in collaboration with:

Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality

Produced by Kleijnen Systematic Reviews Ltd in collaboration with Erasmus University Rotterdam and Maastricht University

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Date completed 12/03/2013

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 11/07/01 STA.

Declared competing interests of the authors
None.

Acknowledgements
The authors acknowledge the clinical advice and expert opinion provided by:
- Dr Dominic Culligan, Aberdeen Royal infirmary, Aberdeen, UK.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Riemsma R, Al M, Blommestein H, Deshpande S, Ryder S, Worthy G, Noake C, Armstrong N, Severens JL, Kleijnen J. Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality: a Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd, 2013.

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Abbreviations

AE	Adverse Events
ANC	Absolute Neutrophil Count
AML	Acute Myeloid Leukaemia
AIC	Akaike Information Criteria
bd/b.i.d	Twice Daily
BSC	Best supportive care
C	Chelation
CE	Cost Effectiveness
CEA	Cost effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CF	Chelation Failure
CI	Confidence Interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSR	Clinical Study Report
Del 5q	Deletion 5q
DFO	Desferroxamine
DVT	Deep Vein Thromboembolism
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EPO	Erythropoietin
ESA	Erythropoiesis Stimulating Agents
EUR	Erasmus University Rotterdam
FAB	French-American-British
FACT-An	Functional Assessment of Cancer Therapy-Anaemia
FACT-G	Functional Assessment of Cancer Therapy-General
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factors
HC	Hepatic Conditions
HR	Hazard ratio
HRQL	Health-related Quality of Life
HTA	Health Technology Assessment
IBS	Integrated Brier Score
IC	Indirect Comparison
ICER	Incremental Cost-effectiveness Ratio
IPSS	International Prognosis Scoring System
ITT	Intention to Treat
IWG	International Working Group
KSR	Kleijnen Systematic Reviews
LEN	Lenalidomide
LYS	Life Year Saved
MDS	Myelodysplastic Syndrome
mg	Milligram
mITT	Modified Intention to Treat
MS	Manufacturer’s Submission

MTC	Mixed Treatment Comparison
N/A	Not Applicable
NC	No Chelation
NCCN	National Comprehensive Cancer Network
NHS	National Health Services
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NOS	Not Otherwise Specified
NR	Not Reported
od	Once Daily
OR	Odds Ratio
ORR	Objective response rate
OS	Overall Survival
PAS	Patient Access Scheme
PCT	Primary Care Trust
PDGFR	Platelet-derived growth factor receptor
POC	Points of clarification
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
QALY(s)	Quality-adjusted Life Year(s)
RA	Refractory Anaemia
RAEB	RA With Excess Blasts
RARS	RA with ringed sideroblasts
RBCs	Red Blood Cells
RCT	Randomised Controlled Trial
RCMD	Refractory Cytopenias With Multilineage Dysplasia
RR	Relative Risk
SAE	Serious Adverse Events
SD	Standard Deviation
STA	Single Technology Appraisal
TD	Transfusion Dependent
TI	Transfusion Independent
TOI	Trial Outcome Index
TTO	Time trade-off
WBCs	White Blood Cells
WHO	World Health Organisation
WPSS	WHO Prognostic Scoring System

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1. SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

In the NICE scope the population was described as "adults with myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality and who are red blood cell transfusion dependent". The manufacturer has restricted the population to patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality. This is in line with the anticipated licence indication.

There were two specific intervention regimens included in the submission, namely:

- Lenalidomide 5mg on days 1 to 28 of a 28-day cycle
- Lenalidomide 10mg on days 1 to 21 of a 28-day cycle

The comparator was 'best supportive care including blood transfusions'. In the base case of the economic model best supportive care (BSC) is considered as per the NICE scope. This was defined as the provision of blood transfusions for transfusion dependent patients. No changes to BSC (in terms of transfusion frequency or iron chelation therapy) were assumed when cardiac conditions, diabetes, or hepatic conditions occur. It is unclear whether BSC as represented in the cost effectiveness analysis is similar enough to actual patient experience in England and Wales.

Most outcomes specified in the NICE scope have been included in the MDS-004 trial and have been reported in the MS. However, frequency of blood-transfusions (including blood-transfusion independence) was not reported in the MS. Serious infections were reported for grade 3 or 4 pneumonia only and health related quality of life was measured in the trial in the form of FACT-An scores. Serious infections and the FACT-An data were not used in the cost-effectiveness analysis.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The MS relies on one trial: MDS-004. MDS-004 is a three-arm study conducted throughout Europe, all patients had lower-risk MDS with del(5q) with or without additional cytogenetic abnormalities, and red blood cell (RBC) transfusion-dependent anaemia. A total of 205 patients were randomised to lenalidomide 10mg on days 1–21, lenalidomide 5mg on days 1–28, or placebo on days 1–28 for each four week cycle. Crossover was allowed at 16 weeks if at least a minor erythroid response was not achieved, and all but 11 patients on the placebo arm crossed over to lenalidomide 5mg. The primary endpoint was RBC transfusion independence for ≥26 weeks and was reached in 56.1%, 42.6%, and 5.9% of patients, respectively (compared with placebo, both $p < 0.001$). Cytogenetic response rates were 50% in the 10mg group and 25% in the 5mg group. Median duration of TI was not reached in either lenalidomide group after a median follow up of 1.55 years, and response was 48% of patients responding after one cycle and an additional 37% after two cycles. Of the patients who initially received placebo and crossed over to lenalidomide 5mg, 30.4% progressed to AML compared with 23.2% in the 5mg group and 21.7 in the 10mg group. Median overall

survival was not statistically significant between the groups and ranged between 35.5 and 44.5 months. The most common adverse events of lenalidomide for MDS with del(5q) were neutropenia and thrombocytopenia with 74% and 36%, respectively.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The two main problems with the clinical effectiveness data reported in the MS are:

1. The possibility of treatment switching after 16 weeks due to dose-limiting toxicities or lack of response, which means that most long term effectiveness data are unreliable.

   Given that 62.3% of patients in the lenalidomide 5mg group and 72.5% in the lenalidomide 10mg group experienced an AE leading to dose reduction or interruption, and one dose reduction in the 10mg group means patients receive effectively the same dose as the 5mg group, it seems there is some difficulty in distinguishing the treatment arms. In addition, patients in the placebo or lenalidomide 5mg groups without minor erythroid response by week 16 or those experiencing erythroid relapse could crossover to lenalidomide 5mg or 10mg, respectively. In the placebo group, only one out of 67 patients completed the 52 weeks double-blind phase. This means that the assessment of effects after 16 weeks is severely compromised.

2. Data were reported for two populations: the ITT and mITT population. The mITT population included patients with centrally confirmed low- or intermediate-1-risk MDS with del(5q) and documented RBC transfusion-dependence, who received ≥1 dose of study drug. The fact that confirmation of del(5q) status (karyotype analysis) and bone marrow morphology was performed by central haematological review after randomisation, means that patients not fulfilling the inclusion criteria are included in the ITT population. It is not clear how differences between these two populations influence results. However, data for the ITT population were used in the economic model as it "more closely matches the relevant NICE scope" (MS, section 7.2.1, page 96).

One of the main concerns for patients treated with lenalidomide is the incidence of increased clonal evolution and progression to AML.[1] Given the short follow-up time (16 weeks) and the subsequent possibility to cross-over from placebo to active drug, chances of detecting prolonged survival or acceleration of leukaemia progression are limited.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer developed a *de novo* model to assess the cost effectiveness of lenalidomide versus best supportive care. This model was a Markov state-transition cost-utility model implemented in Microsoft Excel which compared treatment with lenalidomide with BSC, in line with the decision problem.

The model consists of 14 health states. The main health states relate to transfusion status: Transfusion independent, Transfusion dependent without chelation, Transfusion dependent with chelation. Additional states were defined to reflect chelation failure and the potentially

resulting hepatic and diabetic complications, and cardiac complication due to transfusion. In addition, patients may develop acute myeloid leukaemia (AML). From all health states, patients are at risk to die. The outputs were expressed as cost per quality adjusted life year (QALY). The cycle length of the model was four weeks and the time horizon of the study was 20 years.

The proportion of patients in responding to treatment (i.e. become transfusion independent for at least 56 consecutive days) was derived from the MDS-004 trial, as was the duration of response, probability of developing AML and the mortality (except for AML mortality). All other transition probabilities were derived from literature. For the BSC group, the response rate was increased to reflect the impact of ESA use by 28% of patients in daily practice. In addition, it was assumed that non-responders would receive G-CSF.

Utilities applied to the health states were based on a study among UK MDS patients who evaluate three health states descriptions (relating to transfusion status) using a TTO.

Costs of lenalidomide were based on the dosing observed in trial, where patients might interrupt treatment due to adverse events, after which the dose would be adjusted downwards (initial dose: 10mg per day for 21 days per 28 day cycle; first reduction: 5mg per day 28 days per cycle; second reduction: 5mg per day every other day). In addition, monitoring costs, transfusion costs, chelation costs, costs of treating AML and costs of complications and adverse events were taken into account.

Costs and quality adjusted life years (QALYs) were discounted at 3.5%. The impact of parameter uncertainty was estimated in a deterministic and probabilistic sensitivity analysis. Scenario analyses were run on key parameters, especially relating to the utility values for the transfusion independent and transfusion dependent health state, ESA use in BSC and curve fitting for the response duration, progression to AML and overall mortality.

The base case ICER (cost per QALY gained) was £56,965 per QALY gained. The PSA results showed a 0% probability that the ICER is below £30,000 per QALY gained.

From the univariate sensitivity analysis and the scenario analyses, the manufacturer concluded that the key parameters which changed the ICER included utility values for the transfusion independent and transfusion dependent health state, the proportion of patients having dose interruptions, and the curve fitting for progression to AML and overall mortality. While the ICER appears robust for changes in the method of extrapolation of AML progression and overall mortality, this is not true for the incremental costs and incremental QALYs, these can change substantially. Finally, the scenario analysis on ESA use in BSC indicated clearly that the percentage of patients receiving ESA has no impact on the outcome.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic model described in the MS is considered by the ERG to meet the NICE reference cases to a reasonable extent and is in line with the decision problem specified in the scope.

The ERG assessment indicated that the model was generally well presented and reported. However, a few errors regarding the electronic model were identified that altered the results substantially. Additionally, the ERG did not agree with the manufacturer's decision not to apply a half cycle correction.

The input for the model was derived from MDS-004 trial data and literature. Some input values, such as those associated to transfusion related complication, were not based on a systematic search of the literature. However, a rapid review of the literature by the ERG did not reveal new relevant studies. In general, there was some uncertainty about the values that were used for utilities and cost parameters related to AML, complications and AE; however, sensitivity analysis showed that these parameters have little to no effect on the ICER.

The study on which utilities for the transfusion related health states were based does not conform to the NICE reference case, as valuation was done by MDS patients. The health state descriptions were very broad; so that the transfusion dependent description might already incorporate some of the adverse events associated with, for example, chelation therapy or complications such as cardiac disease, diabetes or hepatic complications. The ERG considers it likely that some double counting is included in the model by assigning the utility value of 0.65 (a value for completely transfusion dependent) to all patients not transfusion independent and use utility decrements on top of this.

The cost-effectiveness results were generally robust under the scenario analyses conducted. The ERG univariate sensitivity analysis and scenario analyses revealed that the ICER is quite sensitive to changes in the utility values applied to the transfusion independent and transfusion dependent health states, the response rate to lenalidomide and the percentage of patients having a second treatment interruption.

The response rate to lenalidomide was directly based on the observed response in the MDS-004 trial, and hence the uncertainty around that parameter may be regarded well quantified. The same is true for the percentage patients having a second treatment interruption, though it must be remembered that in the current model only the costs are directly impacted by treatment interruptions while the effects remain constant; in reality however, treatment interruptions will most likely also impact the effects. However, the uncertainty around the utilities is not limited to the statistical uncertainty that was explored in the univariate and probabilistic sensitivity analysis, as no good source for these utilities was identified. The study on which the utilities were based does not conform to the NICE reference case, and it was not fully clear what is being valued.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The MS provided sufficient detail for the ERG to appraise the searches. Additional searches of conference abstracts and other relevant resources such as Cinahl and the Science Citation Index were undertaken by the manufacturer for the clinical effectiveness, cost effectiveness and HRQL sections. The checking of references lists for the clinical effectiveness searches was also used in order to find additional studies not retrieved by the main searches, along with study reports provided by the manufacturer.

The clinical evidence relied on a direct comparison of lenalidomide with BSC in one good quality trial including 205 patients divided over three arms.

The HE model outcomes showed good consistency with trial outcomes, indicating good internal validity. In addition, the predicted life expectancy in the BSC appears plausible, indicating good external validity.

Extensive sensitivity analyses and scenario analyses were performed, showing the robustness of the results.

1.6.2 Weaknesses and areas of uncertainty

The ERG noted a number of errors in the search strategies regarding line combinations, which may have been consequential to the final recall of results. The ERG was unable to say whether these errors were due to poor reporting or mistakes made during the search process. The use of overly complex searches, where a more simple approach would have answered all points of interest, may also have led to papers being missed. This was of particular concern for both the adverse events and HRQL searches.

The possibility of treatment switching after 16 weeks due to dose-limiting toxicities or lack of response, means that most long term effectiveness data are unreliable.

A great weakness of the current study is the lack of high quality utility data. Given the sensitivity of the ICER to these estimates, this means that there is uncertainty about the correct estimate of the ICER.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG defined a new base case analysis. This new ERG base case included the following adjustments:

- Programming errors have been removed
- Half cycle correction has been included
- Costs of iron chelation therapy have been updated to include deferiperone
- The inclusion of deferiperone changes the proportion of patients receiving oral and IV chelation therapy
- Treatment costs of AML were according to the latest version of the azacitadine STA (£1,451 per 28 day cycle);

- Response distributed over time according to trial instead of all patients from cycle 1 onwards
- Costs of neutropenia (£1,045) and thrombocytopenia (£1,768) were changed
- Uncertainty added to the number of monitoring visits and uncertainty increased around cost estimates complications and adverse events

Combining these changes the ERG base case ICER amounted to £62,674 per QALY gained.

A large number of scenarios were defined by the ERG to explore how various assumptions about input values impact the ICER. These revealed that the ICER is sensitive to changes in the percentage of patients receiving IV chelation; however, the explored percentage of 100% is quite extreme, so this scenario serves as a worst case scenario. Additionally, the time until chelation is required also has a noticeable effect on the ICER, but this scenario was mainly explored due to ambiguity regarding the number of blood transfusions already given before entering the model. Also, an alternative utility assumption was explored, where the transfusion dependent health state is assigned a utility value based on a description as "reduced transfusion burden", and the ICER was also sensitive to this change.

From the various scenario analyses and sensitivity analyses it is clear that utilities and cost parameters related to AML, complications and AE have little to no effect on the ICER.

2. BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem.

The MS describes myelodysplastic syndrome (MDS) as a diverse group of haematological disorders in which the bone marrow functions abnormally causing peripheral blood cytopenia due to insufficient production of mature blood cells.[2, 3] MDS can affect blood elements such as red blood cells, white blood cells and platelets resulting in life threatening diseases, with anaemia, increase in bleeding, infection and disease transformation to acute myeloid leukaemia (AML).[2] MDS can affect patient's quality of life due to symptoms such as fatigue and dyspnoea, due to treatments involving hospitalisation with intravenous drug infusions and blood transfusions.[2]

MDS was formerly referred as pre leukaemia. However, about 30% of patients with MDS progress to acute leukaemia.[4] When the causes of MDS are unknown it is classified as primary MDS. Secondary MDS can develop after chemotherapy or radiation treatments for other diseases. The disorder is mainly caused due to cytogenetic abnormalities found in the bone marrow cells. The most common cytogenetic abnormality in MDS is deletion of chromosome 5q occurring in approximately 15% of patients.[5] Severity of MDS is graded using the International Prognostic Scoring System (IPSS) as either low-risk, intermediate-1-risk, intermediate-2-risk or high risk.[6]

Section 2.1 in manufacturer's submission provides data on median survival in years for patients with low-risk and intermediate-1-risk MDS: "*The low-risk and intermediate-1-risk groups together form approximately 70% of all MDS cases. Median survival with low-risk and intermediate-1-risk MDS is 5.7 years and 3.5 years respectively, and can be less than six months for patients with high-risk MDS.*"[7](MS, Section 2.1, page 16).

It is estimated that about 39% of MDS patients with low risk and about 50% with intermediate-1 risk are blood transfusion dependent.[8] The patients with blood transfusion dependent MDS have shorter survival and higher risk of progressing to AML as compared to the patients who are not blood transfusion dependent.

Section 2.2 in manufacturer's submission provides data on the overall incidence of MDS: "*The incidence of MDS is between two and 13 per 100,000 people*" (MS, Section 2.1, page 18).

According to the UK guidelines group for the diagnosis and therapy of adult myelodysplastic syndromes, the overall incidence of MDS is four per 100,000 people but rises to more than 30 cases per 100,000 people per year for patients over 70 years age.[6] The reference used in the manufacturer submission to support the data on incidence of MDS, is the same paper from the guidelines group.[6] Hence, the actual source based on which the manufacturer have reported the incidence of MDS between two and 13 per 100,000 people is not known. In the UK, there are approximately 11,200 diagnosed MDS patients.[9] In 2009, about 2,204 people were newly diagnosed with MDS in England.[2]

Overall, the evidence presented in this section of the submission is in line with the background information given in the final scope.[4] This is also consistent with the ERG's understanding of the problem.

2.2 Critique of manufacturer's overview of current service provision

There are no licensed treatment options available for the treatment of MDS del(5q) patients. Currently, the treatment for MDS del (5q) is best supportive care which includes blood transfusion to control the symptoms associated with bone marrow failure and antibiotics to treat or prevent infections. Also, low dose standard chemotherapy or immunosuppressive therapies can be administered to some patients.[2] Growth factors such as granulocyte colony-stimulating factors and erythropoietin can be used to stimulate the production of red blood cells and white blood cells. Use of growth factors can be successful in the early stages of MDS. However, over a period of time patients can become less responsive to growth factors.[10] Once patients become unresponsive to the available therapeutic options the only treatment then available is blood transfusion. Many patients with low or intermediate-1-risk can become blood transfusion dependent; increasing the risk of infections, anaemia, iron overload and serious comorbidities.[4] Therefore, the main objective is to improve the prognosis by giving early intervention before patients become chronically transfusion dependent.

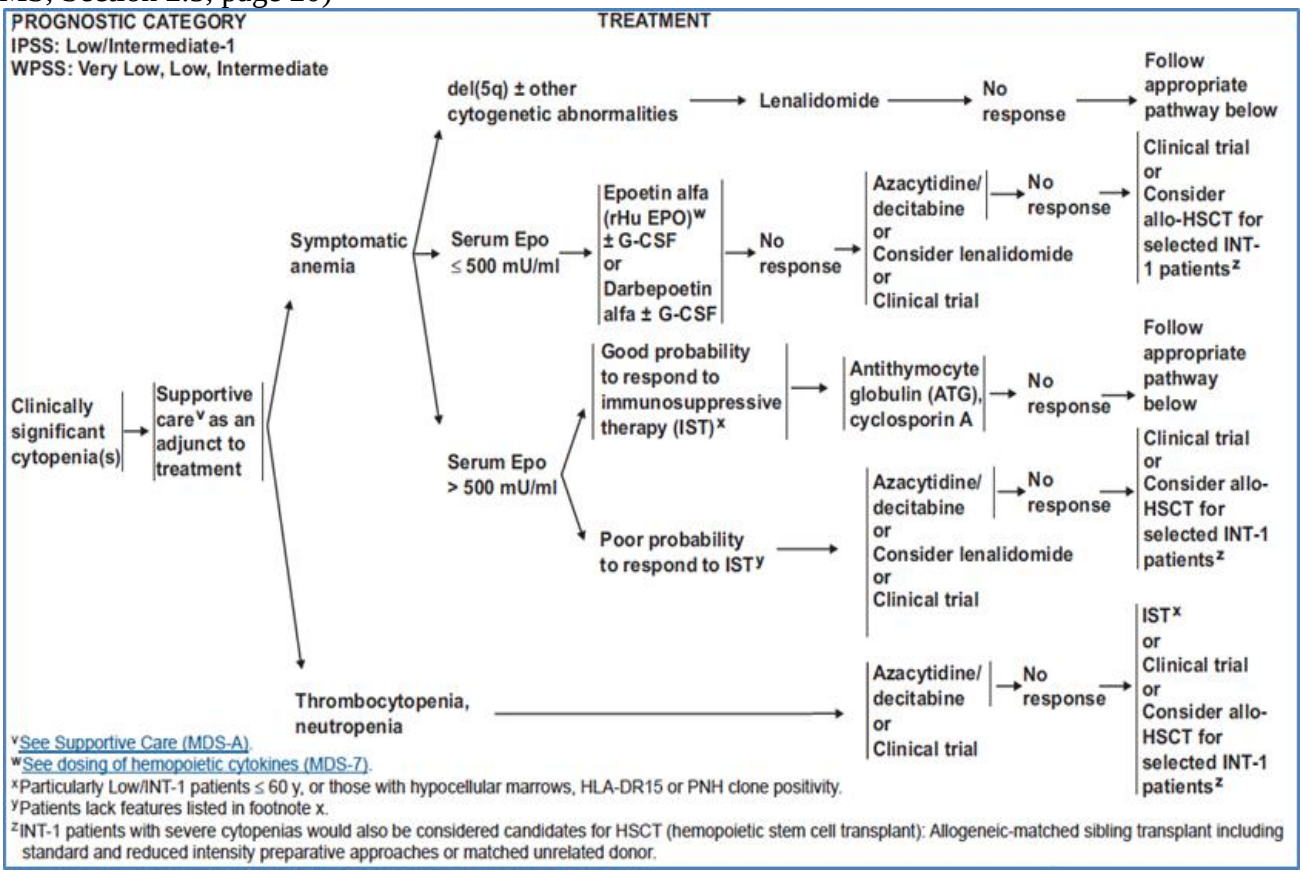
Section 2.5 in the manufacturer's submission states that the main goal of treatment is to achieve transfusion independence: *"The aim of intervention in MDS del(5q) should, therefore, be to reverse transfusion dependence and delay disease progression, and thus prevent the rapid deterioration in patient health and QoL, and the premature mortality associated with it."* (MS, Section 2.5, page 19)

Lenalidomide (Revlimid®) is a structural analogue of thalidomide. This is an oral therapy with anti-neoplastic, anti-angiogenic, pro-erythropoeitic and immunomodulatory properties.[2, 4] Currently lenalidomide does not have UK marketing authorisation for the treatment of MDS.[2] The application is currently under consideration by the European Medicines Agency (EMA) with a Committee for Medicinal Products for Human Use opinion/decision anticipated in April 2013 and European Committee decision in June 2013 (MS, Section 1.3, page 10).

The anticipated indication in the UK is for patients with transfusion-dependent anaemia due to low- or intermediate-1 risk MDS associated with a del(5q) cytogenetic abnormality with or without additional cytogenetic abnormalities – the same indication for which lenalidomide has been approved by the US Food and Drug Administration in December 2005 (MS, Section 1.5, page 10). The final NICE scope for this STA identifies a specific patient group in the licensed indication for this technology; that is, patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a del(5q) cytogenetic abnormality with or without other cytogenetic abnormalities." (MS, Section 2.2, page 18)

The treatment pathway proposed for lenalidomide in patients with del(5q) chromosomal abnormalities and symptomatic anaemia by the National Comprehensive Cancer Network (NCCN) in the United States is displayed in Figure 2.1 below.[2, 11]

Figure 2.1: National Comprehensive Cancer Network guidelines for lenalidomide (See also: MS, Section 2.5, page 20)



According to the manufacturer, in patients with del(5q) MDS lenalidomide modifies the disease mainly by directly targeting the del(5q) clone and by a parallel pro-erythropoietic effect.[2] Lenalidomide targets the cause of the disease, changes the course of the disease and gives relief from the symptoms.[2] Lenalidomide can potentially improve the HRQoL of del(5q) MDS patients by reducing the symptoms associated with comorbid anaemia and by preventing the morbidities associated with anaemia.[2] Therefore, it is believed that early use of the intervention will not only help in avoiding the long term consequences due to chronic anaemia but also remove the potential adverse events associated with blood transfusion.[2] However, there are some serious adverse events associated with the use of lenalidomide, such as venous thromboembolism, grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia.[2]

There are no other licensed treatment options available for the treatment of del(5q) MDS patients. Therefore the main comparator in this submission is best supportive care (BSC) which is in line with the final scope.

3. Critique of manufacturer's definition of decision problem

Table 3.1: Statement of the decision problem (as presented by the manufacturer)

	Final scope issued by NICE	Decision problem addressed in the submission	Comments/rationale if different from the scope
Population	Adults with myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality and who are red blood cell transfusion dependent	Manufacturer has indicated that the population is the same as in final scope issued by NICE. However this does not appear to be the case.	The population identified in the NICE scope includes people with intermediate-2 and high risk MDS, whereas the manufacturer has only sought licence/approval for patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality.
Intervention	Lenalidomide – otherwise not specified	Lenalidomide 10mg and 5mg (2.5mg not available on the market)	Precise intervention not specified by NICE.
Comparator(s)	For people with intermediate-1 or low risk MDS: Best supportive care including blood transfusions For people with intermediate-2 and high risk MDS: Azacitadine Stem cell transplantation	Manufacturer has stated that it is the same as in final scope issued by NICE. This is not the case.	Azacitadine and/or stem cell transplant are not deemed appropriate comparators by the manufacturer as the trial did not include with intermediate-2 and high risk MDS
Outcomes	The outcome measures to be considered include: overall survival progression-free survival (including time to transformation to AML or death) response rates, including haematologic response and improvement frequency of blood-transfusions (including blood-transfusion independence) serious infections adverse effects of treatment health-related quality of life.	Manufacturer has stated that it is the same as in final scope. However there are some areas where incorporation of these results was not evident.	Other than blood transfusion independence, it is not clear how improvement in frequency of transfusions in the dependent population has been accounted for. In addition, whilst serious adverse events were reported they were not accounted for in the economic analysis
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	Manufacturer has stated that it is the same as in final scope.	No deviation

	Final scope issued by NICE	Decision problem addressed in the submission	Comments/rationale if different from the scope
	reflect any differences in costs or outcomes between the technologies being compared. The availability of any patient access schemes for comparators should be taken into account in the economic analysis. Costs will be considered from an NHS and Personal Social Services perspective.		
Other Considerations – including sub groups	Guidance will only be issued in accordance with the marketing authorisation. If evidence allows, subgroups based on different cytogenetic profiles will be considered separately.	Not considered.	No deviation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal 218, March 2011, 'Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia'.[12] Review date decision February 2014. Related Guidelines: Guidance on Cancer Services, Oct 2003, 'Improving outcomes in haemato-oncology cancer'.[13]	Referenced.	No deviation.

3.1 Population

There was a mismatch of population between the scope issued by NICE and the decision problem as identified in the manufacturer's submission. The NICE scope identified a broader population which included people with intermediate-2 and high risk MDS, whereas the manufacturer has only sought licence/approval for patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality.

The manufacturer has provided details of an intention to treat population and a modified intention to treat population. It is not clear which of these populations is more representative of the target population as treated in the NHS in England and Wales.

3.2 Intervention

The final scope issued by NICE only specified the intervention as lenalidomide and did not specify appropriate dose. The manufacturer, on the other hand, specified two intervention regimens namely:

- Lenalidomide 5mg on days 1 to 28 of a 28-day cycle.
- Lenalidomide 10mg on days 1 to 21 of a 28-day cycle.

Lenalidomide does not currently have a UK marketing authorisation for the treatment of MDS. The application is currently under consideration by the European Medicines Agency (EMA) with a Committee for Medicinal Products for Human Use opinion/decision anticipated in April 2013 and European Committee decision in June 2013.

Lenalidomide is implemented in the health economic model as per its anticipated marketing authorisation taking into account the dose interruptions and titrations observed in the MDS-004 trial. In the base case of the model best supportive care (BSC) is considered as per the NICE scope. This is defined as the provision of blood transfusions for transfusion dependent patients.

3.3 Comparators

There are differences between the comparators identified in the final NICE scoping and the manufacturer's submission which relate directly to the population issues identified above, for example, stem cell transplantation for people with intermediate-2 and high risk MDS.

In the base case of the economic model best supportive care (BSC) is considered as per the NICE scope. This is defined as the provision of blood transfusions for transfusion dependent patients. No changes to BSC (in terms of transfusion frequency or iron chelation therapy) are assumed when cardiac conditions, diabetes, or hepatic conditions occur.

It is not clear whether BSC should include ESA (with or without G-CSF) or not. According to independent clinical advice (Personal communication, Dr Culligan, 23 February 2013), there is some doubt about the effectiveness of ESA for patients with MDS del(5q) and including ESA in the model actually improves the ICER for lenalidomide.

In summary, it is difficult to be sure that BSC as represented in the cost effectiveness analysis is similar enough to actual patient experience in England and Wales.

3.4 Outcomes

Most outcomes specified in the NICE scope have been included in the MDS-004 trial and have been reported in the MS: overall survival, progression-free survival (including time to transformation to AML or death), response rates (including haematologic response and improvement), serious infections, adverse effects of treatment, and health-related quality of life. Frequency of blood-transfusions (including blood-transfusion independence) was not reported in the MS. Serious infections were reported for grade 3 or 4 pneumonia only and health related quality of life was measured in the trial in the form of FACT-An scores. Serious infections and the FACT-An data were not used in the cost-effectiveness analysis.

3.5 Other relevant factors

The final scope issued by NICE states: "If evidence allows, subgroups based on different cytogenetic profiles will be considered separately". The manufacturer has indicated that there is no confirmed regulatory sub group at this point and will provide more clarity following on-going discussions on the regulatory process.

The scope does not ask for any specific equity considerations and none are provided in the manufacturer's submission. [redacted]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

An evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), developed by McGowan et al. was used to inform this critique.[14] The submission was checked against the Single Technology Appraisal (STA) specification for manufacturer/sponsor submission of evidence.[15] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1B.

Clinical effectiveness

Searches were reported for all databases required by NICE, except Medline in Process (MS 6.1 & 10.2). The ERG queried this omission in their points of clarification (POC) letter and asked if this resource was included in the Medline search. The manufacturer confirmed that this was the case in their response to points of clarification.[16] Whilst the manufacturers submission (MS) states that no date limits were applied, the ERG asked the manufacturer to provide the full date span for each database searched in order to ensure reproducibility. The MS also provided the date of the week commencing for the clinical effectiveness searches, the ERG requested clarification as to the exact search date for each resource in the points of clarification letter. Both of these requests were addressed in the manufacturer's response to clarification.[16]

The ERG noted errors in the combination of search lines in the following strategies for this section (MS 10.2). The ERG was unclear if these were due to poor reporting or whether they were errors made during searching, which may have affected the recall of results:

- The ERG noted that the systematic reviews facets in line #94 of the Embase search strategy and line #97 in the Medline strategy (MS 10.2) were not included in the final results sets. This may have impacted on the recall of results.

- The logic for the Cinahl search (MS 10.2) appeared to be very confused. Both the RCT and systematic reviews facets (lines #19 and #32) were not included in the final results set. The lines that were included in the final results set also appear to have been combined incorrectly and included some redundant lines.

- The ERG also noted that the final line appeared to have been omitted in the Science Citation Index strategy (MS 10.2). The strategy contained one facet for MDS + 5q (line #5) and one facet for the interventions (line #40), but there was no final line combining the two. It was unclear if this was error in reporting. Line #6 for "best supportive care" also appeared to be an orphan line and was not combined with either facet. It was unclear what effect this may have had on the recall of results.

The manufacturer reported that additional searches were undertaken for this section in the Web of Science Conference Proceedings Citation Index, but there was no record of this in section 10.2. The ERG was unclear if this had been included in the Science Citation Index search and requested clarification in the POC letter. The manufacturer in their response confirmed that this was the case. In addition to the formal searches the MS reported the checking of references lists to identify additional relevant research as well as the use of company study reports pertaining to lenalidomide.

Indirect and mixed treatment comparisons

The MS reported the unsuitability of mixed treatment analysis for this study (MS 6.7). Therefore no strategies were included for this section.

Non-RCT Evidence

The MS reported that non-RCTs were not considered relevant for this submission (MS 6.8). Therefore no strategies were included for this section.

Adverse events

The manufacturer stated that searches for adverse events were not applicable in this case and presented no searches. The ERG requested further explanation for this in their POC letter. The manufacturer responded by stating that adverse events searches were carried out as part of the search for clinical evidence. CRD guidance recommends that if searches have been limited by an RCT filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed.[17] Despite the addition of a systematic review filter the ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits. In light of this recommendation the ERG re-ran the MS clinical effectiveness searches and NOT'ed them against a new strategy designed to identify any papers irrespective of study design that feature the study population of patients with MDS associate with a del(5q) abnormality. An additional 1730 papers were retrieved after de-duplication. The ERG was not able to screen all of the search results due to time constraints, but a cursory look through identified one additional paper which was considered relevant by the ERG (See Appendix 1A & section 4.5 for further details).

Cost effectiveness

Searches were reported for the majority of databases required by NICE, except Medline in Process (MS 7.1 & 10.10). As with the clinical effectiveness searches, the manufacturer confirmed that this was included in the Medline search in their response to POC. The ERG also noted the omission of an EconLit strategy in section 10.2, despite this being a required database and it appearing in a list of searched databases in section 6.2. This omission was queried in the POC letter. The manufacturer confirmed that this resource was searched and provided a strategy. Whilst the MS states that no date limits were applied, the ERG asked the manufacturer to provide the full date span for each database searched in order to ensure reproducibility. The MS also gave Monday 6 February for the date of all cost effectiveness

and HRQL searches, the ERG requested confirmation of the search date for each resource in the POC letter and these were addressed in the manufacturer's response to clarification.[16]

The ERG also noted an error regarding line combinations in the Science Citation Index strategy where lines #4-6; "best supportive care, "clinical practice" & "lenalidomide" respectively appear to have been omitted by error from the interventions facet in line #39. Given that this was an additional resource searched alongside those on the NICE required list, it is unclear what impact this may have had on the overall recall of results.

Measurement and valuation of health effects

Section 10.12 only contained a single generic strategy, the ERG presumed that the individual search strategies for this section were those recorded in 10.10 as "Utility Values Strategies". The manufacturer confirmed that this was the case in their response to POC.

The ERG requested confirmation from the manufacturer that the following NICE required databases were searched to inform the HRQL section and received the following responses:

- Medline in Process: The manufacturer confirmed that this was included in the Medline utilities search
- NHS EED: The manufacturer confirmed that the NHS EED search reported in section 10.10 for cost effectiveness was also used to inform the HRQL section
- EconLit: The manufacturer confirmed that this was searched and provided a strategy following clarification.

The ERG noted that the manufacturer stated in section 10.12.1 that the Web of Knowledge Conference Proceedings Index was included in the list of resources searched for the HRQL section, but no strategy was reported. The manufacturer confirmed that this was included in the Web of Science search in their response to clarification. The ERG also noted an error regarding line combinations in the Science Citation Index strategy where lines #4-6; "best supportive care, "clinical practice" & "lenalidomide" respectively appear to have been omitted by error from the interventions facet in line #39. Given that this was an additional resource searched alongside those on the NICE required list, it is unclear what impact this may have had on the overall recall of results.

The ERG was concerned that some of the strategies reported for this section may have been unduly restrictive. The Medline, Embase and Science Citation Index strategies were developed to retrieve only studies that reported both the condition and the treatment, thus excluding any pure QoL or utility studies in the disease population, this may have led to useful papers being missed.

Resource identification, measurement and valuation

The MS reported that the strategies detailed in 7.4.6 & 10.12 were employed for this section. Therefore the same limitations already discussed applied to these searches.

Summary of searching

The searches documented in the initial manufacturer's submission contained several areas of weakness, only those relating to reproducibility were included in the points of clarification letter forwarded to the manufacturer by NICE. The manufacturer addressed all the points of concern raised by the ERG in their response to clarification.

Given the small number of papers retrieved for this topic, the ERG considered that searches may have been unnecessarily restrictive, potentially leading to useful material being missed. The ERG recommended that a simple search for MDS + del(5q) without a study design filter would have adequately addressed all areas of interest including clinical effectiveness and adverse events, without retrieving large numbers of results. Please see Appendix 1A for example Medline and Embase searches run by the ERG.

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy are described in Table 3, page 34 of the MS (*see MS, Section 6.2.1, page 34-35*; and the Table below).

Table 4.1: Eligibility criteria used in search strategy (MS, Table 3, page 34)

Eligibility criteria	Clinical effectiveness
Inclusion criteria	**Population:** Patients with RBC transfusion-dependent, low- or intermediate-1-risk MDS with del(5q) **Interventions:** Lenalidomide or best supportive care (antibiotics, blood transfusions, growth factor therapies and iron-chelation therapies) **Outcomes:** Frequency of blood transfusions; blood-transfusion independence; overall survival; progression-free survival (including time to transformation to AML; haematological response (including change from baseline in ANC, platelet count and Hb level and haematopoietic cells evaluation); serious infections; adverse effects of treatment; health-related quality of life **Study design:** Randomised controlled trials and systematic reviews **Language restrictions:** No language restrictions were applied
Exclusion criteria	**Population:** Study patients for whom no cytogenetic abnormality was reported; patients with intermediate-2 and high-risk MDS **Interventions:** Azacitadine, chemotherapy and stem cell transplantation **Study design:** Single-arm clinical trials

Abbreviations: AML = acute myeloid leukaemia; ANC = absolute neutrophil count; Hb = haemoglobin; MDS = myeloproliferative disorders; RBC = red blood cell

The NICE scope mentions two populations: 1: people with intermediate-1 or low risk, and 2: people with intermediate-2 and high-risk MDS. However, the second population is explicitly excluded in the search strategy. Prior to the start of this STA, NICE informed the ERG that the manufacturer was only seeking a license for the first population. This is also stated in section 1.5 of the MS: "An application for lenalidomide has been submitted to the EMA for use in the treatment of patients with transfusion-dependent anaemia due to low- or

intermediate-1 risk MDS associated with a del(5q) cytogenetic abnormality with or without additional cytogenetic abnormalities – the same indication for which lenalidomide has been approved by the US Food and Drug Administration in December 2005."

Therefore, the eligibility criteria used in the search strategy are in line with the NICE scope.

4.1.3 Critique of data extraction

One RCT was included, the MDS-004 trial. The data from this trial were extracted from the published journal article by Fenaux et al, 2011[18] and the full clinical study report for study MDS-004.[19]

The main problem with the data extraction is that data are reported separately for two different populations: the intention-to-treat population (ITT) and the modified-intention-to-treat population (mITT). However, not all data are reported fully for both populations. In addition, not all adverse events are reported in the MS. Where necessary, we have requested additional data in the clarification letter, and when provided, further data are reported in this report.

4.1.4 Quality assessment

A summary of the quality assessment of study MDS-004 is presented in Table 10 of the MS (MS, section 6.4.3, page 60). A complete quality assessment for the trial is included in section 10.3, appendix 3 of the MS. The same table is presented below with ERG comments.

Table 4.2: Quality assessment of the MDS-004 trial

Study	**MDS-004**	**ERG comment**
Selection bias		
An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups). Yes, No, Unclear, N.A.	Yes	Yes
There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation). Yes, No, Unclear, N.A.	Yes	Yes
The groups were comparable at baseline, including all major confounding and prognostic factors. Yes, No, Unclear, N.A.	Yes	Yes
Based on answers to above, in your opinion was selection bias present? If so what is the likely direction of effect. Low risk, Unclear/unknown risk, High risk.	Low risk	Low risk
Likely direction of effect.	N/A	N/A
Performance bias		
The comparison between groups received the same care apart from the interventions studied. Yes, No, Unclear, N.A.	Yes	Yes
Participants receiving care were kept 'blind' to treatment allocation. Yes, No, Unclear, N.A.	Yes	Yes, up to 16 weeks
Individuals administering care were kept 'blind' to treatment allocation. Yes, No, Unclear, N.A.	Yes	Yes, up to 16 weeks
Based on answers to above, in your opinion was performance bias present? If so, what is the likely direction of effect? Low	Low risk	Low risk up to 16 weeks. The risk of

risk, Unclear/unknown risk, High risk.		performance bias in the open label phase is high
Likely direction of effect.	N/A	Unknown
Attrition bias		
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up) Yes, No, Unclear, N.A.	Yes	Yes
The groups were comparable for treatment completion Yes, No, Unclear, N.A.	Yes	Yes up to 16 weeks. After 16 weeks groups were no longer comparable due to the crossover study design.
The groups were comparable with respect to the availability of outcome data Yes, No, Unclear, N.A.	Yes	Unclear. Most of the reported data was from the mITT analysis.
Based on answers to above, in your opinion was attrition bias present? If so, what is the likely direction of effect? Low risk, Unclear/unknown risk, High risk.	Low risk	Unclear. The study report says that ITT analysis was performed. However, most data are reported for the mITT which is a concern.
Likely direction of effect.	N/A	Unknown
Detection bias		
The study had an appropriate length of follow-up. Yes, No, Unclear, N.A.	Yes	Yes
The study used a precise definition of outcome. Yes, No, Unclear, N.A.	Yes	Yes
A valid and reliable method was used to determine the outcome. Yes, No, Unclear, N.A.	Yes	Yes
Investigators were kept 'blind' to participants' exposure to the intervention. Yes, No, Unclear, N.A.	Unclear	Unclear
Investigators were kept 'blind' to other important confounding and prognostic factors. Yes, No, Unclear, N.A.	Unclear	Unclear
Based on answers to above, in your opinion was detection bias present? If so, what is the likely direction of effect? Low risk, Unclear/unknown risk, High risk.	Low risk	Low risk
Likely direction of effect.	N/A	N/A

4.1.5 Evidence synthesis

No evidence synthesis is included in the submission. In section 6.6.2, page 74 of the MS, the manufacturer states: "A meta-analysis was not appropriate for this submission. The Phase 3 study, which forms the main evidence base for this submission, is the first randomised, placebo-controlled study of lenalidomide in patients with MDS."

In section 6.7.1, page 76 of the MS, the manufacturer states: "A mixed treatment comparison was not an appropriate analysis for the purposes of this submission. The literature search identified only one RCT of the intervention, lenalidomide, and only one small study of a comparator treatment (best supportive care) relevant to the decision problem."

ERG comment:
The ERG agrees that for the comparison of lenalidomide versus best supportive care in people with intermediate-1 or low risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality and who are red blood cell transfusion dependent, the MDS-004 trial is most likely the best source of clinical effectiveness evidence.

However, for adverse events, other study designs could have been included and longer term data could have been sought.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The manufacturer performed a literature search, which is described in sections 6.1 and 6.2 (pages 32-41). Based on this search, two studies were included:

- Fenaux et al. 2011[18], describing the MDS-004 trial, and
- Balleari et al. 2006[20], a small study with a mixed population. It was not clear how many patients were relevant to the decision problem; therefore, the study was only briefly described.

In section 6.2.3 (page 37) of the MS, the manufacturer states that a number of additional publications were identified that reported on secondary analyses of the MDS-004 trial. It is not reported how these publications were found or why they were not retrieved through the search. In addition, three other studies were identified:

- Revicki et al. 2012[21], describing QoL data from the MDS-004 trial.
- Kuendgen et al. 2012[22], reporting long-term outcomes from two clinical trials (MDS-003/MDS-004), and
- Zeidan et al. 2012[23], an abstract from the American Society of Haematology, examining lenalidomide treatment patterns and their association with reduced transfusion needs in a Medicare-enrolled population with MDS (n=23,855).

Again, it is not reported how these studies were found.

ERG comment:
Overall, it is unclear how studies were identified for inclusion in the submission. However, the ERG is not aware of any relevant trials that have been missed.

MDS-004 trial
The MDS-004 trial is described in sections 6.3 (methods), 6.4 (quality assessment), and 6.5 (results) of the MS. In addition, the adverse events, based on data from the MDS-004 trial, are described in section 6.9 of the MS.

4.2.1 Methodology of the MDS-004 trial

A summary of methodology of the MDS-004 trial is presented in Table 6, page 44 of the MS (see below)

Table 4.3: Summary of methodology of the MDS-004 trial (MS, Table 6, page 44)

Location	Multicentre trial with participating centres in: UK, France, Germany, Italy, Spain, Belgium, Netherlands, Sweden and Israel
Design	Phase 3, randomised, double-blind, placebo controlled trial
Duration of study	Up to 52 weeks
Method of randomisation	Validated interactive voice response system
Method of blinding (care provider, patient and outcome assessor)	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Lenalidomide 10 mg on Days 1–21: n=69 Lenalidomide 5 mg on Days 1–28: n=69 Placebo: n=67 (all 28 day cycles) Crossover from placebo to lenalidomide or higher lenalidomide dose allowed at 16 weeks
Primary outcomes (including scoring methods and timings of assessments)	Red blood cell transfusion-independence for ≥26 weeks
Secondary outcomes (including scoring methods and timings of assessments)	Erythroid response at 16 weeks, duration of red blood cell transfusion-independence, cytogenetic response at Weeks 12, 24 and every 24 weeks thereafter, OS, AML progression, safety, and HRQoL at Weeks 12, 24, 36, 48
Duration of follow-up	Median follow-up 1.55 years.

Key: AML = acute myeloid leukaemia; HRQoL = health-related quality of life; OS = overall survival

<u>Dose</u>

Regarding the dosing within the three arms, the manufacturer reports (page 43-44 MS): "The dose of lenalidomide or placebo was to be reduced if dose-limiting toxicities occurred, and complete blood counts were to be obtained weekly following the development of dose-limiting neutropenia or thrombocytopenia. Lenalidomide dosing was reduced as follows: lenalidomide 5mg (starting dose), dose level −1 (5mg every other day), dose level −2 (5mg twice-weekly), and dose level −3 (5mg weekly); lenalidomide 10 mg (starting dose), dose level −1 (5mg daily), dose level −2 (5mg every other day), and dose level −3 (5mg twice-weekly); patients not tolerating dose level −3 discontinued treatment. For Grade 4 neutropenia, lenalidomide was interrupted and resumed at the next dose level down when ANCs recovered to ≥500/µl. For Grade 4 thrombocytopenia, lenalidomide was interrupted and resumed at a decreased dose level when the platelet count recovered to ≥25,000/µl and <50,000/µl on two or more occasions for seven days or more; or ≥ 50,000/µl at any time. Granulocyte colony-stimulating factors (G-CSF) and granulocyte macrophage-colony stimulating factors (GM-CSF) were allowed for neutropenia."

ERG comment

Given that 62.3% of patients in the lenalidomide 5mg group and 72.5% in the lenalidomide 10mg group experienced an AE leading to dose reduction or interruption, and one dose reduction in the 10mg group means patients receive effectively the same dose as the 5mg group, it seems there is some difficulty in distinguishing the treatment arms. In addition, patients in the placebo or lenalidomide 5mg groups without minor erythroid response by Week 16 or those experiencing erythroid relapse could crossover to lenalidomide 5mg or 10mg, respectively. In the placebo group, only one out of 67 patients completed the 52 weeks double-blind phase. This means that the assessment of effects after 16 weeks is severely compromised.

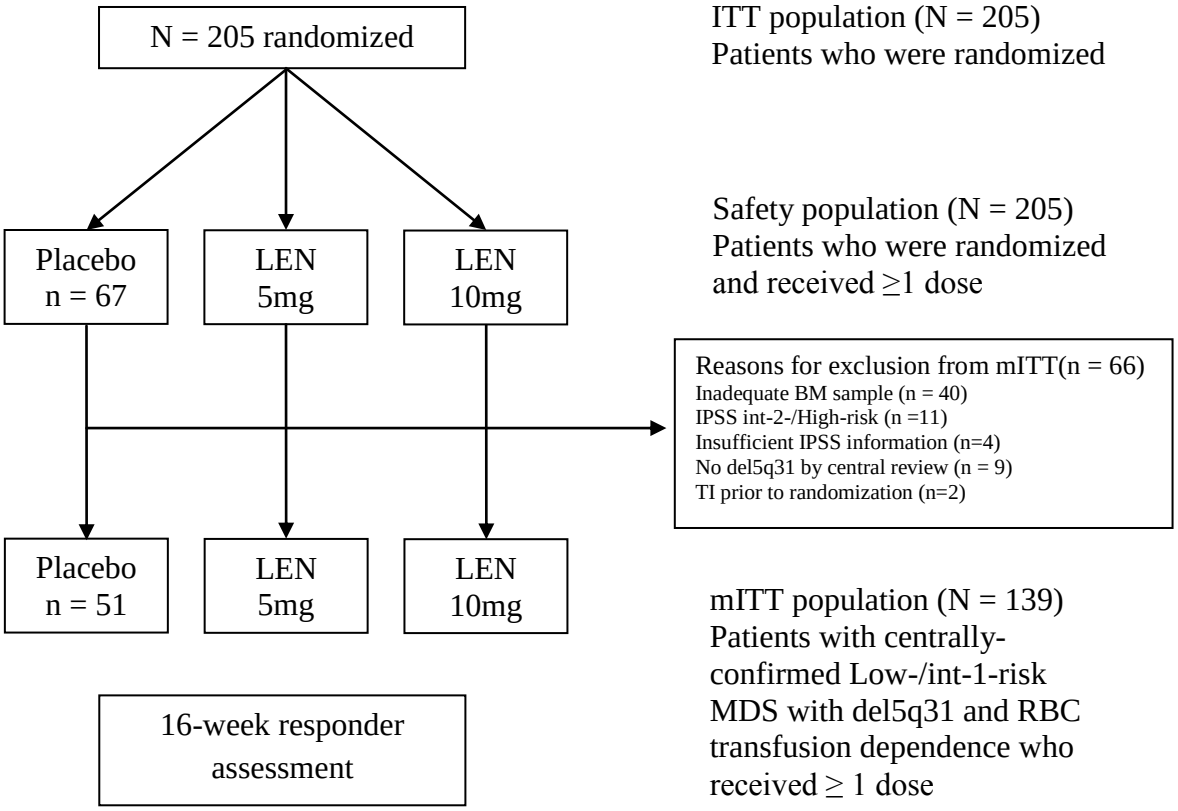
Population

In chapter 6 (clinical evidence), results are reported separately for the intention-to-treat (ITT) population and the modified intention-to-treat (mITT) population; although, not all results are reported for both populations. The difference between both populations is explained in a footnote on page 8 of the MS: "mITT population included patients with centrally confirmed low- or intermediate-1-risk MDS with del(5q) and documented RBC transfusion-dependence, who received ≥1 dose of study drug".

In chapter 7 (cost effectiveness) the manufacturer states: "Using the MITT population was not considered appropriate as it is unlikely that in real-life practice these strict criteria for use of lenalidomide would be met. Additionally the reduction in sample size for analysis (from 69 in the 10 mg arm to 41 and from 67 in the placebo arm to 51) would have lead to increased uncertainty and difficulty in fitting curves." (Section 7.8.5, page 175 MS)

In total, 263 patients were screened for inclusion, and 205 were included. These 205 patients were randomly assigned to receive lenalidomide 10 mg (n=69), lenalidomide 5 mg (n=69) or placebo (n=67) and were included in the ITT and safety populations. A total of 139 patients were included in the mITT population (lenalidomide 10mg, n=41; lenalidomide 5mg, n=47; and placebo, n=51). Figure 4 (page 45) in the MS outlines the reasons for exclusion from the mITT population (see Figure below).

Figure 4.1: Study populations by randomised treatment group in the double blind phase (MS, Figure 4, page 45)



Key: BM = bone marrow; IPSS = International Prognostic Scoring System; LEN = lenalidomide; mITT = modified intention-to-treat; RBC = red blood cell; TI = transfusion independence

ERG comment

Reasons for exclusion from the mITT population are not reported by treatment arm. Furthermore, only one outcome (the primary outcome) is fully reported for both populations (Erythroid response) all other outcomes are reported for only one of the two populations. Baseline patient characteristics of the mITT population are reported in table 7 (page 47-48) of the MS. However, baseline patient characteristics of the ITT population are not reported.

The population is in accordance with the population as defined in the scope. However, confirmation of del(5q) status (karyotype analysis) and bone marrow morphology performed by central haematological review after randomisation, means that patients not fulfilling the inclusion criteria are included in the ITT population.

In response to the clarification letter the manufacturer provided a table with the reasons for exclusion from the mITT analysis by treatment arm (see Table 4.4).

Table 4.4: Reasons for exclusion from the mITT analysis by treatment arm (Response to Clarification Letter, B4, Table 6, page 7)

Category/Description	Placebo QD 28 of 28 Days (N=16)	Lenalidomide 5mg QD 28 of 28 Days (N=22)	Lenalidomide 10mg QD 21 of 28 Days (N=28)
Inadequate BM Sample	12	11	17
INT-2 or Higher IPSS Score	2	5	4
Insufficient IPSS information	0	1	3
No del(5q) by Central Review	2	4	3
Transfusion Independent Prior to Pre-Randomisation	0	1	1

Based on the Clinical Study Report, most baseline characteristics as for the ITT population could be reproduced. These are reported in chapter 4.5 of this report.

Outcomes

Most outcomes specified in the NICE scope have been included in the MDS-004 trial and have been reported in the MS: overall survival, progression-free survival (including time to transformation to AML or death), response rates (including haematologic response and improvement), serious infections, adverse effects of treatment, and health-related quality of life. Frequency of blood-transfusions (including blood-transfusion independence) was not reported in the MS.

Overall survival was reported for the ITT population (MS, page 71-72, Fig 11).

Time to AML progression, defined as the median duration of follow-up for AML progression from date of randomisation to AML, death, or last known contact for non-AML survivors, whichever was earliest, was reported for the ITT population (MS, page 68-70, Fig 10).

Erythroid response was reported for both populations: mITT and ITT (MS, Table 12, page 63). In addition, duration of erythroid response, change in haemoglobin levels, and cytogenetic response and progression were reported for the mITT population only (MS, pages 63-66). Duration of RBC transfusion-independence was defined (IWG 2000 criteria) as the number of days between the last transfusion before the start of the transfusion-independence period or the first dose of lenalidomide, whichever occurred later, and the first transfusion after the transfusion-independence period.

For serious infections, only grade 3 or 4 pneumonia was reported in the MS (Table 17, page 84). Adverse effects of treatment were reported in section 6.9 (MS, pages 79-86) for the safety population.

For health-related quality of life the FACT-An (Functional Assessment of Cancer Therapy-Anaemia) was reported at 12 weeks in 167 randomised patients (MS, Fig 12, page 67). The FACT-G (Functional Assessment of Cancer Therapy-General) was also assessed according to

the clinical study report, but was not reported in the MS. However, for the economic model, the manufacturer concluded that the FACT-An data were not consistent with the reference case and could not be used in the cost-effectiveness analysis (MS, page 140).

ERG comment

Frequency of blood transfusions (including blood transfusion independence) was not reported in the MS. Serious infections were reported for grade 3 or 4 pneumonia only and health related quality of life as measured in the trial in the form of FACT-An scores, was not used in the cost-effectiveness analysis.

Statistical methods

The manufacturer provided the following sample size calculation for the MDS-004 trial: "Assuming response rates (RBC transfusion independence for ≥26 weeks) of 0.400 and 0.100 in the active treatment and placebo groups, respectively, a sample size of 45 patients per group (mITT population) and a two-group continuity corrected chi-square test with a 0.025 two-sided significance level (α split to adjust multiple comparisons) has 80% power to detect differences between each active treatment group and placebo. Descriptive statistics were used to compare lenalidomide 10 mg and 5 mg; the study was not powered to detect differences between the lenalidomide groups. Initial enrolment for the study was 162 patients. On 8 June 2006, the target enrolment was expanded to 205 to ensure the pre-specified number of evaluable patients (n=135) (MS, page 50)."

The Mantel–Haenszel procedure stratified on the IPSS karyotype score (0 versus >0) was used to compare response rates for lenalidomide 10mg and 5mg versus placebo. For the primary endpoint, a stepwise modified Bonferroni procedure controlled the experiment error rate. Patients who discontinued double-blind treatment were considered treatment failures. For erythroid and cytogenetic responses, results are summarised by treatment group. Cytogenetic responses are the best post-baseline responses. Duration of response, AML progression and OS were characterised using Kaplan–Meier curves. Duration for time-to-event analyses was calculated from randomisation to the date of death or censoring (date of last contact), whichever was earliest. For the duration of RBC transfusion independence, data are included until the last date with available information on transfusions. This date is indicated as censored for patients who died or who remained RBC transfusion independent at data cut-off. Analysis of variance was used to analyse changes in haemoglobin concentration from baseline. Response rates were compared within pre-specified subgroups of baseline serum or plasma EPO levels (≤500 versus >500 mIU/ml), and isolated del(5q) versus del(5q) plus at least one additional abnormality using a chi-square test. Analysis of variance was performed to compare changes in the FACT-An score from baseline at Week 12 in each lenalidomide group versus placebo. Longitudinal assessment of FACT-An scores to Week 48 for patients who achieved RBC transfusion independence for ≥26 weeks with lenalidomide is also presented in the MS.

A Cox proportional hazard model was used to evaluate the effect of potential baseline risk factors and RBC transfusion independence for at least eight weeks (IWG 2000 criteria) on

AML-free survival and OS, with RBC transfusion independence (for at least eight weeks) as a time-dependent covariate. A landmark analysis was performed at six months to reduce potential bias regarding the fact that responding patients must have survived long enough to attain a response. Univariate Cox proportional hazard models first assessed each individual risk factor. Once potentially significant ($p<0.15$) risk factors were identified, a multivariate model simultaneously determined the most important prognostic variables using a backward elimination variable-selection approach (variables were eliminated until all remaining variables had a significance of $p<0.15$). These analyses included data through completion of the open label phase for patients randomly assigned to lenalidomide (dose groups combined); patients randomly assigned to placebo were excluded because all, except 11 patients, crossed over to lenalidomide 5mg.

Final data for the double-blind phase are presented for all endpoints except for duration of response, AML progression and OS, which include open label data up to data cut-off (9 July 2010; 156 weeks after last patient accrual).

ERG comment

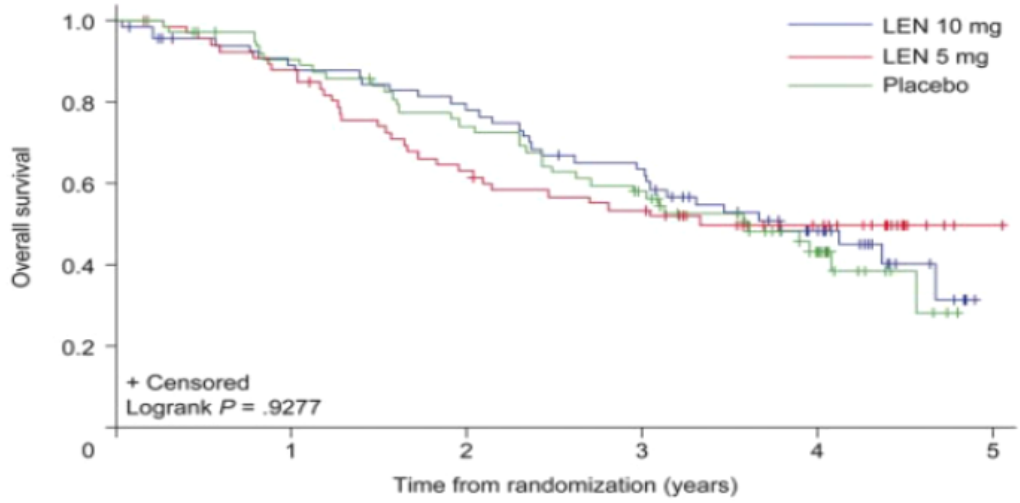
The sample size calculation reported has been checked and verified, it was also checked against the clinical study report. The main analyses of the trial endpoints use standard statistical analysis methods for clinical trials and seem to be appropriate. The only issue of concern is the inconsistent reporting of results for the different patient populations. All results should have been reported in full for both the ITT and mITT populations.

4.2.2 Results of the MDS-004 trial

Overall survival

Overall survival was reported using the Kaplan–Meier curve copied below for the ITT (safety) population (Figure 4.2; see also MS, Figure 11A, page 72) as well as the data reported in Table 4.5.

Figure 4.2: Duration of overall survival; safety population (MS, Figure 11A, page 72)



Patients at risk, n						
LEN 10 mg	69	57	50	35	15	0
LEN 5 mg	69	60	40	31	15	0
Placebo	67	58	46	32	8	0

Table 4.5: Overall survival in the MDS-004 trial (MS, page 71)

	Placebo	**Lenalidomide 5mg**	**Lenalidomide 10mg**
Duration of OS (Median, range)	35.9m (2.1-56.5)	35.5m (1.9-59.4)	36.9m (0.4-57.7)
Length of OS (Median, 95% CI)	42.4m (31.9 - ∞)	≥35.5m (24.6 - ∞)	44.5m (35.5 - ∞)

OS=Overall survival, CI=Confidence Interval, m=months

ERG Comment: "Duration of OS" should probably be: "Duration of follow-up"

Overall, there were 101 (49.3%) deaths during the study period, 10 of which occurred within 30 days of the last dose of study drug. There was no statistically significant difference between lenalidomide and placebo in overall survival (p=0.9277), hazard ratios were not reported.

Table 4.6: Summary of deaths from the DB and OL phases in the MDS-004 trial (Response to Clarification Letter, B6, Table 7, page 8)

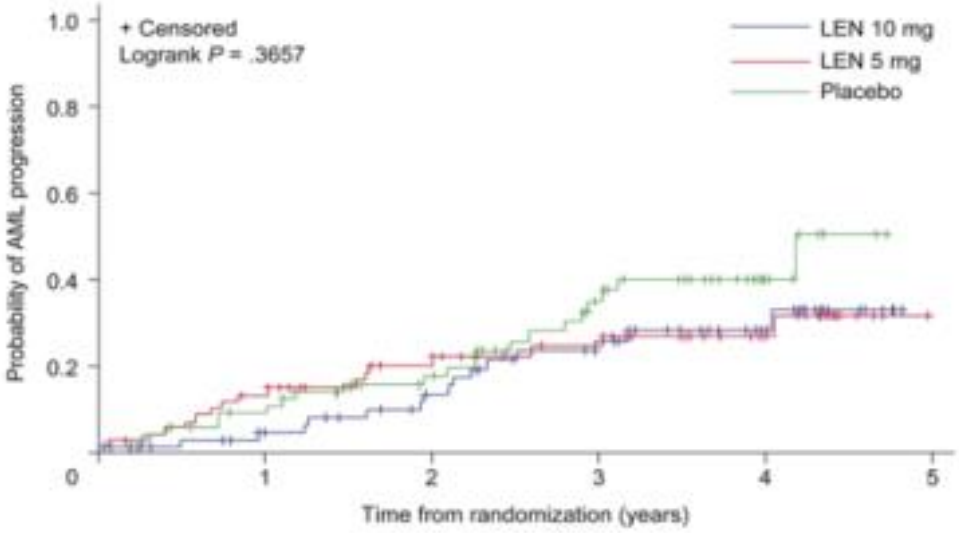
Category	**Placebo QD 28 of 28 Days (N=67) n (%)**	**Lenalidomide 5mg QD 28 of 28 Days (N=69) n (%)**	**Lenalidomide 10mg QD 21 of 28 Days (N=69) n (%)**	**Overall (N=205) n (%)**
All subjects who died during the study	35 (52.2)	32 (46.4)	34 (49.3)	101 (49.3
Number of subjects who died ≤30 days after last dose[a]	4 (6.0)	2[b] (2.9)	4 (5.8)	10 (4.9)

a, b: Information missing in Response to Clarification Letter.

Disease progression

In the ITT (safety) population, median duration of follow-up for AML progression (from date of randomisation to AML, death, or last known contact for non-AML survivors, whichever was earliest) was 30.9 months (range 2.1–56.5 months) in the placebo group, 36.1 months (range 0.4–57.7 months) in the lenalidomide 10 mg group and 31.8 months (range 0.8–59.4 months) in the lenalidomide 5mg group. Time to AML progression was reported using the Kaplan–Meier curve copied below (Figure 4.3; see also MS, Figure 10A, page 70). Median time to progression was not reached in the lenalidomide groups.

Figure 4.3: Time to AML progression; safety population (MS, Figure 10A, page 70)



Patients at risk, n						
LEN 10 mg	69	56	46	33	14	0
LEN 5 mg	69	57	39	30	15	0
Placebo	67	56	43	25	7	0

Response rates

Erythroid response was reported as RBC transfusion independence for ≥26 weeks and ≥8 weeks for both the mITT and ITT populations (see Table 4.7, and MS, Table 12, page 63).

In the economic model, IWG 2000 (response to ≥ 8wks) data were used. For the BSC group the data from the placebo arm were used and for both lenalidomide groups the data from the lenalidomide 10mg arm were used (see MS, Table 23, page 106).

Table 4.7: Erythroid response, as assessed by RBC transfusion independence for ≥26 weeks or ≥8 weeks (double-blind phase; mITT and ITT populations) (MS, Table 12, page 63)

	RBC transfusion independence, n (%) [95% CI]		
	Placebo	Lenalidomide 5mg	Lenalidomide 10mg
mITT population	n=51	n=47	n=41
Protocol-defined (≥26 weeks)	3 (5.9) [1.2–16.2]	20 (42.6) [28.3–57.8]*	23 (56.1) [39.7–71.5]*
IWG 2000 (≥8 weeks)	4 (7.8) [2.2–18.9]	24 (51.1) [36.1–65.9]*	25 (61.0) [44.5–75.8]*
IWG 2006 (≥8 weeks)	3 (5.9) [1.2–16.2]	24 (51.1) [36.1–65.9]*	25 (61.0) [44.5–75.8]*
ITT population	n=67	n=69	n=69
Protocol-defined (≥26 weeks)	4 (6.0) [1.7–14.6]	24 (34.8) [23.7–47.2]*	38 (55.1) [42.6–67.1]•
IWG 2000 (≥8 weeks)	**5 (7.5) [2.5–16.6]**	33 (47.8) [35.6–60.2]*	**42 (60.9) [48.4–72.4]***
IWG 2006 (≥8 weeks)	4 (6.0) [1.7–14.6]	33 (47.8) [35.6–60.2]*	42 (60.9) [48.4–72.4]*

CI = confidence interval; ITT = intention-to-treat, IWG = International Working group; mITT = modified ITT; RBC = red blood cell
p<0.001 versus placebo
Bold: Data used in the economic model (same response for both doses of lenalidomide).

Time to erythroid response was measured at 56 days and at 182 days. Results for time to erythroid response at 56 days are presented in tables 4.8 and 4.9, for the ITT and the mITT population respectively.

Table 4.8: Time to response - subjects who became RBC-transfusion independent for at least 56 days (ITT Population) (Response to Clarification Letter, B7, Table 11, page 9)

	Placebo (N=67)	**5 mg QD (N=69)**	**10 mg QD (N=69)**
Time to transfusion independence (weeks)			
N	5	33	42
Mean	6.4	4.3	5.4
SD	10.33	3.72	3.74
Median	0.3	4.1	4.6
Min, Max	0.3, 24.1	0.3, 12.3	0.3, 14.7

Table 4.9: Time to response - subjects who became RBC-transfusion independent for at least 56 days (mITT Population) (Response to Clarification Letter, B7, Table 10, page 9)

	Placebo (N=51)	**5 mg QD (N=47)**	**10 mg QD (N=41)**
Time to transfusion independence (weeks)			
N	4	24	25
Mean	7.9	3.4	4.9
SD	11.27	3.39	4.06
Median	3.6	3.2	4.3
Min, Max	0.3, 24.1	0.3 12.3	0.3, 14.7

Results for time to erythroid response at 182 days are presented in tables 4.10 and 4.11, for the ITT and the mITT population respectively.

Table 4.10: Time to response - subjects who became RBC-transfusion independent for at least 182 days (ITT Population) (Response to Clarification Letter, B7, Table 9, page 9)

	Placebo (N=67)	**5 mg QD (N=69)**	**10 mg QD (N=69)**
Time to transfusion independence (weeks)			
N	4	24	38
Mean	6.3	3.7	5.1
SD	11.93	3.62	3.74
Median	0.3	3.3	4.3
Min, Max	0.3, 24.1	0.3, 12.3	0.3, 14.7

Table 4.11: Time to response - subjects who became RBC-transfusion independent for at least 182 days (mITT Population) (Response to Clarification Letter, B7, Table 8, page 8)

Statistic	**Placebo (N=51)**	**Lenalidomide 5mg/day (N=47)**	**Lenalidomide 10mg/day (N=41)**
Number transfusion independent (responders)	3	20	23
Mean (weeks)[a]	8.2	3.5	4.5
SD	13.77	3.65	4.03
Median (weeks)[a]	0.3	3.0	4.3
Min, Max	0.3, 24.1	0.3, 12.3	0.3, 14.7

[a] Measured from the day of the first dose of study drug to the first day of the 182+ day RBC transfusion-free period.

Median duration of IWG 2000-defined erythroid response (RBC transfusion independence for ≥8 weeks) for the mITT population is reported in Figure 4.4 (see also MS, Figure 6, page 63).

Figure 4.4: Duration of IWG 2000-defined RBC-TI in patients randomly assigned to lenalidomide 10mg or 5mg (mITT population) (MS, Figure 6, page 64)

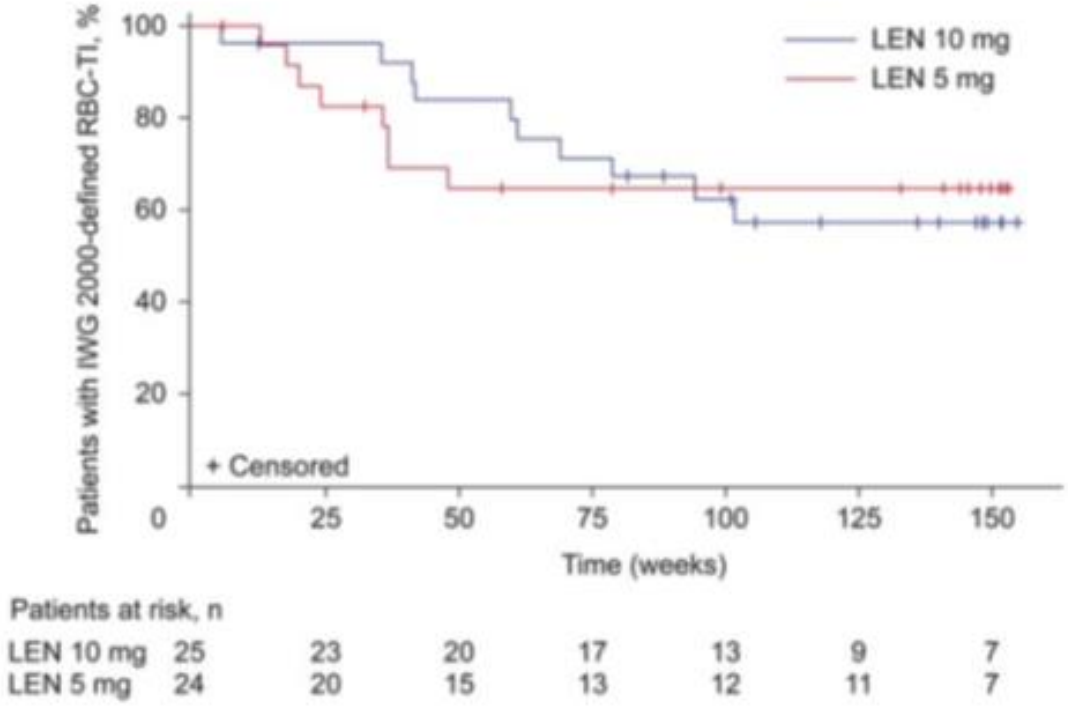


Figure represents patients who achieved RBC-TI during the double-blind phase of the study. For duration of RBC-TI, data are included until the last date with available information on transfusions. This date is indicated as censored for patients who died or who remain RBC-TI at data cut-off. Median duration of RBC transfusion follow-up for all treatment groups combined was 1.55 years (RBC transfusion follow-up for ≥1, ≥2 and ≥3 years was available for 85, 54, and 9 patients, respectively)

IWG = international Working Group; LEN = lenalidomide; RBC-TI = red blood cell transfusion independence

Table 4.12: Duration of 182+ day transfusion independence response by initial dosing regimen (ITT Population) (Response to Clarification Letter, B7, Table 13, page 10)

	Placebo (N=4) n (%)	**5 mg QD (N=24) n (%)**	**10 mg QD (N=38) n (%)**
Kaplan-Meier estimates			
Subjects with Transfusion Independence Response	4	24	38
Subjects who progressed (had a transfusion after response)	0 (0.0)	7 (29.2)	15 (39.5)
Subjects who maintained transfusion independence (censored [1])	4 (100.0)	17 (70.8)	23 (60.5)
Median (weeks)	NA	NA	NA
%95 CI	[NA, NA]	[NA, NA]	[98.3, NA]
Summary statistics (weeks)			
N	4	24	38
Mean	58.6	106.0	106.6
SD	10.60	52.72	42.63
Median	55.1	140.9	105.5
Min, Max	50.0, 74.0	28.3, 157.0	31.3, 158.7

[1]: Information missing in Response to Clarification Letter.

Table 4.13: Duration of RBC-transfusion independence response - subjects who became RBC-transfusion independent for at least 182 Days (mITT Population) (Response to Clarification Letter, B7, Table 12, page 10)

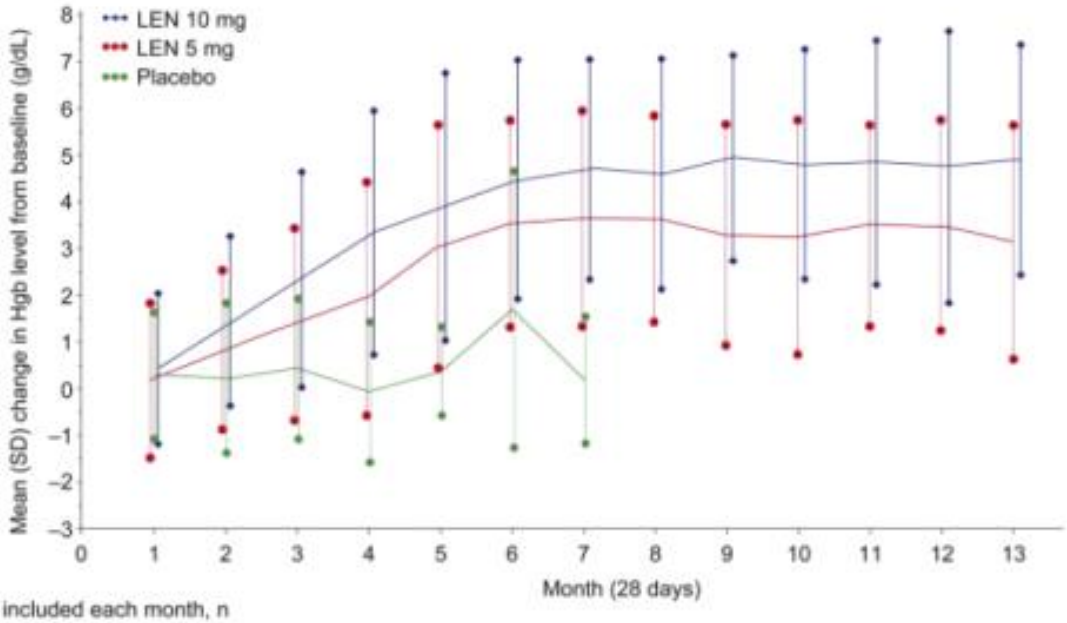
Statistic	**Placebo (N=51)**	**Lenalidomide 5 mg QD (N=47)**	**Lenalidomide 10 mg QD (N=41)**
Kaplan-Meier estimates			
Number of transfusion independent subjects	3	20	23
Number (%) who progressed (had a transfusion after response)	0 (0.0)	5 (25.0)	9 (39.1)
Number (%) who maintained transfusion independence (censored [a])	3 (100.0)	15 (75.0)	14 (60.9)
Median (weeks)	NA	NA	NA
%95 CI (weeks)	NA, NA	NA, NA	98.3, NA
Summary statistics			
N	3	20	23
Mean	61.4	107.7	108.6
SD	10.93	52.35	40.63
Median	56.1	140.9	106.0
Min, Max	54.1, 74.0	28.3, 157.0	40.0, 158.7

Note: measured from the first of the consecutive 182 days during which the subject was free of RBC transfusions to the day before the date of the first RBC transfusion after this period.

[a] Duration of response was censored at the date of last transfusion assessment for subjects who maintained transfusion independence.

Figure 4.5 shows changes from baseline in haemoglobin levels for the mITT population (see also MS, Figure 8, page 66). The data for the ITT population are reported in Table 4.14.

Figure 4.5: Mean haemoglobin change from baseline over time by randomised treatment group; mITT population (MS, Figure 8, page 66)



Patients included each month, n													
LEN 10 mg	40	38	38	36	29	26	24	24	24	24	23	23	18
LEN 5 mg	47	46	43	42	29	24	24	24	23	22	20	18	11
Placebo	51	50	49	47	7	5	4						

Data are mean ± standard deviation but were not calculated if the number of patients was ≤3.
Hgb = haemoglobin; LEN = lenalidomide; SD = standard deviation

Table 4.14: Change in haemoglobin (g/dL) from baseline to maximum value for subjects who became RBC-transfusion independent for at least 182 Days (ITT Population) (Response to Clarification Letter, B7, Table 15, page 11)

		Placebo (N=67)			**5 MG QD (N=69)**			**10 MG QD (N=69)**		
	Stat	**Baseline**	**Max**	**Change**	**Baseline**	**Max**	**Change**	**Baseline**	**Max**	**Change**
Hemoglobin (g/dL)	N	4	4	4	24	24	24	38	38	38
	Mean	10.3	12.4	2.1	8.4	13.9	5.6	8.4	14.5	6.1
	SD	1.03	1.30	0.57	0.86	1.69	1.82	1.00	1.56	1.81
	Median	10.6	12.7	2.2	8.3	14.1	5.5	8.3	14.4	6.5
	Min, Max	8.8, 11.2	10.7, 13.7	1.5, 2.7	6.4, 9.9	10.0, 16.3	1.6, 8.6	6.2, 10.8	11.1, 18.0	2.0, 10.0

Cytogenic response and progression for the ITT and mITT populations are reported in Table 4.15 and 4.16 respectively.

Table 4.15: Cytogenetic response by central review (ITT Population) (Response to Clarification Letter, B7, Table 17, page 12)

	Placebo (N=50)	**5 MG QD (N=48)**	**10 MG QD (N=61)**
Complete response	0 (0.0)	9 (18.8)	15 (24.6)
Partial response	0 (0.0)	4 (8.3)	12 (19.7)
Cytogenetic progression	5 (10.0)	12 (25.0)	12 (19.7)
Cytogenetic relapse	0 (0.0)	0 (0.0)	1 (1.6)
Not evaluable	17	21	8

Table 4.16: Cytogenetic response by central review (mITT Population) (Response to Clarification Letter, B7, Table 16, page 12)

Response category [a]	**Placebo (N [b]=41)**	**5 mg/day (N [b]=37)**	**10 mg/day (N [b]=40)**
	n (%)	**n (%)**	**n (%)**
Major response	0 (0.0)	5 (13.5)	10 (25.0)
Minor response	0 (0.0)	3 (8.1)	7 (17.5)
Cytogenetic progression	5 (12.2)	10 (27.0)	8 (20.0)
Not evaluable/data not available	10	10	1

[a] Best response
[b] Number of subjects evaluable for response

Serious infections

For serious infections, only grade 3 or 4 pneumonia was reported in the MS (MS, Table 17, page 84), see Table below. Adverse effects of treatment were reported in section 6.9 (MS, pages 79-86) for the safety population.

Table 4.17: Grade 3 or 4 adverse events reported in ≥2% of patients by treatment regimen; double-blind safety population (see MS, Table 17, page 84).

System Organ Class/ preferred term*	**Placebo (n=67), n (%)**	**Lenalidomide 5 mg (n=69), n (%)**	**Lenalidomide 10 mg (n=69),n (%)**
Infections and Infestations			
Pneumonia NOS	1 (1.5)	1 (1.4)	3 (4.3)

ERG comment

Serious infections were explicitly mentioned as a relevant outcome in the NICE scope. Therefore, the reporting of serious infections is surprisingly minimal in the MS. We have added additional data for serious infections when we could find them, these are reported below.

The 134-page Clinical Study Report, which was sent as part of the original industry submission, included reporting of infections during the double-blind treatment period in Table 39 (Adverse Events Reported in 10% or More of Patients), see Table 4.18 below.

Table 4.18: Adverse Events Reported in 10% or More of Subjects by Treatment Regimen (Double-Blind Safety Population) (see CSR, Table 39, page 98).

System Organ Class/ preferred term*	Placebo (n=67), n (%)	Lenalidomide 5 mg (n=69), n (%)	Lenalidomide 10 mg (n=69),n (%)
Infections and Infestations			
Urinary tract infection NOS	3 (4.5)	5 (7.2)	8 (11.6)
Respiratory tract infection NOS	2 (3.0)	10 (14.5)	9 (13.0)
Herpes simplex	1 (1.5)	7 (10.1)	0 (0.0)

The following description of infections was reported in the CSR (page 114):
"Infections were identified according to the MedDRA SOC of "Infections and Infestations." The incidence of infections was comparable between the lenalidomide groups (47.8% in the 5-mg group and 49.3% in the 10-mg group) and approximately twice that of the placebo group (26.9%). The most common infection was respiratory tract infection NOS, reported in 2 (3.0%) subjects in the placebo group, 10 (14.5%) subjects in the 5-mg lenalidomide group, and 9 (13.0%) subjects in the 10-mg lenalidomide group. Similarly, the incidence of SAEs in the lenalidomide groups (11.6% for each group) was approximately twice that of the placebo group (4.5%)."

Serious infections during the open-label phase are reported in the 134-page Clinical Study Report in Table 50 (Adverse Events Reported in 10% or More of Patients), 51 (Grade 3/4 Adverse Events Reported in 2 or More Patients), and 52 (Serious Adverse Events Reported in Two or More Patients) see Tables 4.19, 4.20 and 4.21 below.

Table 4.19: Adverse Events Reported in 10% or More of Subjects by Treatment Regimen (Open-label Safety Population) (see CSR, Table 50, page 120).

System Organ Class/ preferred term*	Lenalidomide 5mg QD (n=109), n (%)	Lenalidomide 10mg QD (n=28),n (%)
Infections and Infestations		
Respiratory tract infection NOS	12 (11.0)	3 (10.7)
Urinary tract infection NOS	14 (12.8)	1 (3.6)

Table 4.20: Grade 3/4 Adverse Events Reported in 2 or More Subjects by Treatment Regimen (Open-label Safety Population) (see CSR, Table 51, page 122).

System Organ Class/ preferred term*	Lenalidomide 5 mg QD (n=109), n (%)	Lenalidomide 10 mg QD (n=28),n (%)
Infections and Infestations		
Pneumonia NOS	2 (1.8)	1 (3.6)

Table 4.21: Serious Adverse Events Reported in Two or More Subjects by Treatment Regimen (Open-label Safety Population) (see CSR, Table 52, page 124).

System Organ Class/ preferred term*	Lenalidomide 5 mg QD (n=109), n (%)	Lenalidomide 10 mg QD (n=28),n (%)
Infections and Infestations		
Pneumonia NOS	2 (1.8)	1 (3.6)
Urinary tract infection NOS	2 (1.8)	0 (0.0)

Adverse effects of treatment

Adverse effects of treatment were reported in section 6.9 (MS, pages 79-86) for the safety population.

An overview of the number of patients with at least one adverse event is presented in Table 15 of the MS (page 81), see Table 4.22 below; while grade 3 or 4 adverse events are reported in Table 17 of the MS (page 83), see Table 4.23 below.

Table 4.22: Overview of adverse events (double-blind safety population) (see MS, Table 15, page 81).

AE category*	Placebo (n=67), n (%)	Lenalidomide 5 mg (n=69), n (%)	Lenalidomide 10 mg (n=69), n (%)
Patients with ≥1 AE	63 (94.0)	69 (100.00)	69 (100.0)
Patients with ≥1 AE related to study drug	33 (49.3)	68 (98.6)	66 (95.7)
Patients with ≥1 NCI CTCAE Grade 3–4 AE	29 (43.3)	62 (89.9)	65 (94.2)
Patients with ≥1 related NCI CTCAE Grade 3–4 AE	13 (19.4)	61 (88.4)	62 (88.4)
Patients with ≥1 SAE	14 (20.9)	28 (40.6)	31 (44.9)
Patients with ≥1 SAE related to study drug	1 (1.5)	17 (24.6)	13 (18.8)
Patients with an AE leading to discontinuation of study drug	3 (4.5)	11 (15.9)	6 (8.7)
Patients with an AE leading to a dose reduction or interruption	4 (6.0)	43 (62.3)	50 (72.5)

AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = serious adverse event

* A patient with multiple occurrences of an AE (preferred term using Medical Dictionary for Regulatory Activities version 5.2) is counted only once in the AE category

Table 4.23: Grade 3 or 4 adverse events reported in ≥2% of patients by treatment regimen; double-blind safety population (see MS, Table 17, page 83).

System Organ Class/ preferred term*	Placebo (n=67), n (%)	Lenalidomide 5 mg (n=69), n (%)	Lenalidomide 10 mg (n=69),n (%)
General Disorders and Administration Site Conditions			
Fatigue	1 (1.5)	0 (0.0)	2 (2.9)
Fall	0 (0.0)	1 (1.4)	2 (2.9)
Pyrexia	0 (0.0)	0 (0.0)	2 (2.9)
Infections and Infestations			
Pneumonia NOS	1 (1.5)	1 (1.4)	3 (4.3)
Investigations			
ALT increased	0 (0.0)	2 (2.9)	1 (1.4)
Metabolism and Nutritional Disorders			
Haemochromatosis	2 (3.0)	3 (4.3)	1 (1.4)
Musculoskeletal and Connective Tissue disorders			
Back pain	0 (0.0)	1 (1.4)	2 (2.9)
Respiratory, Thoracic and Mediastinal Disorders			
Dyspnoea NOS	2 (3.0)	1 (1.4)	2 (2.9)
Bronchitis NOS	(0 (0.0)	0 (0.0)	2 (2.9)
Pulmonary embolism	0 (0.0)	2 (2.9)	2 (2.9)
Skin and Subcutaneous Tissue Disorders			
Pruritus	0 (0.0)	0 (0.0)	2 (2.9)
Rash NOS	0 (0.0)	3 (4.3)	0 (0.0)
Vascular disorders			
Deep vein thrombosis	1 (1.5)	1 (1.4)	4 (5.8)

AE = adverse event; ALT = alanine aminotransferase; NOS not otherwise specified
* System Organ Class and preferred term are coded using the Medical Dictionary for Regulatory Activities version 5.2, and are listed in descending order of frequency for the 10 mg lenalidomide column. A patient with multiple occurrences of an AE counted only once in the AE category

ERG comment

More adverse events were reported in the Clinical Study Report. The two tables below show adverse events during the first 16 weeks of the double-blind phase for the safety population (Table 4.24), and grade 3 or 4 adverse events reported in 2% or more of patients in any group during the first 16 weeks of the double-blind phase for the safety population (Table 4.25). Dose reductions and interruptions by double-blind treatment regimen for the safety population are reported in Table 4.26.

Table 4.24: Adverse Events During the First 16 Weeks of the Double-blind Phase by SOC and Treatment Regimen (Double-blind Safety Population) (see CSR, Table 47, page 130).

System Organ Class[a]	**Placebo QD 28 of 28 Days (N=67)**		**Lenalidomide 5mg QD 28 of 28 Days (N=69)**		**Lenalidomide 10 mg QD 21 of 28 Days (N=69)**	
	n	(%)	n	(%)	n	(%)
Subjects with at Least One Adverse Event	64	(95.5)	69	(100.0)	69	(100.0)
Blood and Lymphatic System Disorders	21	(31.3)	59	(85.5)	56	(81.2)
Infections and Infestations	21	(31.3)	35	(50.7)	40	(58.0)
Gastrointestinal Disorders	29	(43.3)	34	(49.3)	36	(52.2)
General Disorders and Administration Site Conditions	25	(37.3)	34	(49.3)	36	(52.2)
Skin and Subcutaneous Tissue Disorders	9	(13.4)	35	(50.7)	33	(47.8)
Musculoskeletal and Connective Tissue Disorders	13	(19.4)	22	(31.9)	28	(40.6)
Nervous System Disorders	13	(19.4)	17	(24.6)	25	(36.2)
Respiratory, Thoracic and Mediastinal Disorders	11	(16.4)	20	(29.0)	17	(24.6)
Vascular Disorders	6	(9.0)	11	(15.9)	15	(21.7)
Investigations	7	(10.4)	10	(14.5)	14	(20.3)
Metabolism and Nutrition Disorders	12	(7.9)	14	(20.3)	11	(15.9)
Psychiatric Disorders	9	(13.4)	7	(10.1)	9	(13.0)
Eye Disorders	2	(3.0)	4	(5.8)	8	(11.6)
Injury, Poisoning and Procedural Complications	7	(10.4)	5	(7.2)	5	(7.2)
Renal and Urinary Disorders	3	(4.5)	3	(4.3)	5	(7.2)
Neoplasms Benign, Malignant, and Unspecified (Incl Cysts and Polyps)	2	(3.0)	2	(2.9)	3	(4.3)
Endocrine Disorders	0	(0.0)	1	(1.4)	3	(4.3)
Reproductive System and Breast Disorders	1	(1.5)	2	(2.9)	2	(2.9)
Cardiac Disorders	6	(9.0)	6	(8.7)	1	(1.4)
Hepatobiliary Disorders	1	(1.5)	4	(5.8)	0	(0.0)
Ear and Labyrinth Disorders	2	(3.0)	3	(4.3)	0	(0.0)
Immune System Disorders	0	(0.0)	1	(1.4)	0	(0.0)

[a] System organ classes are coded using the MedDRA dictionary, and are listed in descending order of frequency in the 10-mg lenalidomide column.

Table 4.25: Grade 3/4 Adverse Events Reported in 2% or More of Subjects in any Group During the First 16 Weeks of the Double-blind Phase (Double-blind Safety Population) (see CSR, Table 49, page 133-4).

System Organ Class/Preferred Term[a]	Placebo QD 28 of 28 Days (N=67)		Lenalidomide 5mg QD 28 of 28 Days (N=69)		Lenalidomide 10 mg QD 21 of 28 Days (N=69)	
	n	(%)	n	(%)	n	(%)
Subjects with at Least One NCI CTC Grade 3 or 4 Adverse Event	**28**	**(41.8)**	**60**	**(87.0)**	**62**	**(89.9)**
Blood and Lymphatic System Disorders	**18**	**(26.9)**	**56**	**(81.2)**	**54**	**(78.3)**
Neutropenia	10	(14.9)	51	(73.9)	51	(73.9)
Anemia	6	(9.0)	2	(2.9)	1	(1.4)
Thrombocytopenia	1	(1.5)	22	(31.9)	25	(36.2)
Febrile neutropenia	0	(0.0)	2	(2.9)	1	(1.4)
Leukopenia	0	(0.0)	8	(11.6)	6	(8.7)
Metabolism and Nutrition Disorders	**4**	**(6.0)**	**5**	**(7.2)**	**2**	**(2.9)**
Iron Overload	2	(3.0)	2	(2.9)	0	(0.0)
Infections and Infestations	**3**	**(4.5)**	**6**	**(8.7)**	**9**	**(13.0)**
Pneumonia	1	(1.5)	1	(1.4)	3	(4.3)
Bronchitis	0	(0.0)	0	(0.0)	2	(2.9)
Respiratory, Thoracic and Mediastinal Disorders	**3**	**(4.5)**	**2**	**(2.9)**	**4**	**(5.8)**
Dyspnea	2	(3.0)	1	(1.4)	2	(2.9)
Pulmonary embolism	0	(0.0)	1	(1.4)	2	(2.9)
General Disorders and Administration Site Conditions	**2**	**(3.0)**	**2**	**(2.9)**	**5**	**(7.2)**
Fatigue	1	(1.5)	0	(0.0)	2	(2.9)
Pyrexia	0	(0.0)	0	(0.0)	2	(2.9)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**1**	**(1.5)**	**2**	**(2.9)**	**2**	**(2.9)**
Acute myeloid leukemia	1	(1.5)	2	(2.9)	0	(0.0)
Skin and Subcutaneous Tissue Disorders	**1**	**(1.5)**	**3**	**(4.3)**	**2**	**(2.9)**
Pruritus	0	(0.0)	0	(0.0)	2	(2.9)
Vascular Disorders	**1**	**(1.5)**	**1**	**(1.4)**	**5**	**(7.2)**
Deep vein thrombosis	1	(1.5)	1	(1.4)	3	(4.3)
Cardiac Disorders	**0**	**(0.0)**	**2**	**(2.9)**	**1**	**(1.4)**
Cardiac Failure	0	(0.0)	2	(2.9)	0	(0.0)
Investigations	**0**	**(0.0)**	**2**	**(2.9)**	**4**	**(5.8)**
Alanine aminotransferase increased	0	(0.0)	2	(2.9)	1	(1.4)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary, and are listed in descending order of frequency in the placebo column. A subject with multiple occurrences of an AE is counted only once in the AE category.

Table 4.26: Dose Reductions and Interruptions by Double-blind Treatment Regimen (Double-blind Safety Population) (see CSR, Table 44, page 125).

Dose Reduction	Placebo QD 28 of 28 Days (N=67)		Lenalidomide 5mg QD 28 of 28 Days (N=69)		Lenalidomide 10 mg QD 21 of 28 Days (N=69)	
	n	(%)	n	(%)	n	(%)
Had at Least One Dose Reduction/Interruption Due to AE						
Yes	2	(3.0)	41	(59.4)	43	(62.3)
No	65	(97.0)	28	(40.6)	26	(37.7)
Time to First Dose Reduction /Interruption (Days) Due to AE[a]						
Mean	79.0		59.2		50.1	
SD	9.90		48.75		56.66	
Median	79.0		43.0		27.0	
Min, Max	72.0, 86.0		7.0, 215.0		10.0, 269.0	
Duration of First Dose Interruption (Days)[b]						
Mean	7.0		16.2		26.8	
SD	8.49		15.50		34.37	
Median	7.0		11.0		14.0	
Min, Max	1.0, 13.0		1.0, 64.0		1.0, 161.0	
Had Second Dose Reduction /Interruption Due to AE						
Yes	0	(0.0)	8	(11.6)	24	(34.8)
No	67	(100.0)	61	(88.4)	45	(65.2)

[a] Time to dose reduction/interruption is the time from first dose of study medication to the start of first reduction/interruption.

[b] Duration of dose interruption is the time from last dose of one dosing regimen to first dose of the next dosing regimen. A dosing change is considered an interruption if the start of the new dosing record is greater than 1 day after the end of the previous dosing record.

ERG comment

The most common adverse events of lenalidomide for MDS with del(5q) were neutropenia and thromobocytopenia with 74% and 36%, respectively.

Health-related quality of life

The manufacturer's submission provides a graph with absolute change in FACT-An scores from baseline among patients who achieved transfusion independence for ≥26 weeks in the placebo group at Week 12 (before crossover) and the lenalidomide 5mg and 10mg groups at Weeks 12, 24, 36, and 48 (see MS, Figure 9, page 67-68).

ERG comment

As stated in the manufacturer's submission (MS, page 67), the double-blind and longitudinal results are descriptive and exploratory, because of the study design and missing data after Week 16. Therefore, we will only reproduce the change in HRQoL from baseline to week 12. These data are reported in Table 4.28 in chapter 4.5 of this report.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison or mixed treatment comparison evidence synthesis was included in the submission.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparison or mixed treatment comparison evidence synthesis was included in the submission.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Baseline patient characteristics (ITT population)

As reported in section 4.2.1, baseline characteristics were only reported for the mITT population. While baseline patient characteristics for the ITT population were not reported in the MS. Based on the Clinical Study Report, most baseline characteristics as for the ITT population could be reproduced. These are reported in Table 4.27 below.

Table 4.27: Baseline Demographic and Disease-related Characteristics by Treatment Group and Overall (ITT Population)

Characteristic	Placebo (N=67)	Lenalidomide 5 mg (N=69)	Lenalidomide 10 mg (n=69)	Overall (n=205)
Age, years: median (range)	68 (39–85)	66 (40–86)	68 (36–84)	67 (36–86)
Female sex, n (%)	54 (80.6)	53 (76.8)	49 (71.0)	156 (76.1)
Time since diagnosis, years: median (range)	2.4 (0.2–14.3)	2.7 (0.2–17.1)	2.5 (0.2–29.2)	2.6 (0.2–29.2)
Transfusion burden, units/8 weeks: median (range)	6 (2–12)	6 (1–25)	6 (2–12)	6 (1–25)
IPSS risk category (central review), n (%)				
Low	30 (44.8)	20 (29.0)	20 (29.0)	70 (34.1)
Intermediate-1	22 (32.8)	29 (42.0)	23 (33.3)	74 (36.1)
Intermediate-2 (1.5 – 2.0)	2 (3.0)	5 (7.2)	3 (4.3)	10 (4.9)
High Risk (≥ 2.5)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.5)
Missing	13 (19.4)	15 (21.7)	22 (31.9)	50 (24.4)
WPSS risk category, n (%)				
Very low	0	0	0	0
Low	2 (3.0)	7 (10.1)	2 (2.9)	11 (5.4)
Intermediate	34 (50.7)	24 (34.8)	26 (37.7)	84 (41.0)
High	16 (23.9)	23 (33.3)	19 (27.5)	58 (28.3)
Very high	1 (1.5)	0 (0.0)	2 (2.9)	3 (1.5)
Missing	14 (20.9)	15 (21.7)	20 (29.0)	49 (23.9)
FAB classification (central review), n (%)				
RA	37 (55.2)	38 (55.1)	32 (46.4)	107 (52.2)
RARS	8 (11.9)	7 (10.1)	9 (13.0)	24 (11.7)
RAEB	4 (6.0)	9 (13.0)	9 (13.0)	22 (10.7)
CMML	1 (1.5)	2 (2.9)	0 (0.0)	3 (1.5)
Specimen not adequate from diagnosis	12 (17.9)	11 (15.9)	17 (24.6)	40 (19.5)
Other or missing	5 (7.5)	2 (2.9)	2 (2.8)	9 (4.4)
WHO classification, n (%)				
RA	NR	NR	NR	NR

RARS	NR	NR	NR	NR
RAEB-1	NR	NR	NR	NR
RAEB-2	NR	NR	NR	NR
RCMD	NR	NR	NR	NR
5q– syndrome	NR	NR	NR	NR
Unknown	NR	NR	NR	NR
Missing	NR	NR	NR	NR
EPO level, n(%)				
≤500 mIU/ml	23 (34.3)	19 (27.5)	23 (33.3)	65 (31.7)
>500 mIU/ml	35 (52.2)	39 (56.5)	33 (47.8)	69 (52.2)
Missing	9 (13.4)	11 (15.9)	13 (18.8)	33 (16.1)
Prior EPO use, n (%)	33 (49.3)	35 (50.7)	40 (58.0)	108 (52.7)
Karyotype, n (%)				
Isolated del(5q)	45 (67.2)	43 (62.3)	47 (68.1)	135 (65.9)
del(5q) + ≥1additional abnormality	18 (26.9)	20 (28.9)	17 (24.6)	55 (26.8)
ANC 0.5–1.0 x 10^9/l, n (%)	NR	NR	NR	NR
Platelet count, n(%)				
<150 x 10^9/l	NR	NR	NR	NR
25–50 x 10^9/l	NR	NR	NR	NR
≥150 x 10^9/l	NR	NR	NR	NR

ANC = absolute neutrophil count; CMML = chronic myelomonocytic leukaemia; EPO = erythropoietin; FAB = French–American–British; IPSS = International Prognostic Scoring System; RA = refractory anaemia; RAEB = RA with excess blasts; RARS = RA with ringed sideroblasts; RCMD = refractory cytopenias with multilineage dysplasia; WPSS = WHO Prognostic Scoring System

Health Related Quality of Life

In the MS, the manufacturer's submission provides a graph with absolute change in FACT-An scores from baseline among patients who achieved transfusion independence for ≥26 weeks in the placebo group at Week 12 (before crossover) and the lenalidomide 5mg and 10mg groups at Weeks 12, 24, 36, and 48 (see MS, Figure 9, page 67-68). No actual data for HRQoL are reported.

In addition, as reported in section 4.2.2, the double-blind and longitudinal results for HRQoL are descriptive and exploratory, because of the study design and missing data after Week 16. Therefore, we will reproduce the change in HRQoL from baseline to week 12 based on the data reported in the Clinical Study Report. These data are reported in Table 4.28 below.

Table 4.28: Health Related Quality of Life – Baseline scores and Change from Baseline at 12 weeks (N, Mean (SD) - Safety Population)

	Placebo		**Lenalidomide 5mg (N=69)**		**Lenalidomide 10mg (n=69)**	
	Baseline N, Mean (SD)	**12-week Change** N, Mean (SD)	**Baseline** N, Mean (SD)	**12-week Change** N, Mean (SD)	**Baseline** N, Mean (SD)	**12-week Change** N, Mean (SD)
FACT Subscales:						
- Physical Well-Being	65, 21.4 (5.18)	54, 0.3 (4.27)	60, 21.8 (4.20)	47, 0.9 (2.84)	63, 21.5 (4.42)	54, 0.8 (4.89)
- Social/Family Well-Being	65, 20.4 (6.29)	53, -0.4 (5.97)	61, 22.4 (5.10)	47, -0.7 (6.28)	62, 20.8 (5.38)	53, 0.0 (4.92)
- Emotional Well-Being	64, 17.6, (4.49)	54, -0.3 (3.18)	60, 17.6, (4.00)	47, 1.1 (2.49)	62, 17.2, (3.84)	52, 1.0 (4.34)
- Functional Well-Being	64, 16.5 (5.75)	54, -1.2 (4.52)	60, 16.5 (5.53)	47, 0.3 (4.35)	62, 16.5 (5.28)	52, -0.1 (4.81)
- Additional Concerns	64, 49.7 (14.90)	54, -1.1 (11.17)	59, 52.1 (12.03)	46, 4.2 (10.59)	64, 50.6 (12.95)	52, 4.2 (12.21)
- Fatigue	64, 30.6 (11.58)	54, -0.4 (9.54)	59, 32.6 (9.24)	46, 3.2 (8.73)	64, 31.5 (9.67)	52, 3.0 (9.39)
FACT-G total score	63, 73.2 (15.57)	50, -1.7 (10.16)	59, 74.9 (13.54)	45, 1.9 (10.26)	59, 73.0 (12.32)	49, 1.9 (13.34)
TOI-An total score	64, 85.7 (24.14)	52, -1.1 (17.13)	59, 88.3 (19.74)	46, 5.6 (15.56)	60, 86.1 (18.45)	49, 4.9 (18.16)
TOI-F total score	64, 67.2 (20.87)	53, -0.8 (14.76)	59, 69.5 (17.18)	46, 4.8 (14.21)	60, 67.9 (15.39)	49, 3.9 (15.47)
FACT-An score	64, 121.5 (28.49)	52, -2.5 (18.50)	59, 125.7 (23.63)	45, 5.9 (18.26)	59, 121.8 (22.24)	48, 5.8 (23.17)

Additional information from the manufacturer regarding the FACT-An scale (see Response to Clarification Letter, B16, page 17):

"The Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire was used to assess HRQoL. The FACT–An is composed of two subscales: the FACT-G (general) and the FACT-An (anemia). The FACT-G measures general HRQoL in cancer patients within four domains: physical, social, emotional and functional. The Anemia subscale measures the cancer-related symptoms of anemia and fatigue. Higher overall scores indicate better HRQoL (Yellen, 1997)[24].

An additional description of FACT-An is obtained from Cella (2002)[25]:

The Functional Assessment of Cancer Therapy—Anemia (FACT-An [47 items]) consists of 5 subscales; physical well-being (PWB; 7 items), social/family well-being (SWB; 7 items), emotional well-being (EWB; 6 items), functional well-being (FWB; 7 items), and anemia symptoms (AS; 20 items). The PWB, SWB, EWB, and FWB subscales can be summed to form the FACT—General (FACT-G) score. The PWB, FWB, and AS subscales can be summed to form the Trial Outcome Index— Anemia (TOI-An)."

ERG comment

According to the manufacturer, an absolute change from baseline in FACT-An scores of seven points is a minimal clinically important difference. As can be seen in Table 4.28, mean change from baseline at Week 12 was 8.3 points higher in the lenalidomide 10mg (5.8 versus –2.5) group than in the placebo group; and 8.4 points higher in the lenalidomide 5mg (5.9 versus –2.5) group than in the placebo group. Both differences were reported as statistically significant ($p<0.05$) by the manufacturer. However, although the difference between the groups in change from baseline was statistically significant the change within each treatment group was smaller than their recommended minimal clinically significant change. The sample size was small and the change from baseline was very variable (indicated by the high standard deviation).

In addition, HRQoL data from the MDS-004 trial were reported in a paper by Revicki et al. (2013).[21] As reported in the manufacturer's submission "the Revicki study results differ from the trial results in two important ways. The Revicki paper reports data for the ITT population, whereas the trial reports HRQoL for the safety population. In addition, FACT-An scores were available for 81% of randomised patients in the Revicki study, while the trial only had available FACT-An scores for 71% of randomised patients." (see MS, section 6.2.3, page 39). The data from the Revicki paper are reproduced in table 4.29 below.

Table 4.29: Mean changes in FACT-An scores from baseline to Week 12 by treatment group

Measure	Treatment	N	Baseline Mean (SD)	Post Baseline Mean (SD)	Mean Change	P-value[1]
FACT-An Total	Placebo	50	124.0 (27.2)	121.0 (27.2)	-2.8	
	Lenalidomide 5 mg	44	126.1 (25.4)	131.8 (25.0)	5.7	<0.05
	Lenalidomide 10 mg	48	122.3 (21.0)	128.0 (23.2)	5.7	<0.05
FACT-An TOI	Placebo	52	85.4 (23.1)	84.3 (23.4)	-1.1	
	Lenalidomide 5 mg	46	87.9 (20.4)	93.5 (20.0)	5.6	<0.05
	Lenalidomide 10 mg	49	85.7 (17.1)	90.6 (19.3)	4.9	0.103
FACT-F TOI	Placebo	53	66.4 (20.0)	65.6 (20.1)	-0.8	
	Lenalidomide 5 mg	46	68.9 (17.7)	73.7 (17.6)	4.8	<0.05
	Lenalidomide 10 mg	49	67.3 (14.4)	71.2 (16.6)	3.9	0.128
FACT-An subscale	Placebo	54	49.0 (13.9)	47.9 (15.0)	-1.1	
	Lenalidomide 5 mg	46	52.6 (12.2)	56.7 (12.2)	4.2	<0.05
	Lenalidomide 10 mg	52	50.2 (12.4)	54.4 (13.4)	4.2	<0.05
FACT-F subscale	Placebo	54	29.9 (10.8)	29.4 (11.4)	-0.4	
	Lenalidomide 5 mg	46	32.8 (9.3)	35.9 (9.6)	3.2	<0.05
	Lenalidomide 10 mg	52	31.2 (9.3)	34.2 (10.3)	3.0	<0.05
FACT-G Total	Placebo	50	74.5 (15.3)	72.8 (15.9)	-1.7	
	Lenalidomide 5 mg	45	73.9 (14.3)	75.8 (14.4)	1.9	0.193
	Lenalidomide 10 mg	49	72.4 (12.6)	74.3 (12.3)	1.9	0.273
FWB	Placebo	54	16.6 (5.9)	15.4 (5.6)	-1.2	
	Lenalidomide 5 mg	47	16.1 (5.8)	16.4 (5.8)	0.3	0.190
	Lenalidomide 10 mg	52	16.1 (5.5)	16.0 (4.5)	-0.1	0.396
PWB	Placebo	54	21.4 (4.9)	21.7 (5.8)	0.3	
	Lenalidomide 5 mg	47	21.6 (4.4)	22.4 (4.4)	0.9	0.628
	Lenalidomide 10 mg	54	21.4 (4.5)	22.2 (4.5)	0.8	0.768
EWB	Placebo	54	17.9 (4.1)	17.6 (4.5)	-0.3	
	Lenalidomide 5 mg	47	17.4 (4.4)	18.5 (4.3)	1.1	0.075
	Lenalidomide 10mg	52	17.0 (4.1)	18.0 (4.5)	1.0	0.163
SWB	Placebo	53	20.7 (5.8)	20.3 (5.6)	-0.4	
	Lenalidomide 5 mg	47	22.1 (5.1)	21.4 (4.8)	-0.7	0.718
	Lenalidomide 10 mg	53	20.7 (5.4)	20.7 (4.4)	0.0	0.844

[1]P-value from ANCOVA, adjusting for baseline score, for lenalidomide 5mg vs. placebo and lenalidomide 10mg vs. placebo

Adverse events

Adverse events from the MDS-004 trial are extensively reported in the manufacturer's submission and in the Clinical Study Report for the MDS-004 trial. However, as reported in our critique of the manufacturer's search strategy (chapter 4.1) the manufacturer's submission did not include separate searches for non-RCT evidence to find evidence for adverse events related to lenalidomide for patients with MDS associated with a deletion 5q cytogenetic abnormality.

Additional adverse events data are reported in the MDS-003[5] trial and in a study by the Groupe Francophone des Myélodysplasies (GFM) in France[26].

In the GFM study in France, 95 RBC transfusion dependent lower risk MDS patients with del(5q) were treated with lenalidomide (10 mg/day, 3 weeks/ 4weeks). Median age was 70.4 years, and median interval from diagnosis 29 months. IPSS was low in 31% and intermediate-1 in 69% patients. Del 5q was isolated, with 1 additional and >1 additional abnormality in 79%, 14%, and 6% patients, respectively. Median follow-up was 18.5 months, and the median number of days of treatment was 183 (range 3 – 1029+).

The following adverse events were reported:

- Main side effects were cytopenias.
- 37.9% of the patients developed grade 3–4 thrombocytopenia.
- Bleeding disorders related to thrombocytopenia were seen in three patients including one nonfatal CNS bleeding, one epistaxis requiring RBC transfusions and one large hematoma.
- 74% of the patients developed grade 3–4 neutropenia.
- 48% of the patients had to stop or reduce Lenalidomide treatment due to side effects.
- Three patients died from cytopenias during the first eight weeks of treatment: two died from sepsis after seven and eight weeks of Lenalidomide.
- Eight patients (9.5%) developed venous thromboembolism (VTE), including leg or arm deep phlebitis in six and pulmonary embolism in two, after a median of 16 weeks (range 8–90) of Lenalidomide treatment all confirmed by imaging.
- Grade 3–4 nonhematological side effects were Quincke's edema (n = 1), rash (n = 1), diarrhea (n = 1) and pruritus (n = 1). Grade 1-2 nonhematological side effects were diarrhea (n = 12), nausea (n = 8) and infectious complications (n = 8) (one oral candidiasis, two skin infections, one herpes zoster, one otitis, three febrile episodes of undetermined origin without neutropenia).
- 11 patients stopped Lenalidomide before week 16, including two who achieved TI. Reasons for early discontinuation of Lenalidomide were non-hematological side effects in four patients, cytopenias (n = 2), DVT (n = 2), patient's decision (n = 1), physician's decision without toxicity after achievement of TI (n = 1) and sepsis (n = 1).
- Six (6.3%) patients progressed to AML during progression and 15 patients died, including six patients who had achieved TI. Three deaths were related to cytopenias during the first weeks of treatment, three resulted from AML, three from sudden death at

home (two of those patients were older than 90 years), five from unrelated causes, and one from unknown cause.

In the MDS-003 trial, 148 patients with a similar profile as those in the GFM-study, received 10mg of lenalidomide for 21 days every four weeks or daily. Grade 3 and 4 treatment-related adverse events are summarised in the Table below.

Table 4.30: Grade 3 and 4 treatment-related adverse events as reported in the MDS-003 trial[5]

Adverse Event	**Grade 3**		**Grade 4**		**Grade 3 or 4**
	Continuous Daily Dosing* (N = 102)	21-Day Dosing* (N = 46)	Continuous Daily Dosing* (N = 102)	21-Day Dosing* (N = 46)	Both Schedules (N = 148)
	Number of patients (percentage)				
Neutropenia	20 (20)	8 (17)	45 (44)	8 (17)	81 (55)
Thrombocytopenia	37 (36)	14 (30)	7 (7)	7 (15)	65 (44)
Anemia (not otherwise specified)	4 (4)	2 (4)	4 (4)	0	10 (7)
Leukopenia (not otherwise specified)	3 (3)	2 (4)	4 (4)	0	9 (6)
Rash	5 (5)	4 (9)	0	0	9 (6)
Febrile neutropenia	2 (2)	1 (2)	2 (2)	1 (2)	1 (1)
Pruritus	2 (2)	2 (4)	0	0	4 (3)
Fatigue	2 (2)	2 (4)	0	0	4 (3)
Muscle cramp	3 (3)	0	0	0	3 (2)
Pneumonia	1 (1)	2 (4)	1 (1)	0	4 (3)
Nausea	3 (3)	1 (2)	0	0	4 (3)
Diarrhea	4 (4)	0	0	0	4 (3)
Deep-vein thrombosis	3 (3)	1 (2)	0	0	4 (3)
Hemorrhage	1 (1)	2 (4)	1 (1)	1 (2)	4 (3)
Hypokalemia	1 (1)	1 (2)	0	0	2 (1)
Pyrexia	1 (1)	0	0	0	1(1)

*The daily dose was 10 mg

In the MDS-003 trial, 16 patients progressed to a more advanced French–American–British (FAB) MDS subtype or AML and 24 developed new chromosomal abnormalities during the course of treatment.[5] With long-term follow up (median of over three years) of 42 patients treated on this trial, 15 patients (36%) progressed to AML and 17 (40%) had karyotypic evolution. With the exception of one patient, all of these patients died within several months of AML diagnosis.[27]

ERG comment

One of the main concerns for patients treated with lenalidomide is the incidence of increased clonal evolution and progression to AML.[1] Given the short follow-up time (16 weeks) and

the subsequent possibility to cross-over from placebo to active drug, changes of detecting prolonged survival or acceleration of leukemia progression are limited.

4.6 Conclusions of the clinical effectiveness section

The MS relies on one trial: MDS-004. MDS-004 is a three-arm study conducted throughout Europe, all patients had lower-risk MDS with del(5q) with or without additional cytogenetic abnormalities, and red bold cell (RBC) transfusion-dependent anaemia. A total of 205 patients were randomised to lenalidomide 10mg on days 1–21, lenalidomide 5mg on days 1–28, or placebo on days 1–28 for each four week cycle. Crossover was allowed at 16 weeks if at least a minor erythroid response was not achieved, and all but 11 patients on the placebo arm crossed over to lenalidomide 5mg. The primary endpoint was RBC transfusion independence for ≥26 weeks and was reached in 56.1%, 42.6%, and 5.9% of patients, respectively (compared with placebo, both $p < 0.001$). Cytogenetic response rates were 50% in the 10mg group and 25% in the 5mg group. Median duration of TI was not reached in either lenalidomide group after a median follow up of 1.55 years, and response was 48% of patients responding after one cycle and an additional 37% after two cycles. Of the patients who initially received placebo and crossed over to lenalidomide 5mg, 30.4% progressed to AML compared with 23.2% in the 5mg group and 21.7 in the 10mg group. Median overall survival was not statistically significant between the groups and ranged between 35.5 and 44.5 months. The most common adverse events of lenalidomide for MDS with del(5q) were neutropenia and thrombocytopenia with 74% and 36%, respectively.

The two main problems with the clinical effectiveness data reported in the MS are:

1. The possibility of treatment switching after 16 weeks due to dose-limiting toxicities or lack of response, which means that most long term effectiveness data are unreliable.

   Given that 62.3% of patients in the lenalidomide 5mg group and 72.5% in the lenalidomide 10mg group experienced an AE leading to dose reduction or interruption, and one dose reduction in the 10mg group means patients receive effectively the same dose as the 5mg group, it seems there is some difficulty in distinguishing the treatment arms. In addition, patients in the placebo or lenalidomide 5mg groups without minor erythroid response by Week 16 or those experiencing erythroid relapse could crossover to lenalidomide 5mg or 10mg, respectively. In the placebo group, only one out of 67 patients completed the 52 weeks double-blind phase. This means that the assessment of effects after 16 weeks is severely compromised.

2. Data were reported for two populations: the ITT and mITT population. The mITT population included patients with centrally confirmed low- or intermediate-1-risk MDS with del(5q) and documented RBC transfusion-dependence, who received ≥1 dose of study drug. The fact that confirmation of del(5q) status (karyotype analysis) and bone marrow morphology was performed by central haematological review after randomisation,

means that patients not fulfilling the inclusion criteria are included in the ITT population. It is not clear how differences between these two populations influence results. However, data for the ITT population were used in the economic model as it "more closely matches the relevant NICE scope" (MS, section 7.2.1, page 96).

One of the main concerns for patients treated with lenalidomide is the incidence of increased clonal evolution and progression to AML.[1] Given the short follow-up time (16 weeks) and the subsequent possibility to cross-over from placebo to active drug, chances of detecting prolonged survival or acceleration of leukaemia progression are limited.

5. COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Objective of cost effectiveness review

A comprehensive systematic review was conducted to identify all economic studies relevant to the decision problem. The search strategies for the cost-effectiveness review are discussed in detail in section 4.1.1.

5.1.2 Inclusion/exclusion criteria used in the study selection

The in- and exclusion criteria of the study selection could not be found in chapter 7 of the MS nor in section 10.10 of appendix 10.

5.1.3 Included/excluded studies in the cost effectiveness review

The manufacturer identified 398 potentially relevant studies of which six remained after removing duplicates and reviewing titles and abstracts. The following table (table 5.1) presents the key characteristics of included studies.

Table 5.1: Study characteristics of the economic evaluations identified

Lead author	Year	Country(ies)	N	Patient group	Type of information
Gidwani[28]	2012	US	n/a	MDS	Cost-effectiveness Markov model tracking hypothetical cohorts of MDS patients treated with azacitidine or decitabine
El Ouagari[29]	2011	Canada	n/a	Low or int-1 risk MDS	Comparing cost-effectiveness of deferasirox with s no chelation therapy in TD patients
Kuhne[30]	2010	Germany	116	TD MDS low/int-1 risk	Economic burden
Lafeuille[31]	2008	USA	3,312	MDS	Cost of treatment with Epoetin Alfa and Darbepoetin Alfa
Goss[32]	2006	USA	n/a	Low/Int-1 risk transfusion dependent MDS associated with del-5q	Decision analytic model to compare costs and outcomes of lenalidomide with BSC
Casadevall[33]	2004	France	60	MDS & anaemia	Cost and QOL (FACT-An) for ESA+G-CSF patients vs standard care

Five of these studies were considered irrelevant since these were not cost-effectiveness studies[30, 31, 33] or because the interventions included were not specified in the current decision

problem[28, 29]. The study of Goss[32] was potentially relevant since it was conducted among the appropriate population and included relevant treatments. According to their results, the ICER was $35,050 per QALY. However, a one year time perspective was chosen which is unlikely to be sufficient to determine the true cost-effectiveness.

5.1.4 Conclusions of the cost effectiveness review

The ERG agrees with the conclusions from the manufacturer that none of the selected studies were relevant for the decision problem. However, it is not entirely clear what the in-and exclusion criteria were.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

Table 5.2 presents a summary of the de novo economic model developed by the manufacturer. The ERG has assessed the manufacturer's economic evaluation using the Philips et al. checklist for quality assessing decision analytic models[34]. This is shown in Appendix 3 and is used to assist the narrative critique in the following sections.

Table 5.2 Summary of the manufacturer's economic evaluation

	Approach	Source/Justification	Signpost (location in MS)
Model	Markov cohort model with transition probabilities based on a patient's transfusion status, iron chelation therapy, progression to AML and death with a 28 day cycle length.	The model structure was chosen to capture the main features of MDS. The cycle length was based on the dosing interval for lenalidomide.	Section 7.2.3 (p97) and 7.2.5 (p99)
States and events	14 health states are distinguished; • Transfusion independence • Transfusion dependency without requirement for iron chelation • Transfusion dependency without requirement for iron chelation and cardiac disease • Transfusion dependency with response to iron chelation • Transfusion dependency with response to iron chelation and cardiac disease • Transfusion dependency with non-response to iron chelation • Transfusion dependency with non-response to iron chelation and cardiac disease • Transfusion dependency with non-response to iron chelation and diabetes • Transfusion dependency with non-response to iron chelation and hepatic complications • Acute myeloid leukaemia • Acute myeloid leukaemia and cardiac disease • AML and diabetes from adverse reaction to iron overload • AML and hepatic complications from adverse reaction to iron overload • Death	Health states were based upon the 3 clinical features of MDS; transfusion status, iron chelation requirements and progression to AML	Section 7.2.4 (p98)
Comparators	Best supportive care including blood transfusions and for 28% of the patients ESA followed by G-CSF (for non-responders).	Blood transfusions, ESA and G-CSF are currently the only treatment options in the UK.	Section 7.2.8 (p101)
Natural history	Based on the Markov model.	Response rate of the placebo group in the MDS-004 trial was used as well as response rates for ESA and G-CSF from the literature.	Section 7.3.1 (p106)
Treatment effectiveness	Treatment influences the proportion of patients becoming transfusion independent and the duration of response. Note that mortality is expressed as a function of initial response and not treatment directly)	Response rate (in terms of proportion that are transfusion independent at 84 days) of the treatment group was obtained from the MDS-004 trial. Duration of response for lenalidomide and BSC was based on the 10mg and 5mg data of the MDS-004.	Section 7.3.1 (p106)

	Approach	Source/Justification	Signpost (location in MS)
Adverse events	• Two adverse events related to lenalidomide were included as onetime events with impact on costs, not on utility. • Complications of transfusion dependence and iron overload were included as separate health states.	• Only two adverse events were included; thrombocytopenia and neutropenia since these were considered serious enough and different between the treatment and comparator group. • Transfusion dependent patients are at risk of complications which were cardiac diseases in the model. Transfusion dependent patients that do not respond to chelation therapy are at risk of iron overload complications that were diabetes and hepatic complications in the model.	• Section 7.3.1 (p125) • Section 7.3.1 (p114,p116)
Health related QoL	Utility scores are assigned to the transfusion independent, transfusion dependent and AML health states and utility decrements for cardiac disease, diabetes and hepatic complications.	Utility values were obtained from the literature since mapping the Fact-An data to EQ-5D reliably failed.	Section 7.4.9 (p148)
Resource utilisation and costs	Treatment cost (e.g. technology costs of lenalidomide and ESA, monitoring cost and tests) and health state cost (treatment cost AML, transfusion cost, unit cost for complications and adverse events).	Based on UK reference costs and literature.	Section 7.4.20 (p154) to 7.4.23 (p158).
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case	Section 7.2.6 p(100)
Sub groups	No subgroup analysis undertaken	Subgroup analyses explored as part of ongoing regulatory discussions with the EMA.	Section 7.8.1 (p174)
Sensitivity analysis	One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis	Ranges based on observed confidence intervals and assumptions.	Section 7.6.7 (p167) to 7.6.11 (p172)

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3 Comparison of the MS model with the NICE reference case

Elements of the economic evaluation	**Reference Case**	**Included in submission**	**Comment on whether de novo evaluation meets requirements of NICE reference case**
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Time horizon is 20 years, average age 67.
Synthesis of evidence in outcomes	Systematic review	No	Most parameters were based on the MDS-004 trial, some were identified by a non-systematic search
Measure of health effects	QALYs	Yes	
Source of data for measurement HRQOL	Reported directly by patients and/or carers.	No	Obtained from literature, general health descriptions are valued
Source of preference data for valuation of changes in HRQOL	Sample of public	No	TTO among 21 UK MDS patients
Discount rate	Annual rate of 3.5 on costs and health effects	Yes	
Equity weighting	No special weighting	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	

5.2.2 Model structure

An Excel-based Markov cohort model was developed to calculate the cost effectiveness of lenalidomide for MDS patients. The model was developed to reflect three key features of MDS del(5q) treatment:

1. A patient's transfusion requirements, i.e. whether they are transfusion independent or transfusion dependent, the latter subject to increased risk of cardiac disease.

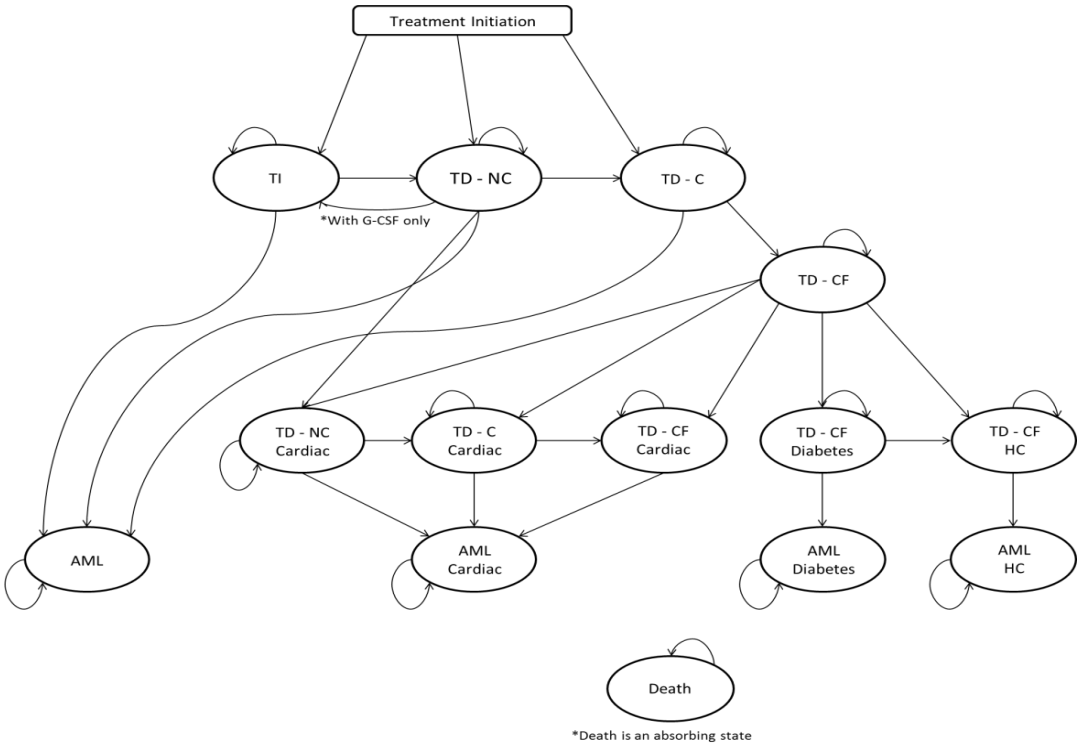
2. Whether a patient requires iron chelation, following a certain number of RBCs and thus is at risk of other complications.

3. Whether a patient has progressed to acute myeloid leukaemia (AML).

These key features together with the complications associated with transfusion dependency and iron chelation translate into a model with 14 health states. The diagrammatical representation of the model as reported by the manufacturer is presented by Figure 5.1.

The model is primarily based on data from the MDS-004 trial, which is supplemented by data from the literature and clinical opinion.

Figure 5.1: Model structure as provided by the manufacturer



TI = transfusion independent, TD = Transfusion dependent, NC = No chelation, C = Chelation, CF = Chelation Failure, Cardiac = cardiac disease, Diabetes = Diabetes, AML = acute myeloid leukaemia, HC = Hepatic conditions.

After treatment initiation, patients respond to treatment and become transfusion independent (TI) or do not respond and become transfusion dependent (TD). Once TI, patients can continue to be TI, stop responding and become TD, progress to AML or die. After progression to AML, patients either stay in the AML state or die.

Patients who become TD, both non responders and patients who stopped responding after an initial response, are at increased risk of cardiac disease and may enter one of the three cardiac health states (TD-NC Cardiac, TD-C Cardiac or TD-CF Cardiac). From one of the cardiac health states patients may progress to AML or die.

A distinction is made between TD patients who do not require chelation (NC) or do require chelation (C). Chelation requirements are dependent on transfusion history and number of transfusions during the modelling period. Patients who respond to chelation therapy remain in the TD-C health state. Patients who fail to respond enter the chelation failure health state (TD-CF). Besides being at risk for cardiac disease, these patients are at risk of iron overload complications which were assumed to be diabetes and hepatic complications. From both complication states, TD-CF Diabetes or TD-CF HC respectively, patients develop AML or die. Separate AML complication states were included in the model, AML Diabetes and AML HC, to account for the complications throughout the modelling period.

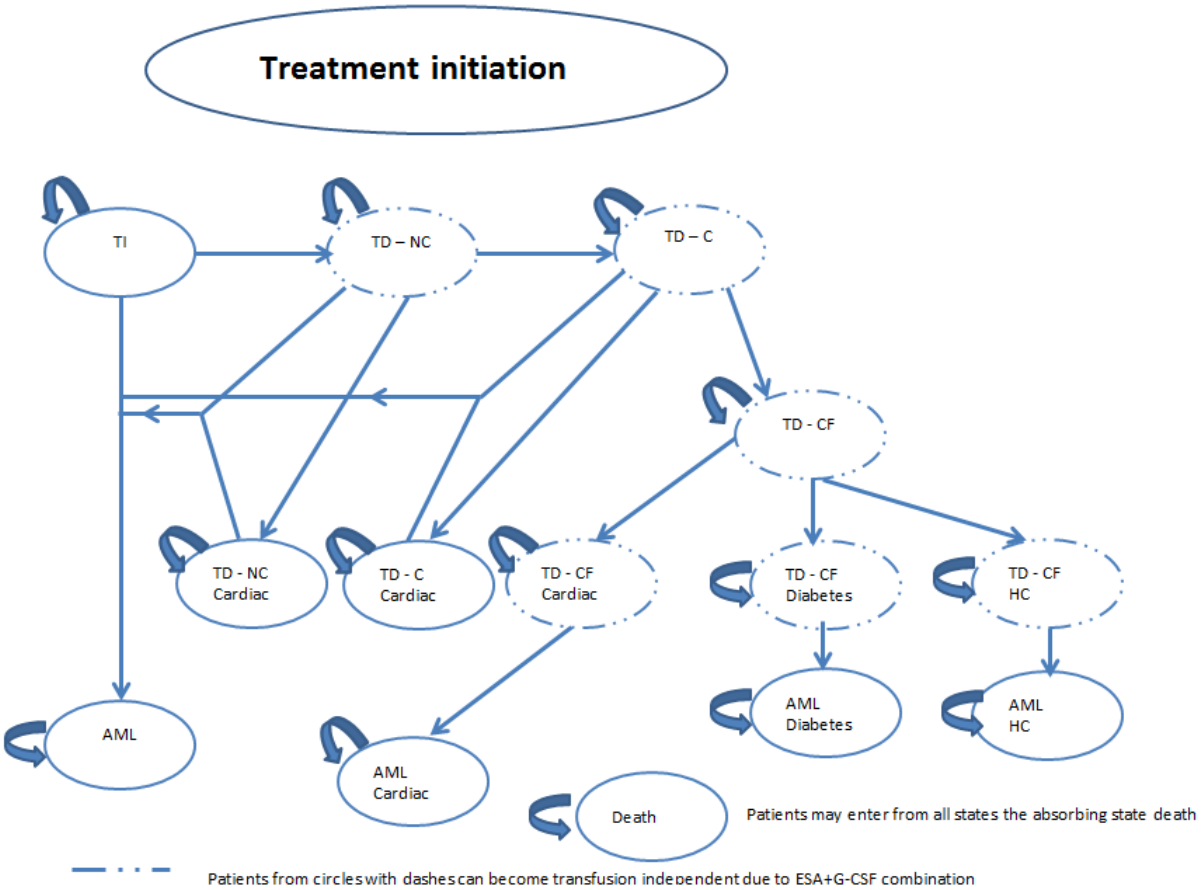
Patients from the lenalidomide group can become TI only during the first cycle when the initial response rate of treatment is applied. Once patients in the lenalidomide group become TD, they cannot become TI again. The model does allow patients in the BSC group to become TI from the TD states after treatment with G-CSF. Based on the diagram of the model this is only allowed from the TD no chelation (TD-NC) state. However, the Excel model also allows people from TD chelation failure (TD-CF) or complication states (TD-CF Cardiac, TD-CF Hepatic and TD-CF Diabetes to become transfusion independent again. Death is an absorbing health state which patients either enter directly or through the AML health states.

No half-cycle correction was applied in the model; in Table 22 of the MS it was stated that this was not required due to the short cycle length.

ERG comment

The model description in the MS and the model structure as found in Excel did not fully match. According to figure 5.1, patients could move from TD chelation failure to TD no chelation Cardiac disease or TD chelation Cardiac disease states. These transitions do not seem logical and were also not included in the Excel model. While the model structure did not show the movements from the TD-C, TD-CF Cardiac, TD-CF Diabetes and TD-CF Hepatic to TI, the Excel model allows patients to move from these health states to the TI state. The ERG has drawn a new outline (figure 5.2) that shows the model structure that matches the Excel model submitted by the manufacturer.

Figure 5.2 Model structure as constructed by the ERG



The Excel model extensively models the complications of TD and iron chelation although the number of patients who spend time in some of these health states is extremely small while more severe forms of MDS were not included. The ERG asked in the clarification letter to explain why progression to more severe forms of MDS was not included. The manufacturer responded with the following explanation:

"We did not include more severe forms of MDS in the model as the model focuses on a particular position within the treatment pathway: low and int-1 risk MDS, that is to say the indication provided in the scope and not the entire treatment pathway. Progression to int-2 and high risk MDS for low risk and int-1 MDS was not measured within the clinical trial and therefore could not be included within the model.

This is probably conservative as it would be expected that more patients in the control arm and non-responders would progress to severe disease which would incur more costs as a result of going onto azacitidine."

While the model might focus on a particular position within the treatment pathway, cost-effectiveness analyses require a life-time perspective to incorporate all future costs and

effects, which includes the possibility of disease progression and reduced transfusion burden. Lack of trial evidence is a handicap to modelling, but does not preclude it. Moreover, since no information was available, the ERG considered it impossible to speculate about whether this is conservative or not and does not agree with this statement of the manufacturer.

The ERG does not agree with the decision of the manufacturer to not include half cycle correction. The reason stated by the manufacturer is the short cycle length. However, whether a cycle length is short or long very much depends on the changes observed inpatient distribution from one cycle to another. In general, with short cycles one would observe relatively small changes between two consecutive cycles. In this model, the first few cycles show a very significant redistribution of patients over the various health states, which indicates that in that part of the time line, 28 days is a rather long cycle length. The ERG has therefore implemented the half cycle correction in the ERG base case that is presented in section 5.3. Adding the correction decreased the base case ICER in favour of lenalidomide.

5.2.3 Population

The economic evaluation was based on the ITT patient population from the MDS-004 trial for lenalidomide in MDS del(5q) patients. Patients aged 18 years or older with IPSS Low- or Int-1-risk MDS with del5q31, with or without additional cytogenetic abnormalities, and RBC transfusion dependent anaemia were included. Median age in the trial was 69 years, range [38 – 86] and 76% of the patients were female. The median time since diagnosis was 2.7 years and the transfusion burden was a median six units per eight weeks.

ERG comment

While the ITT population from the MDS-004 clinical trial (N=205) seems to reflects that of the expected license indication, the article of Fenaux[18] mentioned that this ITT population included patients with inadequate BM sample (N=40), IPSS Int-2-/High-risk MDS (N=11) and no del5q31 by central review (N=9). Information about the ITT and MITT was requested in the clarification letter regarding the reasons for exclusion per group. Table 4.4 shows that the number of patients who do not match the expected licence indication (i.e. INT-2 or higher IPSS score and no del5q by central review) is small, four and seven patients in the placebo group and lenalidomide 10mg respectively, and reasonably balanced. Therefore, the ERG concluded the trial sufficiently represents the target population.

5.2.4 Interventions and comparators

The intervention was lenalidomide 10mg per day, and the dosing schedule for lenalidomide in the model is taken from the MDS-004 trial, in which patients received 21 days of continuous treatment per 28 days. Patients in the trial were allowed up to two treatment interruptions, usually due to adverse events. After the first interruption patients resumed treatment at a lower dose of 5mg for 28 days per 28 day cycle. After a second interruption patients resumed treatment at a dose of 5mg given for 14 days per cycle. Patients in the lenalidomide arm of the model remain on treatment until they stopped responding to treatment.

The intervention is compared to best supportive care (BSC) which was also the comparator arm (i.e. placebo group) in the MDS-004 trial. However, BSC in the MDS-004 trial consisted of the provision of blood transfusion for transfusion dependent patients while BSC in the UK may also include the provision of ESA. Patients receiving ESA have a greater chance of response to treatment (i.e. become transfusion independent) than with transfusions alone although also higher costs are induced. In order to provide the most appropriate comparison in the model, the manufacturer included the provision of ESA in BSC treatment. Within the MDS-004 trial 28% of UK patients had received ESA prior to the trial (52.7% of all patients had received ESA prior to the trial). It is assumed within the base case of the model therefore that 28% of patients will receive ESA for three cycles (as with lenalidomide before response is determined), in addition to transfusions as part of BSC. Initial non-responders receive G-CSF in addition to ESA for three cycles.

ERG comment

Several assumptions were made in order to incorporate the response to ESA. Neither the proportion of patients receiving ESA or the response rate to ESA could be obtained from the trial. This introduced additional uncertainty in the model. According to expert opinion (Personal communication, Dr Culligan, 23 February 2013) there is some uncertainty about the effect of providing ESA to MDS patients with del5q mutations.

5.2.5 Perspective, time horizon and discounting

The model has a NHS perspective and a time horizon of 20 years. Costs and effects were discounted at an annual 3.5% discount rate

ERG comment

The ERG concludes that the discount rate and perspective are in line with the NICE reference case. Considering the average age of 67 years in the MDS-004 trial and median survival for low risk and intermediate 1-risk patients is 5.7 and 3.5 years respectively a time horizon of 20 years is adequate and similar to a lifetime perspective.

5.2.6 Treatment effectiveness and extrapolation

The parameters in the model can be divided into those that are treatment independent and those that are treatment dependent. First the treatment independent parameters are discussed and then the treatment dependent.

Treatment independent parameters

Blood transfusion and complications

Transfusion dependent patients require blood transfusions including RBC and platelet units. The average number of units was obtained from the MDS-004 trial. The average number of RBC and platelet units was 4.57 and 0.06 respectively and required patients to have 1.89 RBC and 0.02 platelet transfusions per 28 day cycle. These transfusion rates are applied to all patients, each cycle, in the transfusion states of the model.

Patients dependent on transfusions have an increased risk of complications. Within the model the risk of cardiac disease is included to represent this increased risk. The risk of individuals dependent on transfusions progressing to cardiac disease is not obtained from the MDS-004 trial but by digitising the graph from Malcovati[35]. The manufacturer determined a Gompertz curve as being the best fit to the data points obtained.

ERG comment

While the report mentioned several curves were tested to show the cumulative probability of cardiac disease this information was not presented in the report. The ERG requested additional information on the methods used to digitise the graph of Malcovati[35]. The following response was obtained from the manufacturer:

"As patient level data was not available and number at risk was not provided in the publication it was assumed that all patients who did not die within the trial were censored at the last time point provided when fitting the curves. Uncertainty was estimated based upon a multivariate normal distribution using the curve fit and variance covariance defined by the estimated patient level data produced using the assumption. As the curves provided a good visual fit and this parameter has only a small impact upon the model further investigation was not considered necessary. Cardiac complications account for <1% of total costs on both arms and the impact on the ICER if utility decrement is not included for cardiac disease is less than £100."

The ERG accepts this approach as reasonable.

Iron chelation

Iron chelation is initiated to avoid complications associated with iron overload after receiving 20 to 25 units of RBCs[36]. The base case model of the manufacturer includes an average threshold of 25 RBC units. Since the patients in the model were already transfusion dependent their history was taken into account. The average number of units of RBCs previously transfused is based on the transfusion history of the UK patients in the MDS-004 trial.

Patients that do start the model in the 'no iron chelation required' health state have received an average of 9.15 units of RBCs per eight weeks over the preceding weeks. Once a patient has received over a threshold of 25 units of RBCs, they are initiated on iron chelation. In the base case model of the manufacturer, patients receive either desferroxamine (DFO) or deferasirox as iron chelation therapy. The proportion on each was estimated from Prescription Cost Analysis: England 2010[37] and is presented below in Table 5.4.

Table 5.4 Iron chelation treatments and dosing

Iron chelator	Market share	Days dosed per week	Dose (mg/kg)
IV – DFO and Desferal	29%	4-7*	40
Oral - Exjade	71%	7	20

** 5 was chosen as the base case value.*

A response rate of 66% is assumed in the model based on the results of Kontoghiorges [38]. Response and determination of non-response to iron chelation is assumed to occur in the first cycle of treatment. Once a patient requires iron chelation they move to either the chelation or chelation failure state depending on their response. Patients that respond to chelation treatment are assumed to continue to receive chelation up to progression to AML or death. A proportion of patients enter the model having previously received iron chelation (8%). These patients continue being chelated if they do not achieve transfusion independence. If they do respond to lenalidomide treatment and achieve transfusion independence then they stop chelation treatment and have their RBC count reset to 0.

ERG comment

According to the MS, patients received 9.15 RBC units over the preceding eight weeks. In the model, this number is multiplied by two to calculate the number of cycles patients are allowed to spent in the no chelation state. It is not clear to the ERG why the 9.15 is multiplied and it seems the model assumed that patients received transfusions for the preceding 16 weeks. This is nowhere clarified in the MS or the model.

The ERG inquired in the clarification letter as to why deferiperone (i.e. a third option for chelation therapy that was listed in the Prescription Cost Analysis: England 2010[37] database) was not considered by the manufacturer. The manufacturer indicated that deferiperone should have been considered within the model. Based on the PCA 2011 database[39] this leads to the following update of the cost of iron chelation (table 5.5):

Table 5.5 Updated cost for iron chelation

Treatment	Market share	Doses per week	Source	Unit Dose Price	Unit Dose Price + Carriage
DFO	5.7%	5	BNF[40]	£25.66	£37.94
Deferiprone	53.6%	7	BNF[40]	£28.43	£40.71
Deferasirox	40.7%	7	BNF[40]	£46.37	£58.64
Total per cycle					**£1,332.45**

The updated total cost per cycle is therefore £1,332.45 compared with the value of £1,383.39 used in the submission. Including the deferiperone not only reduces the cost, it also changes the proportion of patients treated with oral and IV chelation therapy, 94.3% and 5.7% respectively.

It was unclear to the ERG to what extend the market shares presented by the manufacturer reflect current practice in MDS patients, since the database does not show for which disease the drug is prescribed. However, in their submission to the Scottish Medicines Consortium the manufacturer of deferasirox estimated that around 190 patients were receiving iron chelation in Scotland: 19 beta-thalassaemia, 7 sickle cell and 166 MDS patients.[41] If this could be extrapolated to England, it provides a reasonable confidence that the market shares derived from the PCA 2011 database reflect daily practice in MDS patients.

Iron overload complications

Patients that do not respond to iron chelation are at risk of iron overload complications. These are assumed to be diabetes mellitus and hepatic complications. The probability of developing these complications is based on the study by Jaeger[42]. Table 5.6 presents these rates.

Table 5.6 Annual and cycle rates for the incidence of adverse events

Adverse Event	Annual rate - Transfusion Dependent	Cycle rate
Diabetes Mellitus	2.70%	1-(1-2.7%)^(1/13) = 0.21%
Hepatic complications	8.30%	1-(1-8.3%)^(1/13) = 0.66%

ERG comment

The probability of developing diabetes mellitus or hepatic complications is based on a rather outdated study[42] published more than 20 years ago which collected data between 1973 and 1989. It is not entirely clear how the annual adverse event rate was obtained from the data.[42] Additional information was requested in the clarification letter but the response only related to the derivation of cycle probabilities from annual probabilities.

However, the ERG was confused how the annual rate of transfusion dependent adverse events was obtained from the reference.[42] Tolley[43] who quoted the same reference[42] identified an annual rate of 3.2% and 7.6% for diabetes and hepatic complications respectively. Given the incidence of diabetes (N=5) and hepatic complications (N=11), the total patients number (N=46) and the information on follow-up the ERG could not replicate the numbers provided in the MS and remains in doubt how these numbers were derived.

Progression to AML

Patients with MDS are at risk of developing AML. The time to development of AML was derived from individual patient level analysis of the MDS-004 trial and performed separately for transfusion dependent and transfusion independent patients where the latter has a smaller chance of progressing to AML. AML progression curves were fitted to individual patient level data with appropriate choice of curve extrapolated using an extensive set of selected distributions. Although the extreme value distribution had the lowest IBS, the Weibull distribution was chosen by the manufacturer since this was believed to have relatively low IBS and low AIC and offered a more clinically realistic fit since the Weibull predicts 100% AML progression not as quickly as the extreme value distribution.

ERG comment

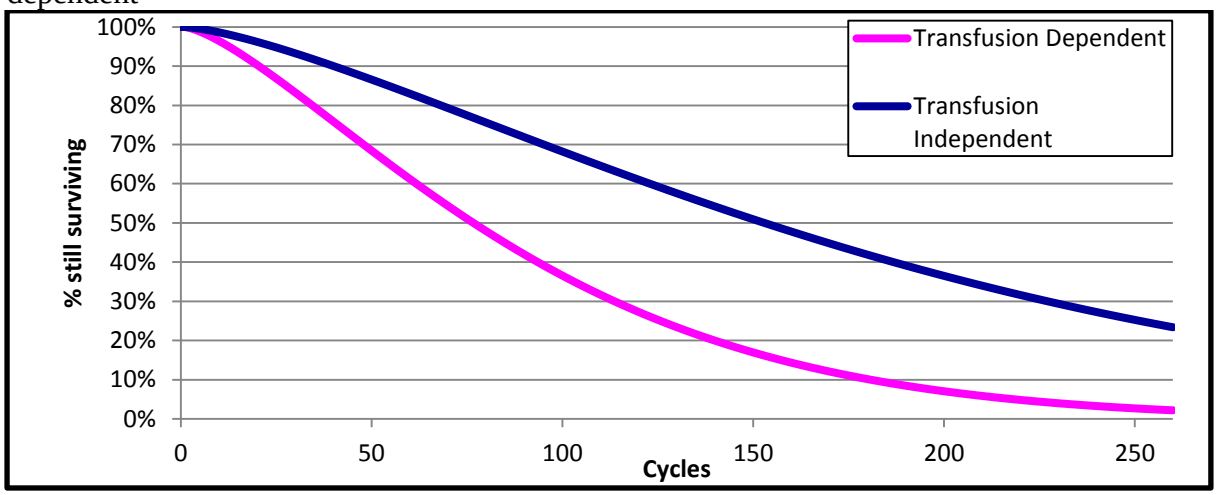
While the manufacturer stated that the Weibull had relatively low IBS and AIC, the Weibull had one of the highest AIC and the highest IBS. The stratified log-normal curve had the lowest AIC and ranked 5th for the IBS, whilst the stratified log-logistic curve had the second lowest AIC and ranked 4th for the IBS. Both also seemed to have the best fit based on visual inspection, especially for the first two years. Thus, given the fact that the manufacturer states on page 108 of the MS (and in Appendix A of the MS) that the IBS is generally considered superior to using AIC, it is surprising that the curve with by far the highest IBS was selected without a clear argument why. The sensitivity of the model to the curve selection was explored in section 5.2.10.

Mortality

According to the manufacturer, survival is significantly influenced by whether the patient is transfusion dependent or not, with transfusion independent patients surviving longer. Therefore, survival curves were fitted to the trial data based upon whether patients achieved transfusion independence at eight weeks or not. The goodness-of-fit measures AIC and IBS were in reverse order, i.e. distributions with the lowest AIC had relatively high IBS and vice versa. The Weibull distribution scored average for both measures and this distribution was assigned to the base case scenario by the manufacturer (see Figure 5.3).

In the model, probabilities of dying during each cycle are derived using a weighted average of the two curves based on the initial response rates, 60.9% for the lenalidomide 10mg group and 7.8% for the BSC group.

Figure 5.3 Kaplan-Meier mortality curves of transfusion independent and transfusion dependent



ERG comment

Mortality rates for TI and TD were obtained from the MDS-004 trial. However, it is important to realise that, since only the initial response rate (that was already too low due to a programming error in the model) is used, the probability of dying in the placebo group is overestimated. In the model, patients who failed to have an initial response, may become TI

after treatment with G-CSF + ESA. The model neglects this positive effect in the comparator group by using only the initial response rate.

Mortality unrelated to the disease is incorporated in the curve used, as it was estimated based on death from all causes in the MDS-004 trial.

AML Mortality

Since AML mortality could not be obtained from the MDS-004 trial (too few patients died from AML), an article by Wahlin[44] was used. Wahlin[44] stratified 211 elderly AML patients into three prognostic categories based on cytogenetics, leukocyte count, and the presence/absence of antecedent haematological disorders. The adverse risk group included 113 patients with inter alia, del(5q) mutations. The manufacturer digitised the published survival curve for the adverse risk group to obtain a set of survival data points. Parametric curves were fitted to these survival points and while the log normal function provided the best fit based upon its AIC score, the Weibull function was chosen to represent AML mortality because it did not exhibit such a long tail, and had only a marginally larger AIC score (470.71 compared to 470.14).

ERG comment

By using the study by Wahlin[44], the sample size from which AML mortality data were obtained doubled from 56 to 113. Nevertheless, the number remains limited and additional uncertainty was introduced since the published curve had to be digitised. Besides, the patients in the adverse prognosis group included del(5q) patients but it was not stated to what extent the patients with other mutations in the adverse prognosis group are representative for the MDS-004 trial population.

Treatment dependent variables

Response to lenalidomide treatment

The response to treatment is obtained from the lenalidomide 10mg arm in the MDS-004 trial. The model uses the ITT population response rates according to the International Working Group (IWG) 2000 criteria[45]; an uninterrupted period of transfusion independence for 56 consecutive days. The response rate was 60.9% for the lenalidomide 10mg group.

The description of the model stated that response to treatment was assumed to occur within the first four week cycle, so all patients spend the first cycle in the transfusion dependent state. However, the model starts with the results of the treatment initiation and patients move immediately from the first cycle onwards to the transfusion independent health state. Since responding to treatment, (i.e. becoming TI) is determined as being TI for 56 consecutive days and was measured after 84 days, this seems overly optimistic, as the overall response rate also includes patients who do not respond immediately.

In the clarification letter, the ERG asked to clarify why 60% of the patients in the lenalidomide group were in the transfusion independent state. The manufacturer stated that:

“As a simplifying assumption in the submitted model, all patients who respond were classed as responders from cycle 1 onwards in both arms.”

The following table (table 5.7) with the number of patients responding per treatment arm was provided by the manufacturer.

Table 5.7 Number of patients responding per treatment arm

	Number of patients			**% transfusion independent**		
	Placebo	**5 mg lenalidomide**	**10 mg lenalidomide**	**Placebo**	**5 mg lenalidomide**	**10 mg lenalidomide**
28	3	16	16	4.5	23.2	23.2
56	4	27	30	6.0	39.1	43.5
84	4	32	41	6.0	46.4	59.4
112	4	33	42	6.0	47.8	60.9
140	4	33	42	6.0	47.8	60.9
168	4	33	42	6.0	47.8	60.9
182	5	33	42	7.5	47.8	60.9

Based on table 5.7, the response rate could be adjusted to follow the proportions in the trial with the assumption that response to ESA occurs at the same rate as response to lenalidomide 10mg.

Response to BSC

BSC in the MDS-004 trial consisted of the provision of blood transfusion for transfusion dependent patients. However, although not included in the MDS-004 trial, BSC may also include the provision of ESA and G-CSF. Therefore, the response to BSC consists of the response to blood transfusions, ESA monotherapy and combination therapy of ESA+G-CSF.

The effectiveness of blood transfusions only was obtained from the MDS-004 placebo group and equal to 7.5%.

The proportion of patients receiving ESA had to be estimated since there was no ESA use in the trial. The proportion of patients treated with ESA in addition to blood transfusion was assumed to be equal to the proportion of UK patients who received ESA prior to the trial, i.e. 28%. The effectiveness of ESA and G-CSF is based on the research of Jädersten[46] who reported response rates after combination therapy by predicted groups. The patient composition of the MDS-004 trial was used to obtain the average response rate for this patient group. Table 5.8 shows the proportion of MDS-004 patients and the response rate for ESA+G-CSF.

Table 5.8 Response rate to ESA+G-CSF for predictive groups

Predictive Group	Proportion of MDS-004 Patients	ESA + G-CSF Response Rate [46]
High probability of response	3%	60%
Intermediate probability of response	36.4%	18%
Low probability of response	60.1%	6%

Predictive groups are defined according to Hellström-Lindberg[47] and as follows:

- High probability of response: Serum erythropoietin (S-Epo) of ≤ 500 U/l, and a prior transfusion requirement of < 2 RBC units per month on average.
- Intermediate probability of response: one of either S-Epo ≤ 500 U/l or a prior transfusion requirement of < 2 RBC units per month.
- Low probability of response: S-Epo of > 500 U/l, and a prior transfusion requirement of ≥ 2 RBC units per month on average.

Since patients in the low predictive group are unlikely to be treated by ESA, the manufacturer weighted the response rates for the high and intermediate probability groups with the proportion of trial patients in those groups. This methodology provided an estimated response rate to ESA + G-CSF of 21.7%. However, the manufacturer considered this as unlikely to be representative of ESA + G-CSF use in the UK because combination therapy is started upon the failure of ESA alone. The response rate to monotherapy with either ESA or G-CSF is based on Balleari[20] and assumed to be half that to combination therapy. Utilising this assumption provides an ESA response rate of 10.8% and a response rate of 10.8% for G-CSF when this is added to ESA monotherapy.

The initial response rate of BSC is calculated by multiplying the proportion of patients receiving ESA (28%) by the monotherapy ESA response rate (10.8%) plus the proportion of patients without ESA (72%) multiplied by the response rate of transfusion only (7.5%) obtained from the placebo rate in the MDS-004 trial. This results in an initial response rate of 8.4%. However, in the model, a second weighting of 28% is applied resulting in a final initial response rate of 7.76% in the BSC group.

There is a chance for initial non-responders to become TI after the combined therapy of ESA+G-CSF. Non-responders in the BSC group will then be given G-CSF in addition to ESA for 3 cycles. The proportion of patients responding to G-CSF was originally determined at 10.8% (i.e. half of the weighted response rate of 21.7%). In the model the response rate for G-CSF was weighted double since the response rate of 8.4% (i.e. which was already weighted) was multiplied again by the proportion of patients receiving ESA (28%). This double weighted response rate was multiplied again by the proportion of patients receiving ESA (28%). This results in 0.66% of the patients.

ERG comment

The original model included an initial response rate which was weighted twice by the 28% of patients that received ESA. Instead of an initial response rate of 8.4% the 7.76% was used in the model. Besides, also the response to GCSF was weighted two times resulting in a response rate of 0.66% instead of 2.36%. An explanation was asked in the clarification letter

and the manufacturer confirmed that these were programming errors. Compared to the base case ICER (£56,965), correcting the programming errors increases the ICER with almost £2,000 to £58,732.

Effectiveness is based on a single trial, the MDS-004 trial that included 67 and 69 patients in the placebo and lenalidomide 10mg arm respectively. The trial seems to reflect the target patient population although BSC in the UK is not limited to blood transfusions only. Nevertheless, the number of patients is relatively small and interpretation of results is complicated by the cross-over design. Due to the limited number of patients, progression to transfusion dependent adverse events or death to AML had to be based on the literature and is not always specific for the MDS-del5q patients. This increases the uncertainty and assumptions that have to be made to model the cost-effectiveness.

The primary endpoint of the study was red blood cell (RBC) transfusion independence (TI) for ≥26 weeks. Instead of the primary endpoint, i.e. RBC-TI for ≥ 26 weeks as defined by the protocol, the manufacturer used one of the secondary endpoints; erythroid response using the IWG 2000 criteria[48]. The response to treatment according to the MDS-004 trial is shown in chapter 4, Table 4.7, and was 7.5% in the placebo group and 60.9% in the lenalidomide group.

The base case model assumes 28% of the patients receive ESA. In the clarification letter the ERG requested information on the rational for assuming that the proportion of patients who received ESA prior to the trial is representative for ESA use during BSC in the UK. The manufacturer provided the following statement:

"As no evidence is available on the use of ESA within MDS and clinical experts indicated that use was low in the NICE scoping meeting the estimates based upon prior ESA use by UK patients within the clinical trial are the most appropriate available. These are consistent with the NICE scoping statement that ESA use is low in the UK for del5q patients.

Subgroup analysis showed that prior ESA did not significantly impact the chance of transfusion independence by treatment group within the trial therefore the overuse of ESA prior to the trial compared to UK practice is unlikely to impact results.

Sensitivity analysis is provided to address the uncertainty around ESA use in the trial analysing 0% and 100% use."

It is clear that there is a lack of data to confidently define which percentage of the MDS-del(5q) patients receives ESA. In addition, the consulted clinical expert (Personal communication, Dr Culligan, 23 February 2013) indicated that there are some data that suggests that 5q- syndrome has a lower response rate than other low risk MDS, which may decrease ESA use in the del(5q) population. The ERG is not confident that the definition of BSC by the manufacturer fully reflects the BSC within the NHS. However, as indicated by

the manufacturer, the model outcomes are not very sensitive to changes in the percentage ESA use (see section 5.2.9).

Response rate to BSC ESA monotherapy was obtained by dividing the response rate to ESA+G-CSF in half. This seems to be a simplistic approach entirely based on the study of Balleari[20] who studied patients who received Erythropoietin (N=15) and Erythropoietin+G-CSF (N=15). Although the response rate after 16 weeks was 33% for the Erythropoietin group and 62.5% for the Erythropoietin +G-CSF, the difference between monotherapy and combined therapy was smaller after 8 weeks, 40% and 73% respectively. In addition, these response rates do not match the weighted response rate of 21.7% meaning the generalisability of the results is limited. Besides, since G-CSF in the UK is only provided to patients who do not respond to ESA monotherapy, it seems more realistic that the proportion of patients responding to monotherapy is higher compared to the combined therapy.

Response duration

The response duration for lenalidomide and BSC in the model is based on patient level data from MDS-004 trial. The time that patients continue to respond, i.e. remain transfusion independent, was for the 10mg lenalidomide group obtained from the ITT patients initially receiving the lenalidomide 10mg dose. The lenalidomide 5mg response duration curve was used to approximate the BSC response time in the model since response curves could not be calculated from patients on the placebo arm as there were insufficient responses (only five patients responded and four of these were censored)

Parametric response duration curves were fitted to the data for all patients starting on either lenalidomide 10mg or 5mg in the trial (Weibull, log logistic, lognormal and exponential functions) and the goodness of fit determined using the Integrated Brier Score (IBS) and Akaike Information Criterion (AIC). The curves with lowest AIC and IBS and the best visual fit were the lognormal distributions and these were used for the base case model for the lenalidomide and BSC group.

ERG comment

In the clarification letter, the ERG requested further rational for why the 5mg dose response duration curves were used for the BSC group. The manufacturer provided this in the clarification letter:

“The response curves have been taken from 5 mg lenalidomide as there were not enough patients responding on the placebo arm of the trial to fit curves. Only five patients responded and of these only one was not censored. This was insufficient to attempt to fit curves.

As lenalidomide 5mg is an active and effective treatment the use of this curve as a proxy for no treatment is likely an over-estimate of response duration for patients receiving only transfusions. The use of this curve as a proxy for ESA response duration is likely also an overestimate of response duration as Kelaidi et al[49] indicated a mean response duration of 13 months for del5q patients, the mean and median durations of response for responding patients

with the 5 mg curve used is considerably longer than this (24 months and 41 months respectively). It should be noted that the Kelaidi[49] population includes patients who are not RBC transfusion dependent (38%) meaning that in reality response duration may be even lower for the transfusion dependent population.

It should be noted that the model is not sensitive to the assumptions regarding response duration due to the low proportions of patients responding to placebo and ESA, to which these curves are applied."

Since there was no other information available, the ERG considered it appropriate to assume that the response duration of the BSC group could be simulated based on date of response duration of the 5mg lenalidomide group although the rational for assuming 5mg response duration instead of for example 10mg seems arbitrary. The ERG explored the impact of assuming the response duration of BSC is similar to the response duration of the 10mg group (see section 5.3).

Adverse events

Safety of lenalidomide is based on the ITT population of the MDS-004 trial and only two adverse events, neutropenia and thrombocytopenia, were included in the model since only these were considered as serious enough to warrant inclusion in the model and different between the placebo and lenalidomide arms in the trial. According to the MS, the rates of grade 3/4 thrombocytopenia and neutropenia (including leukopenia) were taken from published data from the MDS-004 trial. Since MDS is characterized by peripheral cytopenias, the manufacturer considered it unlikely that all instances of neutropenia and thrombocytopenia could be attributed to lenalidomide. Therefore, the number of patients experiencing these AE was adjusted by subtracting the patients who had neutropenia and thrombocytopenia within the placebo group. It was assumed that any lenalidomide adverse events happened during the first 4 cycles with a constant hazard. AEs have a range of severity and thus it is assumed that only a proportion of patients incurring the AE require treatment, 6% for thrombocytopenia and 27.7% for neutropenia. These figures are based on the MDS-004 trial data. It is assumed that the adverse rates for patients receiving ESA are the same as for those receiving transfusions only.

ERG comment

One or more grade 3/4 adverse events were experienced by 94% of the patients in the 10mg lenalidomide arm compared to 43% in the placebo group. While the thrombocytopenia and neutropenia are the most frequent AEs, the ERG requested an explanation why other AEs such as DVT, were not included in the model. The manufacturer provided the following response in the clarification letter:

"There was a low incidence of these adverse events in the trial and clinician opinion is that these can be routinely monitored without incurring many costs.

In the MDS-004 study, DVT occurred in 1 subject each in the 5-mg and placebo groups, in 4 (5.8%) subjects in the 10-mg group, and in 4 (7.1%) subjects who had crossed over from placebo to 5-mg. Pulmonary embolism was reported by the similar proportion of subjects (2 subjects; 2.9%) in the 5-mg group and (3 subjects; 4.3%) in the 10-mg group and by no subjects in the placebo group over the entire study."

Apart from the type of AEs included in the model, questions about the rate of adverse events remained. According to the MS (p124), adverse events grade 3/4 of thrombocytopenia and neutropenia (including leukopenia) were taken. The clarification letter provided an additional table (table 5.9) showing the adverse events during the first 16 weeks and within the entire double blind treatment phase. These numbers were used in the base case analysis.

Table 5.9 Comparison of adverse events occurrences within the first 16 weeks compared to the entire trial

	Within the first 16 weeks			**Within the entire double blind treatment phase**		
	Placebo	**5 mg**	**10 mg**	**Placebo**	**5 mg**	**10 mg**
Thrombocytopenia	2	29	31	2	30	34
Neutropenia	12	53	52	12	53	53

However, the numbers used in table 5.9 and the model deviated from table 4.25 (CSR, Table 49, page 133-4). According to the ERG, the numbers used in the base case were not only grade 3/4 events, but all the AEs (i.e. grade 1-4) since the numbers correspond to the table of all adverse events in the CSR (CSR, Table 48, page 131). Besides, the rate for neutropenia does not seem to include leukopenia. It is unclear if the proportion of patients treated was also based on all patients with AEs or only on patients experiencing grade3/4 AEs. In the first case, the discrepancy between text and numbers used does not lead to problems, but if the proportion AEs is based on all grades whilst the proportion treated is based on grade 3/4 AEs, the current model is incorrect. The ERG has opted not made changes to the model.

Treatment interruptions

As in the trial, the model accounts for two treatment interruptions during which period the patient receives no lenalidomide treatment and no treatment costs should be attributed during this period. After the first dose interruption patients resumed treatment at a lower dose of 5mg given for 28 days per cycle while patients resumed treatment at a dose of 5mg given for 14 days after the second dose interruption. These treatment interruptions and dose adjustments are especially relevant for the treatment costs of lenalidomide. No additional monitoring requirements or costs were associated with the dosing issues. Within the model it is assumed that patients were monitored weekly up to 56, two weekly up to 84 days and four weekly thereafter.

According to the MS, 64% of the patients experienced a first dose interruption and 62% of these patients experienced a second interruption. However, the proportion of patients in the model was 68.7% and 73.8% for first and second time interruptions respectively. In addition,

also the mean time to interruption and length of interruption between the manuscript and model did not correspond. In response to the clarification letter the manufacturer confirmed that the numbers in the model are correct, and thus that the numbers on page 102 and 103 of the MS are incorrect.

The correct values (which were already used in the model) are summarised in table 5.10.

Table 5.10 Proportion of patients experiencing dose interruptions and mean time to interruptions

1st interruption	
Proportion of patients	68.70%
Mean time to 1st interruption in days (SD)	54.2 (113.8)
Length of 1st interruption in days (SD)	17.5 (30.1)
2nd interruption	
Proportion of patients	73.80%
Mean time to 2nd interruption in days (SD)	72.1 (141.9)
Length of 2nd interruption in days (SD)	13.9 (59.6)

ERG comment

The programming of the dose interruptions in the Excel model contained errors. For the ERG base case analyses these were corrected. This increased the base case ICER by over 10% in favour of BSC.

5.2.7 Health related quality of life

The MDS-004 trial assessed HRQoL collecting EQ5D data at baseline and using the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire at baseline and in weeks 12, 24, 36 and 48. Unfortunately, according to the manufacturer, estimating EQ-5D utilities by mapping the FACT-An data resulted in models with an unacceptable level of error. Therefore, utility values had to be obtained from the literature.

A systematic search was designed to identify relevant QoL data for patients with MDS. Four potentially relevant QoL studies were identified: Buckstein[50] Buckstein 2011[51], Goss[32] and Szende[52]. The results from Buckstein were two abstracts that reported utility values of MDS patients. According to the MS, these values were 0.85 for transfusion independence and 0.63 for transfusion dependence. Goss[32] described a cost-effectiveness analysis using utility values obtained from a small study of interviewing 8 MDS patients. According to their results, utility values were 0.5, 0.81 and 0.91 for transfusion dependent, reduced transfusion burden and transfusion independent. Buckstein[50] and Goss[32], were not used in the base case model but explored in a scenario analysis (section 5.2.10).

Utility values in the model were obtained from Szende[52] while utility decrements for chelation therapy (i.e. 21% for DFO and 0% for oral chelator use) were obtained from McLeod[53] and decrements for AEs were obtained from Fryback[54]. Neutropenia and thrombocytopenia occur frequently, both as a characteristics of the disease and also as a result of treatment with lenalidomide. Nevertheless, the model did not incorporate utility decrements for patients who experienced these adverse events since according to the manufacturer, the effects on Qol are typically transient and manageable i.e. the effect is short term. The utility values and decrements are presented in table 5.11

Table 5.11 Utility values and decrements used in the economic model

	Utility value	Confidence interval
Utilities per health state		
Transfusion Independent	0.85	[0.793-0.900]
Transfusion Dependent	0.65	[0.543-0.751]
AML	0.65	[0.543-0.751]
AE utility decrements		
DFO use	21.0%	[0.158-0.263]
Oral Chelator use	0%	Not included in PSA
Cardiac Disease	17.9%	[0.068-0.290]
Diabetes	12.3%	[0.050-0.196]
Hepatic Complications	8.0%	[0.060-0.100]
Thrombocytopenia	0%	Not included in PSA
Neutropenia	0%	Not included in PSA

ERG comment

The study of Szende[52], that was used by the manufacturer, obtained utility values by asking UK MDS patients to evaluate three health states descriptions using a TTO. The utility values per health state aimed to represent the transfusion independence (0.85), reduced transfusion burden (0.77) and transfusion dependence states (0.65). However, the description of the states was in such broad terms that it covered a range of health problems and the level of transfusion dependence was not the only difference (see Table 5.12). Therefore, the difference between the utility values for transfusion independent and dependent cannot be interpreted as the increased QoL of becoming transfusion independent.

Table 5.12 Health State Descriptions used by Szende[52]

Transfusion-independent state
You rely on regular medications and routine medical checkups but you do not need to go to a health care facility to receive blood transfusions. You **rarely** feel that you need to arrange your life around medical appointments. You **rarely** experience fatigue and tiredness that would limit you in performing routine physical activities. Your disease **rarely** interferes with your social functioning and family life. You **occasionally** have concerns about your future due to your health. You **periodically** experience **mild to moderate** discomfort associated with health conditions and their treatment, but you rarely feel that you are at risk of infections. You can take care of yourself and routine activities **most of the time**. You **rarely** feel that you are a burden to your family due to your health condition. You **often** feel positive, motivated, and in control of your life despite your health condition.
Transfusion dependent state
You rely on regular blood transfusions and need to spend **significant** time at a health care provider facility. You depend on availability and accessibility of health care facilities and your health care providers. You **often** feel that you need to arrange your life around medical appointments. You **often** experience fatigue and tiredness that limits you in performing routine physical activities. Your disease **often** interferes with your social functioning and family life. You **often** worry about your future due to your health. You experience **moderate to severe** discomfort associated with health conditions and their treatment, and feel that you are at risk of infections. You rely on family or other caregiver support as you **frequently** may need assistance to take care of yourself and routine activities. You may **often** feel that you are a burden to your family due to your health condition. You **often** feel sad, hopeless, and helpless because of your health condition.

The study of Szende[52] emphasises the importance of distinguishing between the level of transfusion dependence. Assuming a utility value of 0.65 for all non-responders might favour the ICER for lenalidomide by enlarging the difference between QALYs for lenalidomide and BSC since patients in the BSC spend much more time in the transfusion dependant health states. However, if patients treated with lenalidomide spend more time in a reduced transfusion burden state, the effect is the other way around.

Due to the broad descriptions, the transfusion dependant description might already incorporate some of the adverse events associated with for example chelation therapy or complications such as cardiac disease, diabetes or hepatic complications. The ERG considers it likely that some double counting is included in the model by assigning the utility value of 0.65 from Szende[52] (a value for completely transfusion dependent) to all patients not transfusion independent and use utility decrements on top of this.

This idea is supported by the utility values obtained from the study of McLeod[53]. According to their results, mean utility for the oral chelation therapy was 0.84 compared to 0.66 for the IV chelation therapy. While the 0.66 is almost identical to the 0.65 for the transfusion dependant state, the manufacturer estimated a utility decrement of 21% for the subcutaneous chelation therapy which means a subtraction of 0.14 to a utility value of 0.51. There was no

utility decrement applied to patients who received oral chelation implying a utility value of 0.65. However, this is much lower than the utility value of McLeod[53].

In the clarification letter, the ERG asked whether a systematic search was undertaken to obtain more contemporary estimates. The manufacturer stated that:

"A systematic search was not undertaken to obtain more contemporary estimates however this variable has little impact upon the model – removing either of these variables entirely changes the ICER by less than £100."

The ERG performed a rapid review of the literature but this did not reveal new relevant studies.

The manufacturer did not apply utility decrements to the AEs associated with lenalidomide treatment. Although the effect on QoL of neutropenia and thrombocytopenia is short term, the effect of sever neutropenia (grade 3/4) can be substantial and is experienced by 75% of the patients in the lenalidomide group while the proportion of patients is 14.9% in the placebo group[55]. However, the overall effect in the model would be small. A further justification was requested by the ERG and provided by the manufacturer in the clarification letter:

"Clinical opinion confirmed that these were fairly manageable and do not impact the quality of life.

Evidence from the lenalidomide submission in multiple myeloma, which is a more severe disease, indicates that both neutropenia and thrombocytopenia have a very small impact on patient quality of life with utility decrements lasting for seven days on average (Brown, 2012). The utility decrements used within this submission are negligible: 0.003 per patient experiencing neutropenia and 0.006 per patient experiencing thrombocytopenia."

The ERG considered the reference to the study of Brown[56] who obtained the utility values from the study of Lloyd[57] which was conducted among patients with breast cancer not applicable to this patient population. In order to explore what impact a utility decrement for these AE has on the ICER, the ERG explored a scenario with a 25% decrement (see section 5.3).

Utilities for AML were assumed to be same as transfusion dependent, implying being partly or completely transfusion dependent is as bad as having AML. The ERG considers this a questionable assumption. However, since there is no difference between the time spent in AML for the BSC and lenalidomide group, the impact of the utility value assigned to AML is negligible.

5.2.8 Resources and costs

Drug acquisition prices were obtained from the British National Formulary.[40] The frequency of monitoring associated with the initiation of lenalidomide treatment was based on the summary of product characteristics. Visits (and thus blood counts) occur weekly for the first

eight weeks, bi-weekly for the next four weeks, and then four weekly thereafter (at this point they are being monitored at the same frequency as patients who are not receiving treatment). Monitoring for best supportive care was assumed to occur once per cycle throughout treatment. Monitoring in both treatment groups is assumed to take place by a GP. Patients who are on iron chelation accrue the costs of four-weekly liver function tests at the monitoring visits.

The cost for treatment of AML were obtained from an earlier STA for intermediate-2 and high-risk MDS patients.[53] These costs were based on a structured questionnaire among thirteen haematologists who specialised in the treatment of MDS patients. These costs should include routine follow-up, laboratory and disease monitoring, concurrent medication and treatment of disease or treatment related AEs.

The unit prices are presented in table 5.13, whilst table 5.14 presents the treatment costs per cycle.

Table 5.13 Unit prices included in the model

Item	Standard Unit	Unit Price	Source
Drug costs			
Lenalidomide	per 10mg tablet	£180.00	BNF 64th ed. [40]
Lenalidomide	per 5mg tablet	£170.00	BNF 64th ed. [40]
ESA Erythropoeitin (Eprex)	per 20,000 IU vial	£110.62	BNF 64th ed. [40]
G-CSF (Neupogen)	per 300 mg vial	£52.71	BNF 64th ed. [40]
Chelation therapy			
IV iron chelation	per dose	£25.35	BNF 64th ed. [40]
Oral iron chelation	per dose	£46.37	BNF 64th ed. [40]
Monitoring costs			
GP Visit	Per visit	£36.00	PSSRU 2011 GP surgery cost including qualifications[58]
Full Blood Count	Per test (one per visit)	£3.09	NHS 2011/12 reference costs – haematology[59]
Serum Ferritin	Per test (one per visit)	£1.23	NHS 2011/12 reference costs – biochemistry[59]
Blood transfusion cost			
RBC unit		£367.98	Davies (2006) [60]
Platelet transfusion		£312.49	Guest (1998) [61]
AML treatment			
AML treatment	per 28 day	£1,919.40	STA Azacitidine[53]
Transfusion dependent complications			
Cardiac Disease	annual cost	£3,792.30	Luengo-Fernandez et al[62]
Hepatic Complications	annual cost	£1,445.80	Wright (2006) [63]
Diabetes Mellitus	annual cost	£ 3,644.40	Kavanos (2012) [64]

Item	Standard Unit	Unit Price	Source
Adverse events lenalidomide			
Thrombocytopenia	per episode	£1,636.38	NHS 2011/12 reference costs – SA08F[59]
Neutropenia	per episode	£1,636.38	NHS 2011/12 reference costs – SA08F[59]

Table 5.14 Treatment cost per cycle

Item	Cost per cycle
Lenalidomide 10mg 21 days per cycle	£3,780
Lenalidomide 5mg 28 days per cycle	£4,760
Lenalidomide 5mg 14 days per cycle	£2,380
ESA (2 vials per week)	£885
G-CSF (3 vials per week)	£633

ERG comment

The manufacturer referred to an earlier STA for the cost of AML treatment. According to the MS the cost for AML treatment was £1,844 per 28 day cycle. The ERG was only able to find an estimate of £1,814 per five week cycle (page 100 of the MS for the STA of azacitidine) and asked in the clarification letter for an explanation. The manufacturer confirmed that the £1,814 per five week cycle found by the ERG was the most recent cost estimation.

Some uncertainty around the cost for adverse events, AML and transfusion dependent complications remained. Tolley[43] conducted a cost effectiveness analysis and required similar cost components, e.g. treatment costs for AML and transfusion dependent complications. However, there was a large difference between the costs for this study and the submission of the manufacturer. For example, both studies obtained cost for cardiac disease from Luengeo-Fernandez[62] however, according to Tolley[43] cost for cardiac disease were £6,208 (2008 values) while these were £3,792 (2011/2012 values) in the MS. Other references were used for diabetes £4,187 and hepatic complications £2,144.

As for the utilities of these health states, no systematic search was done to find cost estimates for these various items. Again, the ERG performed a rapid review of the literature but this did not reveal new relevant studies.

In the original submission of the manufacturer, costs for thrombocytopenia and neutropenia were £1,636.38 and obtained from NHS reference costs.[59] The ERG requested in the clarification letter an explanation why the more specific codes for neutropenia were not used. In the response the manufacturer stated that:

"Code PA45Z refers to febrile neutropenia with malignancy, this is considerably more severe than neutropenia which is what was seen in the lenalidomide trial."

Additionally, the manufacturer suggested a new source for the cost estimates of the AE:

"It is acknowledged that the costing currently provided is not realistic enough and in fact substantially overestimates the costs of these adverse events as in some cases the events either do not require treatment at all or can be treated as an outpatient appointment rather than requiring admission as an inpatient. Costs have therefore been updated to match those used for grade 4 AEs in the lenalidomide submission for multiple myeloma as published by Brown et al (2012)."

While the code for neutropenia might not be appropriate, the ERG also identified specific costs for thrombocytopenia (code SA12F). Based on the costs for inpatient treatment (i.e. long and short stay) the costs would be £1,768 for thrombocytopenia. Since the febrile neutropenia was not considered appropriate for this population, the ERG prefers the use of the general code (Other Haematological or Splenic Disorders, without CC (SA08F), using the numbers for short and long inpatient stay yielding an estimate of £1,045.

The argument by the manufacturer that these tariffs overestimate the costs as in some cases the events do not require treatment at all is considered invalid by the ERG; the model already takes into account that not all patients were treated by assuming only 6% and 28% of the grade 3/4 thrombocytopenia and neutropenia events receive treatment.

The ERG considered the proportion of patients treated for thrombocytopenia and neutropenia rather low (6% and 28%). These numbers were obtained from the MDS-004 trial. However, since there was some confusion about including all patients experiencing AEs or only grade 3/4 the ERG is uncertain whether the 6% and 27.7% of patients treated applies to all adverse events or grade 3/4 only. Besides, there were no treatment proportions provided for leukopenia. The ERG explored alternative assumptions regarding the AEs in section 5.3.

The ERG requested the manufacturer to clarify how the assumption was derived that all monitoring visits of MDS were completed by a GP. The manufacturer provided the following response:

"Haematology costs are included within the costs for adverse events and transfusions which are the main causes for haematologist visits. To avoid double counting haematology visits are therefore not included for regular monitoring which outside of the above is primarily conducted by GPs."

Based on the manufacturer's response, transfusion dependent patients already see haematologists regularly and therefore the monitoring visits are assumed to occur at the GP. While the costs for adverse events include the costs of a haematologist, only 6% and 28% of the patients with grade 3/4 thrombocytopenia and neutropenia are treated for their adverse event. In other words, only a very small proportion of the patients with AEs are seen by a haematologist while the majority of the patients are regularly monitored by their GP. Based on independent clinical advice (Personal communication, Dr Culligan, 23 February 2013), the ERG is not convinced that this a reasonable assumption. We have therefore explored a scenario in which all consultations are done by the haematologist (see section 5.3).

Finally, the ERG asked the manufacturer why it was assumed that the standard error for all cost estimates without a standard deviation estimate was derived as 10% of the mean. The manufacturer stated that:

"The use of a standard error of 10% of the mean in PSA when estimates of true uncertainty are not available is industry standard practice and has been used and accepted in many previous submissions."

It is indeed the ERG's experience that often a fixed percentage is used to derive a standard error. However, since a standard error indicates how uncertain the estimate of the mean is, it would make more sense to let the actual percentage depend on the cost estimate at hand. For a single item, such as a transfusion or a GP visit, a standard error of 10% might be quite reasonable. However, for cost estimates of events such as cardiac complications, that are an amalgam of various resource use items such as specialist visits, diagnostics, hospital days and medication, a 10% standard error appears too small. The ERG has therefore set the standard errors of the complication and adverse event costs to 20% of the mean in the ERG base case (section 5.3).

In the clarification letter the ERG requested why the monitoring visits for BSC and lenalidomide were not varied in the PSA. According to the manufacturer for simplicity this was covered within the variation of the costs of monitoring rather than the number of visits. According to the ERG the frequency of visits per cycle and the costs of monitoring are two different kinds of uncertainty and should both have been included in the PSA. Therefore, the ERG has defined a 10% standard error was defined for the number of monitoring visits in the ERG base case (section 5.3)

5.2.9 Cost effectiveness results

This section describes the results of the base case analysis. The following table (table 5.15) present the model outputs by clinical outcomes for BSC and lenalidomide. This table provides the LY and reveals that the time spent in AML is almost similar for BSC and lenalidomide, 0.3 and 0.32 respectively. The largest difference in QALYs and LYs gained is observed in the transfusion dependent health state.

Table 5.15 Base case overall results for effectiveness and cost

Treatment	Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
BSC	Transfusion independent	0.17	0.13	£2,415.61
	Transfusion dependent	4.06	2.27	£96,690.57
	AML	0.3	0.17	£6,619.99
	Total	**4.53**	**2.58**	**£105,726.18**
Lenalidomide	Transfusion independent	1.76	1.39	£69,731.35
	Transfusion dependent	3.61	1.9	£79,758.20
	AML	0.32	0.17	£6,818.16
	Total	**5.69**	**3.46**	**£156,307.71**

While Table 5.15 showed the overall costs for transfusion independent, transfusion dependence and AML, the resources by category for both lenalidomide and BSC are presented in table 5.16.

Table 5.16 Resource use by category

Item	Cost lenalidomide	Cost BSC	Increment
Technology cost	£68,261.29	£2,393.04	£65,868.25
Complications: Thrombocytopenia and Neutropenia	£316.14	£0.00	£316.14
Iron Chelation Therapy	£33,110.04	£41,111.57	-£8,001.53
Complications: Cardiac Disease, Diabetes Mellitus and Hepatic Complications	£712.81	£756.88	-£44.07
Blood transfusions	£44,381.48	£52,857.69	-£8,476.21
AML	£6,818.16	£6,619.99	£198.17
General Monitoring	£1,153.93	£22.57	£1,131.36
Monitoring with Best Supportive Care	£1,524.43	£1,927.89	-£403.46
Monitoring with Iron Chelation Therapy	£29.43	£36.55	-£7.11
Total	**£156,307.71**	**£105,726.18**	**£50,581.53**

Based on the results presented in table 5.15 the ICER was calculated. The incremental costs and effects are provided in the following table 5.17.

Table 5.17 Incremental costs and effects

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Best supportive care	£105,726	4.53	2.58	-	-	-	-
Lenalidomide	£156,307	5.69	3.46	£50,582	1.16	0.89	£56,965

ERG comment

The base case analysis of the manufacturer included three programming errors, thus the outcomes, including the ICER presented here, are incorrect. Two of these errors were confirmed by the manufacturer in response to the clarification letter and corrected by the ERG, as was the third programming error. The results of the ERG analyses are shown in section 5.3

5.2.10 Sensitivity analyses

The uncertainties in the economic evaluation were assessed through scenario analysis, deterministic sensitivity analysis and probabilistic analysis.

Scenario analysis

The following scenarios were explored and incorporated in the model:

1. Impact of using inputs based upon all patients in the trial rather than just UK patients.

This scenario changed the following parameters (table 5.18):

Table 5.18 Parameters changing using all patients included in the MDS-004 trial

	UK patients	All trial patients
Proportion of patients using ESA	28%	52.70%
Average number of RBC	9.15	8.97
Average RBC units per cycle	4.57	4.49
Average platelet units per cycle	0.06	0.0049

Using this scenario in the base case analysis resulted in an increased ICER of £59,500. However, according to the ERG there is a mistake in the model. The model uses for the average number of RBC units per cycle for all patients the value 2.9385. However, according to the MS manuscript this should be 8.97. Using the value of the manuscript in the model resulted in an increased ICER of £55,921.

2. Impact of comparing to either all patients using ESA or all patients only receiving transfusions as required

3. Impact of altering the threshold at which chelation is given (range from 20 – 30 units)

4. Impact of using alternative utility sources: Buckstein[50] and Goss[32].

The scenario of Goss[32] used utility values of 0.91 for transfusion independent and 0.5 for AML and transfusion dependent. Although not incorporated in the scenario analyses, Goss[32] also reported utility values for reduced transfusion requirements which was 0.81. The scenario of Buckstein[50] uses age-adjusted utility values: 0.83 for transfusion dependent and 0.66 for transfusion dependent and AML.

5. Impact of selecting alternative curve fits for mortality, AML and response duration (all alternative curves fitted)

Table 5.19 shows the results of all these scenarios (for the full tables containing also the per treatment costs and QALYs we refer to Tables 48 to 54 in the MS).

Table 5.19 Scenario analysis results

Parameter	Base case	Scenario analysis	ICER
Base Case			£56,965
Population used for parameter estimation	UK patients	All trial patients	£59,500
Comparator	Blood transfusion + 28% of patients ESA	All patients ESA	£56,623
		All patients only blood transfusion	£58,913
Iron chelation threshold	25	20	£55,953
		30	£57,761
Source utilities	Szende[52]	Goss[32]	£47,621
		Buckstein[50]	£59,323
Method of extrapolation response duration	Lognormal	Exponential	£56,265
		Weibull	£56,403
		Log-logistic	£56,730
		Extreme value	£55,445
Method of extrapolation AML progression	Weibull	Exponential	£56,717
		Log-logistic	£56,237
		Lognormal	£55,514
		Extreme value	£57,703
Method of extrapolation overall survival	Weibull	Exponential	£56,646
		Log-logistic	£55,813
		Lognormal	£55,536
		Extreme value	£58,117

ERG comment

The ERG would like to note that the results of the scenario analysis are based on the base case model that included programming errors related to the response rate of ESA and GCSF. This is especially relevant for the second scenario.

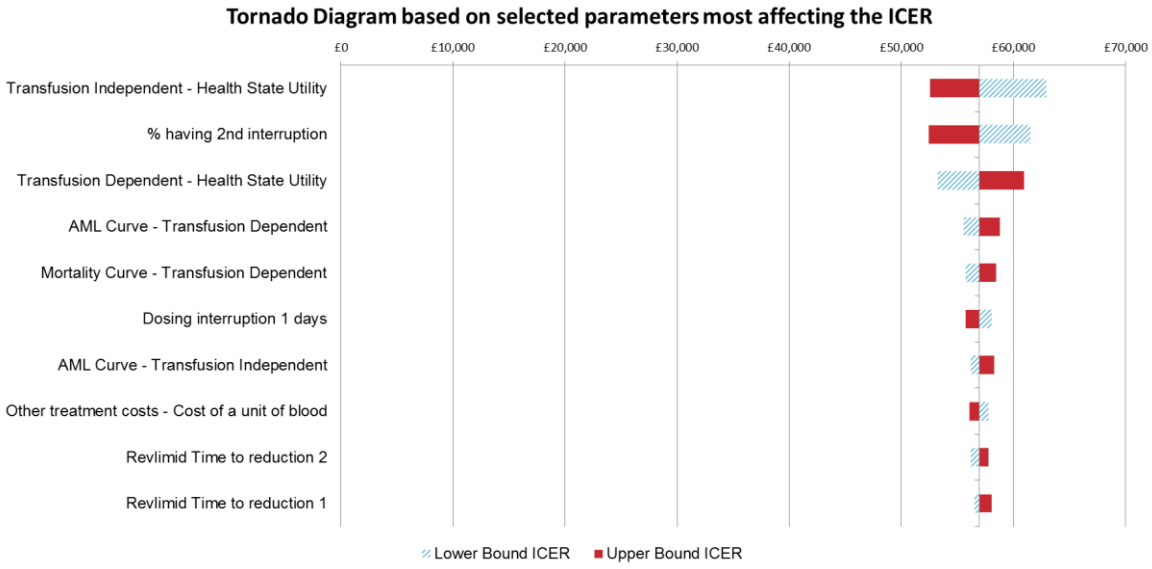
While the scenarios from the manufacturer already incorporated a range of possibilities, the ERG considered the utility value for the transfusion dependent health state low, especially since additional utility decrements for complications such as cardiac disease and diabetes were applied. While two alternative sources were explored, the extent to which these results are applicable remains. The health state descriptions of for example Goss[32] were based on different levels of problems on quality of life domains such as fatigue and tiredness and the need to arrange one's life around medical appointments and disease interference with social life. The descriptions of health states were in such broad terms that the difference between the values for transfusion independence and dependence cannot be interpreted as the reduced utility for transfusion dependence. Therefore, an additional scenario was incorporated by the ERG that applied the utility value of Szende[52] for the reduced transfusion state [0.77 sd 0.21]. This scenario increased the ICER to £59,274. While it might seem unreasonable to apply the utility value for partly transfusion dependent, this might be justified since utility decrements for adverse events are incorporated in the model.

The ICER appears quite robust for changes in curve estimation. However, tables 53 and 54 in the MS, which show costs and QALYs separately, show that for OS and AML progression the lognormal curve leads to a gain in life years of 1.4 whilst an extreme curve leads to a gain of 1 LY. But as the same pattern is true for the incremental costs, the ICERs only differ by about £2,000.

Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted by the manufacturer to establish which variables have the greatest influence on the ICER. Upper and lower bounds were determined using distributions as they were also applied in the PSA. Figure 5.4 shows the top ten parameters affecting the ICER. The most influential parameter is the utility for the transfusion independent health state followed by percentage of patients having a second dose interruption of lenalidomide and the utility for the transfusion dependent health state.

Figure 5.4 Tornado diagram of top ten parameters affecting the ICER



Probabilistic sensitivity analysis

The cost of lenalidomide and monitoring visits were not included in the sensitivity analysis. According to the manufacturer, both were fixed and not subject to uncertainty. Besides, it was assumed that all patients were assumed to have the same monitoring frequency. For all details on the distributions and parameters used for the PSA we refer to table 28 on page 126 of the MS.

The probabilistic sensitivity analysis was conducted using 1000 model runs. The summary results of the PSA performed by the manufacturer are shown in table 5.20 while the following figures show the cost effectiveness scatter plot and acceptability curve (figure 5.5 and 5.6).

Table 5.20 Summary results of PSA

	Outcome
Mean Incremental Costs	£50,178
Mean Incremental QALYs	0.862
Mean ICER	£58,178
% of observations cost-effective at £20,000 threshold	0%
% of observations cost-effective at £30,000 threshold	0%

Figure 5.5 Cost effectiveness scatter plot

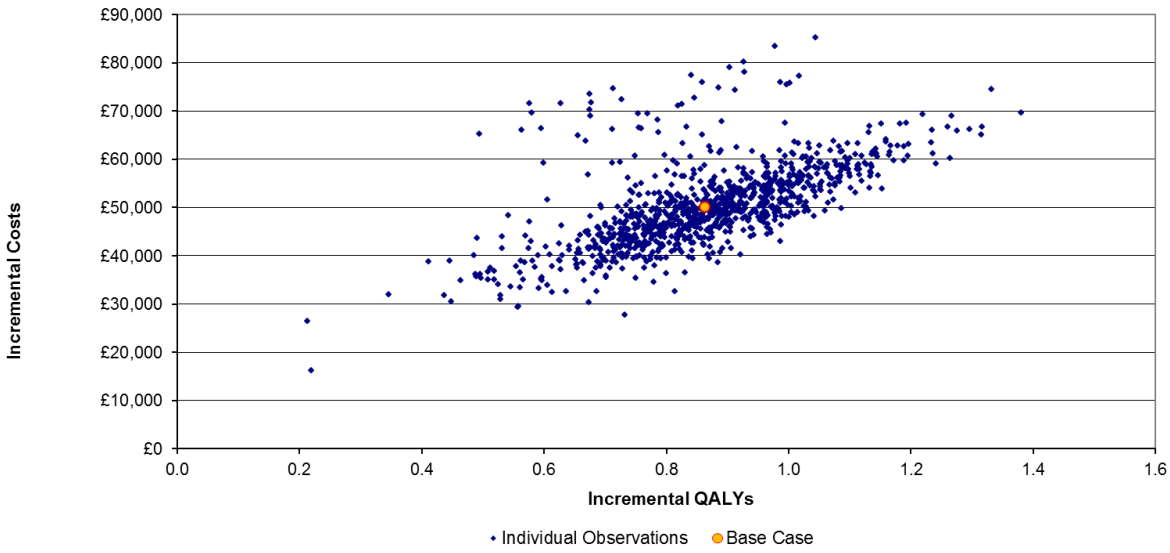
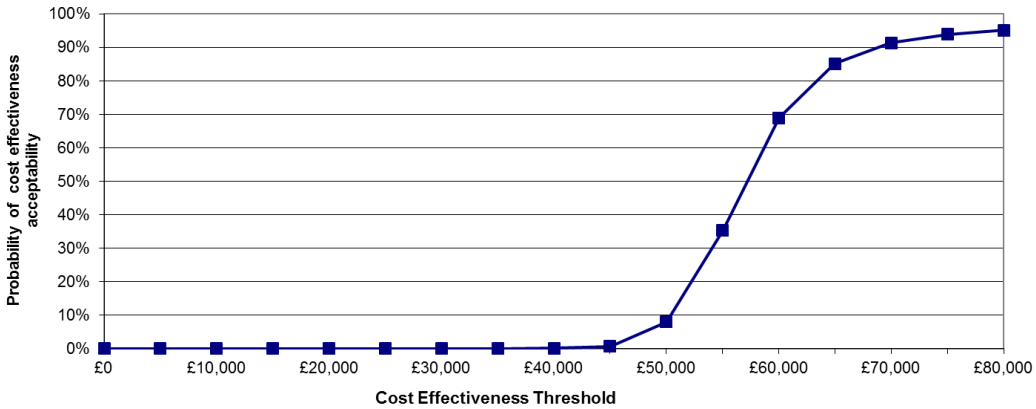


Figure 5.6 Cost effectiveness acceptability curve



ERG comment

In is interesting to see that the percentage of patients having a second dose interruption of lenalidomide is the second most influential parameter, and that other parameters related to the dosing schedule are also in the top 10. This is due to the fact that increasing the percentage of patients interrupting treatment means that the overall costs of the lenalidomide decrease (more patients receive a lower dose) whilst the effect is not influenced in the current model. In reality it seems likely that there is a correlation between the percentage and length of dose interruptions and the effects of the treatment.

The utility values for transfusion independence and transfusion dependence ranked first and third in the deterministic sensitivity analysis. This confirms the results from the scenario analyses, where the ICER was also significantly impacted by changes in utility values.

5.2.11 Model validation and face validity check

In section 7.6.1 of the MS, the model outcomes are compared to the clinical trial results. This comparison is presented in Table 5.21.

In addition, in section 7.7.1 under the heading "Validation", it is explained that multivariate regression analyses were undertaken to compute the magnitude of effect and statistical significance of various explanatory variables on response duration and mortality from other causes than AML. According to the manufacturer, these analyses served as an internal model validation since it enabled checking that the influence of variables obtained from the data adheres to a priori expectations.

Table 5.21 Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Median overall survival lenalidomide	5.2 years (MDS003 + MDS004)	4.7 years
	3.7 years (MDS004)	
Median overall survival Transfusion Only	3.8 years (MDS003 + MDS004)	3.8 years
	3.5 years (MDS004)	
Median time to AML progression for transfusion dependent patients	Not reached in the trial	5.4 years
Median time to AML progression for transfusion independent patients	Not reached in the trial	7.9 years
Median duration of response for patients who initially respond: lenalidomide	Not reached in the trial: lower bound of the 95% CI 1.9 years (MDS 004)	2.1 years
	2.2 years (MDS 003)	
Median duration of response for patients who initially respond: Placebo	Not reached in the trials (lower bound of the 95% CI 0.2 years (MDS 004)	1.5 years (evaluated based upon 5mg data)
% of patients experiencing thrombocytopenia grade 3/4	Lenalidomide 10mg: 44.9%	41.9% (difference between the two arms)
	Placebo: 3%	
% of patients experiencing neutropenia grade 3/4	Lenalidomide 10mg: 75.4%	57.5% (difference between the two arms)
	Placebo: 17.9%	

ERG comment

According to the ERG, the validation of the model was insufficient. The ERG requested information on the methods used to validate the model and how technical validity was assured. While some information on the internal validity was provided in table 5.21, the ERG

missed the discussion on the degree of concurrence between trial data and model results and requested restricted means as an additional measure to compare the trial with model outcomes. Regarding the external validity the ERG asked to compare the model results to data sources outside the clinical trial, especially for the BSC group.

The manufacturer responded as follows in the clarification:

"The median overall survival as provided in Table 40 of the submission is similar to that within the model when looking at the results of both the MDS003 and MDS004 trials (which is the information used within the model). In fact the median is slightly higher for lenalidomide in the clinical trial as response to lenalidomide was slightly higher in MDS003. The median duration of response is similar for lenalidomide to that experienced in the clinical trial and the proportion of patients experiencing adverse events is consistent.

The median survival presented is also consistent with available external information: in the NICE scope it is stated that median survival with low risk and intermediate-1 risk MDS is 5.7 years and 3.5 years respectively. As the median duration of MDS prior to the trial is 2.4 years in the placebo arm of the trial the additional survival takes patients to a median of approximately 6.2 years, consistent with the survival estimates for low risk MDS and the healthier population which would be expected to be enrolled into a clinical trial.

Due to other commitments the company statisticians were not able to provide restricted mean estimates in time to respond to these questions. If this is still required we can provide this at a later date."

The ERG agrees that the information provided in Table 5.21 indicates a good internal validity, i.e. the model outcomes are quite similar to the trial observations. The ERG however regrets that the manufacturer did not provide restricted means as an additional measure to compare outcomes. It is well possible that medians agree whilst means (due to skewness) disagree.

The ERG added a comparison to those presented by the manufacturer, by comparing the percentage of patients transitioned to AML between the model (Table 5.22) and the trial (Figure 10 of MS). In the trial a cumulative risk of AML for the lenalidomide dose groups combined was 25.1% (95% CI 17.1–33.1) at three years. This is slightly higher than the 21.3% observed in the model. In addition, the time to progression curve for lenalidomide 10mg shows a 1-year cumulative risk of approximately 5% and a 5-year cumulative risk of approximately 35%, both quite similar to what was obtained with the model.

Table 5.22 Time to AML progression in model

Treatment	1 year	3 year	5 year	20 year
Lenalidomide	6%	21.3%	33.5%	55.8%
BSC	7.3%	24.7%	36.9%	52.6%

The ERG agrees with the manufacturer that the survival as observed in the model is higher than that reported in literature and that this is most likely related to patient selection during trial enrolment, as the model outcomes and trial outcomes regarding mortality concur.[7]

The ERG also checked the disaggregated outcomes as reported in section 5.2.9 for their plausibility. In Table 5.15 it is observed that with lenalidomide more years are spent being transfusion independent than with BSC, which is a direct result of the higher response rate to lenalidomide and the long duration of response as observed in the MDS-004 study. In addition, one would expect lenalidomide patients to live longer as mortality is related to transfusion status, and this is indeed observed. A priori the expectation was also that the number of patients progressing to AML would be smaller in the lenalidomide group, since this transition is also dependent on transfusion status. However, here the difference between transfusion dependent and independent is smaller than for mortality. In addition, from Table 5.21 we observe that during the first five years, fewer lenalidomide patients develop AML, in line whit the a priori expectations. However, since lenalidomide patients live longer, and are thus at risk for AML over a longer period, at 20 years the number of patients progressed to AML is slightly larger for the lenalidomide group.

Overall, the ERG regards the model outcomes as plausible given the model inputs.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

New base case analysis

Based on several remarks in section 5.2 of this report the ERG defined a new base case analysis. This new ERG base case included the following adjustments:

- Programming errors confirmed by the manufacturer have been removed.
- Programming errors relating to dose reductions and days on active treatment were removed
- An additional cycle was added to the model
- Half cycle correction has been included
- Costs of iron chelation therapy have been updated to include deferiperone
- The inclusion of deferiperone changes the proportion of patients receiving oral and IV chelation therapy
- Treatment costs of AML were according to the latest version of the azacitadine STA (£1,451 per 28 day cycle);
- Response distributed over time according to trial instead of all patients from cycle 1 onwards (see table 5.9)
- Costs of neutropenia (£1,044.73) and thrombocytopenia (£1,768.01) were changed
- Uncertainty added to the number of monitoring visits and uncertainty increased around cost estimates complications and adverse events

The results of the adjusted ERG base case are presented in table 5.23, 5.24 and 5.25 for effects, costs and overall results, respectively. A table with the separate effect of all of these changes can be found in chapter 6.

Table 5.23 Results ERG case effects

	LY (undiscounted)		QALY (discounted)	
Health state	**BSC**	**Lenalidomide**	**BSC**	**Lenalidomide**
Transfusion Independent	0.14	1.64	0.11	1.29
Transfusion Dependent - No Chelation	0.13	0.25	0.08	0.15
Transfusion Dependent - Chelation	2.56	1.95	1.48	1.05
Transfusion Dependent - Chelation Failure	1.41	1.45	0.80	0.78
AML	0.30	0.32	0.17	0.17
Total	**4.54**	**5.61**	**2.64**	**3.45**

Table 5.24 Results ERG case costs

	Costs (discounted)	
	BSC	**Lenalidomide**
Technology Cost	£2,201	£71,318
Complications (Thrombo & Neutropenia)	£0	£184
Cost of Iron Chelation	£39,700	£28,500
Cost of Transfusion and Chelation Complications	£778	£842
Cost of Blood Transfusion	£53,161	£45,121
Cost of AML	£5,011	£5,150
Monitoring Costs	£0	£0
General monitoring costs	£19	£1,059
Monitoring cost with standard care	£1,929	£1,525
Monitoring cost for iron chelation	£37	£27
Total Cost	**£102,834**	**£153,725**

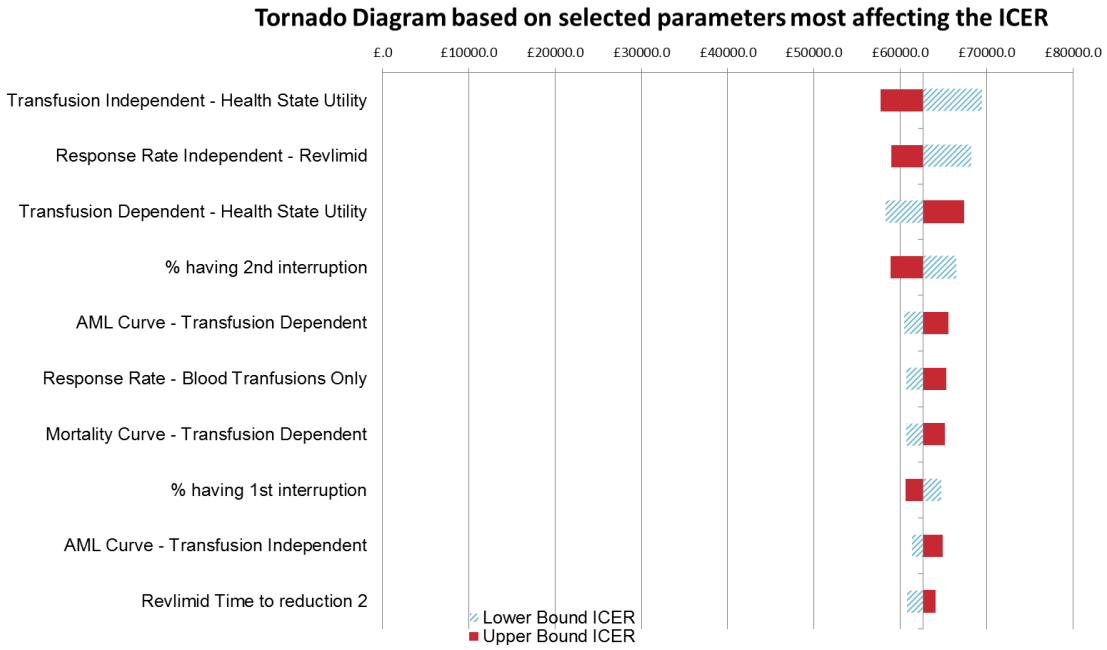
Table 5.25 Summary ERG case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Best supportive care	£102,836	4.10	2.64	-	-	-	-
Lenalidomide	£153,733	4.94	3.45	£50,898	0.84	0.81	**£62,674**

Deterministic sensitivity analysis

With this new ERG base case a new sensitivity analysis was conducted. Figure 5.7 shows the tornado diagram of the ten most influential parameters of the ERG base case. Compared to the base case of the manufacturer (figure 5.4) the response rate to lenalidomide has become much more important and is now the second most influential parameter. In addition, the response rate to BSC is now ranked sixth where previously it was not ranked in the top 10.

Figure 5.7 Tornado diagram – top 10 parameters affecting the ICER



Scenario analysis

The base case model of the manufacturer incorporated five scenarios that were described in detail in section 5.2.10. These scenarios were also explored for the ERG base case. The results are presented in Table 26. The table with detailed output per scenario can be found in Chapter 6.

Table 5.26 Scenarios included in the base case of the manufacturer applied to the ERG case

Parameter	ERG base case	Scenario analysis	ICER
ERG Base Case			£62,674
Population used for parameter estimation	UK patients	All trial patients	£61,396
Comparator	Blood transfusion + 28% of patients ESA	All patients ESA	£60,012
		All patients only blood transfusion	£63,124
Iron chelation threshold	25	20	£64,159
		30	£66,917
Source utilities	Szende[52]	Goss[32]	£51,956
		Buckstein[50]	£65,357
Method of extrapolation response duration	Lognormal	Exponential	£62,470
		Weibull	£62,052
		Log-logistic	£62,465
		Extreme value	£61,591
Method of extrapolation AML progression	Weibull	Exponential	£62,109
		Log-logistic	£61,405
		Lognormal	£60,216

		Extreme value	£63,982
Method of extrapolation overall survival	Weibull	Exponential	£61,970
		Log-logistic	£60,755
		Lognormal	£60,290
		Extreme value	£64,609

Additional scenarios were explored by the ERG. Table 5.27 shows the results. Detailed information is provided in Appendix 4.

Table 5.27 Additional scenarios on the ERG base case explored by the ERG

Parameter	ERG Base case	Scenario analysis	ICER
ERG Base case			£62,674
Utility value for transfusion dependence	Utility value fully transfusion dependent (0.65)	Utility value reduced transfusion burden (0.77)	£68,357
Utility value for AML	Utility AML is similar to transfusion dependence (0.65)	Utility of AML is reduced with 25% (0.49)	£62,753
Cost adverse events	Treatment cost adverse events	Zero cost for treating adverse events	£62,448
Treatment of adverse events	Only a proportion of patients experiencing AEs require treatment	All patients experiencing AEs require treatment	£62,846
Monitoring	Monitoring visits at GP	Monitoring visits at haematologist	£64,079
Cycles before Chelation Threshold reached (non-responders)	2	4	£67,428
Proportion of patients treated with IV chelation	5.70%	100%	£56,750
Response duration BSC	According to 5mg	According to 10mg	£64,164
Utility decrement AE	0% Thrombocytopenia 0% Neutropenia	25% Thrombocytopenia 25% Neutropenia	£63,893

The manufacturer sensitivity analyses have shown that the model is quite sensitive to changes in the utility. We have therefore also explored a scenario in which the utility value for transfusion dependence is increased to 0.77, the value for reduced transfusion burden[52]. The resulting ICER was considerably larger than the ERG base case ICER. Since the time spent in the transfusion dependent state is larger in the comparator group, the accumulated QALYs increased more in the comparator group than in the lenalidomide group.

We also explored a scenario with a decreased utility for AML. According to the ERG, it seems plausible that AML is worse than transfusion dependence and a reduction of 25% was assigned (utility value of 0.49). Compared to the ERG base case, the impact of lowering the

utility value for AML is negligible since life years spend in AML are equal for the lenalidomide and comparator group.

As discussed in section 5.2.8, some uncertainty exists about the cost of adverse events (i.e. thrombocytopenia and neutropenia). As an additional scenario, the impact of zero costs was explored. The ICER is decreased slightly, because although a substantial proportion of patients experienced AEs, the relative small proportion of patients treated reduces the overall impact on the ICER.

The proportion of patients treated with AEs was considered rather low. In order to explore the impact of these treatment proportions, the assumption was made that all patients experiencing AEs required treatment. This led to a minimal increase of the ICER.

The ERG raised some questions on the monitoring of MDS patients by a GP. The manufacturer stated that adverse events are the main causes for haematologist visits and to avoid double counting haematology visits were therefore not included for regular monitoring. However, since most patients are not treated for adverse events, the ERG wanted to explore the impact of using the price for a haematology visit. This increased the ICER slightly.

Earlier it was mentioned that the 9.15 RBC units over the preceding eight weeks was multiplied by two in the model (see section 5.2.6) for the calculation of the number of cycles before the chelation threshold was reached for non-responders. Since the ERG is not sure about the appropriateness of the multiplication, the impact of assuming no multiplication factor (meaning that the number of cycles before non-responders require chelation increases from two to four) was explored as a scenario analysis. This led to a clear increase of the ICER.

As the clinical expert (Personal communication, Dr Culligan, 23 February 2013) stated that chelation therapy consists in most cases of IV treatment, we explored a scenario where instead all patients instead of only 5.7% are treated with IV chelation. This led to a clear reduction in the ICER.

The ERG base case assumed response duration of BSC was similar to response duration of the 5mg lenalidomide group. Since the ERG is not sure about the response duration of BSC, an additional as scenario was explored that assumed response duration of BSC was similar to the 10mg group. This scenario increased the ICER.

Finally, while the manufacturer considered the adverse events as fairly manageable and to have a minimal impact on the quality of life, the ERG explored an additional scenario assuming a 25% decrement on the utility for patients experiencing thrombocytopenia and neutropenia. This scenario increased the ICER.

Probabilistic sensitivity analysis

The summary results of the PSA are shown in table 5.28.

Table 5.28 Summary results of PSA ERG case

Item	Result
Mean Incremental Costs	£51,226
Mean Incremental QALYs	0.79
Mean ICER	£65,052
% of observations cost-effective at £20,000 threshold	0%
% of observations cost-effective at £30,000 threshold	0%

PSA results are presented in figure 5.8 and figure 5.9.

Figure 5.8 ERG Cost effectiveness scatter plot

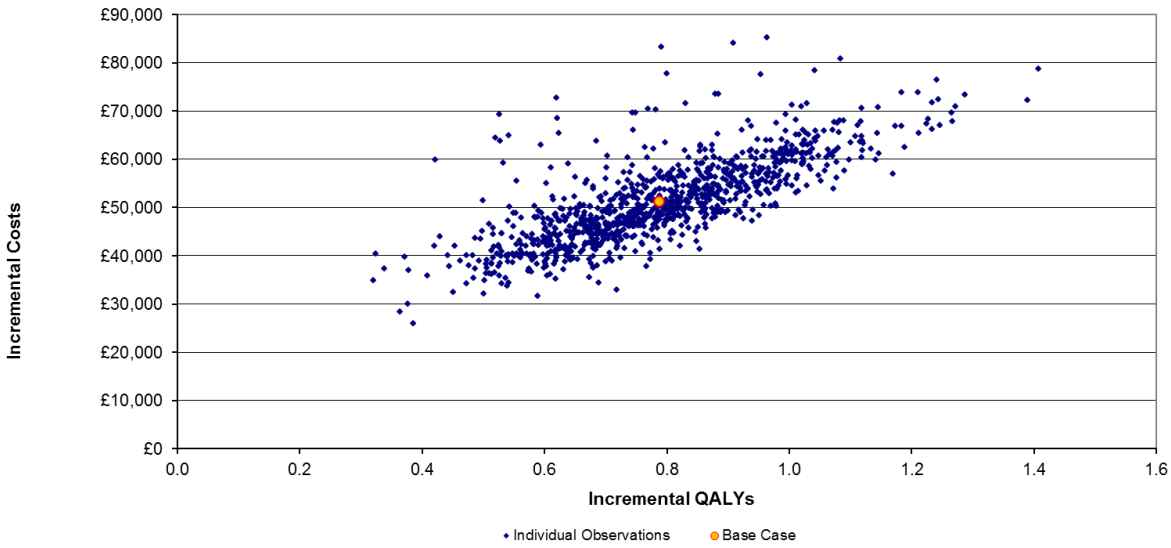
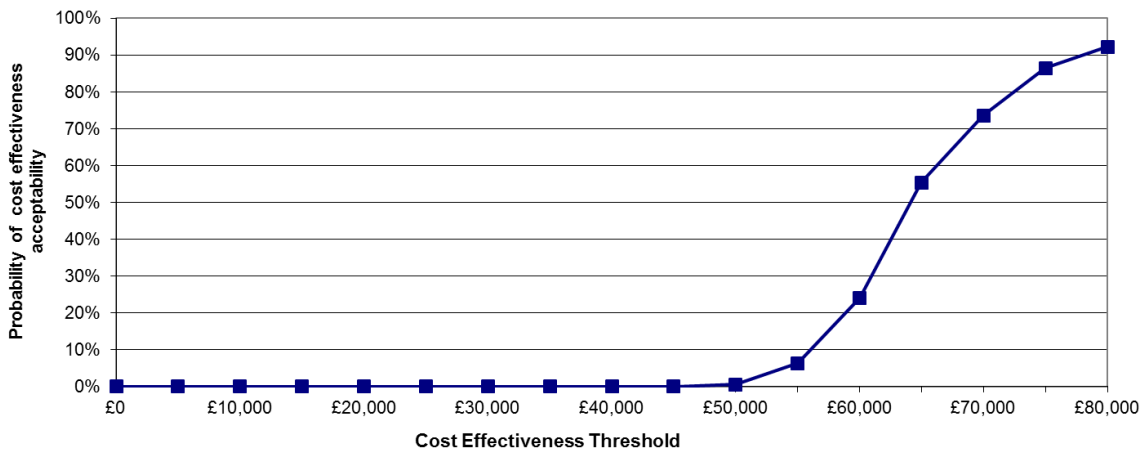


Figure 5.9 ERG Cost effectiveness acceptability curve



Compared to the manufacturer's base case the incremental QALYs in the PSA are a little smaller. The cost effectiveness acceptability curve is shifted to the left meaning that the

probability of lenalidomide being a cost-effective intervention at for example £50,000 has been reduced to almost zero while this was around 10% in the base case analysis.

5.4 Conclusions of the cost effectiveness section

The economic model described in the MS is considered by the ERG to meet the NICE reference cases to a reasonable extent and is in line with the decision problem specified in the scope.

The ERG assessment indicated that the model was generally well presented and reported. However, a few issues regarding the electronic model were identified that altered the results substantially. By correcting these issues, adding a half cycle correction and changing a few input parameters, an ERG base case was defined. The manufacturer base case ICER was £56,965 per QALY gained whilst the ERG base case ICER amounted to £62,674 per QALY gained.

The input for the model was derived from MDS-004 trial data and literature. For some input values, such as those associated to transfusion related complication, were not based on a systematic search of the literature. However, a rapid review of the literature by the ERG did not reveal new relevant studies.

The study on which utilities for the transfusion related health states were based does not conform to the NICE reference case, as valuation was done by MDS patients. The health state descriptions were very broad, so that the transfusion dependant description might already incorporate some of the adverse events associated with for example chelation therapy or complications such as cardiac disease, diabetes or hepatic complications. The ERG considers it likely that some double counting is included in the model by assigning the utility value of 0.65 (a value for completely transfusion dependent) to all patients not transfusion independent and use utility decrements on top of this.

The ERG univariate sensitivity analysis revealed that the ICER is quite sensitive to changes in the utility values applied to the transfusion independent and transfusion dependent health states, the response rate to lenalidomide and the percentage of patients having a second treatment interruption.

The response rate to lenalidomide was directly based on the observed response in the MDS004 trial, and hence the uncertainty around that parameter may be regarded well quantified. The same is true for the percentage patients having a second treatment interruption, though it must be reminded that in the current model only the costs are directly impacted by treatment interruptions while the effects remain constant; in reality however, treatment interruptions will most likely also impact the effects.

The uncertainty around the utilities is not limited to the statistical uncertainty that was explored in the univariate and probabilistic sensitivity analysis, as no good source for these

utilities was identified. The study on which the utilities were based does not conform to the NICE reference case, and it was not fully clear what is being valued.

The cost effectiveness results were generally robust under the scenario analyses conducted, though a few scenarios impacted the ICER noticeably.

The manufacturer defined scenario analyse confirmed that the ICER is mostly sensitive to changes in the utility; when other sources for the utility values are used, the ICER changes significantly. While the ICER appears robust for changes in the method of extrapolation of AML progression and overall mortality, this is not true for the incremental costs and incremental QALYs, these can change substantially. The scenario analysis on ESA use in BSC indicated clearly that this has no impact on the outcome.

The ERG defined scenario analyses also revealed that the ICER is sensitive to changes in the percentage of patients receiving IV chelation; however, the explored percentage of 100% is quite extreme, so this scenario serves as a worst case scenario. Additionally, the time until chelation is required also has a noticeable effect on the ICER, but this scenario was mainly explored due to ambiguity regarding the number of blood transfusions already given before entering the model.

From the various scenario analyses and sensitivity analyses it is clear that utilities and cost parameters related to AML, complications and AE have little to no effect on the ICER.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Chapter 5.3 the ERG base case was presented, which was based on various changes compared to the manufacturer base case. Table 6.1 shows how each individual change impacts the ICER plus the combined effect of all changes simultaneously. Appendix 4 lists the details about the changes made to the model.

Tables 6.2 and 6.3 present the results of the manufacturer defined and ERG defined scenarios, respectively, applied to the ERG base case.

Table 6.1 Revised base case cost-effectiveness analysis, incorporating corrections and amendments identified by the ERG.

	Best supportive care		**Lenalidomide**		**Incremental**		**ICER**
	Cost	QALY	Cost	QALY	Cost	QALY	Cost per QALY gained
Manufacturer's base case analysis	**£105,726**	**2.58**	**£156,308**	**3.46**	**£50,582**	**0.89**	**£56,965**
Corrected confirmed programming errors	£104,753	2.59	£156,308	3.46	£51,555	0.87	£59,196
Correcting programming errors dose reduction	£104,753	2.59	£162,628	3.46	£57,875	0.87	£66,453
Additional cycle added	£104,753	2.59	£162,628	3.46	£57,875	0.87	£66,453
Half cycle correction	£104,052	2.57	£160,343	3.43	£56,292	0.87	£64,929
Chelation therapy deferiperone added	£102,270	2.64	£158,890	3.49	£56,620	0.85	£66,346
Cost AML adjusted	£100,655	2.64	£157,227	3.49	£56,572	0.85	£66,289
Response over time (mortality based on max response)	£102,839	2.64	£153,817	3.45	£50,978	0.81	£62,773
Cost AEs adjusted	£102,836	2.64	£153,733	3.45	£50,898	0.81	£62,674
ERG revised base case	**£102,836**	**2.64**	**£153,733**	**3.45**	**£50,898**	**0.81**	**£62,674**

Table 6.2 ERG base case - Scenario analyses incorporated in the base case model applied to the ERG case

	Best supportive care			**Lenalidomide**			**Incremental**		**ICER**
	Cost	QALY	LYG	Cost	QALY	LYG	Cost	QALY	Cost per QALY gained
ERG Base case	**£102,836**	**2.64**	**4.10**	**£153,733**	**3.45**	**4.94**	**£50,898**	**0.81**	**£62,674**
All trial patients	£108,182	2.67	4.15	£155,809	3.45	4.94	£47,627	0.78	£61,396
All patients ESA	£111,532	2.75	4.25	£153,733	3.45	4.94	£42,201	0.70	£60,012
No patients ESA	£99,949	2.60	4.04	£153,733	3.45	4.94	£53,785	0.85	£63,124
Iron chelation threshold 20	£101,827	2.64	4.10	£153,955	3.45	4.94	£52,127	0.81	£64,159
Iron chelation threshold 30	£102,640	2.64	4.10	£157,136	3.45	4.94	£54,497	0.81	£66,917
Source utility Goss	£102,836	2.06	4.10	£153,733	3.04	4.94	£50,898	0.98	£51,956
Source utility Buckstein	£102,836	2.67	4.10	£153,733	3.45	4.94	£50,898	0.78	£65,357
Curve selection – response duration Exponential	£102,816	2.64	4.10	£153,279	3.45	4.94	£50,464	0.81	£62,470
Curve selection – response duration Weibull	£102,884	2.64	4.10	£152,380	3.44	4.94	£49,496	0.80	£62,052
Curve selection – response duration Log-logistic	£102,855	2.64	4.10	£153,276	3.44	4.94	£50,422	0.81	£62,465
Curve selection – response duration Extreme value	£102,894	2.64	4.10	£151,389	3.42	4.89	£48,495	0.79	£61,591
Curve selection – AML progression Exponential	£106,278	2.71	4.22	£158,387	3.55	5.10	£52,109	0.84	£62,109
Curve selection – AML progression Log-logistic	£103,494	2.65	4.12	£156,725	3.51	5.05	£53,232	0.87	£61,405
Curve selection – AML progression Lognormal	£102,794	2.63	4.09	£158,397	3.55	5.11	£55,603	0.92	£60,216
Curve selection – AML progression Extreme value	£102,141	2.63	4.08	£150,817	3.39	4.83	£48,676	0.76	£63,982

	Best supportive care			Lenalidomide			Incremental		ICER
	Cost	QALY	LYG	Cost	QALY	LYG	Cost	QALY	Cost per QALY gained
ERG Base case	**£102,836**	**2.64**	**4.10**	**£153,733**	**3.45**	**4.94**	**£50,898**	**0.81**	**£62,674**
Curve selection – overall survival Exponential	£108,182	2.76	4.31	£160,072	3.60	5.18	£51,890	0.84	£61,970
Curve selection – overall survival Log-logistic	£105,222	2.70	4.19	£160,088	3.60	5.17	£54,866	0.90	£60,755
Curve selection – overall survival Lognormal	£107,326	2.75	4.28	£163,384	3.68	5.29	£56,058	0.93	£60,290
Curve selection – overall survival Extreme value	£101,134	2.60	4.03	£148,779	3.33	4.76	£47,645	0.74	£64,609

Table 6.3 ERG base case – Scenario analyses additional scenarios

	Best supportive care			Lenalidomide			Incremental		ICER
	Cost	QALY	LYG	Cost	QALY	LYG	Cost	QALY	Cost per QALY gained
ERG Base case	**£102,836**	**2.64**	**4.10**	**£153,733**	**3.45**	**4.94**	**£50,898**	**0.81**	**£62,674**
Utility value for transfusion dependence	£102,836	3.10	4.10	£153,733	3.85	4.94	£50,898	0.74	£68,357
Utility value for AML	£102,836	2.60	4.10	£153,733	3.41	4.94	£50,898	0.81	£62,753
Cost adverse events	£102,836	2.64	4.10	£153,549	3.45	4.94	£50,714	0.81	£62,448
Treatment of adverse events	£102,836	2.64	4.10	£154,681	3.45	4.94	£51,845	0.81	£63,841
Monitoring	£106,324	2.64	4.10	£158,362	3.45	4.94	£52,038	0.81	£64,079
Cycles before Chelation Threshold reached (non-responders)	£101,353	2.64	4.10	£156,246	3.45	4.94	£54,893	0.81	£67,428
Proportion of patients treated with IV chelation	£102,836	2.34	4.10	£153,733	3.24	4.94	£50,898	0.90	£56,750
Response duration BSC	£102,103	2.65	4.10	£153,733	3.45	4.94	£51,631	0.80	£64,164
Utility decrement AE	£102,836	2.64	4.10	£153,733	3.43	4.94	£50,898	0.80	£63,893

7. OVERALL CONCLUSIONS

The two main problems with the clinical effectiveness data reported in the MS are:

1. The possibility of treatment switching after 16 weeks due to dose-limiting toxicities or lack of response, which means that most long term effectiveness data are unreliable.

   Given that 62.3% of patients in the lenalidomide 5mg group and 72.5% in the lenalidomide 10mg group experienced an AE leading to dose reduction or interruption, and one dose reduction in the 10mg group means patients receive effectively the same dose as the 5mg group, it seems there is some difficulty in distinguishing the treatment arms. In addition, patients in the placebo or lenalidomide 5mg groups without minor erythroid response by Week 16 or those experiencing erythroid relapse could crossover to lenalidomide 5mg or 10mg, respectively. In the placebo group, only one out of 67 patients completed the 52 weeks double-blind phase. This means that the assessment of effects after 16 weeks is severely compromised.

2. Data were reported for two populations: the ITT and mITT population. The mITT population included patients with centrally confirmed low- or intermediate-1-risk MDS with del(5q) and documented RBC transfusion-dependence, who received ≥1 dose of study drug. The fact that confirmation of del(5q) status (karyotype analysis) and bone marrow morphology was performed by central haematological review after randomisation, means that patients not fulfilling the inclusion criteria are included in the ITT population. It is not clear how differences between these two populations influence results. However, data for the ITT population were used in the economic model as it "more closely matches the relevant NICE scope" (MS, section 7.2.1, page 96).

The economic model described in the MS is considered by the ERG to meet the NICE reference case to a reasonable extent and is in line with the decision problem specified in the scope.

The ERG assessment indicated that the model was generally well presented and reported, besides a few errors in the model and the lack of a half cycle correction. The manufacturer base case ICER was £56,965 per QALY gained whilst the ERG base case, correcting for the various issues identified, estimated an ICER of £62,674 per QALY gained.

The various sensitivity analyses revealed that the ICER is relatively robust against changes in most input values but quite sensitive to changes in the utility values applied to the transfusion independent and transfusion dependent health states and the response rate to lenalidomide. As the latter was directly based on the observed response in the MDS004 trial, the uncertainty around that parameter may be regarded well quantified.

The uncertainty around the utilities is not limited to the statistical uncertainty that was explored in the univariate and probabilistic sensitivity analysis. The study on which those utilities were based does not conform to the NICE reference case, as valuation was done by

MDS patients. The health state descriptions were very broad, so that it is no fully clear what is being valued.

7.1 Implications for research

Long-term effectiveness data, including survival and leukaemia progression, as well as adverse events data in comparison with best supportive care are warranted.

In order to increase the robustness of the health economic outcome, a quality of life study among MDS patients would be of great value. Ideally, such a study would ask transfusion dependent and independent patients to fill out the EQ-5D, after which outcomes are valued using the UK tariff which is based on the general population.

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Appendix 1: Additional ERG Search Strategies

The ERG undertook the following search as a broad update to supplement the Medline and Embase strategies reported in MS 10.2. The additional search was intended to identify any Non-RCTs missed by errors in line combinations and to identify whether any papers reporting adverse events had been missed by the original MS searches. The ERG searches were designed to identify any papers irrespective of study design that feature the study population of patients with MDS associated with a del(5q) abnormality. For completeness the ERG also added additional synonyms and Emtree terms for del(5q).

Search Strategies

(ERG: MDS AND del(5q)) NOT (MS search 10.2)

Medline search: Lines #1-113 replicate the MS search. The MS search was run in January 2012, so a date facet was inserted (lines #114-117) in order to ensure any new papers retrieved by the original MS strategy would not be removed from the new results set. Lines #118-123 contain the new ERG strategy intended to identify any papers irrespective of study design containing MDS AND del(5q). The MS search is then "NOT"-ed from the ERG search in line #124 in order to remove papers already retrieved by the previous MS search, leaving only new or previously missed references.

Medline (OVIDSP):1946-2013/1/wk02
Searched 18.1.12

1 exp Myelodysplastic Syndromes/ (14856)
2 myelodysplas$.mp. (14503)
3 MDS.ti,ab. (9205)
4 1 or 2 or 3 (22108)
5 5q.mp. (2450)
6 4 and 5 (732)
7 best supportive care.mp. (856)
8 clinical practice.mp. (79576)
9 lenalidomide.mp. (1419)
10 revlimid.mp. (70)
11 active therap$.ti,ab. (1182)
12 Placebos/ (31156)
13 placebo$.mp. (152152)
14 Anti-Bacterial Agents/ (217892)
15 antibiotic$.ti,ab. (197691)
16 Blood Transfusion/ (50548)
17 transfusion$.ti,ab. (69913)
18 "Intercellular Signaling Peptides and Proteins"/ (17106)
19 Receptors, Erythropoietin/ or Erythropoietin/ or Erythropoietin, Recombinant/ (20310)
20 erythropoietin$.ti,ab. (19714)
21 EPO.ti,ab. (7991)
22 darbepoetin alfa.mp. (899)

23 Epoetin Alfa/ (0)
24 epoetin alfa.mp. (1469)
25 epoetin beta.mp. (426)
26 epoetin theta.mp. (2)
27 epoetin zeta.mp. (15)
28 Polyethylene Glycols/ (33786)
29 methoxy polyethylene glycol-epoetin beta.mp. (23)
30 Granulocyte Colony-Stimulating Factor/ (12413)
31 Granulocyte Colony-Stimulating Factor$.mp. (15764)
32 G-CSF.mp. (10711)
33 Filgrastim/ (0)
34 filgrastim.ti,ab. (1248)
35 lenograstim.mp. (309)
36 pegfilgrastim.mp. (375)
37 Iron Chelating Agents/ (4709)
38 Iron/ and Chelation Therapy/ (264)
39 iron chelat$.mp. (8182)
40 Thioctic Acid/ (2697)
41 Alpha lipoic acid.mp. (1366)
42 ALA.ti,ab. (29615)
43 Deferasirox.mp. (449)
44 Deferoxamine/ (5560)
45 Deferoxamine.ti,ab. (2937)
46 Dimercaprol/ (1446)
47 Dimercaprol.ti,ab. (245)
48 BAL.ti,ab. (10089)
49 Succimer/ (1386)
50 Dimercaptosuccinic acid.mp. (2050)
51 DMSA.ti,ab. (1847)
52 Unithiol/ (488)
53 2,3-dimercapto-1-propanesulfonic acid.mp. (56)
54 DMPS.ti,ab. (501)
55 Edetic Acid/ (23650)
56 Ethylenediamine tetraacetic acid.mp. (603)
57 Penicillamine/ (6944)
58 Penicillamine.ti,ab. (6118)
59 or/7-58 (813265)
60 6 and 59 (198)
61 Meta-Analysis/ (36436)
62 meta analy$.tw. (42349)
63 metaanaly$.tw. (1111)
64 meta analysis.pt. (36436)
65 (systematic adj (review$1 or overview$1)).tw. (34426)
66 exp Review Literature/ (1735930)
67 or/61-66 (1769146)
68 cochrane.ab. (20383)
69 embase.ab. (18164)
70 (psychlit or psyclit).ab. (818)
71 (psychinfo or psycinfo).ab. (6570)

72 (cinahl or cinhal).ab. (6869)
73 science citation index.ab. (1500)
74 bids.ab. (315)
75 cancerlit.ab. (527)
76 or/68-75 (33098)
77 reference list$.ab. (7214)
78 bibliograph$.ab. (9630)
79 hand-search$.ab. (3024)
80 relevant journals.ab. (525)
81 manual search$.ab. (1775)
82 or/77-81 (19846)
83 selection criteria.ab. (15833)
84 data extraction.ab. (7416)
85 83 or 84 (22003)
86 review.pt. (1732721)
87 85 and 86 (15329)
88 comment.pt. (484036)
89 letter.pt. (757313)
90 editorial.pt. (306642)
91 animal/ (4993321)
92 human/ (12521286)
93 91 not (91 and 92) (3656510)
94 or/88-90,93 (4762234)
95 67 or 76 or 82 or 87 (1776639)
96 95 not 94 (1622977)
97 60 and 96 (70)
98 randomized controlled trial.pt. (336937)
99 controlled clinical trial.pt. (84917)
100 randomized controlled trials/ (82305)
101 random allocation/ (75868)
102 double blind method/ (117050)
103 single blind method/ (16860)
104 clinical trial.pt. (472343)
105 exp Clinical Trial/ (695229)
106 (clin$ adj25 trial$).ti,ab. (214587)
107 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (118391)
108 placebos/ (31156)
109 placebos.ti,ab. (1638)
110 random.ti,ab. (135219)
111 research design/ (72000)
112 or/98-111 (1137142)
113 60 and 112 (60)
114 (2012$ or 2013$).ed,dc. (800643)
115 (2012$ or 2013$).yr. (531581)
116 114 or 115 (800891)
117 113 not 116 (46)
118 exp Myelodysplastic Syndromes/ (14856)
119 myelodysplas$.mp. (14503)
120 MDS.ti,ab. (9205)

121 or/118-120 (22108)
122 (5q or del5q or del-5q).mp. (2456)
123 121 and 122 (737)
124 123 not 117 (691)

Embase (OVIDSP):1974-2013/wk02
Searched 18.1.12

1 exp myelodysplastic syndrome/ (22107)
2 myelodysplas$.mp. (25496)
3 MDS.ti,ab. (14850)
4 1 or 2 or 3 (33029)
5 5q.mp. (5594)
6 4 and 5 (1705)
7 best supportive care.mp. (1651)
8 clinical practice.mp. (225629)
9 lenalidomide.mp. (6261)
10 revlimid.mp. (948)
11 active therap$.ti,ab. (1730)
12 placebo/ (224082)
13 placebo$.mp. (306001)
14 antiinfective agent/ (152102)
15 antibiotic$.ti,ab. (271446)
16 blood transfusion/ (83894)
17 transfusion$.ti,ab. (100035)
18 signal peptide/ (17755)
19 erythropoietin receptor/ (2484)
20 erythropoietin antibody/ or erythropoietin/ or recombinant erythropoietin/ (39765)
21 erythropoietin$.ti,ab. (25575)
22 EPO.ti,ab. (10774)
23 darbepoetin alfa.mp. (950)
24 epoetin alfa.mp. (1391)
25 epoetin beta.mp. (568)
26 epoetin theta.mp. (10)
27 epoetin zeta.mp. (37)
28 macrogol derivative/ (10633)
29 methoxy polyethylene glycol-epoetin beta.mp. (56)
30 granulocyte colony stimulating factor/ (28392)
31 Granulocyte Colony-Stimulating Factor$.mp. (40631)
32 G-CSF.mp. (15356)
33 recombinant granulocyte colony stimulating factor/ (11930)
34 filgrastim.ti,ab. (1857)
35 lenograstim.mp. (691)
36 pegfilgrastim.mp. (734)
37 iron chelating agent/ (2726)
38 iron/ and chelation therapy/ (585)
39 iron chelation/ (3876)
40 iron chelat$.mp. (10459)
41 thioctic acid/ (5425)

42 Alpha lipoic acid.mp. (1863)
43 ALA.ti,ab. (33936)
44 Deferasirox.mp. (1508)
45 deferoxamine mesylate/ or deferoxamine/ (11773)
46 Deferoxamine.ti,ab. (3625)
47 dimercaprol/ (2555)
48 Dimercaprol.ti,ab. (310)
49 BAL.ti,ab. (13870)
50 succimer diisopentyl ester/ or succimer tc 99m/ or succimer di sec butyl ester/ or succimer dibutyl ester/ or succimer dimethyl ester/ or succimer diisobutyl ester/ or succimer derivative/ or succimer diethyl ester/ or succimer/ or succimer dipropyl ester/ or succimer diisopropyl ester/ (4508)
51 Dimercaptosuccinic acid.mp. (1853)
52 DMSA.ti,ab. (2689)
53 unithiol/ (909)
54 2,3-dimercapto-1-propanesulfonic acid.mp. (65)
55 DMPS.ti,ab. (652)
56 edetic acid/ (33280)
57 Ethylenediamine tetraacetic acid.mp. (740)
58 penicillamine disulfide/ or penicillamine derivative/ or penicillamine/ (17316)
59 Penicillamine.ti,ab. (8027)
60 or/7-59 (1244871)
61 6 and 60 (703)
62 Meta Analysis/ (68279)
63 ((meta adj analy$) or metaanalys$).tw. (63949)
64 (systematic adj (review$1 or overview$1)).tw. (49514)
65 or/62-64 (126418)
66 cancerlit.ab. (667)
67 cochrane.ab. (29089)
68 embase.ab. (26065)
69 (psychlit or psyclit).ab. (959)
70 (psychinfo or psycinfo).ab. (6439)
71 (cinal or cinahl).ab. (8556)
72 science citation index.ab. (1923)
73 bids.ab. (425)
74 or/66-73 (44413)
75 reference lists.ab. (8684)
76 bibliograph$.ab. (13937)
77 hand-search$.ab. (4013)
78 manual search$.ab. (2305)
79 relevant journals.ab. (729)
80 or/75-79 (26773)
81 data extraction.ab. (10680)
82 selection criteria.ab. (19505)
83 81 or 82 (28828)
84 review.pt. (1925463)
85 83 and 84 (17140)
86 letter.pt. (809798)
87 editorial.pt. (423038)

88 animal/ (1811979)
89 human/ (14005991)
90 88 not (88 and 89) (1356181)
91 or/86-87,90 (2575383)
92 65 or 74 or 80 or 85 (157748)
93 92 not 91 (151900)
94 61 and 93 (3)
95 clinical trial/ (879872)
96 randomised controlled trial/ (337600)
97 randomization/ (60373)
98 single blind procedure/ (16849)
99 double blind procedure/ (115091)
100 crossover procedure/ (35920)
101 placebo/ (224082)
102 randomi?ed controlled trial$.tw. (82712)
103 rct.tw. (10767)
104 random allocation.tw. (1242)
105 randomly allocated.tw. (18412)
106 allocated randomly.tw. (1876)
107 (allocated adj2 random).tw. (795)
108 single blind$.tw. (13212)
109 double blind$.tw. (139851)
110 ((treble or triple) adj blind$).tw. (321)
111 PLACEBO$.tw. (189117)
112 prospective study/ (222838)
113 or/95-112 (1320280)
114 case study/ (18281)
115 case report.tw. (246431)
116 abstract report/ or letter/ (873869)
117 or/114-116 (1133675)
118 113 not 117 (1283981)
119 61 and 118 (182)
120 (2012$ or 2013$).yr. (1034527)
121 (2012$ or 2013$).em,dd. (1334986)
122 120 or 121 (1346554)
123 119 not 122 (155)
124 exp myelodysplastic syndrome/ (22107)
125 myelodysplas$.mp. (25496)
126 MDS.ti,ab. (14850)
127 or/124-126 (33029)
128 (5q or del5q or del-5q).mp. (5642)
129 127 and 128 (1746)
130 5q- syndrome/ (407)
131 129 or 130 (1746)
132 131 not 123 (1591)
133 limit 132 to embase (1463)

Additional Economics searches

The Manufacturer referenced cost estimates from the Luengo-Fernandez[62] study of cardiovascular disease in the general population. The ERG ran the following focused searches to look for any studies that would provide cost estimates for cardiac complications due to iron overload for those with MDS.

NHS Economic Evaluation Database (NHS EED) (Wiley): Cochrane Library: up to 2013/Issue 1
Searched 21.2.13

#1 MeSH descriptor: [Iron Overload] explode all trees 123
#2 iron near/3 (overload* or intoxicat* or poison* or toxic*) 252
#3 Hemosideros?s or hemochromatos?s or bronze diabetes 127
#4 #1 or #2 or #3 339

NHS EED search retrieved 20 records

MEDLINE (OvidSP):1946-2013/2/wk1
Searched 21.2.13

1 economics/ (26358)
2 exp "costs and cost analysis"/ (168678)
3 economics, dental/ (1847)
4 exp "economics, hospital"/ (18357)
5 economics, medical/ (8479)
6 economics, nursing/ (3868)
7 economics, pharmaceutical/ (2388)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (377593)
9 (expenditure$ not energy).ti,ab. (15656)
10 (value adj1 money).ti,ab. (18)
11 budget$.ti,ab. (15833)
12 or/1-11 (495821)
13 ((energy or oxygen) adj cost).ti,ab. (2460)
14 (metabolic adj cost).ti,ab. (672)
15 ((energy or oxygen) adj expenditure).ti,ab. (14476)
16 or/13-15 (16958)
17 12 not 16 (491997)
18 letter.pt. (760022)
19 editorial.pt. (308567)
20 historical article.pt. (289066)
21 or/18-20 (1343898)
22 17 not 21 (465729)
23 exp Iron Overload/ (11088)
24 (iron adj3 (overload$ or intoxicat$ or poison$ or toxic$)).ti,ab,ot,hw. (7820)
25 (Hemosideros?s or hemochromatos?s or bronze diabetes).ti,ab,ot,hw. (10408)

26 or/23-25 (15896)
27 22 and 26 (285)

Costs filter:

Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

Appendix 2: Further critique of manufacturer's searches

Clinical effectiveness

Further limitations

- The ERG noted that the Emtree term for lenalidomide was not included in the Embase search. Although a subsequent test by the ERG showed that the omission was unlikely to have impacted on the recall of results due to the inclusion of free-text terms.
- The ERG noted CAS registry numbers were not included in the search strategies.
- The ERG noted a number of missing synonyms for the main interventions including: cc 5013, cdc 501, cdc 5013, enmd 0997, imid 3 and revimid for lenalidomide.

Indirect and mixed treatment comparisons

The MS reported the unsuitability of mixed treatment analysis for this study (MS 6.7). Therefore no strategies were included for this section.

Non-RCT Evidence

The MS reported that non-RCTs were not considered relevant for this submission (MS 6.8). Therefore no strategies were included for this section.

Adverse events (comparators)

See section 4.1 & 4.5.

Cost effectiveness

Further limitations

- The ERG noted that the final line appeared to have been omitted in the EconLit strategy provided by the manufacturer in their response to clarification. There was a facet for MDS (line #3) and a facet for the interventions (line #38), but there was no final line combining the two. It is unclear what impact this may have had on the recall of results.
- The ERG noted that the Emtree term for lenalidomide was not included in the Embase search. Although a subsequent test by the ERG showed that the omission was unlikely to have impacted on recall due to the inclusion of free-text terms.
- The ERG noted CAS registry numbers were not included in the search strategies.
- The ERG noted a number of missing synonyms for the main interventions including: cc 5013, cdc 501, cdc 5013, enmd 0997, imid 3 and revimid for lenalidomide.

Measurement and valuation of health effects

Further limitations

- The ERG noted that the Emtree term for lenalidomide was not included in the Embase search. Although a subsequent test by the ERG showed that the omission was unlikely to have impacted on recall due to the inclusion of free-text terms.
- The ERG noted CAS registry numbers were not included in the search strategies.
- The ERG noted a number of missing synonyms for the main interventions including: cc 5013, cdc 501, cdc 5013, enmd 0997, imid 3 and revimid for lenalidomide.

Resource identification, measurement and valuation

The MS reported that the strategies reported in 7.4.6 & 10.12 were employed for this section. Therefore the same limitations already discussed applied to these searches.

Appendix 3: Phillips et al. Checklist

Results of assessing the manufacturers report based on the checklist by Phillips et al.

1. Is there a clear statement of the decision problem?
Yes, the decision problem is clearly stated.
2. Is the objective of the evaluation and model specified and consistent with the stated decision problem?
The objective of the evaluation and model is the cost-effectiveness of lenalidomide treatment in patients with low-risk and intermediate-1 risk patients with MDS. The population identified in the NICE scope includes people with intermediate-2 and high risk MDS, whereas the manufacturer has only sought licence/approval for patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality
3. Is the primary decision-maker specified?
The term is not used, but implicitly the NHS is assumed
4. Is the perspective of the model stated clearly?
Yes, it is the perspective NHS.
5. Are the model inputs consistent with the stated perspective?
No. the source of data for measurement of HRQOL was not directly by patients and valuation was not done by a sample of the public. Instead 21 UK MDS patients perfromed a TTO on three general health descriptions.
6. Has the scope of the model been stated and justified?
Yes
7. Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?
Yes apart from the deviation of the patient population from the original NICE scope (also intermediate-2 and high risk MDS patients).
8. Is the structure of the model consistent with a coherent theory of the health condition under evaluation?
Yes, although only a limited number of adverse events were included and for simplicity only the distinction between transfusion independent or dependent was made.
9. Are the sources of data used to develop the structure of the model specified?
Yes
10. Are the causal relationships described by the model structure justified appropriately?
Yes
11. Are the structural assumptions transparent and justified?
Yes
12. Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?
Yes, the adverse events not included in the model have a relatively low prevalence and due to limited data available, a distinction between completely or partially transfusion dependent could not be made.

13. Is there a clear definition of the options under evaluation?
Yes
14. Have all feasible and practical options been evaluated?
No, not all possible options have been evaluated, e.g. including all adverse events or a separate health state for reduced transfusion burden.
15. Is there justification for the exclusion of feasible options?
Yes, limited data was available.
16. Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?
Yes
17. Is the time horizon of the model sufficient to reflect all important differences between options?
Yes, it is 20 years and considering the average age of 67 this seems to reflect a lifetime horizon.
18. Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?
Yes
19. Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?
Yes, although there exists a difference between completely transfusion dependent and partially.
20. Is the cycle length defined and justified in terms of the natural history of disease?
Yes it is defined, but justified based on the monitoring frequency of lenalidomide.
21. Are the data identification methods transparent and appropriate given the objectives of the model?
No, for certain transition probabilities non-systematic searches were conducted.
22. Where choices have been made between data sources, are these justified appropriately?
Yes.
23. Has particular attention been paid to identifying data for the important parameters in the model?
No, transition probabilities and costs were based on a non-systematic search using PubMed.
24. Has the quality of the data been assessed appropriately?
Yes
25. Where expert opinion has been used, are the methods described and justified?
No external clinical input was used in the submission. Internal clinical input was sought for model construction. More details about this could have been provided.
26. Is the data modelling methodology based on justifiable statistical and epidemiological techniques?
Yes, except for some programming errors in the initial submission.
27. Is the choice of baseline data described and justified?
Yes

28. Are transition probabilities calculated appropriately?
Yes, except for the programming errors.
29. Has a half-cycle correction been applied to both cost and outcome?
No
30. If not, has this omission been justified?
The explanation was given that the cycle length was short so that a correction was not required. The ERG disagrees with that assessment.
31. If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?
N/A
32. Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?
Yes
33. Have alternative extrapolation assumptions been explored through sensitivity analysis?
Yes
34. Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?
Yes
35. Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?
Yes
36. Are the costs incorporated into the model justified?
Yes
37. Has the source for all costs been described?
Yes, although not all costs obtained from the literature could be reproduced.
38. Have discount rates been described and justified given the target decision-maker?
Yes
39. Are the utilities incorporated into the model appropriate?
No, the utilities assigned to the transfusion dependent state are based on broad health state descriptions while additional disutilities are applied for adverse events.
40. Is the source for the utility weights referenced?
Yes
41. Are the methods of derivation for the utility weights justified?
Yes
42. Have all data incorporated into the model been described and referenced in sufficient detail?
No
43. Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?
N/A
44. Is the process of data incorporation transparent?
Yes

45. If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?
Yes
46. If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?
Yes
47. Have the four principal types of uncertainty been addressed?
No
Methodological uncertainty is not discussed.
Structural uncertainty is explored through different scenarios.
Heterogeneity: no analysis of sub-groups was undertaken.
Parameter uncertainty has been assessed in the PSA.
48. If not, has the omission of particular forms of uncertainty been justified?
No, although the following statement -that is not really a justification- was provided: "No analysis of subgroups was undertaken however, as part of ongoing regulatory discussions with the EMA certain additional analysis are being explored, which may make it possible to undertake such analysis in the future".
49. Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?
No.
50. Is there evidence that structural uncertainties have been addressed via sensitivity analysis?
Yes, some alternative scenarios have been run for different utility values, time horizons and use all the trial patient instead of the UK patients only.
51. Has heterogeneity been dealt with by running the model separately for different subgroups?
No
52. Are the methods of assessment of parameter uncertainty appropriate?
For the most part yes, the ERG considered the SE of the cost estimates for complications too small, these were increased by the ERG. Uncertainty around the frequency of monitoring was also added.
53. If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?
No. Clearly stated, but not justified.
54. Is there evidence that the mathematical logic of the model has been tested thoroughly before use?
No
55. Are any counterintuitive results from the model explained and justified?
No counterintuitive results occurred
56. If the model has been calibrated against independent data, have any differences been explained and justified?
No
57. Have the results of the model been compared with those of previous models and any

differences in results explained?

No prior models have been discussed in the submission, and only briefly in response to the clarification letter.

Appendix 4 Details model changes implemented by the ERG

Issue	Sheet	Cell/name	Old formula	New formula	Comment
Prog error	Response ESA	I50	"=prop_ESA*I49+(1-prop_ESA)*m_RespSC"	"=I49"	Cell I51 changes automatically
Prog error	Response GCSF	Y23:Y283	"=IF(v_IncreasedDose="Yes";IF(B23=p_NonRespTimeESA+1;p_RespTIEsa;IF(B23=p_NonRespTimeESA*2+1;p_RespTIGcsf;0));IF(B23=p_NonRespTimeESA+1;p_RespTIGcsf;0))*p_percentESA"	"=IF(v_IncreasedDose="Yes";IF(B23=p_NonRespTimeESA+1;p_RespTIEsa;IF(B23=p_NonRespTimeESA*2+1;p_RespTIGcsf;0));IF(B23=p_NonRespTimeESA+1;p_RespTIGcsf;0))"	Example row 23, applicable to entire column
Prog error: treatment interruption	PF_Revlimid	BQ23	"=28-SUM(BR23:BU23)"	"=MAX((MIN((B23*28);p_DaysToReduction1) - ((B23-1)*28)); 0) + MAX(((B23*28) - MAX((B23-1)*28; p_DaysToReduction1)); 0) * (1 - p_RevInt1)"	Example row 23, applicable to entire column
Prog error: treatment interruption	PF_Revlimid	BR23	"=IF(BP23=0;0;IF(BP23=1;28-(p_DaysToReduction1-C23);IF(BP23=2;MAX(p_DaysToReduction1+p_RevNT1days-C23;0);0)))*p_RevInt1"	"=MAX((MIN(B23 * 28; p_DaysToReduction1 + p_RevNT1days) - MAX((B23 - 1) * 28; p_DaysToReduction1)); 0) * p_RevInt1"	Example row 23, applicable to entire column
Prog error: treatment interruption	PF_Revlimid	BS23	"=IF(BP23=0;0;IF(BP23=1;0;IF(BP23=2;MIN(28-(p_DaysToReduction1+p_RevNT1days-C23);28)*p_RevInt1;28*p_RevInt1+28*(p_RevInt2)*(1-p_RevInt1)-BT23-BU23)))"	"=MAX(MIN(B23 * 28; p_DaysToReduction1 + p_RevNT1days + p_DaysToReduction2) - MAX((B23-1) * 28; p_DaysToReduction1 + p_RevNT1days); 0) * p_RevInt1 + MAX((B23 * 28) - MAX((B23-1) * 28; p_DaysToReduction1 + p_RevNT1days + p_DaysToReduction2); 0) * p_RevInt1 * (1 - p_RevInt2)"	Example row 23, applicable to entire column

Issue	Sheet	Cell/name	Old formula	New formula	Comment
Prog error: treatment interruption	PF_Revlimid	BT23	"=IF(BP23=0;0;IF(BP23=3;28-(p_DaysToReduction1+p_DaysToReduction2+p_RevNT1days-C23);IF(BP23=4;MAX(p_DaysToReduction1+p_RevNT1days+p_DaysToReduction2+p_RevNT2days-C23;0);0)))*p_RevInt2"	"=MAX(MIN(B23*28; p_DaysToReduction1 + p_RevNT1days + p_DaysToReduction2 + p_RevNT2days) - MAX((B23-1)*28; p_DaysToReduction1 + p_RevNT1days + p_DaysToReduction2); 0) * p_RevInt2 * p_RevInt1"	Example row 23, applicable to entire column
Prog error: treatment interruption	PF_Revlimid	Column BU	"=IF(BP23=4;28*p_RevInt2-BT23;0)"	"=MAX(B23*28 - MAX((B23-1) * 28; p_DaysToReduction1 + p_RevNT1days + p_DaysToReduction2 + p_RevNT2days); 0) * p_RevInt1 * p_RevInt2"	Example row 23, applicable to entire column
Cycle added lenalidomide	PF_Revlimid	Row 283	until row 282	until row 283	
Cycle added BSC	PF_SC	Row 283	until row 282	until row 283	
Adjust sum range	Entire workbook	r_bloodtrans_sc	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_bloodtrans_Rev	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_costsESA	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_costsRev	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_DiscCostsESA	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_DiscCostsRev	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_DiscCostsRev2	"range 23:282"	"range 23:283"	
Adjust	Entire	r_DiscQALYsESA	"range 23:282"	"range 23:283"	

Issue	Sheet	Cell/name	Old formula	New formula	Comment
sum range	workbook				
Adjust sum range	Entire workbook	r_DiscQALYsRev	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_ESARange	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_LifeyearsESA	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_LifeyearsRev	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_QALYsESA	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_QALYsRev	"range 23:282"	"range 23:283"	
Adjust sum range	Entire workbook	r_RevRange	"range 23:282"	"range 23:283"	
Half cycle correction: sum discounted cost lenalidomide	Results_Standard	G23	"=SUMIF(r_RevRange;"<="&IF(p_Timeframe="Lifetime";15;p_Timeframe);r_DiscCostsRev)"	"=((SUM(PF_Revlimid!DD23:DD282))+((SUM(PF_Revlimid!DD24:DD283))))/2"	
Half cycle correction: sum discounted cost BSC	Results_Standard	G24	"=SUMIF(r_ESARange;"<="&IF(p_Timeframe="Lifetime";15;p_Timeframe);r_DiscCostsESA)"	"=((SUM(PF_SC!CI23:CI282))+((SUM(PF_SC!CI24:CI283))))/2"	
Half cycle correction: sum discounted QALYs lenalidomide	Results_Standard	H23	"=SUMIF(r_RevRange;"<="&IF(p_Timeframe="Lifetime";60;p_Timeframe);r_DiscQALYsRev)"	"=((SUM(PF_Revlimid!DE23:DE282))+((SUM(PF_Revlimid!DE24:DE283))))/2"	

Issue	Sheet	Cell/name	Old formula	New formula	Comment
Half cycle correction: sum discounted QALYs BSC	Results_Standard	H24	"=SUMIF(r_ESARange;"<="&IF(p_Timeframe="Lifetime";60;p_Timeframe);r_DiscQALYsESA)"	"=((SUM(PF_SC!CJ23:CJ282))+((SUM(PF_SC!CJ24:CJ283))))/2"	
Half cycle correction: sum discounted LYG lenalidomide	Results_Standard	U23	-	"=((SUM(PF_Revlimid!DT23:DT282))+((SUM(PF_Revlimid!DT24:DT283))))/2"	
Half cycle correction: sum discounted LYG BSC	Results_Standard	U24	-	"=((SUM(PF_SC!CS23:CS282))+((SUM(PF_SC!CS24:CS283))))/2"	
Add deferiperone	Default UK Values	C50	0.290748899	0.05685293	
Add deferiperone	Default UK Values	insert row C51		0.536268757	
Add deferiperone	Default UK Values	old C51 new C52	0.709251101	0.406878313	
Add deferiperone	Unit cost	K36	£1,383.39	£1,322.45	
Cost AML	Default UK Values	C24	£68.55	£51.84	

Issue	Sheet	Cell/name	Old formula	New formula	Comment
Response over time	PF_Revlimid	Insert column AU	0	"=IF(response_assess>=C24;Response!J137*SUM(H23:I23)/SUM(H23:L23);0)"	Example row 23, applicable to entire column
Response over time	PF_Revlimid	Insert column AY	0	"=IF(response_assess>=C24;Response!J137)*SUM(J23:K23)/SUM(H23:L23)"	Example row 23, applicable to entire column
Response over time	PF_Revlimid	Insert column BF	0	"=IF(response_assess>=C24;Response!J137)*SUM(L23)/SUM(H23:L23)"	Example row 23, applicable to entire column
Response over time	PF_Revlimid	Column AW		"=IF(B23=p_cyclesbeforechel_nonresponders;H$23+I$23-SUM(AQ$22:AU23;AV18:AV23);0)+IF(OR(OFFSET(AQ23;-p_cyclesbeforechel_responders;0)=0;ISERROR(OFFSET(AQ23;-p_cyclesbeforechel_responders;0)/1));0;(OFFSET(AQ23;-p_cyclesbeforechel_responders;0)-(SUM(OFFSET(AR23:AS23;-p_cyclesbeforechel_responders;0)))))"	Example row 23, applicable to entire column
Response over time	Response	Insert response table		Table 38 STA report	
Response over time	Response	create new variable :max_TI_10mg	-	0.5945	
Response over time	Response	create new variable :max_TI_BSC		0.1024	

Issue	Sheet	Cell/name	Old formula	New formula	Comment
Response over time	PF_Revlimid			"=AL23*(1-max_TI_10mg)+max_TI_10mg*AM23"	
Response over time	PF_Revlimid			"=AJ23*(1-max_TI_10mg)+max_TI_10mg*AK23"	
Response over time	PF_SC	Column Z	"=PF_Revlimid!AL23*(1-$G$23)+$G$23*PF_Revlimid!AM23"	"=PF_Revlimid!AL23*(1-max_TI_BSC)+max_TI_BSC*PF_Revlimid!AM23"	Example row 23, applicable to entire column
Response over time	PF_SC	Column AA	"=PF_Revlimid!AJ23*(1-$G$23)+$G$23*PF_Revlimid!AK23"	"=PF_Revlimid!AJ23*(1-max_TI_BSC)+max_TI_BSC*PF_Revlimid!AK23"	Example row 23, applicable to entire column
Response over time	PF_SC	Column AJ	"=((H23+I23)-SUM(AH23:AI23))*Y23"	"=IF(response_assess>=C24;Response!M137)*SUM(H23:I23)/SUM(H23:L23)"	Example row 23, applicable to entire column
Response over time	PF_SC	Column AK	"=IF(B23=p_cyclesbeforechel_nonresponders;(H23+I23)-SUM(AE$23:AJ23);0)+IF(OR(OFFSET(AE23;-p_cyclesbeforechel_responders;0)=0;ISERROR(OFFSET(AE23;-p_cyclesbeforechel_responders;0)/1));0;(OFFSET(AE23;-p_cyclesbeforechel_responders;0)-(SUM(OFFSET(AF23:AG23;-p_cyclesbeforechel_responders;0)))))"	"=IF(B23=p_cyclesbeforechel_nonresponders;(H$23+I$23)-SUM(AE$23:AJ23);0)+IF(OR(OFFSET(AE23;-p_cyclesbeforechel_responders;0)=0;ISERROR(OFFSET(AE23;-p_cyclesbeforechel_responders;0)/1));0;(OFFSET(AE23;-p_cyclesbeforechel_responders;0)-(SUM(OFFSET(AF23:AG23;-p_cyclesbeforechel_responders;0)))))"	Example row 23, applicable to entire column

Issue	Sheet	Cell/name	Old formula	New formula	Comment
Response over time	PF_SC	Column AN	"=((J23+K23)-SUM(AL23:AM23))*Y23"	"=IF(response_assess>=C24;Response!M137)*SUM(J23:K23)/SUM(H23:L23)"	Example row 23, applicable to entire column
Response over time	PF_SC	Column AV	"=(L23-SUM(AT23:AU23))*Y23"	"=IF(response_assess>=C24;Response!M137)*SUM(L23)/SUM(H23:L23)"	Example row 23, applicable to entire column
Cost AEs	Default UK Values	D68	1636.38	1,768.01	
Cost AEs	Default UK Values	D69	1636.38	1,044.73	