: (a) the use of jointly fitted models as the base case; (b) the range of alternative models explored; (c) statistical and visual goodness-of-fit; (d) the nature of the underlying hazards; and (e) the long-term clinical plausibility of

the extrapolated survival curves. Heading (f) then summarises the overall concerns regarding the survival extrapolation and presents the EAG's preferred parametric survival models.

As the oral azacitidine LFS and OS models were dependent on the selected HDC/IL-2 models, they were not discussed separately. For the plausibility of the HRs applied to HDC/IL-2 from the ITC to predict oral azacitidine LFS and OS, see critique point (3).

(a) Use of jointly fitted models as base case

In the original CS,[1] the company fitted jointly standard parametric survival models, with treatment included as a covariate, and selected the exponential model as the base case for both LFS and OS. The company justified the use of jointly fitted models by noting that the Schoenfeld residuals tests did not show a statistically significant violation of the PH assumption (i.e., the assumption required for fitting joint proportional models: exponential, Weibull and Gompertz distributions). However, the EAG observed that the complementary log-log plots for both LFS and OS were not entirely parallel, and the smoothed Schoenfeld residuals were not completely horizontal, suggesting that the PH assumption might not necessarily hold. Furthermore, no quantile-quantile (Q-Q) plot was provided by the company to test whether assumption for joint accelerated failure time (AFT) models (i.e., gemma, generalised gamma, log-logistic, log-normal distributions) would hold. Additionally, there is no clinical evidence to suggest that the treatment effect remains constant over time. Therefore, the EAG considered fitting models independently to be a more appropriate approach.

In the updated model,[30] the company fitted independent models as part of the scenario analyses. However, no updated base case results were provided based on any of these independent models.

(b) Range of models assessed

The company fitted seven standard parametric survival models to the available LFS and OS data (see Figure 10 and Figure 16 for jointly fitted models; Figure 13 and Figure 19 for independently fitted models). Other more flexible survival distributions, such as restricted cubic spline (RCS) models, were not considered.

Visual assessment of both jointly and independently fitted models indicated that several models, particularly the Gompertz and generalised gamma distributions, produced highly optimistic extrapolations (note: generalised gamma did not converge). Specifically, these models predicted over 20% survival after 60 years of extrapolation (from a modelled baseline age of 44.2 years) for OS in both HDC/IL-2 and SoC group, and for LFS in the HDC/IL-2 group.

The EAG fitted nine independent RCS models (hazard-, normal-, and odds-scale models with one to three knots each) for both LFS and OS. These models improved internal validity and better aligned with the Kaplan-Meier turning points within the trial follow-up period; however, they were affected by the heavily censored tails. Considering long-term clinical plausibility, the EAG concluded that these models did not offer improved external validity over the independently fitted standard parametric models and were therefore not presented here.

(c) Statistical and visual goodness-of-fit

The EAG notes the following observations regarding the fitted parametric survival models:

- *LFS (see Figure 9, Figure 10, Figure 12,* Figure 13*):* For the jointly fitted models, the Gompertz and generalised gamma distributions had the lowest AIC and BIC values, whereas the exponential, gamma, and Weibull models had the highest. For the independently fitted models, the overall trend in AIC and BIC values was consistent with that observed for the jointly fitted models. Specifically, for the SoC group, the Gompertz and generalised gamma distributions showed the lowest AIC and BIC values, while the exponential, gamma, and Weibull models showed the highest. A similar pattern was observed for the HDC/IL-2 group, except that the independently fitted generalised gamma model did not converge. Visual assessment showed that the jointly fitted standard parametric models provided a suboptimal fit, particularly for the HDC/IL-2 group. The independently fitted standard parametric models offered only marginal improvement, with the Gompertz distribution being the only one that better reflected the shape of the Kaplan-Meier curve within the trial follow-up period, but provided an optimistic extrapolation.
- *OS (Figure 15, Figure 16, Figure 18,* Figure 19*):* For the jointly fitted models, the generalised gamma and log-normal distributions had the lowest AIC and BIC values, while the gamma and Weibull model had the highest. For the independently fitted models, in the SoC group, the Gompertz, exponential, and log-normal showed the lowest AIC/BIC values, whereas gamma, generalised gamma, and Weibull had the highest. In the HDC/IL-2 group, the exponential, log-normal, log-logistic models had the lowest AIC/BIC values, while the Gompertz and Weibull models had the highest. For OS, both jointly and independently fitted standard parametric models provided similar visual fits, though none achieved a satisfactory overall fit. Given that the independently fitted generalised gamma distribution abruptly dropped to zero for both LFS and OS in the HDC/IL-2 group (Figure 13 and Figure 19), the EAG replicated the company's analyses and confirmed that these two models did not converge.

Given the small size of the targeted subgroup (fewer than 40 patients per treatment arm) and the long censoring tails for both LFS and OS, modelled visual fits to the trial follow-up data should be interpreted

with caution. Specifically: (1) the results may not be generalisable to the target subgroup within the general population, and (2) the limited follow-up and high degree of censoring may preclude reliable estimation of the true long-term survival pattern using parametric survival models. Had additional follow-up data been available, given that the trial was first published in 2006,[31] it would have helped to better characterise long-term outcomes and improve the reliability of extrapolations (see point (e) in this section for further discussion of long-term clinical plausibility).

(d) Consideration of nature of hazards

In the CS,[1] the company only provided plots for modelled hazards for the jointly fitted standard parametric models for LFS and OS, without presenting the smoothed or unsmoothed empirical hazards. In the clarification response (question B7)[30], the company updated these plots to include both smoothed and unsmoothed empirical hazards, along with the modelled hazards, and provided hazard plots for both jointly and independently fitted standard parametric models for LFS and OS.

The plots help assess how well the modelled hazard functions align with the observed data. However, a good fit within the trial follow-up period does not guarantee reliable long-term extrapolations, as the empirical hazard shape beyond the observed period is unknown. It is therefore important to also consider the clinical plausibility of the extrapolated hazard trends and the corresponding Kaplan–Meier curves.

With respect to these hazard plots, the EAG makes the following observations:

- *LFS (see Figure 11 and Figure 14):* For both jointly and independently fitted models, the modelled hazards from the Gompertz distribution showed the closest alignment with the smoothed empirical hazards across treatment groups within the trial period, with both groups exhibiting a decreasing hazard over time.
- *OS (see Figure 17 and Figure 20):* For both jointly and independently fitted models, the Gompertz distribution showed the closest alignment with the smoothed empirical hazards, capturing the decreasing hazard observed for the SoC group. However, none of the jointly or independently fitted models adequately represented the increasing–then–decreasing hazard pattern observed for the HDC/IL-2 group.

Apart from these observations, the EAG notes that these plots should be interpreted with caution given the extremely small sample size and high censoring, which produce long tails in the Kaplan-Meier curves. The later portion of the modelled hazard within the follow-up period, which informs the hazard direction during extrapolation, may not reflect the long-term hazard pattern expected in clinical practice. Specifically, the all-cause mortality may begin to increase at older ages. While this may have been

partially accounted for in the economic model, where OS and LFS are capped by the general population's life-table mortality, the EAG considered it highly uncertain whether this adequately adjusted for the long-term hazard behaviour in AML given the limited sample size and follow-up data.

(e) Consideration of long-term clinical plausibility

With respect to long-term clinical plausibility, the EAG makes the following observations:

- *LFS (see Figure 10 and* Figure 13*)*: the company selected the jointly fitted exponential model as base case, which predicted a 10-year LFS of over 25% for HDC/IL-2 and less than 10% for SoC. EAG's clinical advisors suggested that, in current practice, LFS among younger patients is expected to be higher, and a 10-year survival close to 0% is clinically implausible. Both EAG's clinician advisors suggesting 10-year LFS above 25% for both treatment groups.

  As there is no evidence to support a constant treatment effect over a lifetime, the EAG considered independent models more appropriate. If the treatment effect were truly constant, independently fitted models would yield results very similar to jointly fitted ones. Among all independent models, the independently fitted exponential model for HDC/IL-2 was deemed reasonable, with a 10-year LFS slightly above 25% and converging to 0% by 60 years (i.e., average patient being 104 years old). In contrast, all other models for HDC/IL-2 predicted LFS above 5% at the end of the 60-year extrapolation period. For SoC, the EAG considered the independently fitted log-normal and log-logistic models more clinically plausible. These models predicted higher 10-year survival than the exponential, gamma, or Weibull models, which projected 10-year survival close to 0%. In addition, the log-normal and log-logistic models declined to 0% survival by 60 years, which was considered more clinically plausible. In contrast, the independently fitted generalised gamma and Gompertz models produced potentially reasonable 10-year estimates for SoC, but maintained survival above 5% by 60 years, which was considered clinically implausible.

- *OS (see Figure 16 and Figure 19)*: The company selected the jointly fitted exponential model as the base case, which predicted a 10-year OS of nearly 50% for HDC/IL-2 and around 20% for SoC. The EAG's clinical advisors suggest that, in current practice, 10-year OS among younger patients is likely higher (above 30%).

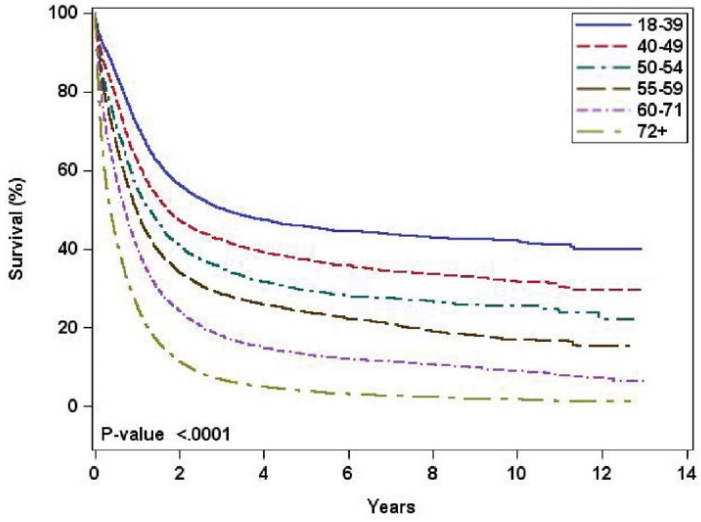
  As there is no evidence to support a constant treatment effect over a lifetime, the EAG considered independent models more appropriate. Among these, the independently fitted Weibull and gamma models for HDC/IL-2 were considered reasonable, predicting 5-year OS about 70%, 10-year OS estimates of 40-45%, and convergence to 0% by 60 years. These

represented more pessimistic projections for HDC/IL-2 among all independently fitted standard parametric models, yet clinically plausible. In contrast, the log-logistic, log-normal, and Gompertz models did not converge to 0% by 60 years, which was considered clinically implausible.

The EAG noted that data from CRUK for people diagnosed with AML in one area of England between 2010 and 2019 indicate that survival in AML is strongly age-dependent, with 5-year OS of approximately 60% for patients under 40 years, decreasing to around 35% for those aged 50-59 years, 15% for those aged 60-69 years, and about 1% for those aged 80 years or older.[25] The EAG also noted evidence from an observational study of patients diagnosed with AML between 2004 and 2007 in the US National Cancer Database, which similarly demonstrated that age has a significant impact on long-term OS in AML patients.[92] Among AML patients treated with chemotherapy only, 10-year OS was 40-45% for those aged 18-39 years, 30-40% for those aged 40-49 years, 20-30% for those aged 50-54 years, and 20-30% for those aged 50-54 years (Figure 23). The EAG noted that this study was conducted approximately 20 years ago, and that the standard of care may have improved since then. Therefore, it was considered possible that the 10-year survival under current practice could be higher than that reported in this observational study. Based on the above evidence, the EAG considered the independently fitted Weibull model appropriate, despite it being the most pessimistic among the independently fitted models for HDC/IL-2, as its 10-year survival estimate remained relatively optimistic given that the average age of AML patients in Brune *et al.* is 44 years. For SoC, the EAG considered the independently fitted Weibull model most plausible. Among models projecting clinically plausible OS at 60 years (i.e., less than 5%; exponential, gamma, and Weibull), the Weibull produced the highest 10-year survival (above 25%), aligning most closely with clinical expectations.

The EAG notes, based on its clinical advisors [redacted][93] that the SoC has evolved substantially since the Brune *et al*. trial was conducted. In current practice, several additional salvage treatments (e.g., fludarabine) are available, which could not be explicitly reflected in the survival projections, as subsequent treatments in the trial were unknown and unlikely to include these newer options. Given the limited data, the EAG prioritised visual inspection and long-term clinical plausibility over short-term data fit, recognising that the available follow-up may not fully capture the hazard patterns relevant to the extrapolation period.

Figure 23: Age-based overall survival of patients treated with chemotherapy only in US National Cancer Database patients diagnosed with AML during years 2004-2007 (reproduced from Khanal et al. Figure 1)



(f) Summary and EAG's preferred parametric survival models

Overall, the EAG considers the company's survival modelling to be subject to substantial uncertainty. Alternative survival models, based on the EAG's preferred models are summarised in Table 28 are explored as part of the EAG's exploratory analyses (see Section 5.2).

Table 28: Summary of EAG's preferred parametric survival models

	Treatment	Company's selected model	EAG's preferred model	Justification for EAG preferred model selection and additional comments
LFS	HDC/IL-2	Exponential, jointly fitted	Exponential, independently fitted	The independently fitted exponential model was considered reasonable, with 10-year LFS slightly above 25% and converging to 0% by 60 years (average patient age ~104 years). Other models predicted >5% LFS at 60 years, which was deemed implausible.
	SoC	Exponential, jointly fitted	Log-normal, independently fitted	Independently fitted log-normal model was more clinically plausible, predicting higher 10-year survival than exponential, gamma, or Weibull models (which projected near-zero survival). It also declined to 0% by 60 years. In contrast, generalised gamma and Gompertz models predicted >5% survival at 60 years, which is clinically implausible.
OS	HDC/IL-2	Exponential, jointly fitted	Weibull, independently fitted	Independently fitted Weibull models were considered reasonable, predicting 10-year OS around 40-45% and declining to 0% by 60 years.

	Treatment	Company's selected model	EAG's preferred model	Justification for EAG preferred model selection and additional comments
	SoC	Exponential, jointly fitted	Weibull, independently fitted	The independently fitted Weibull model was considered most plausible. Among models projecting <5% OS at 60 years (exponential, gamma, Weibull), the Weibull produced the highest 10-year survival (>25%), aligning best with clinical expectations.

EAG - External Assessment Group; LFS – leukaemia-free survival; OS – overall survival; HDC/IL-2 - HDC - histamine dihydrochloride with interleukin-2; SoC – standard of care.

(5) Concerns regarding the treatment discontinuation approach and impact on survival estimates

The company adopted a blended survival approach to account for treatment discontinuation in the HDC/IL-2 and oral azacitidine groups, as discussed in Sections 4.2.2, 4.2.4.1 and 4.2.4.3. The EAG considered this approach problematic because the data used to produce standard parametric models for LFS and OS of HDC/IL-2 already included patients who had discontinued treatment; therefore, the survival estimates reported in Nilsson *et al.*[32] should already reflect outcomes for those who discontinued treatment. Specifically, the company confirmed during the clarification stage for the EAG's additional questions[46] that the IPD used for the parametric survival models for LFS and OS included the 8.3% of patients in the HDC/IL-2 arm who discontinued due to AEs unrelated to relapse. As such, applying the blended survival approach effectively double counts the impact of treatment discontinuation.

The EAG considered that treatment discontinuation should only apply to partitioning between LFS_{on} and LFS_{off} within the LF state to assign the respective HRQoL outcomes and costs for each sub-state, while LFS and OS should be modelled using a non-blended approach, based directly on standard parametric survival estimates. The EAG shows the effect on LFS and OS estimates between the company's base case (blended) and EAG's preferred analysis (non-blended) survival models in Figure 24 and Figure 25, respectively. The EAG notes that the EAG's approach improves estimated survival for HDC/IL-2 and oral azacitidine groups.

Figure 24: Company's base case versus EAG's preferred analysis - LFS, HDC/IL-2 vs SoC and oral azacitidine (generated using the company's model)

BC - base case; EAG - External Assessment Group; HDC/IL-2 - histamine dihydrochloride with interleukin-2; HR - hazard ratio; LFS - leukaemia-free survival; OS - overall survival; PA - preferred analysis; SoC - standard of care.

Figure 25: Company's base case versus EAG's preferred analysis – OS, HDC/IL-2 vs SoC and oral azacitidine

BC - base case; EAG - External Assessment Group; HDC/IL-2 - histamine dihydrochloride with interleukin-2; HR - hazard ratio; LFS - leukaemia-free survival; OS - overall survival; PA - preferred analysis; SoC - standard of care.

(6) Concerns regarding the utility values used in the model

(a) Issues regarding health state utilities

The EAG has concerns regarding the company's approach for HRQoL. As previously described in Section 4.2.4.3, HRQoL data collected in the Brune *et al.* were unavailable to the company, and therefore the utility values for all health states were informed by external data. In the base case, the utility values were obtained from Tremblay *et al.*,[53] an economic evaluation study which in turn also based their utility estimates from external sources. The utility estimates selected by the company for LF on treatment, LF off treatment and post-progressed disease were derived from Batty *et al.*,[64] Leunis *et al.*,[65] and Pan *et al.*,[66] respectively.

The EAG notes that the estimate from Pan *et al.*[66] was derived from QLQ-C30 mapped to EQ-5D using an algorithm by Kontodimopoulos *et al.* 2009.[81] In contrast, the EQ-5D estimate obtained from Leunis *et al.* was based on EQ-5D-5L data, whereas the estimate from Batty *et al.*[64] was obtained from two other economic evaluations (Goss *et al*. and Gidwani *et al*.), both conducted in myelodysplastic syndromes in US settings. In response to clarification question B14(a),[30] the company commented that

the value from Leunis *et al.* is '*methodologically most closely aligned with the preference for EQ-5D data in the NICE Reference Case*', although it uses EQ-5D-5L data. The company also commented that, in terms of face validity, it *'still fall[s] below age- and sex-matched general population norms'*. With regards to the value from Pan *et al.*, the company noted that *'mapping to the EQ-5D is acknowledged as an option in the NICE Reference Case (…) where EQ-5D data are not directly available'*. The value from Batty *et al.*,[64] in turn, was considered by the company to be *'closely aligned (numerically if not methodologically) with the EQ-5D utility value from Leunis et al. (2014), with the difference capturing effects such as the incidence of adverse events arising from treatment.'* The EAG also commented on the estimates for the leukaemia-free states being very high for a population with AML; the company mentioned in response that "*It is also worth noting that the target population consists exclusively of patients who are in first complete remission, which may result in (relatively) buoyant quality of life scores when compared with patients after an initial diagnosis or relapse."*

The three alternative sources for health state utilities included by the company in scenario analyses (Joshi *et al.*,[79] Stein *et al.*[56] and Russell-Smith *et al.*[58]) have also been previously described in Section 4.2.4.3. The first two sources also have limitations related to their valuation methods: Joshi *et al.* used a cTTO methodology instead of EQ-5D, whilst Stein *et al.* used a DCE methodology with participants from the general population in the US. Russell-Smith *et al.,* which was obtained from the SLR of economic evaluations undertaken by the company, sourced the utility values from a previous NICE STA (TA399).[59] This STA used trial-based disease specific EORTC QLQ-C30 data mapped to EQ-5D using published algorithm.[82] The company commented on the limitations of Joshi *et al.* and Stein *et al.* as alternative sources of utilities (clarification response B16)[30] and justified the inclusion of these sources as scenario analyses to provide comparability to TA827. However, the company has not commented on the appropriateness of use of Russell-Smith *et al.* or the face validity of its estimates.

One of the clinical advisors for the EAG commented that the utility values for younger patients in remission whilst off treatment could more likely reflect those of Joshi *et al.* or Stein *et al.,* whilst the other advisor suggested that the estimates for the leukaemia-free used in the base case seemed very high. The EAG notes that the results for these scenarios analyses using alternative utility sources were not presented by the company as part of their clarification response. The EAG considers that, due to the limitations in most sources presented by the company and in the absence of HRQoL data from the clinical study that reflects the specific target population, it is unclear which would be the best source of utilities for this population. The EAG explores the use of different sources in its exploratory analyses (see Section 5.2).

(b) Exclusion of impact of frequent injections to HRQoL

The CS[1] and clarification response[30] do not present any evidence regarding the impact to HRQoL of the number of injections required for the treatment with HDC/IL-2 in patients with AML. In clarification response to question A3, regarding the acceptability and feasibility of the HDC/IL-2 regimen for patients, the company provided only limited evidence, drawing from Brune *et al.* and reported international experience regarding adverse events that resulted in dose reduction or treatment interruption.

The EAG has concerns around the high number of injections required for patients receiving treatment with HDC/IL-2, where 4 daily subcutaneous injections are self-administered for 21 consecutive days for up to 10 treatment cycles, which corresponds to 840 injections in total for those patients who are able to complete all cycles. The EAG notes that during the company's advisory board meeting in February 2025, one of the UK clinicians commented that [redacted][93]

The impact of these injections to patients' HRQoL and how they may influence patients' preferences regarding therapy's choice, however, is unclear.

HRQoL data specific to AML patients which accounted for the impact of daily injections could not be retrieved by the EAG in a quick search of the literature. Nonetheless, one study from Boye *et al.*[94] was identified, which assessed patient preferences for hypothetical health state vignettes related to injection-related attributes (dose frequency, dose flexibility, and injection site reactions) in 151 patients with type 2 diabetes in Scotland. The study used a standard gamble approach, and patients also completed the EQ-5D-3L and 3 other instruments. Utility estimates are presented for the basic health state (patients are at their current weight, have diabetes for many years, and take oral medication only) and eight hypothetical health states that included injectable medication in addition to oral treatment. These eight hypothetical health states varied by three features: how often injections were needed (daily or weekly), how flexible the dosing was (flexible or not), and whether injection site reactions were present or absent.

The EAG considers that although this estimate has some limitations, in particular that it is not directly derived from EQ-5D-3L, is not specific to AML patients, and does not reflect the exact treatment regimen for HDC/IL-2. Nonetheless, given the scarcity of data related to the isolated impact of daily injections to patients in AML, the EAG considers it reasonable to use the data from this study to estimate a utility decrement to explore the impact of daily HDC/IL-2 injections on HRQoL in the model. The decrement was obtained from the difference between the reported utilities from the state with daily injections with the highest utility (basic health state plus injectable medication, daily injections, no injection site reaction, flexible dosing: 0.689) and the basic health state (i.e., oral medications only:

0.813), which leads to a decrement of 0.124. The EAG applied this utility decrement as a proxy for the potential impact of the daily injections to patients as part of the EAG's exploratory analysis (see Section 5.2.1)

(7) Uncertainty around the impact of AEs to costs and HRQoL

The model includes short-term QALY losses and costs in each treatment group associated with selected AEs of Grade 3/4 which occurred in the Brune *et al.* study. The company's approach for selecting specific types of AEs were initially unclear to the EAG. In response to clarification question B12,[30] the company clarified that the company included those AEs which *"showed significant differences between arms in the Brune et al. (2006) study and were considered to result in meaningful costs being incurred from the perspective of NHS England"*. Upon request from the EAG, the company also included the impact of additional AEs (thrombocytopenia, neutropenia and headache), Grade 3/4 AEs with an incidence of ≥5% in either treatment arm from Brune *et al*. As part of the clarification response, the company also included the impact of these AEs to HRQoL, with the assumption of a similar duration of 1 week for all AEs included. The impact of AEs to HRQoL was added to the model in addition to the lower health state utility for patients receiving HDC/IL-2 and oral azacitidine whilst leukaemia-free and on treatment. In addition, the model assumes that patients receiving oral azacitidine incur the same AE incidence rates as patients in the HDC/IL-2.

The EAG has a few concerns related to the approach adopted by the company. The logic for the selection of AEs for inclusion in the model seems unusual, given that in TAs the criteria generally applied involves an incidence rate threshold (≥5% or ≥10% in either treatment arm from the trial). When including the AEs with an incidence of ≥5% at the clarification stage, the company maintained the original AEs in the model, the reasons for this are unclear.

The CS[1] states that the difference of 0.02 between the utility estimates for HDC/IL-2 patients on and off therapy being intended to capture "*an average annual loss of approximately one week in perfect health in those patients receiving treatment. This was considered to be conservative from the perspective of histamine dihydrochloride and low-dose interleukin-2 given the low incidence rates of Grade 3 and 4 adverse events in the Brune et al. RCT".* The EAG commented in clarification question B14[30] that the estimates for LFS on and off treatment were obtained from a cost-effectiveness study evaluating midostaurin versus standard of care in newly diagnosed patients with AML, which may have a different AE profile to HDC/IL-2 being used as maintenance therapy. In response, the company commented that this difference in the health state utility values was considered to present a highly conservative scenario, which was suggested by the very small disutilities due to AEs of 0.001 in the HDC/IL-2 arm versus 0.0003 in the control arm. Despite this argument, the company has not provided

justification for applying the additional impact of AEs to HRQoL on top of the differential utility values for patients on and off treatment. It is unclear what the difference of 0.02 between the HDC/IL-2 patients on and off therapy is intended to reflect.

The EAG considers that the assumption of equivalent AEs between oral azacitidine and HDC/IL-2 may not be ideal, given patients receiving oral azacitidine, an oral therapy, may have a different AE profile to HDC/IL-2, but a result of a pragmatic approach. One of the EAG's clinical advisors noted that the higher incidences in AEs observed in QUAZAR AML-001 compared to Brune *et al.* may be attributable to the different periods when the respective trials were conducted, with improvements over time in clinical trial reporting standards and technology. Given that the differences between the studies are not measurable and outcomes of the ITC (see Section 3.4) did not include AEs, this issue has not been corrected by the EAG. Nonetheless, the EAG exploratory analyses which explore different sources for health state utilities (issue 6) indirectly also address this issue.

(8) Issues related to model costs

(a) Concerns regarding the estimates for the patients' mean weight used to derive some of the drug costs in the model

The estimate for mean weight included in the original and updated versions of the model is informed by the mean weight reported for the general population in England from the NHS HSE 2021,[71] which is not specific for patients with AML. This estimate is used in the model to derive the per cycle drug costs for IL-2 and hydroxycarbamide (regimen included as part of the post-progression SoC).

In response to clarification question B4,[30] the company clarified that the estimate for mean weight was obtained from the reported mean weights of 85.1kg for men and 71.8kg for women for the entire population surveyed in the NHS HSE 2021[71] (using the proportion of males of 50% from the model). The company justifies this approach based on the lack of data related to body weight in the Brune *et al.* study, and in the reports available for other interventions in AML, such as Wei *et al*.[36] (QUAZAR AML-001 trial) and Stone *et al*.[68] (NCT00651261), and stated their preference to use a UK-specific surrogate estimate rather than an AML-specific estimate for the wrong locality. The company also suggests, based on the results from a study by Liu *et al.,*[95] which reported the distribution of people with AML across body mass index (BMI) strata, that the weight distribution of the population with AML is similar to the weight distribution for the general UK population, and therefore the estimate from NHS HSE 2021 is likely to be a reasonable surrogate.

However, the EAG notes that mean weight estimates from the Brune *et al.* study are available from the trial's CSR document shared with the EAG (clarification response A16)[30] for the

[redacted]. The EAG is unclear why these estimates were not included as part of the evidence submitted as part of the CS and clarification responses and considers the estimate for patients in CR1 to be better aligned with the target population in the current appraisal than the one for the general population. The EAG's preferred analysis includes the estimate for patients with CR1 at baseline reported in the Brune *et al.* study (see Section 5.2).

(b) Issues regarding modelled drug administration costs for HDC/IL-2 and oral azacitidine

The administration costs included in the company's model are described in Section 4.2.4.4. In summary, the company included costs of administering the HDC/IL-2 injections from NHS Cost Collection for 2023/24[75] in the form of a 'simple parenteral chemotherapy delivery at first attendance' (currency code SB12Z) applied once per cycle on the same model cycles when patients receive therapy with HDC/IL-2, which is assumed to include patient training in the administration of their first dose given it includes 30 minutes of nurse time and 30 to 60 minutes of chair time. The company also stated that patients would be expected to collect the prescription of HDC/IL-2 from the hospital once per treatment cycle (clarification response, question B17).[30]

The EAG, during the clarification stage, requested any information from the study that may be available regarding incorrect administration or the need for re-training; however, these were not presented by the company. The EAG also notes that the SmPC for HDC/IL-2 (page 14) states regarding the dispensing instructions for IL-2 (aldesleukin) that *"IL-2 (aldesleukin) should be aseptically reconstituted, diluted and dispensed in capped polypropylene tuberculin syringes by the pharmacy based on the individual patient's weight (see administration chart for aldesleukin below) at the recommended dose of 16,400 IU/kg (1 µg/kg). Up to two weeks supply of pre-filled capped tuberculin syringes may be provided to patients for home administration, with instructions that the syringes be stored under refrigeration at 2°C – 8°C prior to administration."* Therefore, the EAG believes that if recommended, patients eligible for HDC/IL-2 would not be able to receive the full 3-week supply once per treatment cycle, instead they would have to collect it at least twice in each 3-week treatment cycle.

In Annex B of the 2025/26 NHS Payment Scheme (NHSPS),[96] guidance is available regarding on the currencies used in the NHSPS and are also used in NHS Cost Collection database. The text regarding the delivery of chemotherapies states that *"current chemotherapy delivery HRGs are assigned for each attendance for treatment to reflect the complexity of treatment and resource use."* Although the explanation for the SB12Z currency ('Deliver simple parenteral chemotherapy') states that it includes the delivery of a complete cycle, the explanation for currency SB15Z (Deliver subsequent elements of

a chemotherapy cycle) mentions that it should be included in regimens with more than one day of delivery (see Table 29). The guidance also mentions that some high-cost drugs and Cancer Drugs Fund drugs are included in separate costing elements (e.g., via API fixed element or paid outside of the NHSPS).

Table 29: Current chemotherapy delivery HRGs (reproduced from Table 1 in NHSPS Annex B)

HRG Code	Definition	Explanation
SB12Z	Deliver simple parenteral chemotherapy	Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle.
SB13Z	Deliver more complex parenteral chemotherapy	Overall time of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle.
SB14Z	Deliver complex chemotherapy, including prolonged infusional treatment	Overall time of 60 minutes nurse time and over two hours chair time for the delivery of a complete cycle.
SB15Z	Deliver subsequent elements of a chemotherapy cycle	Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance, for example day 8 of a day 1 and 8 regimen or days 8 and 15 of a day 1, 8 and 15 regimen.

Following the logic of the company for the administration costs, the EAG believes that for each cycle where patients receive HDC/IL-2, the administration costs should reflect the costs of one 'Deliver simple parenteral chemotherapy' and one 'Deliver subsequent elements of a chemotherapy cycle' (SB12Z and SB15Z currencies) to reflect the reconstitution, dilution and dispensing of the regimen drugs required for IL-2 twice per treatment cycle. This alternative scenario is included in the EAG's exploratory analyses (see Section 5.2).

The model also assumes that no administration costs are incurred by patients receiving oral azacitidine since it corresponds to an oral therapy. For consistency between the approaches for the different treatment groups, the EAG believes administration costs should be included for this treatment group. Therefore, in EAG's exploratory analyses the inclusion of administration costs for oral azacitidine is explored, whereby the 'Deliver Exclusively Oral Chemotherapy' (currency SB11Z, service code 303 - Clinical Haematology Service, £248.76) is applied once in each model cycle where patients receive oral azacitidine (see Section 5.2).

(c) Concerns regarding potential HDC/IL-2 accessories' costs or other issues regarding the delivery of the HDC/IL-2 at home not included in the model

As previously mentioned in Section 4.2.4.4, the company considers that *"under normal circumstances, no accessories are required for the self-administration of HDC/IL-2 as both the HDC and IL-2 components are supplied in or with sterile syringes."*[30] The SmPC for HDC/IL-2, however, specifically mentions that *"Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection can be administered via an ambulatory infusion syringe pump or by controlled manual subcutaneous injection by syringe with a timer."*[28] The EAG notes that patients in Brune *et al.* study have administered the regimen at home, but it is unclear if the use of any accessories to ensure the HDC injection is delivered within the intended timeframe of 5-15 minutes was allowed or implemented, and if so, what proportion of patients required the use of a pump, a timer or any other accessory in the study.

In addition, the EAG's clinical advisors have noted that some patients may not be able to self-administer at home, and the company stated in response that from clinical experience in Sweden, the HDC/IL-2 regimen is feasible and acceptable to patients in routine clinical practice, and that only on exceptional occasions patients were unable to self-administer, in which cases "*a partner and/or carer has been able to assist with the procedure"*. The company also highlighted that administration at home is more feasible given the relatively younger age group of the target population (clarification response, question A3).[30] The EAG considers that although the age group of the target population suggests the implementation of the regimen may be easier compared to older populations, data regarding the acceptability of the regimen and what would happen to patients in clinical practice who are unable to self-administer at home were not provided by the company (e.g., would 2 daily visits from community nurses be required, or would these patients receive all doses at a hospital setting if required).

The EAG believes that, considering that more details regarding these potential additional costs related to the implementation and delivery of the HDC/IL-2 regimen were not provided in the evidence presented by the company within the CS or clarification response, it is difficult to predict their impact to the model results. Therefore, the EAG was unable to explore any changes regarding these issues as part of the EAG's exploratory analyses.

(d) Concerns regarding the exclusion of RDI, wastage and concomitant drugs from drug cost calculations

The EAG notes that the estimates of drug costs included in the company's model does not include any considerations regarding RDI, adherence or compliance, but that the original version of the model did include some consideration of wastage. In response to the EAG clarification question A3(c), regarding how adherence and compliance were assessed in patients who self-administered HDC/IL-2 at home in

the Brune *et al.*, the company shared data from the CSR whereby treatment compliance was assessed at the end of each treatment cycle by investigator's judgement of at least 80% required dose of IL-2 and HDC being taken. The study reported [redacted] However, the CSR did not present RDI or any another measurement of adherence.

The EAG notes that for oral azacitidine an estimate of mean RDI was available from the TA827 committee papers (86.9%, reported in CS Section B.3.5.1.1 - page 191), which is based on the QUAZAR AML-001 trial.[19] Despite the limitations of the approach applied in the model by the company in this appraisal, which used the median treatment duration of 12 months to apply the drug costs for oral azacitidine as a consequence of the data for treatment discontinuation not being available for any of the treatment groups, the EAG considers that including the observed RDI for oral azacitidine would better reflect the modelled drug costs for this regimen, increasing comparability with TA827. Analogously, the EAG considers that the costs of concomitant drugs given alongside oral azacitidine should also include the costs of premedication with ondansetron, which was assumed to be given at the dose of 8mg twice a day for 5 days prior to each cycle of oral azacitidine therapy.[19] These changes to the oral azacitidine costs are explored as part of the EAG's exploratory analyses. The EAG also explored alternative assumptions regarding the RDI for HDC/IL-2 as part of additional scenario analyses (see Section 5.2).

In relation to wastage, in response to clarification question B17(b),[30] the company stated that the original model submitted at CS already included wastage, by applying the full 3-week treatment costs to all patients in the HDC/IL-2 group in the first model cycle, to all patients still in LFS onTx sub-state in subsequent cycles where therapy is assumed to be administered regardless if they discontinue therapy in that cycle due to AE or relapse. The company has revised their approach in the updated version of the model, whereby the costs of the HDC and IL-2 drugs are applied to the number of patients remaining on treatment in the previous cycle. The EAG notes that this revised approach fixes a separate issue, where there was a mismatch in the calculations of the proportion of patients where one cycle was skipped, but is unclear how this approach addressed additional wastage within the model, in particular regarding the costs of IL-2.

The SmPC for HDC/IL-2[28] states that HDC should be dispensed as vials containing 0.70 mL of solution (including overfill) to facilitate the dose extraction of each single 0.5 mL dose with polypropylene syringes, whilst IL-2 should be dispensed in syringes after being reconstituted, diluted and aseptically drawn based on patient's weight and dosage of 1 µg/kg, to be stored under refrigeration at 2°C – 8°C

prior to administration. The SmPC also provides the dosing volumes based on patient weight, which considers a minimum standard dosage volume of 0.25 mL (50 µg) and a maximum dose of 0.5 mL (100 µg), which is reproduced in Table 30. The EAG notes that in the model, IL-2 costs implicitly assumes vial sharing, which may not be feasible due to a number of factors: (i) it is unclear if the same vials could be used for other patients in other indications (given that the company assumes that only 50 to 100 patients in England would be eligible for the regimen in this indication); (ii) vial sharing across cycles for the same patients may not be possible due to limited storage after preparation. In addition, the EAG considers that patient weight can meaningfully influence the total cost of IL-2 if taking into account wastage (the number of vials needed), and therefore the weight distribution should have been taken in consideration instead of only the mean weight for purposes of estimating the mean per cycle costs of IL-2. The EAG explored using a distribution-based mean cost for IL-2 as part of the exploratory analyses (see Section 5.2).

Table 30: Administration chart for IL-2 ([aldesleukin], reproduced from HDC/IL-2 SmPC Table 3)

Patient Weight (kg)	Standard dosage (µg)	Injection volume (mL)*	20% dose reduction injection volume (mL)**
≤50	50	0.25	0.20
>50 to ≤60	60	0.30	0.25
>60 to ≤70	70	0.35	0.30
>70 to ≤80	80	0.40	0.30
>80 to ≤90	90	0.45	0.35
>90 to ≤100	100	0.50	0.40
>100	100	0.50	0.40

**Injection volume rounded up to the nearest 0.05mL.*
***Injection volumes based on 20% reductions are rounded thus actual dose reductions vary from 15%-25%.*

(e) Issues regarding the costs of SoC drugs, allo-SCT and other subsequent therapies

The original model submitted by the company included only the costs of SoC drugs, which are assumed to be received after patients' relapse (post-progression), given that patients are assumed not to receive any active therapy as part of standard of care whilst they are still in the leukaemia-free state. In the model, SoC drugs include hydroxycarbamide (a chemotherapy), ciprofloxacin (an antibiotic), posaconazole, fluconazole (antifungal agents), and tranexamic acid (an antifibrinolytic), based on the approach adopted in TA827,[19] given that information on subsequent therapies was not available from

Brune *et al.*[31] In response to clarification question B20,[30] the company also included the costs of allo-SCT as an one-off cost, which include only the costs of the transplant procedure, applied at the point of relapse to different proportion of patients by treatment group, based on estimates from the QUAZAR AML-001 trial obtained from TA827.[19]

The EAG has a few concerns regarding the approach adopted by the company. The EAG's clinical advisors agree with the view that patients still in remission would not receive any additional therapy, however one of EAG's advisors noted that fluconazole is not commonly used in clinical practice for this indication, and other therapies should have been included (e.g., FLAG-IDA). The EAG agrees that without data on the therapies received by patients in the study, it is difficult to replicate the costs of subsequent treatments which would reflect the outcomes for the patients in the trial. However, other alternatives would be to estimate what patients would receive in current practice in the UK, based either on data from previous TAs in similar populations (the closest may be TA827) or on clinical opinion. The company chose to partially include the costs from TA827 by including only the costs of allo-SCT, which seems limited and to be unfavourable to SoC, due to the higher incidence of transplants in this group in QUAZAR AML-001. By including only the costs of the procedure and not adjusting the subsequent costs of disease management for at least some of the patients receiving transplant, the company is implicitly assuming that the transplant has no impact not only on the health outcomes, but also on downstream costs of treatment for AML. The EAG also considers that the costs of other post-relapse therapies, such as FLAG-IDA or the regimens included in TA827 (cytarabine, injectable azacitidine, and salvage chemotherapy [daunorubicin and cytarabine]), should have been considered by the company to better reflect the subsequent costs of patients in the target population in current clinical practice. The inclusion of these costs is explored in EAG's exploratory analyses (see Section 5.2), however the EAG was unable to incorporate any adjustments to OS related to patients receiving allo-SCT.

(9) Weak characterisation of uncertainty

The EAG has concerns regarding the uncertainty analysis presented in the CS.[1] One of the issues has been partially addressed by the company in the updated version submitted at clarification; however, the results of the analyses (probabilistic and scenario analyses) have not been presented at the clarification response. These are summarised below.

(a) Some uncertain parameters held fixed in PSA.

Uncertainty surrounding most of the cost estimates is not modelled in the original and updated versions of the model submitted by the company. The original version of the model only sampled the values for OS and LFS estimates, utilities, AE incidence rates and treatment discontinuation rates. In response to

clarification question B23,[30] the company justified the exclusion of some parameters in the assessment of uncertainty on the scarcity of data on the variance around cost and resource use data. Nonetheless, the company stated having included the functionality to also sample the SoC drug costs, based on standard deviations presented in the eMIT data, disease management costs, proportion of patients receiving SoC drugs, adverse event treatment costs and disease management resource use based on assumed standard deviations of 10% of the mean.

However, upon inspection of the latest version of the model submitted (dated 30th October 2025), the EAG notes that not all parameters (with non-zero means) in the categories described above have been included (e.g. the frequency of clinical visits in the LF state is varied, whilst these frequencies in the post-progression and the proportion of patients receiving transfusions or bone marrow aspirate/biopsy are held fixed). Another inconsistency seems to relate to some of drug pack prices being varied (e.g., SoC drugs), whilst the cost of the allo-SCT procedure was held fixed. The EAG observes that uncertainty characterisation has also been excluded for the HR values for OS and LFS on the comparison against oral azacitidine, where these values are assumed fixed in the PSA, when they could be varied based on the results from the ITC. Therefore, the EAG is still unclear about the criteria used for the exclusion of some of the parameters still maintained fixed.

Overall, the EAG believes that the company's PSA provides a weak characterisation of parameter uncertainty. Overall, the EAG considers the results of the deterministic model to be more reliable than those obtained from the probabilistic model.

(b) Limited scenario analyses

The CS[1] presents scenario analyses around the discount rates (0% and 6%), the model time horizon (10 to 50 years, by increments of 10), the choice of LFS models and OS models, and the sources of utility values for the health states. The EAG notes that the results for these scenarios were not presented using the updated version of the model, and the inclusion of oral azacitidine as a comparator in the model. The EAG believes that a wider set of scenarios could have been explored to provide a better assessment of decision uncertainty, including around the estimates of treatment effect between oral azacitidine and HDC/IL-2 (LFS and OS), the costs of subsequent treatments included in the model, the impact of AEs to costs and HRQoL, and the discontinuation rates for HDC/IL-2 and oral azacitidine.

Some of these aspects of uncertainty are addressed in the EAG's exploratory analyses presented in Section 5.2.

5 Cost-effectiveness results

This chapter presents the results of the company's economic model (latest updated version submitted at clarification stage), and the methods and results of the EAG's exploratory analyses. Section 5.1 summarises the company's cost-effectiveness results, section 5.2 presents the methods and results of the EAG's exploratory analyses, including the EAG's preferred analyses and additional sensitivity analyses. Section 5.3 presents a brief discussion around disease severity modifiers which are relevant to this appraisal. Section 5.4 presents a brief statement around the comparators with a cPAS discount available. Section 5.5 summarises the conclusions of the economic analyses presented by the company and the EAG.

5.1 Company's cost-effectiveness results

5.1.1 Company's central estimates of cost-effectiveness

Table 31 presents the central estimates of cost-effectiveness generated using the latest version of the updated model which was submitted as part of the company's clarification response. The results presented by the company do not include any disease severity modifiers (DM);[1] the results presented in this section include decision modifiers as applicable. In general, a DM of 1.2 is applied to the comparison SoC whilst the comparison against oral azacitidine is only eligible for a DM of 1.0 (with exceptions for both cases in scenario analyses presented in following section). This issue is discussed in Section 5.3.

The results presented in the table only include list prices for HDC/IL-2 and comparators. The results including the cPAS price for oral azacitidine (see Section 5.4) are presented in a separate confidential appendix. The probabilistic version of the model suggests that HDC/IL-2 is expected to generate an additional 3.17 discounted QALYs at an additional cost of £77,038 against SoC, with a corresponding ICER of £24,323 per QALY gained (£20,269 with a DM of 1.2). In the comparison against oral azacitidine, HDC/IL-2 is expected to generate less [redacted] discounted QALYs and to reduce costs by [redacted], generating an ICER [redacted].

The deterministic version of the model results in a slightly lower ICER versus SoC of £24,183 per QALY gained (£20,153 with DM of 1.2), and a higher ICER [redacted] against oral azacitidine.

Table 31: Company's updated base case results, HDC/IL-2 versus SoC and versus oral azacitidine, pairwise comparisons, post-clarification model (generated by the EAG using the company's updated model)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER incl. DM⁂
Probabilistic model†								
HDC/IL-2	13.96	6.81	£128,745	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	6.59	3.57	£50,620	6.92	3.17	£77,038	**£24,323**	**£20,269**
Deterministic model								
HDC/IL-2	13.51	6.74	£127,658	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	6.45	3.54	£50,341	7.06	3.20	£77,317	**£24,183**	**£20,153**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; N/R - Not reported; SoC - standard of care; SWQ - south-west quadrant.
** Undiscounted LYs, not reported by the company, obtained by the EAG by adapting the company's model.*
⁂ A decision modifier multiplier of 1.0 applies to the comparison against oral azacitidine, and of 1.2 applied to the comparison against SoC.
† The company's updated model includes an error in the probabilistic sampling sub-routine which allows sampled probabilities for health state utilities not to follow logical order (see critique point [1g]).

5.1.2 Company's PSA results

The company did not present the results of the PSA using the updated version of the model as part of the clarification response. The results of the company's PSA are presented in Table 31, generated by the EAG using the company's model, and as cost-effectiveness planes for HDC/IL-2 versus SoC and versus oral azacitidine in Figure 26 and Figure 27, respectively. The cost-effectiveness acceptability curves (CEACs) for the three treatment groups is presented in Figure 28. None of figures include QALY weighting based decision modifiers. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the probability that HDC/IL-2 generates more net monetary benefit than SoC and oral azacitidine is expected to be approximately 0.15 and [redacted], respectively.

Figure 26: Cost-effectiveness plane, HDC/IL-2 versus SoC (drawn by the EAG, does not include a decision modifier)

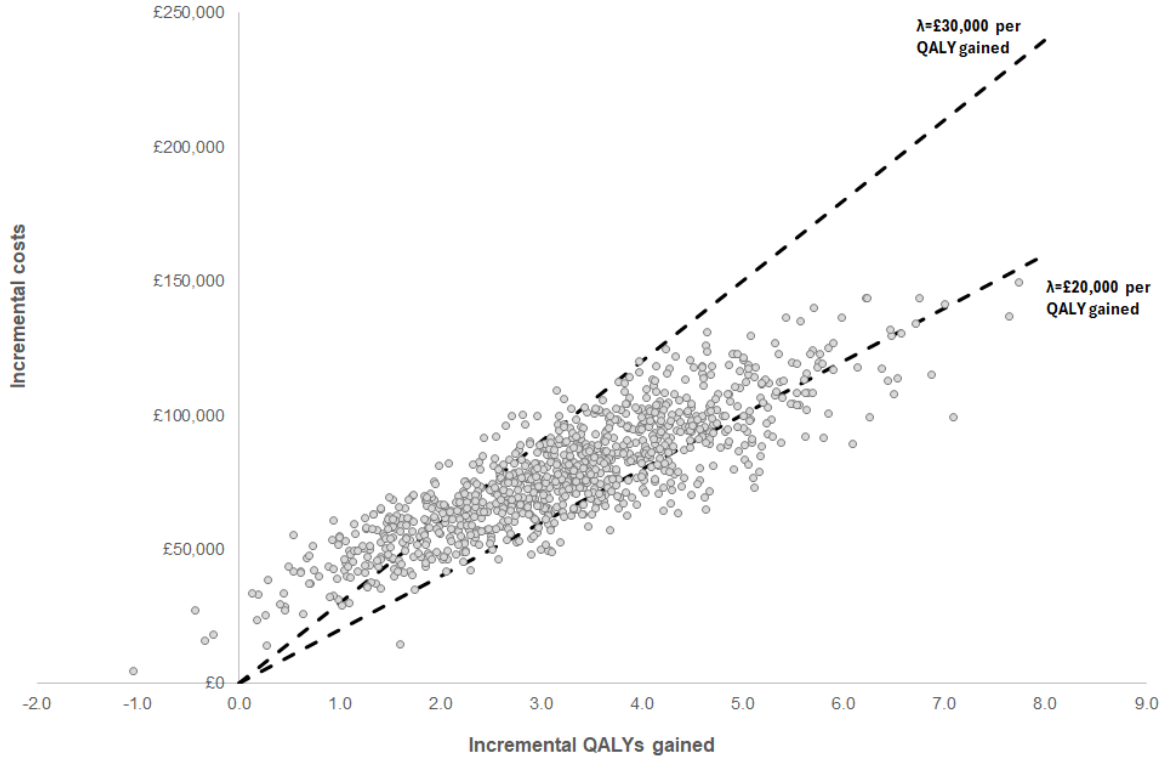


Figure 27: Cost-effectiveness plane, HDC/IL-2 versus oral azacitidine (drawn by the EAG, does not include a decision modifier)

Figure 28: Cost-effectiveness acceptability curves, HDC/IL-2 versus SoC and oral azacitidine (drawn by the EAG)

HDC/IL-2 - Histamine hydrochloride with interleukin-2; SoC - standard of care.

5.1.3 Company's sensitivity and scenario analyses

In the CS,[1] the company presented the results of the company's DSAs for the comparison against SoC (Section 3.11, Table 30). However, these results were not presented at the clarification response using the updated version of the model and for the comparison against oral azacitidine. Tornado plots summarising the results of the company's DSAs for both comparisons against SoC and oral azacitidine were generated by the EAG using the latest version of the company's model and are presented in Figure 29 and Figure 30 (pairwise comparisons). The EAG notes that the results presented do not consider any decision modifiers.

For the comparison of HDC/IL-2 versus SoC, the model is most sensitive to the following parameters: utility values for the LFS health states (on and off treatment), discount rates, the HDC and IL-2 prices and baseline weight. For the comparison of HDC/IL-2 versus oral azacitidine, the parameters of most influence in the model are [redacted]. Using the highest HR value for OS leads to [redacted]. Other parameters with moderate influence correspond to the [redacted]

[redacted]

Figure 29: DSA results, HDC/IL-2 versus SoC, pairwise, does not include decision modifier (generated by the EAG using the company's updated model)

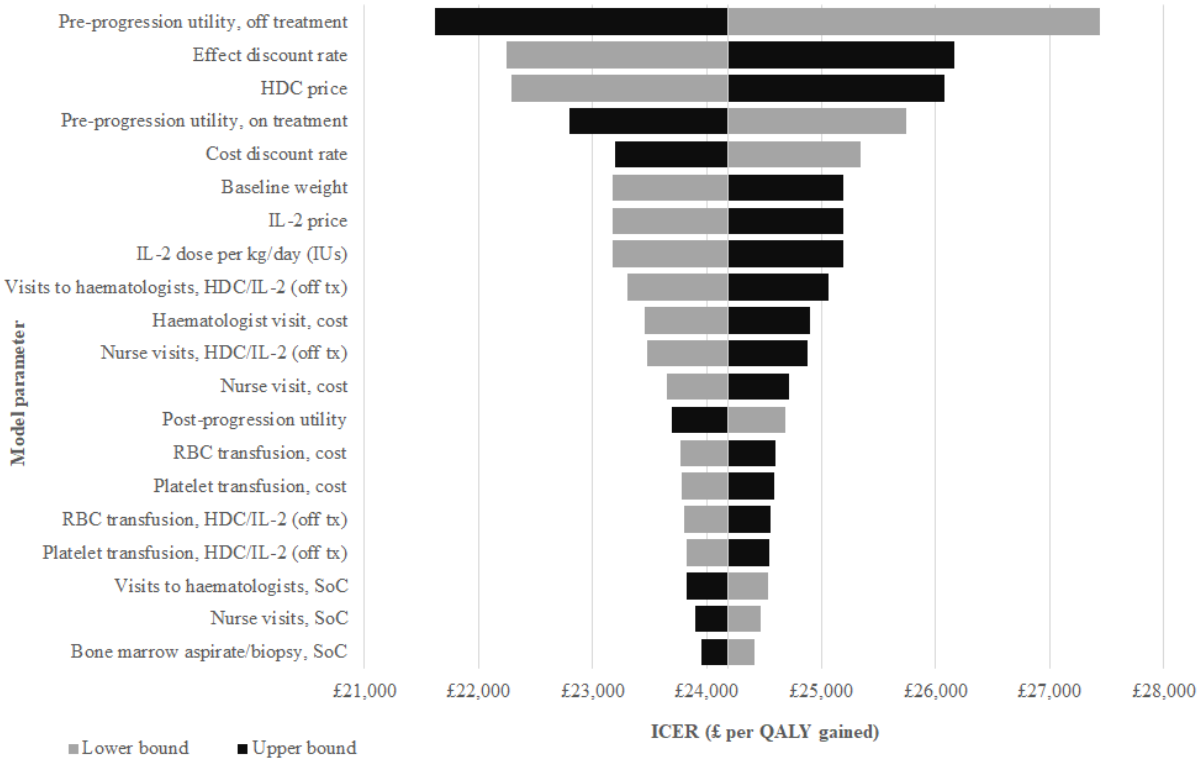


Figure 30: DSA results, HDC/IL-2 versus oral azacitidine, pairwise, does not include decision modifier (generated by the EAG using the company's updated model)

[redacted]

The company also presented the results of scenario analyses which explored alternative values for discounting rates (0% and 6%), different time horizons (between 10 and 50 years, in increments of 10 years), different LFS and OS models (using jointly fitted parametric models), and alternative health state utility values from Joshi *et al.*,[79] Stein *et al.*,[56] and Russell-Smith *et al.*[58] only using the original version of the model. The results of these scenario analyses are summarised in Table 32, and were generated by the EAG using the latest version of the company's model. Without considering any decision modifiers, the ICERs for HDC/IL-2 versus SoC range from £18,854 to £35,133 per QALY gained (£15,712 to £29,277 when considering DMs), whilst the ICERs versus oral azacitidine range from [redacted] ([redacted] when considering DMs). In two scenarios against SoC, the DM of 1.2 ceases being applicable (Gompertz OS model and generalised gamma OS model), whilst only in one scenario against oral azacitidine ([redacted].

Table 32: Results of selected scenario analyses presented in the company's clarification response (generated by the EAG using the company's updated model)

Scenario	HDC/IL-2 versus SoC				HDC/IL-2 versus oral azacitidine			
	Incremental QALYs	Incremental cost	ICER without DM	ICER with DM (DM=1.2)[‡]	Incremental QALYs	Incremental cost	ICER without DM	ICER with DM (DM=1.0)[‡‡]
Company's updated base case model (deterministic)	3.20	£77,317	**£24,183**	**£20,153**	[redacted]	[redacted]	[redacted]	[redacted]
Discount rates = 0.0%	5.12	£104,108	**£20,327**	**£16,939**	[redacted]	[redacted]	[redacted]	[redacted]
Discount rates = 6.0%	2.45	£67,840	**£27,634**	**£23,028**	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon = 10 years	1.58	£55,628	**£35,133**	**£29,277**	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon = 20 years	2.61	£67,647	**£25,929**	**£21,607**	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon = 30 years	3.00	£73,863	**£24,580**	**£20,484**	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon = 40 years	3.15	£76,405	**£24,262**	**£20,219**	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon = 50 years	3.19	£77,239	**£24,189**	**£20,158**	[redacted]	[redacted]	[redacted]	[redacted]
LFS model = Gamma	3.69	£69,575	**£18,854**	**£15,712**	[redacted]	[redacted]	[redacted]	[redacted]
LFS model = Gompertz	3.56	£68,654	**£19,280**	**£16,067**	[redacted]	[redacted]	[redacted]	[redacted]
LFS model = Log-logistic	3.35	£73,032	**£21,786**	**£18,155**	[redacted]	[redacted]	[redacted]	[redacted]
LFS model = Log-normal	3.27	£74,065	**£22,647**	**£18,873**	[redacted]	[redacted]	[redacted]	[redacted]
LFS model = Weibull	3.59	£70,017	**£19,479**	**£16,232**	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	HDC/IL-2 versus SoC				HDC/IL-2 versus oral azacitidine			
	Incremental QALYs	**Incremental cost**	**ICER without DM**	**ICER with DM (DM=1.2)‡**	**Incremental QALYs**	**Incremental cost**	**ICER without DM**	**ICER with DM (DM=1.0)⁂**
LFS model = Gen. gamma	2.79	£72,528	**£25,950**	**£21,625**	[redacted]	[redacted]	[redacted]	[redacted]
OS model = Gamma	3.29	£79,031	**£24,033**	**£20,028**	[redacted]	[redacted]	[redacted]	[redacted]
OS model = Gompertz	3.47	£82,600	**£23,788**	**£23,788**	[redacted]	[redacted]	[redacted]	[redacted]
OS model = Log-logistic	3.21	£77,733	**£24,179**	**£20,150**	[redacted]	[redacted]	[redacted]	[redacted]
OS model = Log-normal	3.37	£80,613	**£23,931**	**£19,942**	[redacted]	[redacted]	[redacted]	[redacted]
OS model = Weibull	3.39	£81,026	**£23,871**	**£19,892**	[redacted]	[redacted]	[redacted]	[redacted]
OS model = Gen. gamma	3.01	£73,854	**£24,541**	**£24,541**	[redacted]	[redacted]	[redacted]	[redacted]
Utility values from Joshi *et al.*	3.42	£77,317	**£22,621**	**£18,851**	[redacted]	[redacted]	[redacted]	[redacted]
Utility values from Stein *et al.*	3.42	£77,317	**£22,633**	**£18,861**	[redacted]	[redacted]	[redacted]	[redacted]
Utility values from Russell-Smith *et al.*	2.93	£77,317	**£26,381**	**£21,984**	[redacted]	[redacted]	[redacted]	[redacted]

EAG - External Assessment Group; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; SoC – standard of care.
‡ DM of 1.2 applies to most comparisons against SoC, except when using OS models using generalised gamma or Gompertz, where a DM of 1.0 applies.
⁂DM of 1.0 applies to most comparisons against oral azacitidine, except when using a time horizon of 10 years, where DM of 1.2 applies.

For both comparisons, the scenarios with most impact on the ICERs relate to scenarios in which non-Reference Case discount rates are used and shortening the time horizon to 10 years. The EAG's has concerns regarding the applicability of these alternative discount rates, since they are not supported by the NICE Methods guide. Applying a shorter time horizon, in particular of only 10 years, may not capture all the costs and HRQoL incurred in the patient's lifetime. The ICER for HDC/IL-2 is also sensitive to some of the selected parametric survival models for LFS (e.g. Gompertz, gamma and Weibull in the comparison against SoC, and Gompertz and generalised gamma in the comparison against oral azacitidine). The impact of alternative OS models was limited, with the largest impact corresponding to the use of the jointly fitted log-logistic in the comparison against oral azacitidine. The use of alternative utility values had a limited impact on the ICERs (<10%), with Russell-Smith *et al.* having the largest impact versus SoC, but more limited impact against oral azacitidine. The company did not present the results of using alternative using independently fitted LFS and OS models; these are explored in the EAG exploratory analyses (see Section 5.2).

5.2 EAG's additional analyses

5.2.1 EAG's exploratory analyses – methods

The EAG undertook exploratory analyses (EAs) using the updated version of the model which was provided as part of the company's clarification response.[30] All analyses were undertaken by one modeller and checked by a second modeller. Results are presented with and without QALY weighting when applicable (decision modifier = 1.2 for comparisons against SoC and [redacted] for comparisons against oral azacitidine).

The EAG's preferred analysis is comprised of 9 sets of amendments to the company's updated model. EA1 includes the correction of errors; EA2 to EA9 are conducted independently but include the error corrections from EA1. EA10 combines all the EAG's amendments together in a single analysis.

EA1: Correction of errors

The following corrections were applied to the company's updated model:

- *EA1a:* General population mortality risks were amended to use life tables for England for the period 2021-2023 (rather than England and Wales).
- *EA1b:* The formula used to draw the OS estimates from the coefficients of the independently fitted log-logistic model was amended to use the corrected estimates from the curves presented by the company at the clarification response. The EAG notes that this correction only applies if the independent log-logistic OS model for HDC/IL-2 is selected.

- *EA1c:* The formulae in the oral azacitidine trace worksheet used to estimate OS before and after the general population mortality risk constraint is applied were amended to include the OS HR of oral azacitidine vs HDC/IL-2 before the constraint, instead of after.
- *EA1d:* The costs of oral azacitidine were amended to adjust the 28-day treatment cycle to the monthly cycles (approximately 30.4 days) employed in the model.
- *EA1e:* The trace worksheets for the three treatment groups were amended to include age-adjustment of utility values using Hernandez Alava *et al.*[86]
- *EA1f:* The mean weight used in the model was amended to use the mean weight estimate informed for the CR1 population in the Brune *et al.* study (75.94kg from CSR [redacted]).[34]
- *EA1g:* The per cycle OS risk programming issue was fixed for all 3 treatment groups.

These model corrections are included in all subsequent exploratory analyses.

EA2: Application of the ITC OS HR based on stratified HR for OS from QUAZAR AML-001 to estimate outcomes for oral azacitidine group

In this analysis, the OS HR for HDC/IL-2 versus oral azacitidine from the ITC of QUAZAR AML-001 ITT population vs Brune *et al.* ITT population was assumed to be based on the stratified HR for OS from QUAZAR AML-001 instead of the unstratified HR ([redacted] instead of [redacted]).

EA3: Use of alternative models for LFS and OS

Based on the goodness-of-fit of the fitted distributions and clinical expectations of survival, the model was amended to use the following models for LFS and OS in HDC/IL-2 and SoC groups:

- LFS, HDC/IL-2: independently fitted exponential
- LFS, SoC: independently fitted log-normal
- OS, HDC/IL-2: independently fitted Weibull
- OS, SoC: independently fitted Weibull

A structural constraint was also included to ensure that, in any cycle, the OS estimates for the SoC group do not to exceed OS for HDC/IL-2.

EA4: Inclusion of additional cost elements for oral azacitidine

Within this analysis, additional cost elements for oral azacitidine were included in the model, such as RDI, costs of premedication and administration costs, which have been omitted in the company's model. The RDI estimate (0.869) was sourced from TA827 committee papers,[19] whilst the premedication costs included the same assumptions for dosage and number of administrations for ondansetron also based on TA827. Patients are assumed to receive ondansetron 8mg twice a day for five days in each 28-day treatment cycle with oral azacitidine. The administration costs for oral

azacitidine were based on the National Cost Collection for the NHS 2023/24[75] currency SB11Z (deliver exclusively oral chemotherapy, service 303). When this change is applied, the per cycle cost of oral azacitidine decreases from £11,734 to £10,449.

EA5: Inclusion of wastage-based costs for IL-2

The EAG estimated the total costs for IL-2 using the method of moments, whereby the patients' weight distributions from Brune *et al.*[34] were used to estimate the distribution of patients who would receive different number of vials for IL-2 (500mg, 1000mg and 2000mg) and their associated costs. These calculations, as in the company's base case, do not include RDI estimates for IL-2. The total acquisition costs were estimated at £2,167, instead of £1,909 per three-week treatment cycle.

EA6: Alternative assumption regarding administration costs for HDC/IL-2

Within this scenario analysis, the EAG assumed that patients would have to collect their prescribed medication at least twice per 3-week treatment cycle, in line with the dispensing instructions for IL-2 in the SmPC for HDC/IL-2[28] (see Section 4.3.5, issue 8[b]). Therefore, patients in the HDC/IL-2 treatment group are assumed to incur the administration costs of one 'Deliver simple parenteral chemotherapy' and one 'Deliver subsequent elements of a chemotherapy cycle' (SB12Z and SB15Z currencies) in every cycle where treatment is assumed to be given. This change leads in an increase on administration costs from £250 to £542.

EA7: Alternative assumptions regarding the SoC drugs

In this scenario analysis, the EAG removed the proportion of patients who receive fluconazole as part of the SoC drug regimens, based on clinical opinion from one of the EAG's clinical advisors. The EAG also reweighted the proportion of patients receiving the other regimens to maintain the overall proportion of patients who receive SoC drugs. The per cycle costs increased from £19 to £22.

EA8: Removal of the impact of the discontinuation approach to health outcomes

As discussed in Section 4.3.5 issue 5, upon an additional request for clarification from the EAG, the company clarified that the IPD used to inform the parametric survival models for LFS and OS included the 8.3% of patients in the HDC/IL-2 arm who discontinued due to AEs unrelated to relapse. In this scenario, the EAG removed the 'blended models' approach adopted by the company, with the LFS and OS models including only the data from the corresponding treatment groups, with treatment discontinuation still being used to inform treatment costs and HRQoL outcomes for the LFS on treatment state.

EA9: Inclusion of disutility related to frequency of HDC/IL-2 injections

In this scenario analysis, the EAG included an additional utility decrement related to the high frequency of injections required for the treatment of patients with HDC/IL-2 of 0.124 (see Section 4.3.5 issue 6[b]), based on the difference between the reported utilities for basic health state with oral medication only (0.813) and basic health state with oral medication plus daily injections, flexible dosing and no injection site reaction (0.689) from Boye *et al.*[94] This utility decrement is applied to patients in the HDC/IL-2 treatment group who remain on treatment (in LF on treatment state), in the cycles where patients are assumed to receive treatment.

EA10: EAG-preferred analysis

The EAG's preferred analysis combines EAs 1-9. A summary of the approaches adopted by the EAG are summarised in Table 33.

Table 33: Summary of EAG's exploratory analyses using company's base case

EA number	Company's base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	Correction of errors – see list above		Remaining errors identified by the EAG in the updated version of the model	4.3.5, issue (1)
2	Use of unstratified HR for OS from QUAZAR AML-001	Use of stratified HR for OS from QUAZAR AML-001	The EAG aimed to fix an inconsistency issue in the original approach where it used the stratified HR from QUAZAR AML-001 to inform the ITC for LFS, whilst and the unstratified HR to inform the OS ITC. The company's currently approach was more in favour of HDC/IL-2.	4.3.5, issue (3)
3	Use of jointly fitted exponential models for extrapolation of LFS	Use of independently fitted exponential model for HDC/IL-2 and independently fitted log-normal model for SoC	The complementary log-log plots for both LFS and OS and the smoothed Schoenfeld residuals suggest that the PH assumption might not necessarily hold. Independently fitted chosen models were more clinically plausible based on visual fit and considering the substantial uncertainty related to the company's survival modelling.	4.3.5, issue (4)
	Use of jointly fitted exponential models for extrapolation of OS	Use of independently fitted Weibull models for both HDC/IL-2 and SoC		
4	Drug costs for oral azacitidine do not include RDI, premedication and administration costs	Inclusion of RDI, premedication and administration costs for oral azacitidine	The EAG adopted an approach more in line with the assumptions in TA827.	4.3.5, issue (8[b] and [d])

5	No wastage considered for IL-2 drug costs	IL-2 drug costs based on method of moments	The company's approach did not consider the weight distribution and wastage involving the costs of IL-2, a drug with dosage based on patients' weight.	4.3.5, issue (8[d])
6	Administration costs includes 1 dispensing of HDC/IL-2 per treatment cycle	Model assumes that HDC/IL-2 is dispensed twice every treatment cycle	EAG's assumption in line with the dispensing instructions for IL-2 in the SmPC for HDC/IL-2[28]	4.3.5, issue (8[b])
7	Proportion of patients receiving each regimen in SoC from TA827	Proportion of patients slightly revised (exclusion of fluconazole)	EAG's assumption based on opinion from clinical advisor.	4.3.5, issue (8[e])
8	Blended approach for LFS and OS outcomes, based on rate of discontinuation	Blended approach removed, LFS and OS informed by respective data from Nilsson *et al.*	Company clarified that data from Nilsson *et al.*[32] includes patients who have discontinued early on from AEs.	4.3.5, issue (5)
9	No disutility included related to the frequency of injections for HDC/IL-2	Inclusion of disutility of 0.124 in cycles where HDC/IL-2 treatment is assumed to be given.	The company's approach did not consider the impact of daily injections to patients' HRQoL.	4.3.5, issue (6[c])

Additional sensitivity analyses

The following additional sensitivity analyses (ASAs) were conducted using the deterministic version of the EAG's preferred model (EA9), which are summarised in these are summarised in Table 34.

- *ASA1a-c:* These analyses apply all alternative sources for health state utility values used by the company: Joshi *et al.* (ASA1a), Stein *et al.* (ASA1b) and Russell-Smith *et al.* (ASA1c).
- ASA2: This analysis applies alternative HR estimates for LFS and OS, based on the lower range of the 95%IC estimated from the ITCs conducted by the company.
- ASA3: This analysis assumes same LFS and OS estimates for oral azacitidine to those for HDC/IL-2 (LFS and OS HRs=1.0).
- ASA4a: This analysis excludes the costs of allo-SCT for all treatment groups
- ASA4b: This analysis reintroduces the costs of allo-SCT and includes the costs of other subsequent treatment regimens (low-dose cytarabine, injectable azacitidine and salvage chemotherapy) based on data from TA827.
- ASA5: In this analysis, the EAG reintroduces the company's preferred models for LFS and OS (jointly fitted exponentials).
- ASA6a: In this analysis, the EAG includes the RDIs for HDC and IL-2, assuming they are the same as for oral azacitidine (86.9%).
- ASA6b: In this analysis, the EAG assumes RDIs of 95% for HDC and IL-2.

Table 34: Summary of EAG's scenario analyses using EAG's preferred assumptions

-	EAG's base case assumption	EAG's scenario
1a	Health state utility values from Tremblay *et al.*	Health state utility values from Joshi *et al.*
1b		Health state utility values from Stein *et al.*
1c		Health state utility values from Russell-Smith *et al.*
2	Use the mean estimates for OS and LFS HRs from the ITC of oral azacitidine versus HDC/IL-2.	Use the lower range estimates for OS and LFS HRs from the ITC of oral azacitidine versus HDC/IL-2
3		Oral azacitidine assumed equivalent to HDC/IL-2 (HRs assumed =1.0)
4a	Inclusion of allo-SCT costs as the only costs of subsequent therapies	Exclusion of allo-SCT costs
4b		Inclusion of the costs of other therapies, based on TA827
5	Use of independently fitted LFS exponential model for HDC/IL-2 and independently fitted LFS log-normal model for SoC; for OS, independently fitted Weibull models were used for both HDC/IL-2 and SoC	Use of jointly fitted exponential LFS and OS models for HDC/IL-2 and SoC (company's base case)
6a	RDIs for HDC and IL-2 are assumed 100%	Use of alternative RDIs for HDC and IL-2 (86.9% for both drugs, based on oral azacitidine)
6b		Use of hypothetical RDIs for HDC and IL-2 (95%)

Allo-SCT - allogenic stem cell transplant; HDC/IL-2 - histamine dihydrochloride with interleukin-2; HR - hazard ratio; ITC - indirect treatment comparison; LFS - leukaemia-free survival; OS - overall survival; SoC - standard of care.

5.2.2 EAG's exploratory analyses - results

The results of the EAG's preferred analysis for the comparison of HDC/IL-2 versus oral azacitidine and versus SoC are presented in Table 35. Each of analyses EA2-8 include the error corrections included in EA1, and all of the EAG's preferred assumptions are combined in EA10. All results reported for the comparison against SoC include a decision modifier of 1.2; the comparison against oral azacitidine was [redacted].

Correcting the remaining errors in the company's updated model leads to an estimated ICER for HDC/IL-2 versus SoC of £20,915 per QALY gained (EA1, £25,098 without the DM). Changing preferences around the LFS and OS models used for HDC/IL-2 and SoC (EA3) had the most impact on the ICER (£27,357, or £32,828 without the DM). All the other analyses (EA2 and EA4 to EA8) have only a minor impact on the ICER for this comparison. Under the EAG's preferred scenario (EA10), the deterministic ICER for HDC/IL-2 versus SoC is estimated to be £28,918 per QALY gained (£34,701 without the DM), which is moderately higher than the company's base case ICER.

In the comparison against oral azacitidine, all results generated indicate that HDC/IL-2 generates [redacted] QALYs and is [redacted] compared to oral azacitidine, and all results are

[redacted]. Correcting the errors in the company's updated model leads to an estimated ICER of [redacted]. The analysis with most impact on the ICER for this comparison was the removal of the impact of the discontinuation approach to health outcomes (EA8, [redacted]). Using the stratified HR for OS from QUAZAR AML-001 to estimate outcomes for oral azacitidine group (EA2) leads to an ICER of [redacted]. Including a utility decrement related to the HDC/IL-2 injections leads to an ICER of [redacted]. The inclusion of RDI and other cost elements to oral azacitidine also has a moderate impact to the ICER (EA4, [redacted]). Under the EAG's preferred scenario (EA10), the deterministic ICER for HDC/IL-2 versus oral azacitidine is estimated to be [redacted], which is considerably lower than the company's base case ICER.

Table 35: EAG preferred analysis results – HDC/IL-2 versus oral azacitidine and versus SoC, pairwise comparisons

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER‡ (excl. DM)	ICER‡ (incl. DM)
Company's updated base case model								
HDC/IL-2	13.51	6.74	£127,658	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.54	£50,341	7.06	3.20	£77,317	**£24,183**	**£20,153**
EA1: Correction of errors								
HDC/IL-2	13.51	6.55	£127,150	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.49	£50,340	7.06	3.06	£76,809	**£25,098**	**£20,915**
EA2: Use of stratified HR for OS from QUAZAR AML-001 to estimate outcomes for oral azacitidine group								
HDC/IL-2	13.51	6.55	£127,150	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.49	£50,340	7.06	3.06	£76,809	**£25,098**	**£20,915**
EA3: Use of alternative LFS and OS models for HDC/IL-2 and SoC								
HDC/IL-2	10.35	5.87	£112,638	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.13	£55,591	2.33	1.74	£57,046	**£32,828**	**£27,357**
EA4: Inclusion of additional elements for oral azacitidine costs								
HDC/IL-2	13.51	6.55	£127,150	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.49	£50,340	7.06	3.06	£76,809	**£25,098**	**£20,915**
EA5: Inclusion of wastage-based costs for IL-2								
HDC/IL-2	13.51	6.55	£129,834	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.49	£50,340	7.06	3.06	£79,494	**£25,975**	**£21,646**
EA6: Alternative assumption regarding administration costs for HDC/IL-2								
HDC/IL-2	13.51	6.55	£129,584	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.49	£50,340	7.06	3.06	£79,244	**£25,894**	**£21,578**
EA7: Alternative assumptions regarding the SoC drugs								
HDC/IL-2	13.51	6.55	£127,299	-	-	-	-	-

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER‡ (excl. DM)	ICER‡ (incl. DM)
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.49	£50,464	7.06	3.06	£76,835	**£25,106**	**£20,922**
EA8: Removal of the impact of the discontinuation approach to health outcomes								
HDC/IL-2	14.15	6.83	£129,711	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.49	£50,340	7.70	3.34	£79,370	**£23,767**	**£19,806**
EA9: Inclusion of disutility related to HDC/IL-2 injections								
HDC/IL-2	13.51	6.47	£127,150	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.49	£50,340	7.06	2.97	£76,809	**£25,824**	**£21,520**
EA10: EAG-preferred analysis (EAs 1-9 combined)								
HDC/IL-2	10.57	5.94	£118,569	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.13	£55,718	2.55	1.81	£62,851	**£34,701**	**£28,918**

LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; DM – decision modifier; Inc. – incremental.
** Undiscounted*
‡ All ICERs for HDC/IL-2 against oral azacitidine are in SWQ (£ per QALY lost).

5.2.3 Scenario analyses using EAG's preferred assumptions

The results of the EAG's additional sensitivity analyses for the pairwise comparisons of HDC/IL-2 versus oral azacitidine and SoC are presented in Table 36. All analyses include a DM of 1.2 in the comparisons against SoC, and 1.0 in the comparison against oral azacitidine.

In the comparison against SoC, most scenarios have only a modest impact on the ICER. The exceptions are the application of the utility values from Russell-Smith *et al.* (£34,276 per QALY gained, or £41,131 without the DM), and using the company's preferred model choices for OS and LFS, which leads to a lower ICER of £21,647 per QALY gained (or £25,977 without the DM). In the comparison against oral azacitidine, the analyses with the higher impact were the changes in assumptions regarding the HRs for OS and LFS: using lower range of estimates led to a lower ICER of [redacted], whilst assuming equivalency between oral azacitidine and HDC/IL-2 leads to an ICER of [redacted].

Table 36: EAG's additional sensitivity analysis results – HDC/IL-2 versus oral azacitidine and versus SoC, pairwise comparisons, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER‡ (excl. DM)	ICER (incl. DM)
EAG-preferred analysis								
HDC/IL-2	10.57	5.94	£118,569	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.13	£55,718	2.55	1.81	£62,851	**£34,701**	**£28,918**
ASA1a: Use of Joshi *et al.*								
HDC/IL-2	10.57	6.29	£118,569	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.25	£55,718	2.55	2.03	£62,851	**£30,895**	**£25,746**
ASA1b: Use of Stein *et al.*								
HDC/IL-2	10.57	6.39	£118,569	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASA1c: Use of Russell-Smith *et al.*								
HDC/IL-2	10.57	5.50	£118,569	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	3.98	£55,718	2.55	1.53	£62,851	**£41,131**	**£34,276**
ASA2: Use of alternative HRs for LFS and OS to estimate the outcomes for oral azacitine (based on lower range of estimates from ITC)								
HDC/IL-2	10.57	5.94	£118,569	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.13	£55,718	2.55	1.81	£62,851	**£34,701**	**£28,918**
ASA3: Oral azacitidine's treatment effect assumed equivalent to HDC/IL-2								
HDC/IL-2	10.57	5.94	£118,569	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.13	£55,718	2.55	1.81	£62,851	**£34,701**	**£28,918**
ASA4a: Costs of allo-SCT excluded								
HDC/IL-2	10.57	5.94	£118,336	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.13	£54,769	2.55	1.81	£63,567	**£35,096**	**£29,247**
ASA4b: Costs of subsequent treatments included (based on TA827)								
HDC/IL-2	10.57	5.94	£118,875	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	8.02	4.13	£56,670	2.55	1.81	£62,204	**£34,344**	**£28,620**
ASA5: Company's preferred LFS and OS models reintroduced								
HDC/IL-2	14.15	6.75	£134,981	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	6.45	3.49	£50,464	7.70	3.25	£84,517	**£25,977**	**£21,647**
ASA6a: Alternative RDI assumption for HDC/IL-2 (68.9%, based on oral azacitidine)								
HDC/IL-2	10.57	5.94	£112,208	-	-	-	-	-

Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.13	£55,718	2.55	1.81	£56,490	**£31,189**	**£25,991**
ASA6b: Alternative RDI assumption for HDC/IL-2								
HDC/IL-2	10.57	5.94	£116,141	-	-	-	-	-
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡
SoC	8.02	4.13	£55,718	2.55	1.81	£60,423	**£33,361**	**£27,800**

LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; DM – decision modifier; Inc. – incremental.
** Undiscounted*
‡ All ICERs for HDC/IL-2 against oral azacitidine are in SWQ (£ per QALY lost).

5.3 Decision modifiers

In the CS,[1] the company did not present a case for a QALY weighting for severity, and all results did not include any disease severity modifiers. In response to clarification question C1,[30] the company stated that *"on the grounds that HDC/IL-2 already fell within a cost-effective range based on the survival assumptions in the base case analysis, the severity modifier was not applied in the base case analysis"*, but would be open to reconsider in case "*where the shortfall calculation is deemed to be sufficiently robust and if subsequent scenario analyses show a less favourable cost-effectiveness profile for HDC/IL-2"*.

The expected total QALYs for the general population were based on the 2021-23 National life tables for England and Wales from the ONS,[72] and the mean age and proportion of females from the baseline characteristics from the company's model (Table 37). The EAG used the York (online) shortfall calculator[85] to calculate the general population QALYs, absolute (AS) and proportional shortalls (PS), using the population EQ-5D-3L data adjusted by age and sex from the Health Survey from England (HSE) 2014. The QALY shortfall analysis for the company's base case and EAG's preferred analyses are presented in Table 38.

Table 37: Summary of company's or EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source	Reference to section in submission or rationale
Sex distribution	0.50	Population baseline characteristics (section 4.2.1)
Starting age	44	
Discount rate	3.5%	section 4.2.1

Table 38: Summary of company's and EAG's base-case QALY shortfall analyses and preferred QALY weighting

-	Expected years of life*	Expected total QALYs for the general population	Expected total QALYs for people living with a condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight (York calculator)
Company's base case						
SoC	6.45	17.62	3.54	14.08	79.91%	1.2
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred analysis						
SoC	8.02	17.62	4.13	13.49	76.56%	1.2
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The resulting AS and PS for each of the comparators were compared to the criteria stated in the NICE Methods Guidance (Table 39). Whilst the results for the comparison against oral azacitidine indicate that the criteria for a DM [redacted], the results for the comparison against SoC suggest that a DM of 1.2 is appropriate in both company's and EAG's preferred analysis.

Table 39: QALY weightings for severity (reproduced from NICE Methods Guidance, Table 6.1)

QALY weight	Proportional shortfall	Absolute shortfall
x1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

5.4 Confidential comparator and subsequent treatment prices

The company has not proposed a Patient Access Scheme (PAS) discount for HDC/IL-2. All the results of all analyses included in this report use list prices from BNF or discounted prices publicly available in eMIT where applicable.

A cPAS discount is available for oral azacitidine; the results of the analyses including the discounted price for oral azacitidine are presented in a separate confidential appendix to this EAG report.

5.5 Conclusions of the cost-effectiveness section

The CS presents an SLR of existing economic studies of treatments for adult patients with AML and details the methods and results of a de novo model-based health economic analysis of HDC/IL-2 versus SoC and versus oral azacitidine in patients in CR1, aged ≤60 years, with normal karyotype, and who were not eligible for allo-SCT.

The company's SLR identified three existing economic models in AML.[52, 53, 58] None of the identified studies include HDC/IL-2 as the intervention and one of the identified studies corresponded to a publication derived from NICE TA827, which compared oral azacitidine against watch and wait plus BSC in the overall population with AML who reached remission and were ineligible for HSCT. The other two studies compared technologies for patients with FLT3 or CD33 mutations in different points of the treatment pathway for AML to this appraisal.

The company's updated model, provided as part of the clarification process, assesses the cost-effectiveness of HDC/IL-2 (plus SoC) versus oral azacitidine (plus SoC) and SoC alone for maintenance treatment of AML patients in CR1, aged ≤60 years, with normal karyotype, and who were not eligible for allo-SCT. The model uses a partitioned survival approach which includes four health states: (i) leukaemia-free (further subdivided into treatment on and treatment off for patients receiving HDC/IL-2 or oral azacitidine), (ii) progressed disease, and (iii) dead. The model includes an implicit initial decision tree component which accounts for patients who discontinue HDC/IL-2 or oral azacitidine early due to AEs not related to relapse; these patients are assumed to accrue the outcomes for SoC. The economic analysis adopts an NHS and PSS perspective, including QALYs accrued by AML patients; caregiver effects are not included.

Clinical outcomes for patients in the HDC/IL-2 and SoC are based on parametric survival models jointly fitted to data on LFS and OS from a *post-hoc* subgroup analysis of patients with AML in CR1, ≤60 years old, and normal karyotype from the Brune *et al*. study, as reported by Nilsson *et al.* Outcomes for oral azacitidine were modelled by applying HRs for LFS and OS from the company's Bucher ITC to the parametric survival models for the HDC/IL-2 group. Health state utility values are based on utility values from Tremblay *et al.* Resource use and cost parameters are informed by a range of sources including standard costing sources, NICE TA827, published literature, and assumptions. Model results are presented in the CS in the form of pairwise comparisons between HDC/IL-2 and each comparator; a fully incremental analysis is not presented.

The probabilistic version of the company's revised model suggests pairwise ICERs for HDC/IL-2 versus SoC of £20,269 per QALY gained, including a DM of 1.2. In the comparison against oral azacitidine, HDC/IL-2 is expected to generate [redacted], generating an ICER [redacted]. The corresponding ICERs based on the deterministic version of the revised model are slightly lower in the comparison against SoC (£20,153 per QALY gained), and higher against oral azacitidine [redacted].

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's model. The EAG notes the following key concerns regarding the company's economic model:

- The EAG considers that there is considerable uncertainty regarding the applicability of the study outcomes to current UK clinical practice, given the substantial advances in AML management in the UK since the Brune *et al.* study was conducted, as well as the use of data from a non-pre-specified (*post-hoc*) subgroup analysis to inform the outcomes of the target population in this appraisal.
- The EAG disagrees with the company's selection of the jointly fitted exponential for LFS and OS. The EAG prefers the following models for each endpoint and treatment groups:
    - LFS, HDC/IL-2: independently fitted exponential
    - LFS, SoC: independently fitted log-normal
    - OS, HDC/IL-2: independently fitted Weibull
    - OS, SoC: independently fitted Weibull
- The EAG considers that the estimated treatment effect between HDC/IL-2 and oral azacitidine is highly uncertain for the target population of this appraisal, with the main concerns relating to (i) limited overlap between the QUAZAR AML-001 and Brune *et al.* trial populations and age being a potential effect modifier; (ii) potential differences in the common comparator (SoC) between the two trials due to significant changes in the treatment landscape for AML between the periods when the studies were conducted; (iii) absence of subgroup results from QUAZAR AML-001 for patients with AML in CR1, aged ≤60 years, with normal karyotype, necessitating reliance on Bucher ITC results based on the ITT populations of QUAZAR AML-001 and Brune et al., which are not representative of the company's proposed population; and (iv) the use of an inconsistent approach to inform the ITC by using a mixture of stratified and unstratified HRs from the two studies. The EAG prefers that all the HRs used are based on the stratified HRs from the studies.
- The EAG considers that most sources of health state utility values presented by the company have limitations, and in the absence of HRQoL data from the clinical study that reflects the specific target population, it is unclear which would be the best source of utilities for this population. In addition, the EAG has concerns about the impact on HRQoL for patients with AML arising from the high number of injections required for treatment with HDC/IL-2, which was not included in the company's model. The EAG retained the company's preferred source for utility values but explored the use of alternative sources as part of additional sensitivity analyses. The EAG also prefers to include an additional utility decrement for the high number of injections, based on published estimates for patients with type 2 diabetes who receive daily injections (versus those managed with oral medication alone).

- The EAG disagrees with the company's approach for modelling the outcomes for patients who discontinue early due to AEs, given that the data used to inform the LFS and OS standard parametric models for HDC/IL-2 included patients who had discontinued treatment. The EAG considers that LFS and OS for the HDC/IL-2 (and as a consequence, for oral azacitidine) should be modelled based directly on standard parametric survival estimates for each respective group (i.e., removal of the 'blended' approach).

The EAG also identified further issues relating to model programming errors and several approaches related to modelling drug and subsequent treatment costs for HDC/IL-2, oral azacitidine and SoC groups. In addition, the EAG considers the results of the company's PSA to be unreliable.

The EAG undertook exploratory analyses using the company's revised model to address some of the issues described above. The EAG's preferred model includes: (i) correction of errors; (ii) use of alternative parametric survival models for LFS and OS in HDC/IL-2 and SoC groups; (iii) use of HR for OS for HDC/IL-2 versus oral azacitidine from the company's ITC of QUAZAR AML-001 vs Brune *et al*. ITT populations based on the stratified HR for OS from QUAZAR AML-001; (iv) inclusion of additional cost elements for oral azacitidine (RDI estimate, costs of premedication and administration costs); (v) change in the approach for acquisition costs for IL-2 to one based on the patients' mean weight and distributions from the CR1 population in Brune *et al*. using the method of moments; (vi) inclusion of a higher administration costs for HDC/IL-2 based on dispensing instructions for IL-2; (vii) inclusion of alternative assumptions regarding SoC costs; (viii) removal of the 'blended' approach to health outcomes for patients in the HDC/IL-2 and oral azacitidine groups; and (ix) inclusion of the impact of higher number of HDC/IL-2 injections on HRQoL.

The deterministic version of the EAG's preferred model suggests that, based on a DM of 1.2, the ICER for HDC/IL-2 versus SoC is estimated to be £28,918 per QALY gained, whilst the ICER for HDC/IL-2 versus oral azacitidine is estimated to be [redacted]. These estimates are substantially less favourable to HDC/IL-2 than the company's base case ICER.

The EAG's additional sensitivity analyses indicate that the ICER is sensitive to the choice of utility values, the choice of parametric models for LFS and OS, and to the choice of HRs for LFS and OS in the comparison against oral azacitidine.

The EAG cautions the interpretation of the results from the economic analyses informing this appraisal, due to substantial uncertainty related to the evidence used to inform LFS and OS in the model. However, the exact impact of this uncertainty on the ICER is unknown.

6 References

1. Brancaster Pharma. Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]. Company evidence submission. Lingfield, UK: Brancaster Pharma:; 2025.
2. Cancer Research UK. What is acute myeloid leukaemia (AML)? ; 2025. https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/about-acute-myeloid-leukaemia (Accessed 20/10/2025).
3. Z Abuhelwa, Q Al Shaer, S Taha, K Ayoub, R Amer. Characteristics of De Novo Acute Myeloid Leukemia Patients in Palestine: Experience of An-Najah National University Hospital. *Asian Pac J Cancer Prev* 2017;18:2459-64.
4. A Vakiti, SB Reynolds, P Mewawalla. Acute Myeloid Leukemia. In: Stat Pearls. Treasure Island (FL): StatPearls Publishing; 2024.
5. Cancer Research UK. Acute myeloid leukaemia (AML) statistics. 2025. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml (Accessed
6. Institute for Health Metrics and Evaluation. GBD Results. In. 09/10/2025 ed. Seattle, USA: IHME, University of Washington; 2025.
7. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF*, et al.* The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia* 2022;36:1703-19.
8. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H*, et al.* Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022;140:1345-77.
9. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka H-M*, et al.* International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood* 2022;140:1200-28.
10. Cancer Research UK. Types and risk groups of acute myeloid leukaemia (AML). 2025. https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/types-aml (Accessed 20/10/2025).
11. Cancer Research UK. Risks and causes of acute myeloid leukaemia (AML). 2025. https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/risks-causes (Accessed 06/10/2025).
12. Wierzbowska A, Czemerska M. Clinical Manifestation and Diagnostic Workup. In: Röllig C, Ossenkoppele GJ, editors. *Acute Myeloid Leukemia*Cham: Springer International Publishing; 2021:119-26.
13. Cancer Research UK. Symptoms of acute myeloid leukaemia (AML). 202506/10/2025).
14. Cancer Research UK. Treatment for acute myeloid leukaemia (AML). 2025. https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/treating-aml (Accessed 06/10/2025).
15. National Institute for Health and Care Excellence. Liposomal cytarabine–daunorubicin for untreated acute myeloid leukaemia [TA552]. London, UK; 2018.
16. National Institute for Health and Care Excellence. Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [TA545]. London, UK; 2018.
17. National Institute for Health and Care Excellence. Midostaurin for untreated acute myeloid leukaemia [TA523]. London, UK; 2018.
18. National Institute for Health and Care Excellence. Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [TA1013]. London, UK; 2024.
19. National Institute for Health and Care Excellence. Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [TA827]. NICE: London, UK; 2022.

20. . Sorafenib maintenance for adults with FLT3-internal tandem duplication (FLT3-ITD) acute myeloid leukaemia (AML) undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT) [URN:2262]. London, UK; 2023.
21. National Institute for Health and Care Excellence. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia [TA218]. London, UK; 2011.
22. National Institute for Health and Care Excellence. Venetoclax with low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [TA787]. London, UK.; 2022.
23. National Institute for Health and Care Excellence. Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [TA765]. London, UK; 2022.
24. National Institute for Health and Care Excellence. Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [TA979]. London, UK.; 2024.
25. Cancer Research UK. Survival for acute myeloid leukaemia (AML). 2025. https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/survival (Accessed 28/10/2025).
26. Grover S, Rina K, Malhotra P, Khadwal A. Caregiver Burden in the Patients of Acute Myeloblastic Leukemia. *Indian Journal of Hematology and Blood Transfusion* 2019;35:437-45.
27. Nielsen IH, Tolver A, Piil K, Kjeldsen L, Grønbæk K, Jarden M. Family caregiver quality of life and symptom burden in patients with hematological cancer: A Danish nationwide cross-sectional study. *European Journal of Oncology Nursing* 2024;69:102538.
28. . Summary of Product Characteristics. Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection. PL 41542/0012. London, UK; 2025.
29. Martner A, Rydström A, Riise RE, Aurelius J, Anderson H, Brune M, *et al.* Role of natural killer cell subsets and natural cytotoxicity receptors for the outcome of immunotherapy in acute myeloid leukemia. *OncoImmunology* 2015;5:e1041701.
30. Brancaster Pharma. Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]. Clarification response. Lingfield, UK: Brancaster Pharma:; 2025.
31. Brune M, Castaigne S, Catalano J, Gehlsen K, Ho AD, Hofmann W-K, *et al.* Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. *Blood* 2006;108:88-96.
32. Nilsson MS, Hallner A, Brune M, Nilsson S, Thorén FB, Martner A, *et al.* Immunotherapy with HDC/IL-2 may be clinically efficacious in acute myeloid leukemia of normal karyotype. *Human Vaccines & Immunotherapeutics* 2020;16:109-11.
33. National Institute for Health and Care Excellence. Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]. Final scope. London, UK; 2025.
34. EpiCept Corporation. Multicenter Randomized Open-Label Study to Evaluate the Safety and Efficacy of Immunotherapy with Subcutaneous Ceplene™ (Histamine Dihydrochloride) plus Proleukin™ (Interleukin-2) Versus No Treatment in Patients with Acute Myeloid Leukemia in First or Subsequent Complete Remission (CR). Clinical Study Report; 2006.
35. Richard F Schlenk, Konstanze Döhner, Jürgen Krauter, Stefan Fröhling, Andrea Corbacioglu, Lars Bullinger, *et al.* Mutations and Treatment Outcome in Cytogenetically Normal Acute Myeloid Leukemia. *The New England Journal of Medicine* 2008;358:1909-18.
36. Wei AH, Döhner H, Sayar H, Ravandi F, Montesinos P, Dombret H, *et al.* Long-term survival with oral azacitidine for patients with acute myeloid leukemia in first

remission after chemotherapy: Updated results from the randomized, placebo-controlled, phase 3 QUAZAR AML-001 trial. *American Journal of Hematology* 2023;98.
37. ClinicalTrials.gov. Multi-Center, Randomized Open-Label Study to Evaluate the Safety and Efficacy of Immunotherapy With Subcutaneous Maxamine (Histamine Dihydrochloride) Plus Proleukin (Interleukin-2) Versus No Treatment (Standard of Care) in Patients With Acute Myeloid Leukemia in First or Subsequent Complete Remission (CR). In; 1999.
38. Li T, Higgins JPT, Deeks JJ. Chapter 5: Collecting data [last updated October 2019]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ*, et al.*, eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.5.: Cochrane; 2024.
39. Mathes T, Klaßen P, Pieper D. Frequency of data extraction errors and methods to increase data extraction quality: a methodological review. *BMC medical research methodology* 2017;17:152.
40. JAC Sterne, J Savović, MJ Page, RG Elbers, NS Blencowe, I Boutron*, et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. . *BMJ* 2019;366.
41. Boutron I, Page MJ, Higgins JPT, Altman DG, Lundh A, Hróbjartsson A. Chapter 7: Considering bias and conflicts of interest among the included studies [last updated August 2022]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ*, et al.*, eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.5.: Cochrane; 2024.
42. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. In: CRD, University of York; 2009.
43. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ*, et al.* Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). In: Cochrane; 2024.
44. Buyse M, Squifflet P, Lucchesi KJ, Brune ML, Castaigne S, Rowe JM. Assessment of the consistency and robustness of results from a multicenter trial of remission maintenance therapy for acute myeloid leukemia. *Trials* 2011;12:86.
45. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G*, et al.* The Importance of Diagnostic Cytogenetics on Outcome in AML: Analysis of 1,612 Patients Entered Into the MRC AML 10 Trial. *Blood* 1998;92:2322-33.
46. Brancaster Pharma. Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]. Additional clarification questions (v2). 2025.
47. Othman J, Potter N, Ivey A, Tazi Y, Papaemmanuil E, Jovanovic J*, et al.* Molecular, clinical, and therapeutic determinants of outcome in NPM1-mutated AML. *Blood* 2024;144:714-28.
48. Othman J, Potter N, Ivey A, Jovanovic J, Runglall M, Freeman SD*, et al.* Postinduction molecular MRD identifies patients with NPM1 AML who benefit from allogeneic transplant in first remission. *Blood* 2024;143:1931-6.
49. Shimony S, Stahl M, Stone RM. Acute Myeloid Leukemia: 2025 Update on Diagnosis, Risk-Stratification, and Management. *Am J Hematol* 2025;100:860-91.
50. Oliva EN, Candoni A, Salutari P, Di Raimondo F, Reda G, Capelli D*, et al.* Azacitidine for Post-Remission Therapy in Elderly Patients with Acute Myeloid Leukemia : Final Results of the Qoless AZA-Amle Randomized Trial. *Blood* 2019;134:117.
51. European Medicines Agency. Ceplene: European public assessment report (EPAR). London: EMA; 2008. Report No: EMA/519759/2008.; 2008. https://www.ema.europa.eu/en/documents/assessment-report/ceplene-epar-public-assessment-report_en.pdf (Accessed
52. Witlox W, Grimm S, Howick J, Armstrong N, Ahmadu C, McDermott K*, et al.* Oral Azacitidine for Maintenance Treatment of Acute Myeloid Leukaemia After Induction Therapy: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *PharmacoEconomics* 2023;41:857-67.

53. Tremblay G, Dolph M, Patel S, Brandt P, Forsythe A. Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom. *Cost Effectiveness and Resource Allocation* 2018;16.
54. Matza LS, Deger KA, Howell TA, Koetter K, Yeager AM, Hogge D*, et al.* Health state utilities associated with treatment options for acute myeloid leukemia (AML). *Journal of Medical Economics* 2019;22:567-76.
55. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health and Quality of Life Outcomes* 2008;6:84.
56. Stein EM, Yang M, Guerin A, Gao W, Galebach P, Xiang CQ*, et al.* Assessing utility values for treatment-related health states of acute myeloid leukemia in the United States. *Health and Quality of Life Outcomes* 2018;16.
57. National Institute for Health and Care Excellence. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [TA642]. London, UK; 2020.
58. Russell-Smith TA, Brockbank J, Mamolo C, Knight C. Cost Effectiveness of Gemtuzumab Ozogamicin in the First-Line Treatment of Acute Myeloid Leukaemia in the UK. *PharmacoEconomics - Open* 2021;5:677-91.
59. National Institute for Health and Care Excellence. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [TA399]. 2016.
60. Kurosawa S, Yamaguchi H, Yamaguchi T, Fukunaga K, Yui S, Wakita S*, et al.* Decision Analysis of Postremission Therapy in Cytogenetically Intermediate-Risk Acute Myeloid Leukemia: The Impact of FLT3 Internal Tandem Duplication, Nucleophosmin, and CCAAT/Enhancer Binding Protein Alpha. *Biology of Blood and Marrow Transplantation* 2016;22:1125-32.
61. Ara R, Brazier JE. Populating an Economic Model with Health State Utility Values: Moving toward Better Practice. *Value in Health* 2010;13:509-18.
62. National Institute for Health and Care Excellence. Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [TA541]. London, UK; 2018.
63. Uyl DEG, LÖwenberg, Vellenga, Suciu, Willemze, Rutten. Cost-effectiveness and quality-of-life assessment of GM-CSF as an adjunct to intensive remission induction chemotherapy in elderly patients with acute myeloid leukaemia. *British Journal of Haematology* 1998;100:629-36.
64. Batty N, Yin Y, Wetzler M. Decitabine is more cost effective than cytarabine and daunorubicin in elderly acute myeloid leukemia patients. *Journal of Cancer Research & Therapy* 2014;2:68-73.
65. Leunis A, Redekop WK, Uyl-de Groot CA, Löwenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. *European Journal of Haematology* 2014;93:198-206.
66. Pan F, Peng S, Fleurence R, Linnehan JE, Knopf K, Kim E. Economic Analysis of Decitabine Versus Best Supportive Care in the Treatment of Intermediate- and High-Risk Myelodysplastic Syndromes From a US Payer Perspective. *Clinical Therapeutics* 2010;32:2444-56.
67. Grulke N, Albani C, Bailer H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. *Bone Marrow Transplantation* 2012;47:473-82.
68. Stone Richard M, Mandrekar Sumithra J, Sanford Ben L, Laumann K, Geyer S, Bloomfield Clara D*, et al.* Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *New England Journal of Medicine*;377:454-64.
69. Scottish Medicines Consortium. histamine dihydrochloride, 500 microgram/0.5ml, vial (Ceplene®). SMC No. (666/10). Glasgow, UK: Scottish Medicines Consortium,; 2011.
70. Tikhonova IA, Hoyle MW, Snowsill TM, Cooper C, Varley-Campbell JL, Rudin CE*, et al.* Azacitidine for Treating Acute Myeloid Leukaemia with More Than 30 % Bone Marrow Blasts: An Evidence Review Group Perspective of a National Institute for

Health and Care Excellence Single Technology Appraisal. *PharmacoEconomics* 2017;35:363-73.
71. NHS England. Health Survey for England 2021. In. 15 Dec 2022 ed. Kew, UK: NatCen Social Research and UCL; 2022.
72. Office for National Statistics (ONS). National life tables: England and Wales - 2021-2023. In. ONS: London, UK; 2024.
73. Stafford MR, Hareendran A, Ng-Mak DS, Insinga RP, Xu R, Stull DE. EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of migraineurs. *Health and Quality of Life Outcomes* 2012;10:65.
74. Joint Formulary Committee. British National Formulary. In; 2025.
75. NHS England. National Cost Collection for the NHS - 2023/24. In. London, UK: NHS England; 2025.
76. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). In. London, UK; 2025.
77. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliative Medicine* 2015;29:899-907.
78. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A. Unit Costs of Health and Social Care 2024 Manual. Technical report. Kent, UK: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2025.
79. Joshi N, Hensen M, Patel S, Xu W, Lasch K, Stolk E. Health State Utilities for Acute Myeloid Leukaemia: A Time Trade-off Study. *PharmacoEconomics* 2018;37:85-92.
80. Wallhult E, Whisnant J, Rowe JM, Szer J, Bhagwat D, Hellstrand K*, et al.* Impact on Quality of Life of Postconsolidation Immunotherapy with Histamine Dihydrochloride and Interleukin-2 in Acute Myelogenous Leukemia. *Blood* 2007;110:4381.
81. Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the Cancer-Specific EORTC QLQ-C30 to the Preference-Based EQ-5D, SF-6D, and 15D Instruments. *Value in Health* 2009;12:1151-7.
82. McKenzie L, van der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D Instrument: The Potential to Estimate QALYs without Generic Preference Data. *Value in Health* 2009;12:167-71.
83. National Institute for Health and Care Excellence. NICE health technology evaluations: The manual. NICE: London, UK; 2022.
84. National Institute for Health and Care Excellence. NICE health technology evaluations: The manual [PMG36]. NICE: London, UK; 2022.
85. Paul Schneider, Simon McNamara, James Love-Koh, Tim Doran, Nils Gutacker. QALY Shortfall Calculator. In. York, UK; 2021.
86. Monica Hernandez Alava, Steve Pudney, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU report. Sheffield, UK.: Decision Support Unit, ScHARR, University of Sheffield; 2022.
87. Ren S, Minton J, Whyte S, Latimer N, Stevenson M. How To Sample Ordered Parameters In Probabilistic Sensitivity Analysis. *Value in Health* 2017;20:A758.
88. Potter N, Jovanovic J, Ivey A, Othman J, Thomas A, Gilkes A*, et al.* Molecular monitoring versus standard clinical care in younger adults with acute myeloid leukaemia: results from the UK NCRI AML17 and AML19 randomised, controlled, phase 3 trials. *The Lancet Haematology* 2025;12:e346-e56.
89. Juliusson G, Jädersten M, Deneberg S, Lehmann S, Möllgård L, Wennström L*, et al.* The prognostic impact of FLT3-ITD and NPM1 mutation in adult AML is age-dependent in the population-based setting. *Blood Advances* 2020;4:1094-101.
90. Nicholas Latimer. SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA. NICE DSU TECHNICAL SUPPORT DOCUMENT 14. Sheffield, UK: School of Health and Related Research, University of Sheffield.; 2011.
91. Mark J Rutherford, Paul C Lambert, Michael J Sweeting, Becky Pennington, Michael J Crowther, Keith R Abrams*, et al.* Flexible Methods for Survival Analysis. NICE DSU

TECHNICAL SUPPORT DOCUMENT 21. Sheffield, UK: Decision Support Unit, ScHARR, University of Sheffield; 2020.
92. Khanal N, Shostrom V, Dhakal P, Upadhyay Banskota S, Chaulagain C, He F*, et al.* Determinants of ten-year overall survival of acute myeloid leukemia: a large national cancer database analysis. *Leukemia & Lymphoma* 2022;63:939-45.
93. Brancaster Pharma. Histamine dihydrochloride (HDC) Advisory Board meeting minutes; 2025.
94. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *The European Journal of Health Economics* 2011;12:219-30.
95. Liu H, Stanworth SJ, McPhail S, Bishton M, Rous B, Bacon A*, et al.* Impact of patient demographics on treatment outcomes in AML: a population-based registry in England, 2013-2020. *Blood Advances* 2024;8:4593-605.
96. NHS England. 2025/26 NHS Payment Scheme – Annex B: Guidance on currencies. London, UK: NHE England; 2025.

Appendix 1: Cochrane Risk of Bias (RoB2) assessment of Brune *et al*.[31] (modified from CS, company's clarification response to question A15)

Domain	Signalling Question	CS Assessment	EAG Assessment
Randomisation process	1.1. Was the allocation sequence random?	Yes	Yes – 'Country-specific randomization schedules were produced electronically based on a block size of 4 and stratified by CR status'.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned?	No	Yes – 'treatment assignment from a centralized randomization center', thus no indication of allocation concealment issues.
	1.3 Did baseline differences suggest a problem with randomisation?	No	No – 'The study arms were well balanced for demographics and potential prognostic factors such as age, sex, previous high-dose cytarabine treatment, previous autologous stem cell transplantation, leukemic karyotypes, time from CR to inclusion, and frequency of antecedent hematologic disorder. Cox modelling did not reveal any imbalances between treatment and control arms…'
	Risk-of-bias judgement (randomisation)	Some concerns	Low risk – Randomisation and allocation sequence concealed, and no baseline imbalances for key prognostic factors.
Deviations from intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes	Yes – 'This open-label, randomized, multicenter phase 3 study…'
	2.2. Were carers and people delivering interventions aware of assignments?	Yes	Yes – as above
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations arising from trial context?	No	No – No deviations noted, treatment adherence good with median 6 cycles completed; dose reductions and interruptions were protocol-specified responses to adverse events.
	2.4. If Y/PY to 2.3: Could deviations have affected outcome?	NA	NA

	2.5. If Y/PY/NI to 2.4: Were deviations balanced between groups?	NA	NA
	2.6. Was an appropriate analysis used to estimate effect of assignment?	Yes	Yes – 'The efficacy analyses were performed according to the intent-to-treat principle, and all reported *P* values are 2-sided' In addition, Nilsson *et al.,*[32] re-analysed subgroups using Kaplan-Meier method (log rank test)
	2.7. If N/PN/NI to 2.6: Potential substantial impact of misanalysis?	NA	NA
	Risk-of-bias judgement (effect of assignment)	Low risk	Some concerns – The open-label design inherently allows for potential bias due to awareness, but the objective, hard clinical outcomes and lack of observed deviations reduce concern in practice.
Deviations from intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes	Yes – 'This open-label, randomized, multicenter phase 3 study…'
	2.2. Were carers and people delivering interventions aware of assignments?	Yes	Yes – 'This open-label, randomized, multicenter phase 3 study…'
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations arising from trial context?	No	No – No deviations noted, treatment adherence good with median 6 cycles completed; dose reductions and interruptions were protocol-specified responses to adverse events.
	2.4. If Y/PY to 2.3: Could deviations have affected outcome?	NA	NA
	2.5. If Y/PY/NI to 2.4: Were deviations balanced?	NA	NA
	2.6. Was an appropriate analysis used to estimate effect of adhering?	Yes	Yes – 'The efficacy analyses were performed according to the intent-to-treat principle, and all reported *P* values are 2-sided'

	2.7. If N/PN/NI to 2.6: Potential substantial impact of misanalysis?	NA	NA
	Risk-of-bias judgement (effect of adhering)	Low risk	Low risk – Adherence to intervention well documented; objective outcomes minimize bias risk despite open-label design.
Missing outcome data	3.1 Were data available for nearly all participants?	Yes	Yes – 'Eight patients, 4 in each study arm, were lost to follow-up or withdrew their consent; these patients were censored at the time of last assessment', thus follow-up data for >97% of randomized patients; very few lost to follow-up or withdrew consent.
	3.2. If N/PN/NI to 3.1: Evidence result not biased by missing data?	NA	NA
	3.3. If N/PN to 3.2: Could missingness depend on true value?	NA	NA
	3.4. If Y/PY/NI to 3.3: Likely missingness depended on true value?	NA	NA
	Risk-of-bias judgement (missing data)	Low risk	Low risk – Nearly complete data capture and appropriate censoring applied.
Measurement of outcome	4.1 Was measurement method inappropriate?	No	No – '…on the LFS of all patients. The secondary objectives included LFS rates at 12, 24, and 36 months after random assignment, effects of treatment on LFS of patients in CR1 and subsequent CR, overall survival…', thus objective outcomes
	4.2. Could measurement differ between groups?	No	No – Assessments consistent across groups; objective and standardized outcome definitions.
	4.3 Were outcome assessors aware?	No	No – Outcome measurement involved objective clinical criteria, reducing bias despite potential assessor knowledge.
	4.4. Could assessment be influenced by knowledge?	NA	NA
	4.5. Likely assessment influenced by knowledge?	NA	NA

	Risk-of-bias judgement (measurement)	Low risk	Low risk – Objective measures, consistently applied.
Selection of reported result	5.1. Analysed according to pre-specified plan?	Yes	No – Nilsson *et al.*[32] explicitly states that "*The exploratory nature of these results should be emphasized…'*
	5.2. Multiple eligible outcome measurements?	No	Yes, numerous potential subgroups were explored *post-hoc* according to CS, Nilsson *et al.*[32] and Nilsson *et al.*[44]
	5.3. Multiple eligible analyses?	No	Unclear
	Risk-of-bias judgement (selection)	Low risk	High risk – potential for selective reporting of results, primarily due to *post-hoc* exploratory analyses
Overall risk of bias	-	Low risk	High risk – Although most domains (randomisation process, deviations from intended interventions, missing data, and outcome measurement) were at low risk or had some concerns, the overall risk of bias was considered high, driven primarily by the potential for selective reporting of results based on *post-hoc* exploratory subgroup analyses.

Single Technology Appraisal

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 25 November 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Under section 1.3 - EAG's key issues - Uncertainty regarding the generalisability of the results from Brune et al. and Nilsson et al. to the current patients with AML who would currently be eligible for AML maintenance treatment in the NHS (page 14), it states (emphasis added): *'In addition, given the **substantial** advances in the AML management in the UK since the Brune et al. study was conducted, the population included in the Brune et al. subgroup of patients with normal karyotype, in CR1, ≤60 years old and ineligible for allo-SCT may not entirely reflect the current population of patients with AML who would be eligible for maintenance therapy with*	Brancaster propose that this statement should be slightly amended to: *'In addition, given the advances in the AML management in the UK since the Brune et al. study was conducted, the population included in the Brune et al. subgroup of patients with normal karyotype, in CR1, ≤60 years old and ineligible for allo-SCT may not entirely reflect the current population of patients with AML who would be eligible for maintenance therapy with HDC/IL-2 in the NHS clinical practice in England. As such, the EAG considers that there is uncertainty regarding the applicability of the study outcomes to current UK clinical practice, affecting both the*	There are two types of treatment that have been introduced (or modified) since the publication of the Brune et al study in 2006 as indicated in 2.1.1 (Disease overview) commencing on page 26 of the EAG report: 1. Targeted treatment is now available for subgroups of patients. For those AML patients with FLT-3 and FLT-3 ITD mutations there are now approved FT3-3 inhibitors available to treat these patients. As confirmed by the EAG's clinical advisors in 2.2.2 (EAG's critique of the company's treatment pathway and positioning of HDC/IL-2) on page 32 of the EAG report, patients with FLT-3 mutations would preferably receive targeted therapies which would preclude the use of HDC/IL-2	This is not a factual inaccuracy. Consistent with the views of the EAG's clinical advisors, Döhner *et al.* (2022) states that *"Since the 2017 report from the European LeukemiaNet (ELN),[1] there has been substantial progress in our knowledge of acute myeloid leukemia (AML). Recent advances significantly influence clinical practice. These advances include insights into the clinical value of genomic abnormalities for diagnosis and prognosis, the clinical significance of inherited predisposition to AML, technological advancements in the quantitative assessment of measurable residual*

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
HDC/IL-2 in the NHS clinical practice in England. As such, the EAG considers that there is ***considerable*** *uncertainty regarding the applicability of the study outcomes to current UK clinical practice, affecting both the clinical evidence and the economic analyses for this appraisal.'* Similar statements are repeated on page 58 under section 3.2.1.3 Summary of the critique of the company's quality assessment, and on page 71 under section 3.6 Conclusions of clinical effectiveness section.	*clinical evidence and the economic analyses for this appraisal.'*	maintenance treatment in this sub-group. 2. Alternative or modified chemotherapy during induction or consolidation. Cytarabine plus an anthracyclin remains the backbone of induction and consolidation therapy, although dosing, the method of administration and timing are continuously discussed and modified. In addition, gemtuzumab ozogamicin (GO) has become available, given in induction and sometimes in consolidation. The combination of ludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida) with GO has been reported to improve the early response in younger patients from the UK AML19 trial.	*disease (MRD) and their utility for assessing therapeutic response and disease risk, the development of a range of novel therapeutic agents, and developments in allogeneic hematopoietic cell transplantation (HCT), resulting in new disease classification,[2] diagnostic and prognostic algorithms, and updated therapeutic practices."* The EAG maintains its view that significant advances in AML management have been made since the Brune *et al.* study, and that the evidence for the normal-karyotype population in Brune *et al.* may not accurately represent a contemporary normal-

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		In the subgroup of patients with normal karyotype, in CR1, ≤60 years old and ineligible for allo-SCT around 90% of patients received high-dose cytarabine as defined by at least 2 g/m^2 per day for 3 or more days during induction or consolidation therapy and this was similar in both treatment and control arms. In this context the advances in AML management may therefore not be considered substantial. The use of high-dose cytarabine in the sub-group more closely reflects contemporary treatment in the UK and hence reduces the uncertainty (from considerable) regarding the applicability of the study outcomes to current UK clinical practice.	karyotype cohort in which patients with specific mutations would be excluded from receiving HDC/IL-2. Therefore, the text in the report was slighlty amended to: *'In addition, given the significant advances in the AML management in the UK since the Brune et al. study was conducted, the population included in the Brune et al. subgroup of patients with normal karyotype, in CR1, ≤60 years old and ineligible for allo-SCT may not entirely reflect the current population of patients with AML who would be eligible for maintenance therapy with HDC/IL-2 in the NHS clinical practice in England. As such, the*

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			EAG considers that there is considerable uncertainty regarding the applicability of the study outcomes to current UK clinical practice, affecting both the clinical evidence and the economic analyses for this appraisal.'

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Under section 1.3 - EAG's key issues - Use of *post-hoc* subgroup analysis to inform the treatment effects for HDC/IL-2 and SoC (page 15), it states (emphasis added): *'However, the EAG notes that the lack of pre-specification for the post-hoc analysis introduces the potential for a* ***high*** *risk of bias (e.g., from selective reporting or data-driven identification of subgroup effects).'* This sentiment is repeated on page 71 under section 3.6 Conclusions of clinical effectiveness section.	Brancaster propose that a qualifying remark precedes this statement and that it should also be slightly amended to: '*The EAG notes that the Brune et al 2006 study met its primary endpoint and the analysis of the outcome data from the study demonstrated that certain prognostic factors had a significant effect on the outcome of HDC/IL-2 versus best supportive care. However, the EAG notes that the lack of pre-specification for the post-hoc analysis introduces the potential for a risk of bias (e.g., from selective reporting or data-driven identification of subgroup effects).'*	The Brune et al 2006 study met its primary endoint by demonstrating a statistically significant improvement in leukaemia-free survival (LFS) in favour of HDC/IL-2 over best supportive care in the ITT population. The CR1 subgroup was pre-specified in the original protocol whereas karyotype status (normal vs aberrant) and age less than 60 were not. In a multivariate analysis from the original study by Brune et al 2006 two factors, that is, age (≥60 versus <60) and karyotype (adverse versus other), were found to have a significant effect on LFS. As a result of the above analyses the post hoc analysis including patients with normal karyotype in CR1 and <60	The EAG agrees that Brune *et al.* (2006) met its primary endpoint and that the study included a pre-specified stratification by CR1. However, this does not address the issue raised in Section 1.3 issue 2, which relates specifically to the non-pre-specified post-hoc subgroup analyses used to inform the model (CR1, aged ≤60 years and with normal karyotype). Section 3.2.1.3 of the report discusses the assessment of the design, conduct, and internal validity of the Brune *et al.* study. Although age and karyotype were identified as prognostic factors, the subgroup applied by the company was not pre-

		years was a rational approach to further define which patients benefitted more from HDC/IL-2 treatment and those who derived little or no benefit from the therapy.	specified and remains data-driven, introducing a non-negligible risk of bias. Therefore, the EAG maintains its view and no changes were made to the text in the EAG report.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The brand name “Ceplene®” is used to describe the technology under 2.1.3 Description of the technology (page 29) and 2.3.2 Intervention (page 45).	Brancaster propose to remove these references to “Ceplene®” and just refer to histamine dihydrochloride (HDC).	The UK approval of HDC is based on the generic name only – histamine dihydrochloride – and not on a brand name.	The EAG has removed any mentions to the brand name, except in Section 3.1.1, referring to the searches conducted by the company. Since the marketing authorisation from EMA is related to brand name *Ceplene*®, the text in Section 2.3.2 (page 46) was also amended to read *“HDC was first granted a licence with the European Medicines Agency (EMA) on 7th October 2008 (under the brand name Ceplene®), and has received an UK marketing authorisation on 1st August 2025.”*

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 31 under subsection 2.2.1 Current treatment pathway and proposed positioning of HDC/IL-2 it states: *'The company estimates that 50 to 100 people with AML in England would be eligible for treatment with HDC/IL-2, excluding patients with a FLT3 mutation.'*	Brancaster propose that this statement should be slightly amended to: *'The company estimates that annually 50 to 100 people with AML in England would be eligible for treatment with HDC/IL-2, excluding patients with a FLT3 mutation.'*	The estimated number of patients refers to an annual number and hence this is made clear in the proposed amendment.	The EAG has amended the text as suggested by the company.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 47 under 2.3.3 Comparators it states: *'Evidence that the use of oral azacitidine in clinical practice in England is restricted only to patients aged 55 years and older was not provided by the company.'*	Brancaster proposes that this statement should be amended to: '*The company provided some evidence in the CS showing that UK haematologists are aware that the evidence from the pivotal QUAZAR randomised controlled study only supports the use of oral azacitidine in patients who are 55 years or older. The company also supplied data indicating that there was limited use of oral azacitidine in the UK. Clinical opinion independently provided for the Budget Impact Assessment (BIA) conducted by NHS England confirmed that the uptake of oral azacitidine has been limited due to the evidence only supporting treatment in patients who are 55 years or older and hence*	The company does not believe it is accurate to state that 'Evidence that the use of oral azacitidine in clinical practice in England is restricted only to patients aged 55 years and older was not provided by the company.' The CS stated that during interviews held between May and August 2024 with 17 UK haematologists specialising in the treatment of AML patients, about the current maintenance treatment landscape and the use of oral azacitidine, it was mentioned by 15 out of 17 haematologists that the evidence from the pivotal QUAZAR randomised controlled study included, only older AML patients who were ≥55 years and these UK haematologists were therefore curious why this was not reflected	The EAG maintains its view that quantitative evidence of a restriction to patients aged 55 years and older in England was not provided by the company; i.e., no age-stratified real-world usage data (e.g., a clinical audit or patient registry data) was presented, which allowed the EAG to verify which age groups of patients are currently receiving treatment with oral azacitidine in the UK. The EAG also notes that NICE guidance TA827 applies to all adults, and clinical opinion does not constitute a formal restriction. However, the EAG acknowledges the clinical context provided regarding the QUAZAR-

	there is clinical reluctance to use a product with significant toxicity where there is no clear evidence of benefit. The same clinical opinion stated that younger patients with favourable and intermediate risk AML are more likely to benefit from HDC/IL-2 whereas older and adverse risk patients based on the available evidence (the QUAZAR trial) are more likely to benefit from oral azacitidine and hence the majority of use will be in non-overlapping patient populations.'	in the NICE recommendation (TA827). The CS included a peer-reviewed study of AML maintenance therapy with decitabine, a structurally and pharmacodynamically related analogue of azacitidine, in AML patients in CR1 after induction and consolidation treatment and who were <60 years old that determined no benefit was provided overall compared with historical controls. It was concluded by the company that this data may have contributed to the rationale for assessing the efficacy of oral azacitidine in an older population of AML patients. The CS included prescription data from NHS Business Services Authority (NHSBSA) Secondary Care Medicines Data (SCMD): in March 2024, 840 azacitidine tablets were prescribed at a cost of £704,040, corresponding to treatment courses for approximately 60 patients; in March 2025, 908 tablets were	AML 001 trial population. To reflect this nuance, the text in the EAG report was amended to: *"Quantitative evidence that the use of oral azacitidine in clincial practice in England is restricted only to patients aged 55 years and older was not provided (i.e., no age-stratified real-world usage data of patients currently receiving treatment was presented, such as clinical audit or patient registry data), although the company provided qualitative clinician feedback suggesting uptake in patients aged 55 years and older may be limited as the QUAZAR AML-001 trial only included patients aged 55 years and older."*

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		prescribed at a cost of £761,034, corresponding to treatment courses for approximately 65 patients. The company's evidence was then independently reinforced in the Budget Impact Assessment conducted by NHS England that advised that clinical opinion had confirmed the uptake of oral azacitidine has been limited due to the evidence only supporting treatment in patients who are 55 years or older and hence there is clinical reluctance to use a product with significant toxicity where there is no clear evidence of benefit in patients who are younger than 55 years and where even in those who are 55 years or older the evidence suggests that oral azacitidine delays relapse rather than preventing relapse. In the same document clinical opinion stated that younger patients with favourable and	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		intermediate risk AML are more likely to benefit from HDC/IL-2 whereas older and adverse risk patients based on the available evidence (the QUAZAR trial) are more likely to benefit from oral azacitidine and hence the majority of use will be in non-overlapping patient populations.	

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Under 3.4.1 Oral azacitidine on page 66 it states: *'The company clarified the quote was from the Budget Impact Assessment document, which was not shared with the EAG as part of the CS.'*	Brancaster propose that this statement should be slightly amended to: *'The company clarified the quote was from the Budget Impact Assessment document which was received by the company after their evidence submission to the EAG/NICE.'*	The Budget Impact Assessment document was sent to the company on 15th October 2025 by Commercial Liaison at NICE, which was after the deadline for the company's submission (CS) on 4th September 2025 and therefore could not be shared in the CS. In addition, the company asked NICE on the 5th November 2025 for the Budget Impact Assessment document including notes to be shared with the EAG. Commerical Liaison at NICE confirmed on 15th November 2025 that the Budget Impact Test (BIT) does not get shared with any stakeholders other than the company and NHSE.	This is not a factual inaccuracy. The Budget Impact Assessment document was not shared with the EAG. Nonetheless, the text was amended as follows: "*The company clarified the quote was from the Budget Impact Assessment document, which was not shared with the EAG as part of the CS. At the factual accuracy check stage, the company further clarified that this document was received by the company after the CS and it is not usually shared with any stakeholders other than the company and NHSE."*

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Under 4.1.1 Critique of company's searches on page 73 it states: '*The EAG would also stress that while EMBASE has adequate coverage of clinical congresses, it does not index the proceedings of health economics conferences such as The Professional Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Health Technology Assessment international (HTAi), except where abstracts are compiled into supplements by a journal such as Value In Health'.*	Brancaster propose that this statement should be slightly amended to: *'The EAG would also stress that EMBASE has adequate coverage of clinical congresses, and also includes abstracts of The Professional Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Health Technology Assessment international (HTAi), where abstracts are compiled into supplements by a journal such as Value In Health'*.	Abstracts from ISPOR are always compiled into a Value in Health supplement.	For clarity, the text in the report was amended as follows: *'The EAG acknowledges that EMBASE has adequate coverage of clinical congresses and also includes abstracts of health economics conferences from The Professional Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Health Technology Assessment international (HTAi) following their publication in supplements to Value In Health and International Journal of Technology Assessment in Health Care (IJTAHC), respectively.'*

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Under 5.2.1 under EAG's exploratory analyses – methods and EA3: Use of alternative models for LFS and OS on page 154 it states: '*A structural constrain was also included.....'*	Brancaster propose that this statement should be corrected to: *'A structural constraint was also included.....'*	'constrain' is a typo and should be amended to 'constraint'.	The EAG agrees. The text has been amended as suggested.

Committee Briefing

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name:	**Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia**
Topic ID:	**1627**
Managed Access Lead:	[redacted]
Date of assessment(s):	**18/11/2025**

Feasibility of successful managed access	Comments / Rationale	
No managed access proposal	**Rationale for rating**	There is no proposal for managed access for this technology. If the company, committee or other stakeholder wishes to explore managed access, they should contact the Managed Access Team as soon as possible.
	Previous ratings and rationale for change	

Managed Access Proposal	No	
Managed Access Team input at Committee meeting	Low	The Managed Access Team does not intend to actively engage at the ACMs unless a desire to pursue managed access is highlighted ahead of the meeting.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, though no proposal has been made to enable this
Are there outstanding uncertainties that could be resolved with further data collection?	Low	The evidence underpinning this appraisal appears, by the EAG's assessment, to be highly uncertain, with little to suggest that time in the CDF would resolve the uncertainties. It is plausible that a managed access agreement could be designed to reduce uncertainty about long-term survival estimates, but this has not been proposed and may not achieve a great deal with regard to the overall uncertainty.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	No	Trial complete, evidence package is mature
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	Low	As there is no proposal, this has not been investigated in detail

Are there any other substantive issues (excluding price) that are a barrier to a MAA?	Not applicable	As there is no proposal, this has not been investigated in detail

Key questions for committee if Managed Access is considered	
1	
2	
3	
4	
5	
6	

Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	
2	
3	
4	
5	
6	