This briefing presents the key issues arising from the manufacturer’s submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to:
- provide information on the protocols, randomisation and blinding used in the main trial
- provide information on the survival and health-related quality of life of a subgroup identified within a trial of azacitidine which was excluded from the submission
- provide information on any additional trials
- provide or confirm values for a number of variables within the economic model
- clarify and justify the methods used to calculate and model overall survival
- clarify assumptions within the model, including those related to the transition to acute myeloid leukaemia (AML), time spent in AML and health-related quality of life associated with treatment
- clarify the source for utility estimates used in the mapping exercise
- discount costs
- correct discrepancies between the text in the submission and the Excel model
- return full functionality to the economic model
- provide a more detailed reference list
Licensed indication
As described in the summary of product characteristics (SPC), azacitidine (Vidaza, Celgene Europe) is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

- intermediate-2 and high-risk myelodysplastic syndrome (MDS) according to the International Prognostic Scoring System (IPSS)
- chronic myelomonocytic leukaemia (CMML) with 10–29% marrow blasts without myeloproliferative disorder
- acute myeloid leukaemia (AML) with 20–30% blasts and multilineage dyplasia, according to the World Health Organization classification.

Key issues for consideration

Clinical effectiveness
- What is the Committee view of the standard approaches to treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia?
- What is the Committee’s view of the validity of the results of the main trial for azacitidine, given:
  - the possible bias introduced by lack of blinding and,
  - the imbalance between the treatment arms in loss to follow-up?
- What is the Committee’s view of the comparison between azacitidine and the use of different conventional care regimens in pre-selected patient subgroups?

Cost effectiveness
- What is the Committee’s view of the use of EQ–5D scores derived from patients with lower-risk myelodysplastic syndrome than those patients for which this treatment is indicated?
• What is the Committee’s view of the face validity of the cost-effectiveness analysis, in particular:
  – the curves used to fit survival
  – the calculation of mortality in acute myeloid leukaemia/myelodysplastic syndrome
  – the exclusion of age-related mortality
  – the characterisation of uncertainty
• What does the Committee consider to be the relevant comparators for patients eligible for low-dose chemotherapy? Should best supportive care (BSC) be included?
• What does the Committee consider to be the relevant comparators for patients eligible for high-dose chemotherapy? Should BSC and low-dose chemotherapy be included?
1 Decision problem

1.1 Decision problem approach in the manufacturer’s submission

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult patients who are not eligible for haematopoietic stem cell transplantation with:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>• intermediate-2 and high-risk MDS according to the IPSS</td>
</tr>
<tr>
<td></td>
<td>• CMML with 10–29% marrow blasts without myeloproliferative disorder</td>
</tr>
<tr>
<td></td>
<td>• AML with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Azacitidine</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Comparators</th>
<th>The comparators considered in this application are:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• BSC alone</td>
</tr>
<tr>
<td></td>
<td>• BSC and low-dose chemotherapy</td>
</tr>
<tr>
<td></td>
<td>• BSC and standard chemotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>The outcome measures to be considered include:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• overall survival</td>
</tr>
<tr>
<td></td>
<td>• progression-free survival</td>
</tr>
<tr>
<td></td>
<td>• response rates</td>
</tr>
<tr>
<td></td>
<td>• time to transformation to AML</td>
</tr>
<tr>
<td></td>
<td>• adverse effects of treatment</td>
</tr>
<tr>
<td></td>
<td>• health-related quality of life</td>
</tr>
</tbody>
</table>

| Economic evaluation | A Markov cohort-based economic model will be used to assess the cost-effectiveness of azacitidine compared with three conventional care regimens in the treatment of MDS: |
|                     | • BSC                                             |
|                     | • low-dose chemotherapy                            |
|                     | • standard-dose chemotherapy                        |
|                     | Cost effectiveness will be expressed in terms of incremental cost per QALY. Costs will be considered from an NHS and personal social services perspective. The time horizon will be the lifetime of a patient owing to the chronic nature of the condition. |
|                     | Consideration will be given to the subgroup of patients with chromosome 7 abnormalities to the extent that the data permit. |

MDS, myelodysplastic syndrome; IPSS, International Prognostic Scoring System (type of classification system for MDS); CMML, chronic myelomonocytic leukaemia; AML, acute myeloid leukaemia; BSC, best supportive care.
1.2 Evidence Review Group comments

1.2.1 Population
The ERG considers the population in the MS to be consistent with the scope, both of which are consistent with the marketing authorisation.

1.2.2 Intervention
The ERG considers the intervention to be consistent with the scope. The marketing authorisation indicates the dosage and route of azacitidine to be 75 mg/m² subcutaneously daily for 7 days followed by a rest period of 21 days (28-day treatment cycle). The SPC recommends that patients be treated for a minimum of six cycles, continuing for as long as the patient continues to benefit or until disease progression.

1.2.3 Comparators
The ERG considers the comparators in the MS to be consistent with the scope. Treatment with azacitidine is compared with treatment with conventional care regimens, which comprise BSC alone (including transfusions, antibiotics and growth factors), or in combination with either low-dose chemotherapy (cytarabine) or standard-dose chemotherapy (cytarabine plus daunorubicin [or idarubicin or mitoxantrone]).

1.2.4 Outcomes
The ERG considers the outcomes in the MS to be consistent with the scope.

1.2.5 Timeframe
The ERG considers the timeframe adopted to be consistent with the scope, with attempts in the economic model to extrapolate to a lifetime time horizon.

1.2.6 Subgroups
The ERG notes that the MS considers the main genetic subgroup identified, chromosome 7 abnormalities (especially -7/del(7q)), as a subgroup in the
evidence of clinical effectiveness. The MS does not consider this subgroup in
the cost-effectiveness analysis.

1.3 Statements from professional/patient groups and nominated experts

Patient and professional groups noted that the average age at diagnosis is
approximately 70–75 years, and that prognosis is poor. Although there is
considerable variation within subgroups of patients, expected survival without
treatment ranges from less than 6 months for patients with IPSS high-risk
MDS to approximately 12–18 months for patients with IPSS intermediate-2
and CMML-2 (defined according to the WHO classification scale as 5% to
19% blasts in the peripheral blood and 10% to 19% marrow blasts).

Patient and professional groups confirmed that supportive care is the
treatment for most patients, and usually comprises transfusions (platelet
and/or red cell) and erythropoietin. Professional groups confirmed that low-
intensity therapy is offered less often than supportive care. Low-intensity
therapy often includes the use of low-dose chemotherapy or biological
response modifiers. High-intensity therapy is generally restricted to younger
and fitter people and includes intensive induction chemotherapy and
sometimes haematopoietic stem cell transplantation.

Professional groups noted that draft European LeukemiaNet guidelines
recommend azacitidine in:

- patients with intermediate-2 or high IPSS risk disease who are not
  eligible for chemotherapy regimens used in AML and

- fit patients with intermediate-2 or high IPSS risk and poor risk
cytogenetics (associated with a high risk of progression) for whom
there is no stem cell donor.
2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer’s submission

The key evidence in the manufacturer's submission (MS) comes from one open-label randomised controlled trial (RCT) of azacitidine, referred to in the MS and hereafter as AZA-001. AZA-001 compared treatment with azacitidine in 358 patients with higher-risk MDS, CMML and AML (20–30% blasts) with treatment with conventional care regimens. Azacitidine was given as a subcutaneous injection at a dosage of 75 mg/m² per day on days 1–7 of a 28-day cycle. Conventional care regimens consisted of best supportive care (BSC) alone (including transfusions, antibiotics and growth factors), or with the addition of either low-dose chemotherapy (initial dose of cytarabine 20 mg/m² per day for 14 days, repeated every 28 days for at least four cycles) or standard-dose chemotherapy (induction with 100 mg/m² per day of cytarabine for 7 days plus 3 days of 45–60 mg/m² per day daunorubicin [or 9–12 mg/m² per day of idarubicin or 8–12 mg/m² per day of mitoxantrone] followed by a maximum of two consolidation cycles; also referred to as ‘intensive chemotherapy’ in the MS). Treatment with azacitidine was given until relapse, unacceptable toxicity or disease progression.

Before randomisation, patients were pre-selected by the investigators for treatment with one of the conventional care regimens based on their age, Eastern Cooperative Oncology Group (ECOG) performance status and the presence of comorbidities. The patients treated with azacitidine were stratified according to their pre-randomisation arm. Comparison was made between those receiving a particular conventional care regimen and those pre-selected for the same respective group, but randomised to azacitidine. The MS reports that patients randomised to either azacitidine or one of the conventional care regimens were comparable in terms of age, baseline severity of MDS, ECOG performance status and time since original diagnosis. Randomisation and
subsequent analyses were stratified according to the French–American–British classification (FAB) subtype and IPSS group. Of the 179 patients receiving a conventional care regimen, 105 were pre-selected for BSC alone, 49 for low-dose chemotherapy and 25 for standard-dose chemotherapy.

The primary endpoint in the RCT was overall survival, defined as time from randomisation to death from any cause. Secondary endpoints included: time to transformation to AML; haematological response; independence from red blood cell transfusions for 56 consecutive days or more; number of infections needing intravenous antibiotics; and the occurrence of adverse events. The primary intention-to-treat analysis of overall survival used the stratified Cox proportional hazards model with covariate adjustments to estimate the hazard ratio. The final Cox proportional hazards model included ECOG performance status, lactate dehydrogenase, haemoglobin, number of previous red blood cell transfusions and the presence or absence of chromosome 7 abnormalities as parameters. Time-to-event curves were estimated with the Kaplan–Meier method. A complete description of the trial and its analyses is given in section 6.3 of the MS.

The literature review conducted by the manufacturer identified another RCT of azacitidine, CALGB 9221. The manufacturer excluded the results of this trial from the submission because the study sample did not have at least 50% of patients with higher-risk MDS.

The MS reports the results of seven phase III trials of comparator therapies, which include BSC, low-dose chemotherapy and standard-dose chemotherapy. No meta-analyses were carried out on the survival results of these trials. Median overall survival and time to transformation to AML are reported for individual treatment arms in the various studies and are subsequently compared with the results for the comparable treatment groups (BSC, low-dose chemotherapy, standard-dose chemotherapy) in the AZA-001
trial. The results are presented in sections 6.6.1 and 6.6.2 of the MS. These results did not inform the economic model.

2.1.1 Results

The MS reports results for the total intention-to-treat (ITT) population. The MS states the median overall survival was 24.5 months with azacitidine compared with 15.0 months for participants receiving conventional care regimens (p = 0.0001, hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.43 to 0.77; see figure 1). The median time to transformation to AML was 17.8 months (interquartile range [IQR] 8.6 to 36.8, 95% CI 13.6 to 23.6) with azacitidine, compared with 11.5 months (IQR 4.9 to not reached, 95% CI 8.3 to14.5) with conventional care regimens (p < 0.0001; HR 0.50, 95% CI 0.35 to 0.70). The MS states that of the participants who were dependent on red blood cell transfusions at baseline, 45% of those on azacitidine became transfusion-independent during treatment, compared with 11.8% in the group receiving conventional care regimens (p < 0.0001).

Figure 1. Overall survival

![Figure 1. Overall survival](image)

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Azacitidine</th>
<th>Conventional care regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>179</td>
<td>132 130 66 52 30 10 1 0</td>
<td>132 95 66 32 14 5 0 0</td>
</tr>
</tbody>
</table>
The MS reports in that in participants with the -7/del(7q) chromosomal abnormality, median Kaplan–Meier overall survival was 13.1 months (IQR 3.9 to 24.5, 95% CI 9.9 to 24.5) in the 30 people on azacitidine, compared with 4.6 months (IQR 2.9 to 9.3, 95% CI 3.5 to 6.7) for the 27 receiving conventional care regimens, giving a hazard ratio of 0.34 (95% CI 0.17 to 0.67, p = 0.0017).

The MS also reports results according to pre-selected treatment group. These results are summarised in table 1, which is adapted from table 6.7 of the MS.

**Table 1. Comparison of overall survival and time to transformation to acute myeloid leukaemia (AML) according to investigator pre-selection in the AZA-001 trial**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Azacitidine (n = 117)</th>
<th>BSC (n = 105)</th>
<th>HR; p value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (months)</td>
<td>21·1 (10·5–NR)</td>
<td>11·5 (5·7–NR)</td>
<td>0·58; 0.0045 (0·40–0·85)</td>
</tr>
<tr>
<td>Time to transformation to AML</td>
<td>15·0 (8·8–27·6)</td>
<td>10·1 (3·9–19·8)</td>
<td>0·41; &lt;0.0001 (0·27–0·63)</td>
</tr>
</tbody>
</table>

**LOW-DOSE CHEMOTHERAPY (n = 94)**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Azacitidine (n = 45)</th>
<th>LDC (n = 49)</th>
<th>HR; p value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (months)</td>
<td>24·5 (8·4–34·7)</td>
<td>15·3 (4·9–25·8)</td>
<td>0·36; 0.0006 (0·20–0·65)</td>
</tr>
<tr>
<td>Time to transformation to AML (months)</td>
<td>15·0 (7·3–25·5)</td>
<td>14·5 (4·9–19·2)</td>
<td>0·55; 0.097 (0·28–1·11)</td>
</tr>
</tbody>
</table>

**STANDARD-DOSE CHEMOTHERAPY (n = 42)**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Azacitidine (n = 17)</th>
<th>SDC (n = 25)</th>
<th>HR; p value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (months)</td>
<td>25·1 (10·0–NR)</td>
<td>15·7 (8·2–24·1)</td>
<td>0·76; 0.51 (0·33–1·74)</td>
</tr>
<tr>
<td>Time to transformation to AML</td>
<td>23·1 (6·4–25·4)</td>
<td>10·7 (4·6–15·4)</td>
<td>0·48; 0.19 (0·16–1·45)</td>
</tr>
</tbody>
</table>

Data are median (interquartile range); hazard ratios (HRs) calculated with stratified Cox proportional hazards model adjusted for treatment, subgroup, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase, haemoglobin, number of previous red blood cell transfusions, and presence or absence of –7/del(7q) chromosomal abnormality.

No subgroup-by-treatment interactions were significant (p > 0.20)

AML, acute myeloid leukaemia; BSC, best supportive care; HR, hazard ratio; LDC, low-dose chemotherapy; NR, not reached; SDC, standard-dose chemotherapy.

The MS states that no subgroup-by-treatment interactions were significant.

The MS reports that the response rates for participants treated with azacitidine were low (any remission 29%, p = 0.0001), but were higher than for patients in the group receiving conventional care regimens (any remission...
12\%, p = 0.0001). Further results on response rates, both for the total population and according to pre-selected treatment group, are listed in table 6.8 on page 51 of the MS.

The manufacturer reports that the most common grade 3 or 4 adverse events observed for all treatments in the trial were peripheral blood cytopenias. The most common non-haematological adverse events related to treatment were infection site reactions with azacitidine, and nausea, vomiting, fatigue and diarrhoea with azacitidine, low-dose chemotherapy and standard-dose chemotherapy. For further information on adverse events observed in the trial, see table 6.9 on page 53 of the MS.

### 2.2 Evidence Review Group comments

The ERG reported that despite minor problems, the literature search appeared generally comprehensive. No additional studies were identified by the ERG.

The ERG reported that the inclusion and exclusion criteria for study selection were clearly stated and consistent with the decision problem. It noted that no detailed list of the excluded studies was provided. The ERG reported that there was no structured assessment of validity, and that this was particularly true for the comparator section.

The ERG reported that for the trials identified to establish comparator effectiveness, data for the treatment arms of the trials were included in isolation, effectively breaking randomisation. The ERG noted that these data did not contribute to the overall conclusions, as they did not inform the economic model.

The ERG considered it appropriate for the submission to be based mainly on the result from the AZA-001 trial. It stated that the evidence from AZA-001 is reasonably robust, but expressed three main concerns:
• The ERG noted that the study was open to bias from lack of complete blinding (see response to 8 April clarification question A5). It acknowledged that complete blinding was made impossible by the nature of the condition and its treatment, but reported that caution is required in the interpretation of trial results, because the measured size of the effect of azacitidine treatment could be overestimated for outcomes with subjective elements such as haematological response.

• The ERG noted that bias might have been introduced by an imbalance in the loss to follow-up between arms of the trial (see ‘number at risk’, figure 1). The manufacturer’s response to a clarification request indicated that there was [redacted]; the ERG considered that reasons for this, such as [redacted] might be associated with higher death rates. The ERG considered that if these participants were included in the number at risk, there might have been a reduction in the stated effect of azacitidine. The ERG also reported that participants were censored at the time of their last bone marrow assessment, and that there was [redacted] performed in the azacitidine group and the group receiving conventional care regimens, indicating a risk of bias associated with the estimate of time to progression (TTP).

• The ERG considered that the evidence of effect in the different groups pre-selected by the investigators was unreliable because of the small size of some of the groups, the imbalance in the baseline characteristics and the lack of a statistically significant difference between the groups. For more information on the ERG’s analysis of the validity of the clinical effectiveness evidence, see appendix 2 of the ERG report.

The ERG noted that in the overall survival curves presented in figure 6.5 of the MS, the azacitidine curve is below that for conventional care regimens for the first few months, only crossing over to indicate improved survival for those receiving azacitidine after 4 months. They also noted that statistically
significant superiority for azacitidine versus standard-dose chemotherapy was not established (95% CI for HR 0.33 to 1.74).

### 2.3 Statements from professional/patient groups and nominated experts

Patient experts report that myelodysplastic syndrome (MDS) causes significant fatigue and difficulty with daily activities. Clinical experts report that because of the poor prognosis of most people with MDS and the limitations of existing therapies, a large number receive best supportive care (BSC) only, which is primarily based on red blood cell transfusions. The professional groups considered that conventional care regimens offered in the AZA-001 trial reflect current treatments in the NHS. Patients are managed by haematologists and most are cared for in district hospitals.

Clinical experts report that treatment with azacitidine provides clinical advantages, including being independent of transfusion and an increased time to transformation to acute myeloid leukaemia (AML). Patients report the benefits associated with relief from fatigue, decreased hospitalisations because of infections, decreased need for blood and platelet transfusion, and increased ability to perform normal activities of daily living. Both patients and professionals note that this latter benefit is very important to patients and their families, and that azacitidine meets an unmet need.

Patient and clinical experts both consider the adverse events associated with azacitidine treatment to be well tolerated. Myelosuppression is the most common adverse event, but patients note that this is also a characteristic of the disease itself. Grade 3 or 4 cytopenias are common, but patients note that these are also experienced with chemotherapy. Nausea, vomiting and injection site reaction are considered to be easily managed.

Clinical experts indicate that azacitidine would be administered at haematology clinics on an outpatient basis, and that no additional training or
equipment would be needed. They note that if treatment protocols are followed, aseptic pharmacies would be needed to prepare the drug at weekends, because the drug has a life-span of only about 6 hours once reconstituted. They indicate that at present this facility is not readily available at many UK centres. Clinical experts report that alternative dosing schedules appear equally efficacious, but are currently outside the licence.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer’s submission

The manufacturer reported that a systematic search was undertaken, but no studies were identified that matched the decision problem. The manufacturer submitted a de novo economic model that reflects the main therapeutic options for treatment of higher-risk MDS patients (IPSS risk categories intermediate-2 or high), comparing azacitidine with BSC, low-dose chemotherapy (plus BSC), and standard-dose chemotherapy (plus BSC).

3.1.1 Model structure

The MS presents a two-arm health-state transition model. The first arm is designed to capture the costs and outcomes associated with treatment with azacitidine; the second arm is designed to capture the costs and outcomes associated with treatment with conventional care regimens, which include BSC alone, low-dose chemotherapy (and BSC), and standard-dose chemotherapy (and BSC), as defined in the AZA-001 trial. The MS reports that the proportion of patients modelled to receive each of the conventional care regimens reflects those observed in AZA-001. The model is divided into three states. A schematic diagram of the model is presented in figure 7.1 on page 75 of the MS and in figure 2 below.
All modelled patients enter the model in the MDS health state at the start of treatment and leave the model at death, irrespective of the treatment regimen. Patients on active therapy enter the model at the first dose. Patients on BSC alone are assumed to enter the model at the same time as they would have entered the model if they had been randomised to one of the active therapy arms. The median time in AML is assumed to be the same for all patients, regardless of the treatment arm from which they progressed. However, the mean time in AML may differ depending on the treatment received. Once they progress to the AML health state, all patients receive BSC, regardless of the previous treatment arm. Some patients are assumed to die without progressing the AML.

The MS reports that patients are assumed to have been treated with other appropriate medications before entering the model. They are assumed to receive treatment for MDS until the end of the treatment period, as observed in the clinical trial, after which they receive BSC until disease progression and then treatment for AML until death.
The MS states that the model uses a 35-day cycle, based on the median cycle length of 36.1 days observed in the AZA-001 trial. Patients treated with azacitidine receive 7 days of treatment per cycle. A lifetime horizon was adopted for the base-case analysis. Alternative timeframes are explored in sensitivity analyses.

Outcomes for costs include those relating to drugs and other medications, monitoring, routine follow-up and management of adverse events. No wastage is assumed with the use of chemotherapy; but wastage is included in the costs of treatment with azacitidine. Health effects are expressed in terms of life years and quality-adjusted life years (QALYs). The model outcomes are expressed in terms of cost per life year and per QALY gained.

The MS reports that an annual discount rate of 3.5% was used for costs and for health benefits. The perspective of the economic evaluation is that of the NHS and personal social services in England and Wales. For further description of the model, see pages 69–80 of the MS.

3.1.2 Model inputs: effectiveness

The MS reports that clinical effectiveness was entered into the model via survival curves calculated from estimates of overall survival from the AZA-001 trial. The survival curves were built by using the maximum-likelihood estimate-generating parameter estimates in STATA to construct a log-logistic fit to the data. The use of a Weibull function is explored in sensitivity analysis. The MS states that preliminary results for patients treated with azacitidine from follow-up of the AZA-001 extension study for further information on the curve fitting, see appendix 4 of the MS.

The manufacturer notes that modelled median survival times are different from the trial medians. The manufacturer states that this was caused by the
number of censored data points around the median survival in the observed data and in the tail of the survival curve. These are reported to be the main influences on the shape of the survival curve.

The MS reports that the model calculates the pooled time in AML across all treatment arms in the AZA-001 trial. This figure is then subtracted from the survival curves to produce the time to progression to AML. This results in a pooled median time spent in AML across all treatments of 3.65 cycles. The manufacturer states that clinical advice suggests there is no difference between treatment arms in the time spent in AML.

The MS states that the rate of adverse events while on treatment is time dependent and based on data from the AZA-001 trial. Once off treatment, patients assume an annualised rate of adverse events for BSC. The manufacturer reports that this estimate is subject to a great degree of uncertainty, and is therefore explored in sensitivity analyses. For further information on effectiveness input, see pages 80–90 of the MS.

3.1.3 Model inputs: utilities

The manufacturer reports that no usable utility data were collected in the AZA-001 trial. The MS reports that data were acquired from the CALGB 9221 trial (previously excluded from the review of clinical effectiveness), in which patients with MDS were treated with either azacitidine or BSC and in which European Organisation for Research and Treatment of Cancer (EORTC) scores were collected. In a separate publication by Sekeres et al., SF–12 scores were reported for patients receiving low-dose and standard-dose chemotherapy. The MS presents a mapping exercise using published algorithms to derive EQ–5D values from the EORTC and SF–12 scores. The manufacturer notes that patients in the CALGB 9221 trial were slightly younger and healthier at baseline than those in the AZA-001 trial. The MS therefore reports a sensitivity analysis that adjusts the utility scores downwards from the CALGB 9221 results, mapping to reflect the reduced
health status of patients in the AZA-001 trial. For further description of the utility mapping exercise, see appendix 5 of the MS.

Based on the utility data from the CALGB 9221 trial, the manufacturer states that patients treated with azacitidine have a better quality of life than those receiving BSC, and this difference increases with the length of treatment. The utility scores seen at 182 days are assumed to remain constant for the remainder of the patient’s time in the MDS health state.

There are no reported utility values for patients with AML. The MS assumes that the AML utility value is the same as that of patients with MDS at baseline (0.67). The effect of varying the AML utility score is examined in a sensitivity analysis.

Disutility associated with adverse events is not included in the cost-effectiveness model. The manufacturer states that the mapped utility data are based on longitudinal recordings and will likely include utility decrements for patients experiencing adverse events. For further information on utility inputs, see pages 93–95 of the MS.

3.1.4 Model inputs: costs

The MS states that costs are applied on a per-cycle rate, and include: routine follow-up appointments; laboratory and monitoring tests; administration of BSC, chemotherapy and azacitidine; and medication, which itself includes premedication, treatment, and concurrent medication. A summary of the per-cycle costs are presented in table 7.14 of the MS.

The manufacturer reports that when possible, health care resource use was determined from AZA-001 protocol regimens. When data were not available from the clinical trial, estimates of resource use were based on expert opinion elicited though a resource use questionnaire (see appendices 7 and 8 of the MS).
Drug costs were taken from the ‘British national formulary’ (BNF). NHS costs were taken from the NHS Reference Costs 2006–07 and indexed to 2008 prices using the 2008 pay and price index from the Personal Social Services Research Unit (PSSRU). The cost of treatment using the NHS 2009–10 tariff is presented as a sensitivity analysis. Azacitidine costs £321 per 100-mg vial.

The MS reports that additional infrastructure is required for drug administration. Azacitidine requires a 7-day continuous treatment cycle, which means that patients will need treatment over a weekend. It is assumed in the model that no additional costs will be incurred above the cost of normal administration. For further description of cost inputs, see pages 96–105 of the MS.

3.1.5 Results

A summary of the base-case cost-effectiveness results is presented in table 2 below. Only the revised results submitted in the manufacturer’s final response to the 29 May 2009 clarification queries are presented.

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Costs incurred</th>
<th>QALYs gained</th>
<th>Marginal costs</th>
<th>Marginal QALYs gained</th>
<th>Cost per QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE-SELECTED FOR BSC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azacitidine</td>
<td>£122 035</td>
<td>3.00</td>
<td>£83 677</td>
<td>1.64</td>
<td>£51 139</td>
</tr>
<tr>
<td>BSC</td>
<td>£38 358</td>
<td>1.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE-SELECTED FOR LOW-DOSE CHEMOTHERAPY</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Azacitidine</td>
<td>£126 061</td>
<td>3.12</td>
<td>£73 826</td>
<td>1.56</td>
<td>£47 178</td>
</tr>
<tr>
<td>LDC</td>
<td>£52 235</td>
<td>1.55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE-SELECTED FOR STANDARD-DOSE CHEMOTHERAPY</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Azacitidine</td>
<td>£113 216</td>
<td>2.56</td>
<td>£48 328</td>
<td>1.41</td>
<td>£34 207</td>
</tr>
<tr>
<td>SDC</td>
<td>£64 888</td>
<td>1.15</td>
<td></td>
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</tr>
</tbody>
</table>

BSC, best supportive care; LDC, low-dose chemotherapy; SDC, standard-dose chemotherapy
For a detailed breakdown of the results, see table 7.18 on page 15 of the response to 29 May 2009 clarification request.

In response to a clarification request by the ERG, the manufacturer estimated that the incremental cost-effectiveness ratio (ICER) for azacitidine compared with conventional care regimens was £47,945. For further information, see page 18 of the response to 29 May 2009 clarification request.

Uncertainty was explored in one-way sensitivity and probabilistic sensitivity analysis (PSA). One-way sensitivity was performed by applying the upper and lower boundary given by the distribution around each parameter. For the PSA, values were sampled from the uncertainty distributions. When there were no estimates of parameter uncertainty, intervals of plus or minus 30% were assumed. Analyses were presented exploring the following parameters: the choice of parametric curve for extrapolation of overall survival estimates; azacitidine having a disease-modifying effect; the modeling of adverse events; the modelled time horizon; the utility value assigned to AML; longitudinal utility scores; adjusted azacitidine and BSC utility values from the CALGB 9221 trial; updated reference costs; and [redacted]. The tornado diagrams for each treatment group are shown below (figure 3), as presented on pages 22 and 23 of the response to the 29 May 2009 request for clarification.
Figure 3. Tornado diagrams for the one-way sensitivity analysis

**Azacitidine vs BSC**
- Comparator OS curve fit
- BSC utility
- Azacitidine Utility
- Azacitidine on treatment cost
- Azacitidine OS curve fit
- Azacitidine off treatment cost
- BSC cost
- Azacitidine acquisition cost
- AE treatment cost
- Progression to AML median time
- Treatment period curve fits

**Azacitidine vs LDC**
- Comparator OS curve fit
- Azacitidine on treatment cost
- Azacitidine Utility
- Azacitidine off treatment cost
- Azacitidine OS curve fit
- LDC utility
- LDC on treatment cost
- LDC off treatment cost
- Azacitidine acquisition cost
- AE treatment cost
- Progression to AML median time
- Treatment period curve fits
The manufacturer reports that for patients pre-selected for BSC, treatment with azacitidine has less than a 10% probability of being cost effective at £30,000 per QALY gained. In patients pre-selected for treatment with low-dose chemotherapy, treatment with azacitidine has less than a 20% chance of being cost effective, and in patients pre-selected for treatment with standard-dose chemotherapy, a 60% chance of being similarly cost effective.

For further information, see pages 19–30 of the response to 29 May 2009 request for clarification.

### 3.2 Evidence Review Group comments

The ERG states that although the search strategy for the literature review suggests that some studies might have been missed, its search identified no additional studies. The ERG reports that an RCT of azacitidine (CALB 9221) was appropriately excluded from the analysis of clinical effectiveness because of differences in the patient characteristics. However, the ERG expressed concern that because the CALB 9221 trial is one of the few sources of data on health-related quality of life, it is repeatedly treated as though it were included when discussing the impact of azacitidine on health-related quality of life. The ERG notes that patients in the CALGB 9221 trial had lower-risk MDS and that the effects on health-related quality of life were likely to be different and less
severe than those experienced by patients with higher-risk MDS who are the population of interest in this appraisal.

The ERG reported major flaws with the economic model, including coding errors, the non-provision of critical information and the removal of complete functionality from the model. For a full list of errors identified, see the 29 May 2009 clarification letter. The ERG reports that because of these errors, the model is not fully executable and presents results which cannot be independently validated at this time.

The ERG noted these concerns were reinforced by issues with the face validity of the results of the model relative to the results of the main source of evidence on clinical effectiveness. For example, the AZA-001 trial (with a median follow-up of 21.1 months) suggests an increase in median overall survival of 9.5 months with azacitidine. However, the model predicts an increase in mean survival of 32–34 months, which is considerably different from the observed difference, notwithstanding that one figure is a median and the other a mean. The ERG considers that this discrepancy may arise because the model is incorporating the survival data inappropriately.

As a result, the ERG concludes that no weight can be placed on the ICERs provided in the current submission.

3.3 Further considerations following premeeting briefing teleconference

3.3.1 Addendum to ERG report based on response to the clarification request on 29 May 2009

In response to the clarification letter of 29 May 2009, the manufacturer provided both a text submission and a revised executable model addressing the issues raised by the ERG concerning the model. The comments are summarised below.
The ERG noted that the manufacturer’s base-case analysis employed the log-logistic parametric function to extrapolate the survival data from the AZA-001 trial. In a sensitivity analysis, the Weibull parametric function was alternatively explored.

When the log-logistic distributions were extrapolated over the 271-cycle (25–year) time horizon of the economic model, the ERG noted that azacitidine generates survival benefit beyond that which might be expected for patients with this severity of disease. For example, 4–5% of patients are modelled to survive into their tenth decade.

The ERG considered that clinical opinion might consider that Weibull extrapolation would produce more clinically consistent results. This was because this azacitidine-dependent improvement is not observed when Weibull distributions are fitted.

In addition, the ERG explored the use of exponential, Gompertz and log-normal distributions to extrapolate the overall survival data. The results of this exploratory analysis are presented on page 7 of the ERG addendum. They report that according to the Akaike’s information criteria (which assess the goodness of fit of curves), the exponential fit was superior in three of the six pre-selected subgroups (BSC, low-dose chemotherapy, standard-dose chemotherapy, BSC plus azacitidine, low-dose chemotherapy plus azacitidine, standard-dose chemotherapy plus azacitidine), further indicating that the use of the log-logistic function in the base case is inappropriate.

The ERG noted that the model assumed a median value of 3.65 cycles for time to progression (TTP) in the AML state. This value was back-calculated from the median observed overall survival (OS) (median TTP in AML equals median OS minus median time in AML). The ERG noted that this value did not
match the observed TTP in the publication of the AZA-001 trial\(^1\) (11.5 months) or the value reported in the MS (17.8 months). The manufacturer stated that this back-calculation was used because excessive censoring resulted in unreliable estimates of TTP. The ERG commented that reliable identification of patients who progressed and reliable estimates of their TTP are needed to calculate a reliable estimate of the median time in AML. The ERG considered that the back-calculation incorporates the problem associated with excessive censoring rather than remedying it. For further information on TTP, see pages 11, 12 and 19 of the ERG addendum.

The ERG further noted that the manufacturer’s modelled time in AML (median 3.65 cycles) used the log-logistic shape parameter for overall survival. The ERG conversely noted that on page 78 of the MS, a pooled mortality rate of 0.135 per cycle is described, which defines an exponential overall survival relationship with a median of 5.1 cycles. This is inconsistent with the log-logistic 3.65 cycle median that was used to model TTP. The ERG also reported that it was unable to replicate the median value of 3.65 cycles from the data in the model.

The ERG noted that in the model, overall mortality was calculated and the 0.135 per cycle figure was used to allocate this typically lower mortality to the AML state. However, when the calculated total overall mortality is lower than 0.135, MDS mortality is reduced to zero and the AML mortality is reduced to match the overall mortality data. The ERG noted that this occurs in the vast majority of cycles. They noted that this could result in an overestimate of survival. For further information on time in AML, see pages 9–12 and 19–20 in the ERG addendum.

The ERG noted several issues with the utility mapping exercise used to calculate the utilities in the model. The ERG reported that the algorithm used

in the mapping exercise is considered by its developers to be less reliable for predicting the utility values for patients in more-severe health states than alternatives suggested in appendix 5 of the MS. The ERG noted that this can lead to bias in the results. The ERG also reported that the algorithm was developed using data from patients with oesophageal cancer. The ERG noted that patients eligible for azacitidine are of a similar age to the patients on which the algorithm was based. However, the underlying conditions and comorbidities are potentially very different. The ERG stated that the results of the mapping algorithm should be treated with caution. For further information on the mapping exercise, see pages 22–25 of the ERG addendum.

The ERG noted that the utility for the AML state is assumed to be equal to the baseline utility for MDS (0.670), which may be considered high.

The ERG reported that the revised model includes no estimate of age-dependent mortality. They commented that given the age of the relevant patient population, it is reasonable to expect that the underlying mortality differs between patients (for example, between people aged 70 and those aged 90). The ERG reported that survival is therefore overestimated in the manufacturer’s model, particularly in older age groups.

The ERG reported that in the revised model, cost and outcome discount rates were calculated according to 'years' of either ten or eleven 35-day cycles. The ERG stated that a cycle-specific discount rate of 0.46% (3.5% x 35/365) would be more appropriate.

Characterisation of uncertainty
The ERG reported that the manufacturer failed to consider correlations among the utility estimates over time, and in doing so underestimated the level of associated uncertainty. The manufacturer assumed an approximately linear correlation between the parameters (for both the log-logistic and Weibull distributions) for the probabilistic sensitivity analysis of TTP in AML. The ERG reported that the survival analysis does not support this assumption, therefore
the model misrepresents uncertainty in this regard. The ERG stated that the manufacturer did not account for the heterogeneity in the approach to treatment of MDS, and in doing so may have overestimated the level of variation in cost estimates. For more information, see pages 28–32 of the ERG addendum.

**ERG exploratory analysis**

The ERG corrected the errors regarding discount rate and covariance. The results of the model incorporating these corrections are presented below in table 3, which is taken from page 38 of the addendum.

**Table 3. Summary of base-case cost-effectiveness results**

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Outcomes</th>
<th>Marginal differences</th>
<th>ICER (adjunct therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Costs (£)</td>
<td>QALYs</td>
<td>Costs (£)</td>
</tr>
<tr>
<td>Azacitidine BSC</td>
<td>120,007</td>
<td>2.90</td>
<td>81,694</td>
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<tr>
<td>BSC</td>
<td>38,313</td>
<td>1.33</td>
<td></td>
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<tr>
<td>Azacitidine LDC</td>
<td>123,491</td>
<td>3.01</td>
<td>72,414</td>
</tr>
<tr>
<td>LDC</td>
<td>51,077</td>
<td>1.52</td>
<td></td>
</tr>
<tr>
<td>Azacitidine SDC</td>
<td>110,472</td>
<td>2.47</td>
<td>46,503</td>
</tr>
<tr>
<td>SDC</td>
<td>63,968</td>
<td>1.12</td>
<td></td>
</tr>
</tbody>
</table>

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; low-dose chemotherapy; standard-dose chemotherapy.

As an indicative analysis, the ERG further considered the impact of incorporating age-specific mortality rates. The results of this are presented below in table 4, taken from page 54 of the addendum.
Table 4. Summary of cost-effectiveness results incorporating age-specific mortality rates

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Outcomes</th>
<th>Marginal differences</th>
<th>ICER (adjunct therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Costs (£)</td>
<td>QALYs</td>
<td>Costs (£)</td>
</tr>
<tr>
<td>Azacitidine BSC</td>
<td>112,932</td>
<td>2.65</td>
<td>76,036</td>
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<tr>
<td>BSC</td>
<td>36,887</td>
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<tr>
<td>Azacitidine LDC</td>
<td>115,497</td>
<td>2.72</td>
<td>66,516</td>
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<td>LDC</td>
<td>48,981</td>
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<tr>
<td>Azacitidine SDC</td>
<td>104,844</td>
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<tr>
<td>SDC</td>
<td>63,710</td>
<td>1.11</td>
<td></td>
</tr>
</tbody>
</table>

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; low-dose chemotherapy; standard-dose chemotherapy.

The ERG noted that the figures in table 4 are similar in magnitude to those provided in the revised manufacturer’s model (see section 3.1.5). The ERG noted that the models generated the most favourable ICER for standard-dose chemotherapy, but statistically significant superiority for azacitidine versus standard-dose chemotherapy was not established (see table 1).

The ERG reported that the results provided by the manufacturer do not necessarily correspond to the clinical question, in which the choice is probably between (in order of treatment intensity): BSC, BSC plus azacitidine, low-dose chemotherapy, low-dose chemotherapy plus azacitidine, standard-dose chemotherapy, standard-dose chemotherapy plus azacitidine. The ERG commented that although not all these options are available for all patients, more than two options are available to many. These options are not addressed within the model. The ERG presented a cost-effectiveness frontier (reproduced below in figure 4) to illustrate the results of such an incremental comparison.
For each value of the cost-effectiveness threshold, the top solid line identifies the outcome with the highest net benefit. The ERG reports that for patients for whom all six options are available, the most cost-effective option is BSC for all values of the threshold up to £51,135 per QALY. Above £51,135 per QALY, low-dose chemotherapy and azacitidine becomes the most cost-effective option. No standard-dose chemotherapy option is cost effective. At £30,000 per QALY, the model suggests a 100% chance that BSC is cost effective. For more information, see pages 39–41 and appendix 1e of the ERG addendum.

The ERG reported that given the time constraints, there were a number of issues which it was not able to explore. These are listed on page 37 of the addendum.

3.3.2 End-of-life criteria

In order to allow the Appraisal Committee to consider the applicability of the end-of-life criteria, the following section summarises the pertinent parameters:
• The marketing authorisation for azacitidine is for adult patients who are not eligible for haematopoietic stem cell transplantation with:
  - intermediate-2 and high-risk MDS, according to the IPSS
  - CMML with 10–29% marrow blasts without myeloproliferative disorder
  - AML with 20–30% blasts and multilineage dysplasia, according to the WHO classification

• Disease incidence is approximately 3.3 per 100,000 in England and Wales. In 2004, 1993 people in England were diagnosed with MDS; 38% of people with MDS in the UK are estimated to have higher-risk (IPSS intermediate-2 or high-risk) disease.

• For patients with IPSS intermediate-2 or high-risk disease, the median overall survival in the absence of treatment is 14.4 months and 4.8 months, respectively.

• The median overall survival in the pivotal trial of azacitidine (AZA-001) was 11.5 months (95% CI 5.7 to not reached) for those treated with BSC only, 15.3 months (95% CI 4.9 to 25.8) for those also treated with low-dose chemotherapy and 15.7 months (95% CI 8.2 to 24.1) for those also treated with standard-dose chemotherapy. The median overall survival observed in the AZA-001 trial for the comparable patient groups treated with azacitidine were 21.1 months (95% CI 10.5 to NR), 24.5 months (95% CI 8.4 to 34.7) and 25.1 months (95% CI 10.0 to not reached), respectively. These represent respective increases in median overall survival of 9.6 months, 9.4 months and 9.2 months.

• The mainstay of treatment for MDS is BSC (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, and low-dose standard chemotherapy for some patients. Stem cell
transplant is not an option for most patients because the patients’ age and/or comorbidities usually preclude this treatment option.

4 Authors

Whitney Miller and Prashanth Kandaswamy, with input from the Lead Team (Dr John Pounsford, Professor John Cairns and Mr Terence Lewis).
Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A  The evidence review group (ERG) report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration:


B  Submissions or statements from the following organisations

I  Manufacturer/sponsor

- Celgene Europe

II  Professional/specialist, patient/carer and other groups:

- Royal College of Physicians/National Cancer Research Institute/Royal College of Radiologists/Joint Collegiate Council for Oncology/Association of Cancer Physicians
- MDS UK Patient Support Group
- Rarer Cancers Forum
- The Leukaemia Society (UK)
- Royal College of Pathologists
- British Committee for Standards in Haematology

C  Additional references used: