Lenalidomide (Revlimid®) for multiple myeloma in people who have received at least one prior therapy

Single technology appraisal (STA) submission to the National Institute for Health and Clinical Excellence

Final after Board sign-off 17 May 2006

13 August 2008 revision

Celgene Limited

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Instructions for manufacturers and sponsors

This specification for submission of evidence to the National Institute of Health and Clinical Excellence (NICE, or the Institute) as part of the single technology appraisal (STA) process is designed to indicate to manufacturers and sponsors the information required by the Institute and the format in which it should be presented. Use of the specification and completion of Appendices 9.1 to 9.3 are mandatory, and the format should be adhered to wherever possible. Reasons for not adhering to this format must be clearly stated. Sections that are not considered to be relevant should be marked 'N/A' and a justification given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise the Institute immediately of any variation between the preliminary and final approval.

A submission should be as succinct and informative as possible. It is expected that the main body of the submission will not usually exceed 75 pages. The submission should be sent to the Institute electronically in Word or a compatible format, and not as a PDF file. A list of all references must be provided, together with paper or electronic copies.

For model-based economic evaluations, a transparent and fully executable electronic copy of the model should be submitted. The Evidence Review Group should have full access to the programming code, and running of the model should be unhindered. Please ensure that the submitted versions of the model program and the content of the submission match. The model should be constructed using standard software, such as Excel or DATA. If non-standard software is required for the construction of the model, please discuss this with the Institute at the earliest opportunity in advance of submission.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but which is considered to be relevant to the submission. Any additional appendices should be clearly referenced in the body of the submission and should not be used to present core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the efficacy section with 'see Appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID rather than relying on numerical referencing alone (for example, 'Trial 123/Jones et al. [126] found ABC' rather than 'One trial [126] found ABC').

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to the Institute at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by the Institute.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to the Institute with all confidential information highlighted and underlined

- a fully executable electronic copy of the economic model has been submitted
- all key references have been made available (electronic or hard copy versions as appropriate)
- the checklist of confidential information has been completed and submitted.

Disclosure of information

To ensure that the appraisal process is as transparent as possible, the Institute considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. The Institute recognises, however, that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the Final Appraisal Determination (FAD) or Appraisal Consultation Document (ACD) to consultees and commentators, all the evidence seen by the Committee should ideally be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). As a minimum, a structured abstract will need to be made available for public disclosure, using a recognised format such as that provided by the CONSORT statement (www.consort-statement.org).

Where data are commercial in confidence or academic in confidence, it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The NICE checklist of confidential information should be completed. If no checklist of confidential information is provided, the Institute will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor will be requested to supply a second 'stripped' version of the submission from which any information that is to remain confidential has been removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear how much data have been removed and where they have been removed from.

The Institute will request the stripped version of the submission at least 2 weeks before the anticipated date of issue of the FAD or ACD to consultees and commentators. The stripped version will be issued to consultees and commentators along with the ACD or FAD, and made available on the Institute's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the stripped version of the submission does not contain any confidential information. **No further amendments or corrections may be made to the submission at this stage.** The NICE checklist of confidential information should be updated and submitted at the same time. The Institute will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for the Institute

to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Appraisal Committee. Confidential information may be distributed to consultees with the permission of the manufacturer or sponsor. The Institute will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by the Institute that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges the Institute to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to the Institute. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed as commercial in confidence before making any decision on disclosure.

For further information, please see the NICE website (www.nice.org.uk).

Abbreviations List

ACD	Appraisal Consultation Document
AE	Adverse Event
AFSSAPS	Agence Francaise de Securite Sanitaire des Produits de Sante
ASCO	American Society of Clinical Oncology
ASH	American Society of Haematology
AWMSG	All Wales Medicines Strategy Group
CE mark	Conformité Européené mark
CI	Confidence Interval
CR	Complete Response
CRD	Centre for Reviews and Dissemination
CSRs	Clinical Study Reports
CTC	Common Toxicity Criteria
DT	Drug/Combination
DVT	Deep Vein Thrombosis
EAP	Expanded Access Program
EBMT	European Group for Blood and Marrow Transplantation
ECOG PS	Eastern Cooperative Oncology Group performance status
EHA	European Haematology Association
EMEA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer Core Questionnaire
EPAR	European Public Assessment Report
ERG	NICE Evidence Review Group
FAD	Final Appraisal Determination
FDA	US Food and Drug Administration
G-CSF	Granulocyte Colony-stimulating Factor
HDD	High-dose Dexamethasone
HDT	High Dose Therapy
HR	Hazard Ratio
ICER	Incremental Cost-effectiveness Ratio
IDMC	Independent Data Monitoring Committee
IMiD	Immunomodulatory Drugs
IMW	International Myeloma Workshop
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-Treat
IVRS	Integrated Voice-response System
LB	Lab based
LY	Life Year
MAA	Marketing Authorization Application
MM	Multiple myeloma
NCI	National Cancer Institute
nCR	Near Complete Response
NE	Not Evaluable
NEJM	New England Journal of Medicine
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NK	Natural Killer
NR	Not reached
NRR	National Research Register
ORR	Overall response rate

OS	Overall Survival
OTT	Overall treatment time
PD	Progressive disease
PFS	Progression free survival
PP	Patient Population/Indication
PR	Partial Response
PT	Publication Type
QALY	Quality Adjusted Life Year
RCTs	Head-to-head Randomised Trials
RMP	Recommended Monitoring Procedure
SCT	Stem Cell Transplantation
SD	Stable disease
SRE	Skeletal-related Event
STA	Single Technology Appraisal
TNF	Tumor necrosis factor
TTP	Time to Progression
TTPFDA	TTP based on an FDA definition
VAD	Vincristine, Doxorubicin, High-dose Dexamethasone
VAT	Value Added Tax
VGPR	Very Good Partial Response
VTE	Venous Thromboembolism

Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the 'Guide to the single technology appraisal process' – www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see Appendix 1, section 9.1).

1 Description of technology under assessment

1.1 *Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.*

Name: Revlimid® (lenalidomide).

Pharmacotherapeutic group: Immunomodulating agent.

ATC code: L04 AX04.

1.2 *Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).*

Lenalidomide was granted EMEA marketing authorisation on 14th June 2007.

1.3 *What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.*

The licensed indication is as follows:

"Revlimid in combination with Dex is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy"

1.4 *To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.*

Lenalidomide was launched in the UK on 25th June 2007

It is very difficult to calculate, from sales data, the exact numbers of patients receiving therapy in the NHS because some patients are receiving lenalidomide in the private sector. However, based on the data available at 15th May 2008, we estimate that approximately 60 patients are currently receiving lenalidomide in the NHS.

1.5 *Does the technology have regulatory approval outside the UK? If so, please provide details.*

As of 15th May 2008, lenalidomide has regulatory approval in 7 countries outside the UK. These countries are listed below:

Date **Approval** *Submission*	Country/ region	Indication
29 Jun 2006 *30 Dec 2005*	US	REVLIMID® (lenalidomide) in combination with Dex is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.
11 Jul 2007 *28 Feb 2006*	Iceland	REVLIMID® (lenalidomide) in combination with Dex is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.
13 Jul, 2007 *28 Feb 2006*	Norway	REVLIMID® (lenalidomide) in combination with Dex is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.
29 Aug 2007 *28 Apr 2006*	Switzerland	Revlimid in combination with Dex is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy
17 Sep 2007 *28 Apr 2006*	Liechtenstein	Revlimid in combination with Dex is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy
13 Dec 2007 *13 Oct 2006*	Australia	Revlimid is indicated for use in combination with Dex in patients with multiple myeloma whose disease has progressed after one therapy.
15 Feb 2008 *24 Jan 2008*	Argentina	REVLIMID® (lenalidomide) in combination with Dex is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy

1.6 *Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?*

Lenalidomide has been appraised by the Scottish Medicines Consortium and the advice issued on 12th May 2008 did not recommend the use of the technology in Scotland. A resubmission is planned.

Lenalidomide is currently being appraised by the All Wales Medicines Strategy Group (AWMSG) and will be considered by the AWMSG at their meeting on 11th June 2008.

1.7 *For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?*

Lenalidomide is available in hard capsules of 5, 10, 15 and 25 mg. Each pack contains three foil blisters with seven capsules for a total of 21 capsules per pack.

1.8 *What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.*

Dose and administration

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of Dex is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings. Dose adjustments are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

Lenalidomide capsules should be taken at about the same time each day. The capsules should not be broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. In the registrational trials lenalidomide treatment was continued until the occurrence of disease progression or unacceptable toxic effects.

1.9 *What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.*

Revlimid 5mg hard capsules containing 5 mg lenalidomide and 147 mg anhydrous lactose. List price 21 capsules x 5 mg £3,570.

Revlimid 10mg hard capsules containing 10 mg lenalidomide and 294 mg anhydrous lactose. List price 21 capsules x 10 mg £3,780.

Revlimid 15mg hard capsules containing 15 mg lenalidomide and 289 mg anhydrous lactose. List price 21 capsules x 15 mg £3,969.

Revlimid 25mg hard capsules containing 25mg lenalidomide and 200mg anhydrous lactose. List price 21 capsules x 25 mg £4,368

1.10 *What is the setting for the use of the technology?*

Lenalidomide must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma (i.e., hospital specialists).

1.11 *For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?*

Additional tests or investigations needed for selection

Due to the structural similarities with thalidomide (a known human teratogen), lenalidomide is contraindicated in women of child bearing potential, or male partners of women of child-bearing potential, unless appropriate contraceptive measures and pregnancy testing are carried out. Females of childbearing potential should have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL).

Need for monitoring

To monitor for potential haematological toxicity, patients are required to undergo routine blood tests to assess full blood counts once per week for the first 8 weeks of therapy, and monthly thereafter. This type and frequency of monitoring is common in the setting of multiple myeloma treatment, and can be conducted remotely – patients can have a blood sample taken at their general practitioner's surgery, with the sample then sent to the haematology clinic for full blood counts.

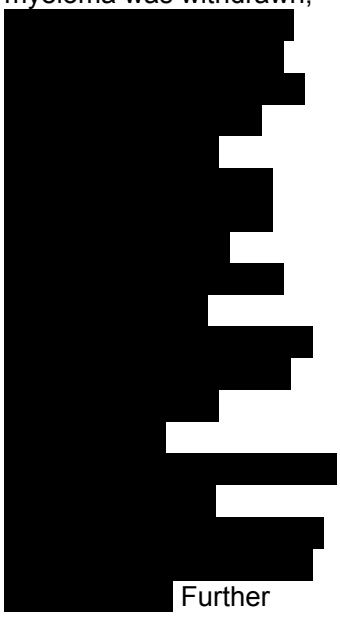
Other therapies administered at same time

Lenalidomide is used in combination with Dex (a steroid).

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with multiple myeloma who have received at least one prior therapy.	Data will be submitted on the clinical and cost effectiveness of lenalidomide in combination with high-dose Dex (HDD) for the treatment of multiple myeloma patients who have received at least one prior therapy.
Intervention	Lenalidomide in combination with high dose dexamethasone.	As per final scope.
Comparator(s)	• High dose Dex • Bortezomib monotherapy and bortezomib in combination with Dex • Thalidomide-containing regimens • Repeat initial chemotherapy including regimens based on mephalan, vincristine, cyclophosphamide and doxorubicin	The principal comparator considered in our submission is high-dose Dex monotherapy as this represents our most robust comparison utilizing data from the registrational trial programme for lenalidomide. An additional comparison is made with bortezomib monotherapy using indirect methods. It is important to consider this comparison as informative only due to the indirect methods used. We do not consider a comparison with bortezomib in combination with high-dose Dex to be appropriate, as this combination is not licensed and data are only currently available from Phase II studies. A comparison with thalidomide is not considered. Thalidomide is licensed only in the first-line treatment of multiple myeloma and a marketing

	Final scope issued by NICE	Decision problem addressed in the submission
		authorization application for thalidomide in relapsing or refractory multiple myeloma was withdrawn,  Further information on this discussion with the regulators can be provided on a commercial in confidence basis. Other conventional therapies, including repeat initial chemotherapy are not included because they are non-superior to Dex monotherapy, in terms of myeloma control and in terms of their tolerability profile. In addition, there are no standard regimens in use but rather a wide variety making meaningful comparisons difficult.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: • time to disease progression • overall survival • response rates • health-related quality of life • adverse effects of treatment	The outcome measures considered include: *Primary Efficacy Outcome* • time to disease progression *Secondary Efficacy Outcomes* • overall survival • response rates • adverse effects of treatment
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Data from the registrational trials were used to develop a cost effectiveness model for lenalidomide use in England & Wales. The economic model calculates the incremental cost-effectiveness ratio (ICER) per quality adjusted life year (QALY) and per life year (LY) gained. The model calculates overall survival and time to disease progression in order to establish the ICERs. In order to capture the full costs and benefits of prescribing lenalidomide in multiple myeloma patients who have received at least one prior therapy we have adopted a lifetime time horizon. Utilities for the model health states were derived from a study that used EQ-5D and all costs are from the NHS and Personal

	Final scope issued by NICE	Decision problem addressed in the submission
		Social Services perspective. Both deterministic and probabilistic sensitivity analyses are performed.
Special considerations and other issues	If evidence allows subgroups of patient populations in whom the technology is clinically effective and cost effective should be considered. These may include subgroups by the type and number of prior therapies (for example whether or not thalidomide has been used at first line), treatment response and duration of remission, severity of disease and cytogenetic features. Consideration should be given to number of treatment cycles and continuation and stopping rules for treatment. Consideration should be given to measurement scales for assessing treatment response including the use of serum-M protein, urinary free light chain levels and EBMT criteria. Guidance will only be issued in accordance with the marketing authorisation.	Subgroups to be considered are: 1) patients who have received one prior therapy 2) patients who have received one prior therapy and are unsuitable for treatment with bortezomib 3) patients who have received at least two prior therapies 4) patients who have previously been treated with Thalidomide (by number of prior therapies) The number of prior therapies was a stratification factor in the registrational trials and a predefined sub-group for analysis in the study protocols. Response rates in the registrational trials were based on the EBMT criteria, where responses are measured by confirmed paraprotein reduction in both serum and urine as well as other clinical parameters.

Section B

3 Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

- *The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.*
- *The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.*
- *The indication(s) and any restriction(s).*
- *The recommended course of treatment.*
- *The main comparator(s).*
- *Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.*
- *The main clinical results of the randomised trials and any relevant non RCTs.*
- *In relation to the economic evaluation, details of:*
  - *the type of economic evaluation and justification for the approach used*
  - *the pivotal assumptions underlying the model/analysis*
  - *the incremental ratios from the evaluation.*

Multiple myeloma is incurable and is the second most common haematological cancer in the UK (1). Overall survival from diagnosis typically ranges from 3–5 years, depending on the mode of treatment employed (2;3). Patients suffer from a range of debilitating symptoms and while treatment frequently results in remission of disease, relapse is inevitable and patients are rarely cured (4). For patients whose disease has progressed following initial treatment, prognosis is particularly poor, and survival is typically less than 1.5 years (2;3).

The prognostic outlook is one where patients will relapse after initial treatment, or discontinue therapy due to adverse events or toxicity, for example peripheral neuropathy, and the disease also becomes refractory to current treatments. There is therefore an unmet need for new therapies throughout the care pathway.

Lenalidomide in combination with dexamethasone is an orally administered therapy, for the treatment of patients whose disease has progressed following previous treatment.

In two Phase III clinical trials (MM-009 and MM-010), the combination of lenalidomide and dexamethasone resulted in consistent and significant improvements in response rate, time to disease progression, and overall survival in relapse or refractory patients compared to treatment with high-dose dexamethasone alone (5;6). The results of these studies are impressive given the prior treatment history of these patients and the severity of the disease.

The trials themselves are also important because they represent a large and significant body of evidence for a rare disease. On the basis of these two clinical studies, lenalidomide has been granted orphan drug status for the treatment of multiple myeloma in both the EU and the USA.

An economic evaluation indicates that in a number of patient populations lenalidomide in combination with dexamethasone represents a good use of NHS resources, given the rare prevalence and severity of this disease and the orphan drug status granted to lenalidomide. The cost effectiveness ratios for five different patient populations range from £22,589 to [redacted] per QALY gained.

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.

Lenalidomide (Revlimid®) is an immunomodulating agent (ATC code: L04 AX04) and belongs to a class of agents often referred to as IMiDs, which are all structural derivates of thalidomide. The exact molecular target of lenalidomide has to be fully elucidated however the mechanism of action is understood to involve anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Lenalidomide was granted EMEA marketing authorisation on 14th June 2007.

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.

Lenalidomide is available as 5mg, 10mg, 15mg & 25mg capsules, in 21 capsule packs. The pack prices are as follows:

Revlimid 5mg hard capsules, list price 21 capsules x 5mg £3,570.

Revlimid 10mg hard capsules, list price 21 capsules x 10mg £3,780.

Revlimid 15mg hard capsules, list price 21 capsules x 15mg £3,969.

Revlimid 25mg hard capsules, list price 21 capsules x 25mg £4,368

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended starting dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings. Dose adjustments are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

The indication(s) and any restriction(s).

“Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one therapy.” In the Phase III registrational trials (5;6) receipt of at least one prior therapy was defined by the inclusion criteria “had progressive multiple myeloma after at least 2 cycles of antimyeloma treatment or to have relapsed with progressive disease after treatment”.

It is important to clarify that patients who had received prior therapy had disease which progressed during and despite their treatment or who had relapsed following a remission period induced by the prior therapy.

There is no experience in children and adolescents. Therefore, lenalidomide should not be used in the paediatric age group (0-17 years).

Lenalidomide is structurally related to thalidomide and is therefore contraindicated in women who are pregnant and in women of childbearing potential unless all of the conditions of the risk minimisation plan (RMP) are met.

The recommended course of treatment.

It is recommended that treatment with lenalidomide is continued until the occurrence of disease progression or the occurrence of unacceptable toxic effects; this was the treatment approach used in the pivotal clinical studies (5;6). This is a novel approach to the treatment of multiple myeloma and reflects the potential for patients to continue to tolerate and respond to lenalidomide over the longer term. Dosing is continued or modified based upon clinical and laboratory findings and the Summary of Product Characteristics provides recommended dose adjustments and interruptions to manage adverse reactions and toxicity.

The main comparator(s).

The principal comparator considered in our submission is high-dose dexamethasone monotherapy as this represents our most robust comparison utilising data from the registrational trial programme for lenalidomide.

An additional comparison is made with bortezomib monotherapy using indirect methods. It is important to consider this comparison as informative only due to the indirect methods used.

Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.

The key clinical evidence is taken from two identical RCT's (5;6) in which lenalidomide in combination with dexamethasone is compared to dexamethasone alone for patients whose disease has progressed following previous treatment.

There are no head-to-head comparative trials with other active treatments, so indirect evidence from a randomised controlled trial of bortezomib has been used for comparison.

The main clinical results of the randomised trials and any relevant non RCTs.

Efficacy

- The MM-009 and MM-010 clinical trials demonstrate that the addition of lenalidomide to dexamethasone significantly increases response rates, time to progression, and overall survival in patients with multiple myeloma following at least one prior therapy. The trials included 692 patients – representing a significant body of evidence, particularly given the orphan nature of the disease.

- The overall response rate seen in patients treated with lenalidomide in combination with dexamethasone was approximately three-fold higher than was seen with dexamethasone only (MM-009: 61.0% versus 19.9%, P<0.001) and (MM-010: 60.2% versus 24.0%, P<0.001) (5;6).

- There was a highly statistically significant improvement in median time to progression (the primary endpoint of the clinical studies) among patients enrolled in the lenalidomide plus dexamethasone arms, compared to the dexamethasone only arms of the two trials. In fact, median time to progression was more than doubled with the combination treatment (MM-009: 11.1 versus 4.7 months, P<0.001) and (MM-010: 11.3 versus 4.7 months, P<0.001) (5;6).

- Data for the difference in overall survival between the study arms in the clinical trials continues to mature. The most recent data were reported in December 2007 (7) and estimated a statistically significant improvement in median overall survival for lenalidomide in combination with dexamethasone compared with those patients who were initially treated with dexamethasone only (35 versus 31 months, P=0.015). These data are impressive given that 170 out of 351 patients in the dexamethasone only arm opted to receive lenalidomide when they developed disease progression or at study unblinding. These patients remained assigned to and were analysed as dexamethasone only patients, despite subsequently receiving lenalidomide. It is highly likely the overall survival is prolonged in this group of patients due to the addition of lenalidomide. Indeed, historical retrospective analyses indicate that the median OS of multiple myeloma patients from first relapse is 14–17 months (2;3).

Safety

- Lenalidomide, in combination with dexamethasone, has a manageable tolerability profile. The most common adverse events ascribed to lenalidomide are haematological in nature – principally neutropenia and thrombocytopenia. Adverse events of this nature are familiar to, and well managed by, haemato-oncologists. The frequency of febrile neutropenia, was low illustrating that neutropenia can be effectively managed with monitoring and appropriate intervention, including dose reduction and dose interruption.

- Importantly, the clinical studies did not report any increase in the incidence of peripheral neuropathy for lenalidomide treated patients. This finding is in contrast to other agents used in the treatment of multiple myeloma where the increased occurrence of peripheral neuropathy can be treatment limiting. This finding suggests lenalidomide may fill an important gap in current unmet medical needs.

- Owing to the structural similarities between lenalidomide and thalidomide, a risk management programme has been put place to reduce the risk of foetal exposure to lenalidomide. The programme employs a simple process that requires the physician and pharmacists to sign a prescription authorisation form to follow the risk minimisation plan (RMP). Given the average age at diagnosis of multiple myeloma for female patients, in practice, very few females of child bearing potential are treated and therefore very few pregnancy tests are required (8).

In relation to the economic evaluation, details of:

- the type of economic evaluation and justification for the approach used

In the economic evaluation, we consider a number of different patient populations who might be expected to receive treatment with lenalidomide in the NHS. These are:

1) Patients with multiple myeloma who have received one prior therapy only. This group is subdivided into (I) all those who have had 1 prior therapy and (II) those with pre-existing peripheral neuropathy

2) Patients with multiple myeloma who have received at least two prior therapies

3) Patients with multiple myeloma who have previously been treated with thalidomide (by number of prior therapies)

The model is constructed as a discrete-event simulation that utilises patient-level information, rather than using an aggregated cohort approach. The model predicts a patient's disease course following a treatment decision in patients who have received at least one prior therapy. With the patient-level simulation, milestones of disease course are defined as events (e.g., response to treatment, progression of disease, death, adverse events), which are not mutually exclusive (patient can respond and also have an adverse event at the same time). The model considers the impact of these events (e.g. disease progression) on patients' health and on other components of the system, such as resource consumption. This approach was chosen because it permits the development of a more realistic model that avoids the over-simplification required by a cohort Markov model.

- *the pivotal assumptions underlying the model/analysis*

In the calculation of quality-adjusted life years, no difference is modelled between response levels (CR, PR and SD) in terms of utility, although it could be argued that better response is associated with higher quality of life. In the current setting, this assumption favours the dexamethasone only treated patients since there were more complete and partial responders with patients that received combination therapy with lenalidomide and dexamethasone and a longer duration of response.

In the model, only Grade 3 and Grade 4 adverse events observed in the clinical trials are considered assuming that those will be the ones that will have the greater impact on resource use profiles, and therefore overall management costs.

For this economic evaluation, the patients from trials, MM-009 and MM-010 were pooled, regardless of trial or treatment assignment to create single starting population. This population was then subdivided into four datasets, one for each best response category (CR, PR, SD, PD) again irrespective of treatment. This implies that treatment has no effect beyond the best response. In other words, within each response level, the course is not influenced by whether the response was obtained with lenalidomide and dexamethasone treatment or dexamethasone treatment alone. This assumption is conservative for lenalidomide since it is understood that dexamethasone has no disease modifying effect.

In the MM-009 and MM-010 trials patients in the dexamethasone only group were allowed to cross-over to treatment with lenalidomide either when progression was observed or after unblinding by the IDMC. Thus, the observed survival for the

dexamethasone only group in the trials includes a strong lenalidomide effect rather than the pure dexamethasone only therapy outcomes. The Medical Research Council (MRC) Myeloma trials were selected to calibrate the post-progression survival predictions derived from the MM-009 and MM-010 trials for the one prior and two or more prior therapy dexamethasone only groups in order to estimate the post-progression survival in the absence of cross-over to treatment with lenalidomide as the MRC trials provide long term follow-up, reflect a large UK patient population, are multi-centre and only include treatment options comparable to dexamethasone. These data represent an important improvement over the data used in previous evaluations in multiple myeloma to estimate survival in routine practice.

- *The incremental ratios from the evaluation.*

An economic evaluation indicates that in a number of patient populations lenalidomide in combination with dexamethasone represents a good use of NHS resources, given the rare prevalence and severity of this disease and the orphan drug status granted to lenalidomide. The cost effectiveness ratios for the five different patient populations range from £22,589 to [redacted] per QALY gained.

Table 1: Summary of the cost-effectiveness results

Population – patients with multiple myeloma who have received:	Comparator	Incremental cost per QALY Gained	Incremental cost per Life Year Gained
One prior therapy only	Len/Dex vs. bortezomib	[redacted]	[redacted]
One prior therapy only and have pre-existing peripheral neuropathy	Len/Dex vs.Dex	£ 46,865	£ 32,501
At least two prior therapies	Len/Dex vs.Dex	£ 24,584	£ 16,301
Prior treatment with thalidomide (1 prior therapy only)	Len/Dex vs.Dex	£ 38,861	£ 26,421
Prior treatment with thalidomide (2 or more therapies)	Len/Dex vs.Dex	£ 22,589	£ 14,927

It is estimated that the net incremental budget impact following the introduction of lenalidomide in combination with dexamethasone, for the different patient populations considered will range from £7.8m in Year 1 for patients who have received one prior therapy only and who have pre-existing peripheral neuropathy through to £17.9m in Year 5. The net incremental budget impact is highest for the patient group who has had at least two prior therapies, ranging from £46.3m in Year 1 through to £66.4m in Year 5.

Table 2: Summary of the budget impact results

Population - patients with multiple myeloma who have received:	Year 1: Net Budget Impact (£m)	Year 5: Net Budget Impact (£m)
One prior therapy only	[redacted]	[redacted]
One prior therapy only and have pre-existing peripheral neuropathy	£7.8	£17.9
At least two prior therapies	£46.3	£66.4
Prior treatment with thalidomide (1 prior therapy only)	£11.9	£23.2
Prior treatment with thalidomide (2 or more therapies)	£16.8	£22.2

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 *Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.*

Epidemiology

After non-Hodgkin's lymphoma, multiple myeloma is the second most common haematological cancer. Based on the GLOBOCAN (9) data, there are 4033 cases of multiple myeloma in the UK, with age standardized rates of 4.3 and 3.1 for males and females respectively (Table 3). More recent data specifically for England and Wales from Cancer Research UK presented in Table 4 show that during 2004, 3353 cases were diagnosed (1).

Table 3: Table 1: Incidence of Multiple Myeloma in UK according to GLOBOCAN 2002 (9)

	Cases	Crude Rate	Age standardized rates
Males	2,087	7.1	4.3
Females	1,946	6.4	3.1
Persons	4,033	-	-

Table 4: Number of new cases of multiple myeloma in the UK in 2004 (Cancer Research UK)(1)

	England		Wales	
Cases				
Males	1,691		142	
Females	1,394		126	
Persons	3,085		268	
Crude rate per 100,000 population				
Males	6.9		9.9	
Females	5.5		8.3	
Persons	6.2		9.1	
Age-standardised rate per 100,000 population				
Males	5.7		7.4	
CI 95%	5.4	5.9	6.2	8.6
Females	3.7		5.3	
CI 95%	3.5	3.9	4.4	6.2
Persons	4.6		6.2	
CI 95%	4.4	4.7	5.5	7.0

Table 5: Number of newly diagnosed patients by sex from 2001 to 2005 in England (10)

	Incidence		Increase	
Year	**Males**	**Females**	**Males**	**Females**
2001	1528	1331	NA	NA
2002	1567	1361	2.49%	2.20%
2003	1657	1404	5.43%	3.06%
2004	1691	1394	2.01%	-0.72%
2005	1739	1504	2.76%	7.31%
Average increase rate			3.17%	2.97%

There has been a gradual increase in the incidence of multiple myeloma (Table 5) from 2001 to 2005 in England (10).

The median age at presentation is 70 years and 15% of patients are under 60 years of age, the disease is rarely diagnosed in patients under the age of 30 (8;10). A recent review of the epidemiologic literature concluded there was still little robust evidence on disease etiology and epidemiologic risk factors, though there was some evidence to support the role of obesity and family history of lymphatohematopoietic cancers (11).

Overall survival from diagnosis typically ranges from 3–5 years for patients with multiple myeloma, depending on the mode of treatment employed (2;3). According to data from the Office of National Statistics, in the year 2005 mulitple myeloma was the cause of death for 2181 people across England and Wales (Table 6).

Table 6: Number of deaths and mortality rates of multiple myeloma, England and Wales, 2005 (Cancer Research UK)(1)

	England		Wales	
Deaths				
Males	1,061		61	
Females	1,006		53	
Persons	2,067		114	
Crude rate per 100,000 population				
Males	4.3		4.2	
Females	3.9		3.5	
Persons	4.1		3.8	
Age-standardised rate (European) per 100,000 population				
Males	3.4		3.0	
CI 95%	3.2	3.6	2.3	3.8
Females	2.4		2.1	
CI 95%	2.2	2.5	1.5	2.7
Persons	2.8		2.5	
CI 95%	2.7	2.9	2.0	2.9

Following first relapse, historical data demonstrate that median overall survival is less than 1.5 years (14–17 months) (2;3), although there is evidence to suggest that newer licensed therapies can significantly extend survival (6;12-15).

A recent publication from the Mayo clinic in the US, has demonstrated that the prognosis of patients multiple myeloma remained unchanged between 1971 and 1994 (14)). This observation has also been demonstrated using UK MRC trial data (Appendix 10). There was a trend in the Mayo clinic data toward improvement in survival during 1995 and 2000, and a statistically significant improvement in survival was seen during the period 2000-2006. The trend to an improvement between 1995 and 2000 coincided with increased use of high dose therapy (with stem cell transplant), which likely contributed to this change (14). The significant improvement in survival observed between 2000-2006 is believed to be due to the introduction of novel therapies (14). These analyses support the use of these historical data as a robust indicator of the survival likely to be achieved today with traditional therapies.

Signs and symptoms

Multiple myeloma is a haematological malignancy that arises from the monoclonal expansion of plasma cells in the bone marrow (16). Patients with mulitple myeloma suffer from a range of debilitating symptoms. Chief among these is skeletal destruction, which arises from activation of osteoclasts by multiple myeloma cells – leading to painful lytic bone lesions, pathological fractures and hypercalcaemia. Secretion of monoclonal proteins by plasma cells results in renal insufficiency, and patients are also more susceptible to infection, due to a compromised B-cell lineage (4;16;17).

Current treatments and guidelines

Multiple myeloma is a disease for which there is no formally established treatment pathway, and clinical practice is known to differ substantially between treating centres.

The currently available standard options for induction and subsequent chemotherapy include melphalan and prednisolone, alkylator-based combination chemotherapy regimens, the vincristine, doxorubicin, high-dose Dex (VAD) regimen, high-dose dexamethasone, bortezomib and thalidomide.

At presentation, standard treatment depends heavily on the health status of the patient. Younger, fitter patients are likely to receive an induction therapy of vincristine, adriamycin and dexamethasone, or combinations containing thalidomide and dexamethasone, followed by high dose chemotherapy with melphalan and autologous stem cell transplantation (SCT) (4). For patients not suitable for high dose therapy and autologous SCT, initial therapy is usually with a combination of melphalan and prednisolone. Recent clinical data (18-20) and licensing of thalidomide for the first-line treatment of untreated myeloma has lead an increase in the use of triple combination of thalidomide with an alkylating agent (melphalan or cyclophosphamide) and a steroid (prednisolone or dexamethasone). Treatment of multiple myeloma frequently results in remission of disease, but relapse is inevitable and patients are rarely cured (4). Upon relapse, patients may be re-treated with the initial therapy (which includes repeat autologous SCT), although response rates are reduced.

From a historical perspective, survival in patients receiving one prior therapy for multiple myeloma has been estimated at between 14.4 months (1.2 years) and 17.1 months (2;3). The former figure is derived from a retrospective analysis of 2,528 patients enrolled in the UK Myeloma IV, V, VI and VIII trials between 1980 and 1997 (2), while the latter is derived from a retrospective analysis of patients (n=578) treated at the Mayo Clinic between 1985 and 1997 (3).

Of the newer agents, that have been granted EMEA marketing authorization for specific indications within mulitple myeloma, bortezomib has previously been reviewed by NICE (21). Thalidomide in combination with melphalan and prednisone was recently granted EMEA marketing authorisation for first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy (22). Lenalidomide in combination with Dex is indicated for the treatment of mulitple myeloma patients who have received at least one prior therapy (23). Bortezomib has EMEA marketing authorisation for monotherapy treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation (24). The NICE recommendation (TA129) considers bortezomib monotherapy as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation (under specific circumstances) (21).

4.2 What was the rationale for the development of the new technology?

While the development of new therapies has improved the quality of life and duration of remission for many patients with multiple myeloma, the prognosis for these

patients remains poor. The major challenge in the management of myeloma is that most patients will relapse after initial treatment; discontinue therapy due to adverse events or toxicity; or the disease becomes refractory to current treatments. There is an unmet need for new therapies throughout the care pathway that can alter the course of the disease, prevent severe complications, enhance the effectiveness of stem cell transplantation or avoid the need for it altogether, delay disease progression, and improve survival.

Lenalidomide is a structural derivative of thalidomide, and was developed with the rationale to produce a compound with greater efficacy and an improved tolerability profile. Lenalidomide and thalidomide are believed to share common modes of action. However, lenalidomide has been shown to be many times more potent than thalidomide with respect to immune modulation and antiproliferation (25;26).

Lenalidomide appears to have a greatly reduced incidence of many of the adverse events typically associated with thalidomide such as peripheral neuropathy, and also has more potent effects on a number of processes thought to underlie the pathogenesis of multiple myeloma (5;6;25).

Lenalidomide has been granted orphan status by the Committee for Orphan Medicinal Products, on the basis that multiple myeloma is not only rare (occurring in fewer than 5 in 10,000 persons in the European Union), but is both life threatening and debilitating, in addition to representing a disease with significant unmet medical need. Treatment of mulitple myeloma with lenalidomide was entered in the Community Register of Orphan Medicinal Products under the number EU/3/03/177 on 12 December 2003.

4.3 What is the principal mechanism of action of the technology?

Lenalidomide is an immunomodulating agent (ATC code: L04 AX04) and belongs to a class of agents often referred to as IMiDs, which are all structural derivates of thalidomide. The exact molecular target of lenalidomide is currently unclear however the mechanism of action is understood to involve anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide has been shown to elicit the following responses (27-30):

- Inhibits proliferation of certain haematopoietic tumour cells including multiple myeloma plasma tumour cells and those with deletions of chromosome 5.
- Enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells.
- Inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels,
- Augments foetal haemoglobin production by CD34+ haematopoietic stem cells.
- Inhibits production of pro-inflammatory cytokines (e.g., TNF-alphạ and IL-6) by monocytes.
- Block the stimulatory effect of insulin like growth factor-1 on NF-Kappa B.

This health technology assessment considers lenalidomide in combination with high-dose dexamethasone. High dose Dex is an effective licensed monotherapy agent that has proven efficacy in multiple myeloma patients (31)

There is a demonstrated synergy between IMiDs and the parental compound thalidomide with Dex that appears to produce more pronounced effects compared with either treatment alone (28;32-34). The mechanism of this additive effect appears to be due to a combined inhibitory action of IMiD plus Dex on NF-Kappa B activity in multiple myeloma cells (29). This additive effect was also seen in cells treated with lenalidomide plus bortezomib or TNF-related apoptosis-inducing ligand (TRAIL/Apo2L) (29).

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Lenalidomide in combination with high-dose dexamethasone is licensed in the UK for the treatment of patients with multiple myeloma who have received at least one prior therapy, as defined in the inclusion criteria of the MM-090 and MM-010 trials ("had progressive multiple myeloma after at least 2 cycles of antimyeloma treatment or to have relapsed with progressive disease after treatment"). There are several other treatments in use for these patients and guidelines (4) suggest that the choice of treatment must be determined on an individual basis depending on the timing of relapse, age, prior therapy, bone marrow function and other clinical circumstances.

Given the recent EMEA approval for thalidomide in first-line treatment and the anticipated uptake of bortezomib following one prior therapy (given recent NICE guidance) (21), current clinical practice suggests, lenalidomide in combination with high-dose Dex (Len/Dex) is most commonly used in patients who have received at least two prior therapies.

The oral administration of lenalidomide in combination with high-dose Dex makes this combination particularly suitable among patients living in remote areas or with an aversion to intravenously-administered treatment. Many chemotherapeutic regimes in the relapsed and refractory myeloma setting require parenteral administration, for example bortezomib requires intravenous administration on days 1, 4, 8 and 16 of a 21 day cycle – this can be given in a day case or outpatient setting, but still requires four hospital visits per month.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

There is no clear consensus on the best practice for treating relapsed and/or refractory mulitple myeloma in the UK. The British Society of Haematology has issued management guidelines for mulitple myeloma, and list a number of possible options for second-line treatment including bortezomib, thalidomide and dexamethasone, but with no clear treatment pathway or drug preferences (4). This guideline from 2005 is currently being updated. Bortezomib monotherapy is recommended by NICE for patients who have progressed following one prior therapy,

however, the appropriate therapy for patients who progress or are intolerant to bortezomib is uncertain at present (21).

Thalidomide in combination with melphalan and prednisolone was recently licensed in Europe for the treatment of newly diagnosed patients but the role in relapsed and or refractory mulitple myeloma is currently uncertain due to lack of robust clinical data. Furthermore, a marketing authorization application for thalidomide in relapsing or refractory multiple myeloma was withdrawn [redacted]

4.6 Provide details of any relevant guidelines or protocols.

The British Society of Haematology developed a guideline on the diagnosis and management of mulitple myeloma in 2005 (4), and within that guideline have a recommendation for the management of patients with relapsed or refractory disease. This guideline is considered outdated and is currently being revised by UK Myeloma Foundation, therefore the strategy it outlines is likely to change given the recent license of thalidomide in first-line treatment and the NICE recommendation for bortezomib for one prior therapy only. The current guideline outlines a strategy dependant on types of prior therapies, speed of relapse and the number of prior therapies.

5 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUORUM statement checklist (www.consort-statement.org/QUOROM.pdf).

The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.

The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. Where no head-to-head RCTs are available, consideration will be given to indirect comparisons, subject to careful and fully described analysis and interpretation.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data.

5.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

A systematic literature review was undertaken to identify randomised controlled trials of lenalidomide in combination with Dex for the treatment of multiple myeloma patients who have received at least one prior therapy. Exact details are provided in Appendix 2, section 9.2.

5.2 Study selection

5.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The systematic review identified two RCTs of lenalidomide in combination with Dex (Len/Dex) in multiple myeloma patients who received at least one prior therapy. Both are active comparator studies that compare Len/Dex to Dex plus placebo (Dex). The systemic review did not identify any trials of Len/Dex compared with other interventions. The two trials are termed MM-009 and MM-010 and the associated publications identified during the systematic review are listed in Table 7 below.

Table 7: List of studies relevant to the decision problem identified by the systematic review

Author/Date (Reference)	RCT data source	Relationship to RCT	Publication type	Publication source
Primary publications				
Weber et al. (2007) (6)	MM-009	Primary publication	Full publication	NEJM
Dimopoulos et al. (2007) (5)	MM-010	Primary publication	Full publication	NEJM
Updates on primary publications				
Weber et al (2007) (35)	Pooled data for MM-009 and MM-010	Update on data in primary publications	Abstract	ASH/Blood
Dimopoulos et al. (2007) (36)	MM-010	Update on data in primary publications	Abstract	IMW
Interim analyses				
Dimopoulos et al. (2005) (37)	MM-009 and MM-010	Pre-planned interim analysis	Abstract	EHA
Dimopoulos et al. (2005) (38)	MM-010	Pre-planned interim analysis	Abstract	ASH/Blood
Sub-group analyses				
Channan-Khan et al. (2006) (39)	Pooled data for MM-009 and MM-010	Pre-specified sub-group pooled analysis of elderly patients	Abstract	ASH/Blood
Channan-Khan et al. (2006) (40)	Pooled data for MM-009 and MM-010	Pre-specified sub-group pooled analysis of non-stem cell transplant patients (none vs. ≥1)	Abstract	ASH/Blood
Stadtmauer et al. (2006) (41)	Pooled data for MM-009 and MM-010	Pre-specified sub-group pooled analysis of number of prior therapies (1 vs. ≥2)	Abstract	ASH/Blood
Miguel. et al. (2007) (42)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of Dex dose adjustments	Abstract	ASH/Blood
Harousseau et al. (2007) (43)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of clinical response status	Abstract	ASH/Blood
Foa et al. (2007) (44)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of IgA patients	Abstract	ASH/Blood
Chanan-Khan et al. (2007) (45)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of ECOG performance status	Abstract	ASH/Blood
Niesvizky et al. (2006) (46)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of thrombotic events	Abstract	ASCO
Weber et al. (2006) (47)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of patients with impaired renal function	Abstract	ASH/Blood

Author/Date (Reference)	RCT data source	Relationship to RCT	Publication type	Publication source
Wang et al. (2007) (48)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of patients resistant to thalidomide	Abstract	IMW
Wang et al. (2006) (49)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of patients who previously received thalidomide	Abstract	ASCO
Wang et al. (2006) (50)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of patients who previously received thalidomide	Abstract	ASH/Blood
Blade et al. (2006) (51)	Pooled data for MM-009 and MM-010	Post-hoc sub-group analysis of patients who previously received thalidomide	Abstract	EHA

NEJM=New England Journal of Medicine EHA=European Haematoogy Association ASH=American Society of Hematology ASCO=American Society Clinical Oncology IMW=International Myeloma Workshop

5.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Inclusion criteria:

- Randomised controlled trials (RCTs) or systematic review/meta-analyses of RCTs
- Sub-group analyses and open label extensions from relevant RCTs
- Studies comparing Len/Dex with another therapy or placebo
- Patients with mulitple myeloma who have received at least one prior therapy
- Full text publications and studies available only as abstracts

Additional inclusion criteria for systematic review:

- Studies that report Overall Survival (OS), Time To Progression (TTP), Progression-Free Survival (PFS), clinical response, quality of life or safety outcomes

Exclusion criteria:

- Non-systematic reviews, editorials, comments and letters.
- Animal, *in vitro* or pharmacodynamic / pharmacokinetic studies
- Patient population is treatment-naïve / newly diagnosed mulitple myeloma

5.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 5.2.1

The list of relevant studies is presented in Table 7 in the preceding section.

All potential hits for RCT identified and screened for retrieval = 1071

Database	Hits
Embase	464
Medline including (R) In-Process and Old Medline	215
The Cochrane Library - Clinical trials	25
ISI Science Citation Index web of knowledge	80
ISI Biosis Preview	81
ISI Proceedings	12
National Research Register	7
Current Controlled Trials	1
ClinicalTrials.gov	55
ASH	80
ASCO	11
Company literature	19
EHA	25

Total hits excluded based on Phase I review (title/abstract) = 924

Database	Include	Exclusion Reasons					
		PT	PP	SD	LB	DC	Total Excluded
Embase	11	219	78	2	23	131	453
Medline including (R) In-Process and Old Medline	9	97	46	10	29	24	206
The Cochrane Library - Clinicaltrials	20				1	4	5
ISI Science WOK	8	48	9	3	5	7	72
ISI Biosis Preview	18	14	9	3	19	18	63
ISI Proceedings	9	1			2		3
NRR	2		2	1		2	5
Current Controlled Trials	1						0
ClinicalTrials.gov	16		2	35		2	39
ASH	28	10	12	5	1	24	52
ASCO	3	1	1	2		4	8
Company literature	19						0
EHA	4	6	2	4	4	2	18

Total hits included for Phase II review (abstract/full text) = 148
After removing duplicate records =53

Reasons for Phase II exclusions:
DC =16
PP =10
SD =8

RCTs meeting the inclusion criteria = 2

- MM009
- MM010

Total publications relating to relevant RCTS =19

PT=Publication type
PP=Patient population or line of therapy
SD=Study design
LB=Lab based/basic science
DC=Drug class or combination

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Two relevant RCTs were identified that examined Len/Dex for the treatment of multiple myeloma patients who have received at least one prior therapy. The trials are termed MM-009 and MM-010. These studies are identical in design but were conducted in different locations. MM-009 took place in the USA and Canada, while MM-010 took place in Europe, Israel and Australia. A number of abstracts, sub-analyses and updated analyses have also been published (Table 5.1).

Most of the published data however have been updated, or additional information is added since initial publication.

5.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

The preliminary results of an expanded access program and two associated studies have been presented at the ASH Annual Meeting. This Phase IIIb study in North American patients provides additional data on safety relevant to the decision problem (23;52;53). All three studies are discussed further in section 5.7

5.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months

A number of studies are ongoing at present to explore the use of lenalidomide in patients with newly diagnosed multiple myeloma. However, in all cases, these studies are in the early stages of implementation and will not, therefore, report any efficacy data within a 6–12 month period. A European leg of the Phase IIIb expanded access study in relapsed/refractory multiple myeloma has completed recruitment and the study is now closed. The data collection is ongoing and database lock and analysis is estimated for completion by the end of 2008. However, this study does not include any efficacy outcomes and will report safety/tolerability data and quality of life measured by the European Organization for Research and Treatment of Cancer Core Questionnaire (EORTC) QLQ-C30 and EORTC MY-24.

5.3 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

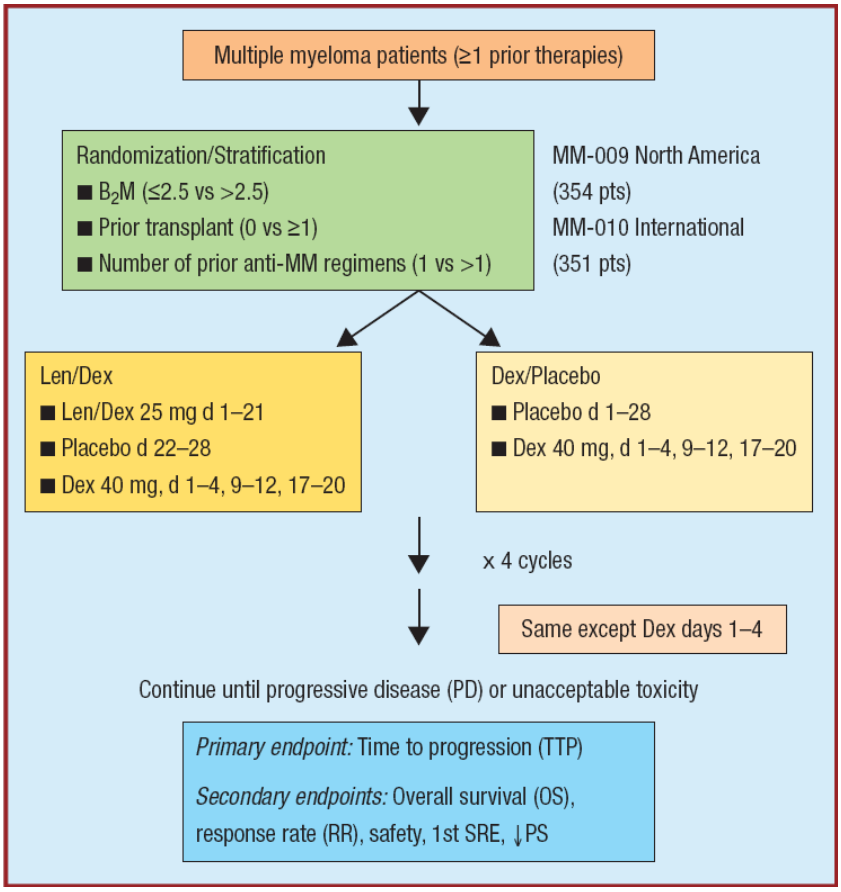
5.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

Study design

The MM-009 and MM-010 studies were identically designed multicentre Phase III, double-blind, randomised, placebo-controlled clinical trials designed to evaluate the efficacy and safety of Len/Dex compared with Dex in patients with relapsed multiple myeloma. Study MM-009 was conducted in the United States and Canada and enrolled 353 patients. Study MM-010 was conducted in Europe, Israel, and Australia and enrolled 351 patients.

Figure 1: Design summary for studies MM-009 and MM-010 (41)



Central randomisation was performed with a block size of four and the use of an integrated voice-response system (IVRS). The IVRS ensures that registration and randomisation were performed quickly and conveniently. In order to reduce selection bias, the random assignment of patients to treatment groups was stratified according to the level of serum β2-microglobulin (<2.5 mg per litre versus ≥2.5 mg per litre), previous stem cell transplantation (none versus ≥one), and the number of previous antimyeloma therapies (one versus ≥two). Patients were assigned to receive either lenalidomide or placebo by randomization at a 1:1 ratio.

This was a double-blind study. The lenalidomide and placebo capsules were identical in appearance, and the subjects, investigators, other study site personnel, and Celgene personnel who were responsible for the study were blinded to each subject's treatment assignment until the study was unblinded.

Outcomes

The primary outcome for MM-009 and MM-010 was time to progression (TTP), with a protocol-specified interim analysis planned for when 50% of the subjects had reached the primary endpoint – to determine if the study should be stopped for superiority, futility, or unfavourable toxicity. Prospectively-defined secondary analyses of TTP were conducted, according to the number of lines of prior therapy and according to whether patients had previously received stem-cell transplantation (SCT) and chemotherapy and according to category of baseline serum β2-microglobulin. Post-hoc analyses of outcome according to the type of prior therapy (thalidomide or bortezemib) were also undertaken. A number of other sub-group and pooled analyses have been conduced and presented at conferences. These are discussed further in the following sections.

The eligibility criteria, which require the subjects to have measurable disease to facilitate the accurate assessment of TTP (the primary efficacy endpoint), are consistent with those used in the earlier Phase I and II studies of lenalidomide in subjects with relapsed or refractory multiple myeloma. Measurable disease was defined as a serum monoclonal protein (M protein) level of at least 0.5 g per deciliter or a urinary Bence Jones protein level of at least 0.2 g per day. A complete list of patient inclusion/exclusion criteria are described in detail in sections 5.3.7 below.

Power calculation

The number of patients was calculated so that a one-sided log-rank test at the 0.025 level, allowing for one interim analysis, would have a statistical power of 85% to detect a difference between the TTP for each group with a constant hazard ratio of 1.5, reflecting an increase of 50% in the median TTP. The number of events required was 222. Events are described in detail in sections 5.3.9.

On the basis of the planned accrual rate, a log-rank test of OS that was performed 18 months after the last patient had been enrolled, when 194 deaths were expected, would have a power of 80% to detect a hazard ratio for death of 0.67.

Interim analysis

An interim analysis of safety and efficacy was planned when disease had progressed in 111 patients in both studies MM-009 and study MM-010 (half of the 222 events required for 85% power). The safety and efficacy data were reviewed by an Independent Data Monitoring Committee (IDMC). If the predetermined O'Brien–Fleming boundary for the superiority of lenalidomide over placebo was crossed, the study would be unblinded at the discretion of the IDMC, and patients would be allowed to receive lenalidomide at the time of disease progression or at the investigator's judgment.

Interventions

The selection of combination therapy with lenalidomide and Dex was based on the available data regarding the additive or synergistic effects of immunomodulatory

drugs (IMiDs) and Dex in the treatment of multiple myeloma (28;32;33;54) at the time the study was initiated.

Dexamethasone was adopted as the control arm because it represented an accepted standard antimyeloma therapy for the treatment of subjects with relapsed or refractory disease (31;55;56). At the time the trials were designed, Dex represented a bench-mark for the degree of multiple myeloma control which can be achieved by the current standard of care in these patients, including combinations such as VAD (55;56). This VAD combination and other multiple myeloma therapies are not superior to high-dose Dex with respect to the degree of myeloma control achieved and the tolerability profile (55;56).

The use of single agent, high-dose Dex as the control therapy allowed for a direct comparison with the lenalidomide plus high-dose Dex experimental treatment in order to determine the contribution of lenalidomide to the efficacy and safety of the combination.

The dose and schedule of Dex administration used in these studies represent a pulse high-dose regimen that is used to treat subjects with advanced multiple myeloma (31;54). The intensity of high-dose Dex therapy was decreased after four cycles of therapy. This dose of Dex was chosen since it represents a monotherapy, which would be ethically acceptable as an active comparator (31).

Timing

Patients received a starting dose of 25mg of daily oral lenalidomide or placebo on days 1–21 of each 28-day cycle. All patients also received 40mg of daily oral Dex on days 1–4, 9–12, and 17–20. After the fourth cycle, 40mg of Dex was administered only on days 1–4. Treatment was continued until the occurrence of disease progression or unacceptable toxic effects.

Blood counts and physical examination were performed on Days 1, 8 and 15 during Cycle 1, Days 1 and 15 during Cycles 2 and 3; and on Day 1 of each cycle thereafter. Serum and urinary protein electrophoresis studies were performed on Day 1 of each cycle and at the end of treatment.

Adverse events

Toxic effects were graded according to the National Cancer Institute's Common Toxicity Criteria, version 2.1 (57). In the case of a Grade 3 or 4 adverse events, treatment was withheld and restarted at the next lower daily dose. The dose of lenalidomide was modified as follows:

- 15mg (dose level, –1)
- 10mg (dose level, –2)
- 5mg (dose level, –3)

For Grade 3 or 4 neutropenia without other toxic effects, the first dose-modification step was:

- daily granulocyte colony-stimulating factor (G-CSF) at 5µg per kilogram of body weight and 25mg of lenalidomide (dose level –1)

- G-CSF at 5μg/kg and 15mg (dose level, –2)
- G-CSF at 5μg/kg and 10mg (dose level, –3)
- G-CSF at 5μg/kg and 5mg (dose level, –4).

Dose levels –2 to – 4 included daily administration of 5μg per kilogram of G-CSF at the investigator's discretion. Thromboprophylaxis was not required, although it was used on an individual basis.

Modifications in the dose of Dex because of toxic effects were:

- 40mg daily for 4 days every 2 weeks (dose level, –1)
- 40mg daily for 4 days every 4 weeks (dose level, –2)
- 20mg daily for 4 days every 4 weeks (dose level, –3).

Assessment of response

The response of patients was assessed according to the criteria of the European Group for Blood and Marrow Transplantation (EBMT) (58;59).

Myeloma paraprotein: serum and urine protein electrophoresis were performed at baseline, on Day 1 of each cycle; Day 15 of cycles 1, 2 and 3; and at the end of treatment. Quantitative immunoglobulins were determined and serum and urine fixation studies performed at baseline and Day 1 of each cycle beginning with cycle 2.

A partial response (PR) was defined as a reduction of M protein by at least 50% in serum, 90% in urine, or both, as confirmed by at least two electrophoretic measurements. A complete response (CR) was defined as the complete disappearance of M protein in serum and urine by immunofixation, as confirmed by two measurements, and the presence of less than 5% marrow plasma cells; the criteria for near CR (nCR) were identical to those for CR but without confirmation of marrow plasmacytosis of less than 5% or the disappearance of M protein.

The TTP was measured from randomisation to the date of the first assessment showing disease progression. Progressive disease (PD) was defined as an increase of at least 25% in M protein from nadir; an absolute increase in serum M protein of more than 500mg per deciliter, as compared with the nadir value; an absolute increase in urinary M protein of more than 200mg per 24-hour period; and either a new bone lesion or plasmacytoma (or an increase in the size of such lesions), or a serum calcium level of more than 11.5mg per deciliter (2.9mmol per liter).

Data for patients who died before there was evidence of disease progression were censored at the time of the last evaluation for assessment of protocol-specified TTP. Survival status was determined every 6 months after the discontinuation of treatment, and OS was calculated as the time from randomisation until death from any cause or the date of the last visit.

Statistical analyses

All primary analyses were based on the intention-to-treat population (ITT), and subgroup analyses were planned on the basis of stratification variables. An

unstratified log-rank test was used to compare the time-to-event variables between the two study groups. Both the TTP and OS were estimated by Kaplan–Meier methods, and a Cox proportional-hazards regression model was used to assess the effect of demographic and prognostic variables on differences in treatment responses between the two study groups. Exact tests were used to compare response rates. All reported P values are two-sided.

5.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

Inclusion criteria

MM-009 and MM-010 are identically-designed studies in patients who have received at least one prior therapy for multiple myeloma. MM-009 took place in the USA and Canada, while MM-010 took place in Europe, Israel and Australia. Patients were eligible for the study if they had all of the following characteristics:

- Were at least 18 years of age and able and willing to sign an informed consent form.
- Had progressive multiple myeloma after at least 2 cycles of antimyeloma treatment or to have relapsed with progressive disease after treatment.
- Had measurable disease that was not resistant to dexamethasone.

Patients were considered to have disease that was resistant to Dex if they had undergone disease progression during previous therapy containing high-dose Dex (total monthly dose, >200mg). Measurable disease was defined as a serum monoclonal protein (M protein) level of at least 0.5g per decilitre or a urinary Bence–Jones protein level of at least 0.2g per day.

Additional eligibility criteria included:

- an Eastern Cooperative Oncology Group performance status (ECOG PS) of no more than 2,
- a serum aspartate aminotransferase or alanine aminotransferase level that was no more than three-times the upper limit of the normal range,
- a serum bilirubin level that was less than two-times the upper limit of the normal range,
- a serum creatinine level of less than 2.5mg per deciliter (221µmol per litre),
- an absolute neutrophil count of at least 1.0 x 10^9 /l,
- a platelet count of more than 75,000 per cubic millimetre for patients with less than 50% bone marrow plasma cells and more than 30,000 per cubic millimetre for patients with 50% or more bone marrow plasma cells.

Women of childbearing potential were eligible if they agreed to use contraception, had a negative pregnancy test before enrolment, and agreed to undergo monthly pregnancy testing until 4 weeks after the discontinuation of the study drug.

Exclusion criteria

Patients who were previously exposed to lenalidomide or whose disease was refractory to Dex were excluded in both studies (MM-090 and MM-010). This was important to ensure that there was no bias in the trial based on previous Dex exposure. Additional exclusion criteria included:

- Known hypersensitivity (immunologic reaction) to thalidomide or dexamethasone
- History of uncontrollable side effects to dexamethasone
- Use of any standard/experimental antimyeloma drug therapy within 28 days of initiation of study drug
- Use of any experimental non-drug therapy within 56 days of initiation of study drug treatment.

Baseline patient and disease characteristics

In MM-009, patients were enrolled from 27 February 2003 at 48 sites in the United States (44 sites) and Canada (four sites). In MM-010, patients were enrolled from 22 September 2003 at 50 sites in Australia (six sites), Europe (41 sites), and Israel (three sites).

Table 8 and Table 9 (below) shows patient characteristics for the study subjects for Len/Dex and Dex study groups in Study MM-009 and Study MM-010. The two treatment groups were well balanced with respect to baseline characteristics including age, sex, stage, ECOG scores, serum β2-microglobulin level, and prior therapy. There were no significant differences ($p>0.05$) between the two groups (Len/Dex versus Dex) according to a pooled t-test for continuous variables (age, age from diagnosis) and Fisher's exact test for categorical variables.(60;61).

The number and types of prior antimyeloma therapies (Table 9) were consistent between Studies MM-009 and MM-010. No significant differences were observed between the Len/Dex and Dex groups in the number or type of prior antimyeloma therapies in Study MM-010. Significantly more of the subjects in the Len/Dex group (80.0%; 136/170) than in the Dex group (70.2%; 120/171) in Study MM-009 had received prior therapy with Dex ($p=0.045$; Fisher's exact test); other than this, no significant differences were observed between the treatment groups in prior antimyeloma therapies in Study MM-009 (60;61).

Of note are the figures for the number of prior therapies that patients had received on entry into the study. Although there was an inclusion criterion for patients to have received at least one prior therapy, approximately 35% of patients had received one prior therapy only (first relapse), while greater than 65% of patients had received at least two prior therapies. Use of prior therapy with thalidomide was extensive in both studies (43.6% of patients in MM009 and 34.2% in MM010).

Table 8: Demographic and clinical characteristics of patients enrolled in MM-009 and MM-010(60;61)

Characteristic	Study MM-009			Study MM-010		
	Len/Dex N=170	Dex N=171	p-Value [a]	Len/Dex N=176	Dex N=175	p-Value [a]
Age (yrs) n Mean SD Median Min, Max	 170 63.3 9.86 64.0 36.0, 86.0	 171 62.6 9.61 62.0 37.0, 85.0	0.505	 176 62.2 10.12 63.0 33.0, 84.0	 175 62.9 8.80 64.0 40.0, 82.0	0.453
Sex Male Female	 102 (60.0%) 68 (40.0%)	 101 (59.1%) 70 (40.9%)	0.912	 104 (59.1%) 72 (40.9%)	 103 (58.9%) 72 (41.1%)	1.000
Race/ethnicity White Black Hispanic Asian/Pacific Islander Other	 134 (78.8%) 25 (14.7%) 3 (1.8%) 5 (2.9%) 3 (1.8%)	 143 (83.6%) 17 (9.9%) 5 (2.9%) 2 (1.2%) 4 (2.3%)	0.455	 172 (97.7%) 2 (1.1%) 0 (0%) 1 (0.6%) 1 (0.6%)	 175 (100.0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%)	0.247
Time from first pathologic diagnosis (yrs) n Mean SD Median Min, Max	 170 3.6 2.47 2.9 0.5, 14.7	 171 3.9 2.76 3.1 0.4, 19.7	0.327	 176 4.2 2.86 3.4 0.4, 15.7	 175 4.8 3.55 4.0 0.3, 26.6	0.079
Baseline multiple myeloma stage I II III Missing	 3 (1.8%) 53 (31.2%) 113 (66.5%) 1 (0.6%)	 4 (2.3%) 53 (31.0%) 114 (66.7%) 0 (0%)	1.000	 11 (6.3%) 50 (28.4%) 115 (65.3%) 0 (0%)	 8 (4.6%) 57 (32.6%) 110 (62.9%) 0 (0%)	0.613

Characteristic	Study MM-009			Study MM-010		
	Len/Dex N=170	Dex N=171	p-Value [a]	Len/Dex N=176	Dex N=175	p-Value [a]
Multiple myeloma progression manifested [b]	161 (94.7%)	162 (94.7%)	1.000	162 (92.0%)	156 (89.1%)	0.367
Rising M-paraprotein levels	30 (17.6%)	38 (22.2%)	0.343	43 (24.4%)	56 (32.0%)	0.124
Worsening lytic bone disease	7 (4.1%)	7 (4.1%)	1.000	5 (2.8%)	7 (4.0%)	0.574
Worsening extramedullary plasmacytoma disease						
ECOG PS			0.131			0.596
0	70 (41.2%)	83 (48.5%)		78 (44.3%)	65 (37.1%)	
1	81 (47.6%)	80 (46.8%)		72 (40.9%)	79 (45.1%)	
2	13 (7.6%)	6 (3.5%)		23 (13.1%)	27 (15.4%)	
3	0 (0%)	0 (0%)		0 (0%)	1 (0.6%)	
Missing	6 (3.5%)	2 (1.2%)		3 (1.7%)	3 (1.7%)	
Lytic bone lesions			0.096			0.603
Present	118 (69.4%)	133 (77.8%)		136 (77.3%)	140 (80.0%)	
Absent	51 (30.0%)	38 (22.2%)		40 (22.7%)	35 (20.0%)	
Missing	1 (0.6%)	0 (0%)		0 (0%)	0 (0%)	
Bone marrow aspirate/ biopsy						
Cellularity			0.966			0.945
Normal	71 (41.8%)	72 (42.1%)		107 (60.8%)	102 (58.3%)	
Hyperplasia	65 (38.2%)	64 (37.4%)		41 (23.3%)	41 (23.4%)	
Hypoplasia	26 (15.3%)	27 (15.8%)		26 (14.8%)	28 (16.0%)	
Missing	4 (2.4%)	6 (3.5%)		2 (1.1%)	3 (1.7%)	
% plasma cells			0.371			0.090
n	165	165		172	169	
Mean	34.5	31.8		36.2	31.1	
SD	28.13	26.79		28.39	26.37	
Median	28.0	25.0		30.0	22.0	
Min, Max	0.0, 95.0	0.0, 100.0		0.0, 100.0	0.0, 100.0	

Characteristic	Study MM-009			Study MM-010		
	Len/Dex N=170	Dex N=171	p-Value [a]	Len/Dex N=176	Dex N=175	p-Value [a]
Baseline β_2-microglobulin ≤2.5 mg/L >2.5 mg/L	49 (28.8%) 121 (71.2%)	50 (29.2%) 121 (70.8%)	1.000	51 (29.0%) 125 (71.0%)	48 (27.4%) 127 (72.6%)	0.813

[a] For continuous variables (age, time from first pathologic diagnosis, and percent plasma cells), the p-value is based on a pooled t-test. For the categorical variables, the p-value is based on Fisher's exact test.
[b] More than one category could be selected. Therefore, percentages may total to more than 100%.

Table 9: Prior antimyeloma therapy – studies MM-009 and MM-010 (60;61)

Type of Therapy	Study MM-009			Study MM-010		
	Len/Dex N=170	Dex N=171	p-Value [a]	Len/Dex N=176	Dex N=175	p-Value [a]
No. of prior antimyeloma therapies			1.000			0.909
1	64 (37.6%)	64 (37.4%)		56 (31.8%)	57 (32.6%)	
2 or 3	106 (62.4%)	107 (62.6%)		120 (68.2%)	118 (67.4%)	
Prior antimyeloma regimens or SCT			0.491			0.661
1	23 (13.5%)	22 (12.9%)		19 (10.8%)	21 (12.0%)	
2	42 (24.7%)	34 (19.9%)		40 (22.7%)	39 (22.3%)	
3	39 (22.9%)	35 (20.5%)		55 (31.3%)	45 (25.7%)	
>3	66 (38.8%)	80 (46.8%)		62 (35.2%)	70 (40.0%)	
Prior SCT			0.631			0.312
0	68 (40.0%)	69 (40.4%)		77 (43.8%)	81 (46.3%)	
1	28 (16.5%)	18 (10.5%)		31 (17.6%)	21 (12.0%)	
2	25 (14.7%)	28 (16.4%)		30 (17.0%)	23 (13.1%)	
3	15 (8.8%)	17 (9.9%)		4 (2.3%)	4 (4.0%)	
>3	34 (20.0%)	37 (21.6%)		34 (19.3%)	43 (24.6%)	
Prior radiotherapy			0.653			0.305
Yes	60 (35.3%)	65 (38.0%)		62 (35.2%)	52 (29.7%)	
No	110 (64.7%)	106 (62.0%)		114 (64.8%)	123 (70.3%)	
Prior thalidomide therapy			0.586			0.091
Yes	72 (42.4%)	78 (45.6%)		52 (29.5%)	67 (38.3%)	
No	98 (57.6%)	93 (54.4%)		124 (70.5%)	108 (61.7%)	
Prior Dex therapy			0.045			0.650
Yes	136 (80.0%)	120 (70.2%)		116 (65.9%)	120 (68.6%)	
No	34 (20.0%)	51 (29.8%)		60 (34.1%)	55 (31.4%)	
Prior bortezomib (Velcade®) therapy			0.864			1.000
Yes	18 (10.6%)	20 (11.7%)		8 (4.5%)	7 (4.0%)	
No	152 (89.4%)	151 (88.3%)		168 (95.5%)	168 (96.0%)	

[a] For continuous variables (age, time from first pathologic diagnosis, and percent plasma cells), the p-value is based on a pooled t-test. For the categorical variables, the p-value is based on Fisher's exact test.

5.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

The consort flow charts for MM-009 and MM-010 are presented respectively in Figure 2 and Figure 3 below.

Figure 2: CONSORT flow chart for MM-009 (62)

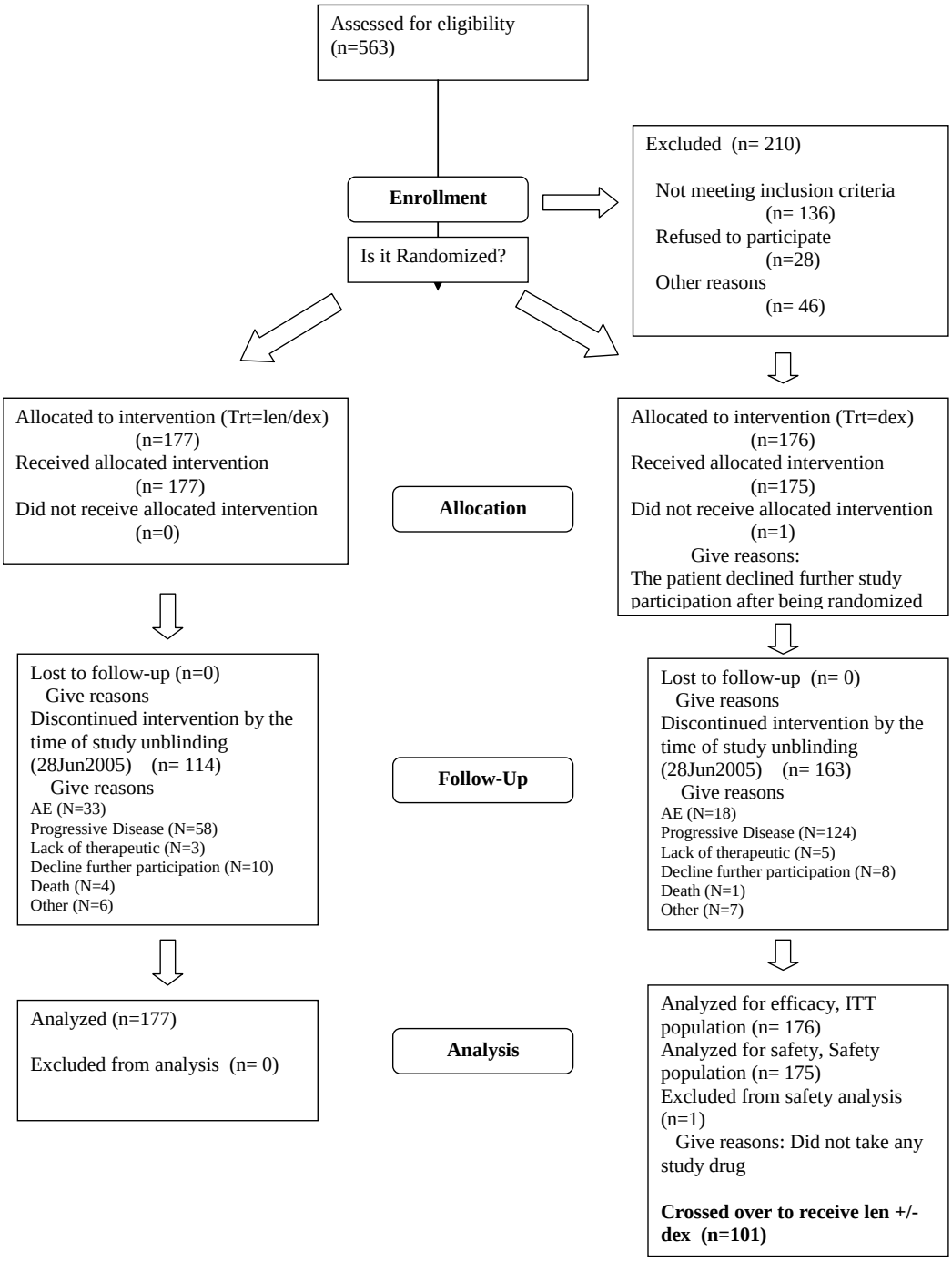
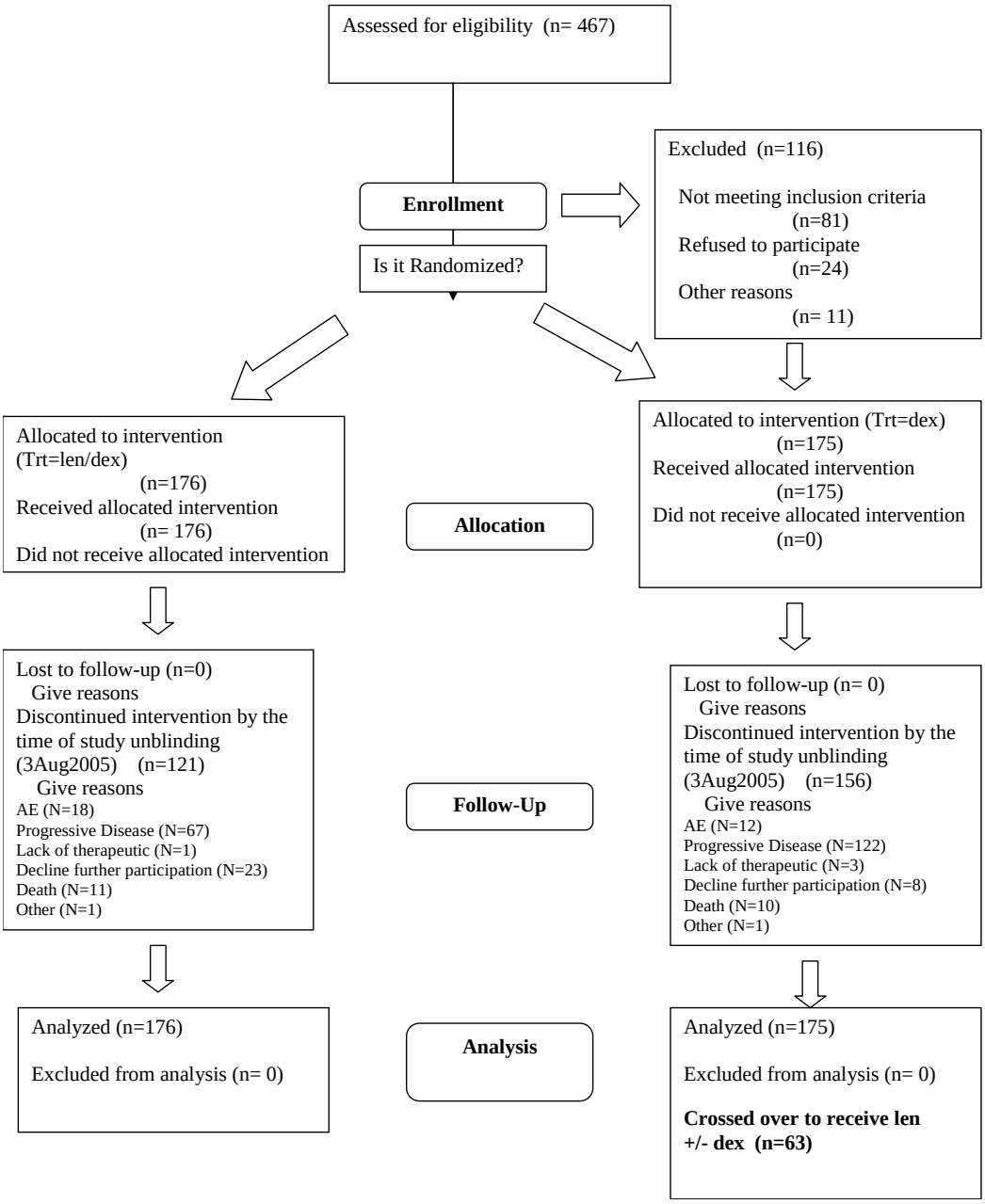


Figure 3: CONSORT flow chart for MM-010 (62)



5.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to

measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

The efficacy outcomes used in the phase III studies MM-009 and MM-010 are an international standard for the assessment of multiple myeloma and represent criteria that were specifically designed for use in efficacy studies. The design features, endpoints, and plans for interim analysis of these studies and the regulatory strategy for lenalidomide were discussed with the Irish Medicines Board, the Swedish Medicinal Products Agency, the German Federal Institute for Drugs and Medical Devices, and the French Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS).The protocols for Studies MM-009 and MM-010 were subjected to a Special Protocol Assessment review by the US Food and Drug Administration (FDA), Division of Oncology Drug Products. Thus, the planned endpoints, statistical analyses and other methodologies were determined and agreed to prospectively with both EU and US regulatory bodies.

A number of post-hoc analyses were undertaken to investigate the effect of known prognostic variables in multiple myeloma and these are explicitly stated as such in this submission.

Primary efficacy outcome

The primary efficacy outcome in studies MM-009 and MM-010 was time to disease progression (TTP), which was chosen due to its wide acceptance as a surrogate endpoint that is often used in haematology and oncology studies. A reduced sample size and duration of follow up can be used to estimate TTP. Furthermore, TTP remains a useful marker in clinical practice for the length of time a patient could be expected not to experience disease progression.

Time to progression, as specified in the protocol, was calculated as the time from randomisation to the first occurrence of any of the following events:

- Disease progression based on the myeloma response criteria developed by EBMT.(58;59) The TTP was measured to the date of the first assessment in the battery of tests required to determine progression.

- Discontinuation from the treatment phase due to disease progression according to the investigator whether or not confirmed by the EBMT criteria. The TTP was measured to the last date of visit.

- Death due to disease progression during the treatment period. The TTP was measured to the date of death if death occurred on or before treatment discontinuation.

The TTP was censored at the date of the last response assessment for subjects who:

- Had not progressed at the time of analysis.

- Withdrew from the treatment phase before documented progression, including those who died of causes not related to multiple myeloma.

- Were given another antimyeloma therapy without documented progression or intolerable adverse events (for these subjects, the date of their last response assessment prior to taking antimyeloma therapy was used as the censor date).

For both MM-009 and MM-010, the analysis of TTP was based on the intention-to-treat population. Median follow-up varies depending on the data-cut presented and will be specified in the results tables.

Secondary efficacy outcomes

1. Overall survival

Overall Survival (OS) is defined as the time from randomisation until death from any cause, and was measured in the ITT population. OS is defined as the time from randomisation until death from any cause, and is measured in the ITT population. Survival is considered the most clinically meaningful cancer endpoint, and when studies can be conducted to adequately assess OS, it is usually the preferred endpoint. This endpoint is precise and easy to measure, documented by the date of death. OS is generally evaluated in randomised controlled studies. Demonstration of a statistically significant improvement in OS can be considered to be clinically important if the toxicity profile is acceptable, and has often supported new drug approval. Difficulties in performing and analysing survival studies include the requirement for long follow-up periods and large patient numbers, and the issue of subsequent cross-over of cancer therapy potentially confounding analyses.

2. Response rate

Response to therapy was assessed using the myeloma response determination criteria developed by EBMT (58;59), which are summarized in Table 10. These criteria provide an international standard for the assessment of treatment response in multiple myeloma, thereby ensuring consistency in the reporting and evaluation of data across study sites. Initially the trial protocols were planning to use the earlier Blade criteria (58). However, an updated version was released in 2006 and these were used to define the response rate (59). The response criteria were assessed by collecting blood and urine samples for protein electrophoresis to quantify the proportion of M-protein and immunofixation. New bone lesions and serum calcium levels were also assessed to determine response.

Table 10: The myeloma response determination criteria used, based on the International Uniform Response Criteria (58;59)

Outcome	Criteria for Classification [a]
Complete response (CR)	A CR required: • Disappearance of M-paraprotein in serum and/or urine by electrophoresis maintained for ≥6 weeks. • Documentation of the following findings within ±2 weeks of the confirmatory electrophoresis studies: o Absence of M-paraprotein confirmed by immunofixation studies of serum and urine. o Less than 5% plasma cells in the bone marrow aspirate or biopsy. o Disappearance of soft tissue plasmacytomas. o No increase in size of number of lytic bone lesions (the development of bone fractures did not exclude a response). If some, but not all, of the criteria for a CR were fulfilled, the response was classified as a PR or RR, provided that all other requirements were satisfied.
Remission response (RR)	An RR required: • A 75% to 99% reduction from baseline in serum M-paraprotein and, if present, a 90% to 99% reduction from baseline in 24-hour urinary light chain excretion or a reduction in the 24-hour urinary light chain excretion to <200 mg by electrophoresis, which was maintained for ≥6 weeks. • Documentation of the following findings within ±2 weeks of the confirmatory electrophoretic studies: o If present, at least a 50% reduction from baseline in the sum of the products of perpendicular diameters of measurable soft tissue plasmacytomas by radiography or clinical examination [b]. If present, there must be no clear progression of evaluable soft tissue plasmacytomas or non-evaluable disease [c, d]. o No increase in the size or number of lytic bone lesions (the development of bone fractures did not exclude a response). o No evidence of disease progression by bone marrow aspirate/biopsy findings (see PD, below).

Outcome	Criteria for Classification [a]
Partial response (PR)	A PR required: • A 50% to 74% reduction from baseline in serum M-paraprotein and, if present, a 50% to 89% reduction from baseline in 24-hour urinary light chain excretion by electrophoresis, which was maintained for ≥6 weeks. • Documentation of the following findings within ±2 weeks of the confirmatory electrophoretic studies: o At least a 50% reduction from baseline in the sum of the products of perpendicular diameters of measurable soft tissue plasmacytomas by radiography or clinical examination [b]. If present, there must be no clear progression of evaluable soft tissue plasmacytomas or non-evaluable disease [c, d]. o No increase in the size or number of lytic bone lesions (the development of bone fractures did not exclude a response). o No evidence of progressive disease (PD) by bone marrow aspirate/biopsy findings (see PD, below).
Outcome	Criteria for Classification [a]
Stable disease (SD)	Criteria for PR or PD were not met.
Plateau phase of response	For subjects who achieved at least a confirmed PR, plateau phase of response was defined by stable M-paraprotein values (within 25% above or below nadir value) and, if present, stable measurements for measurable soft tissue plasmacytomas (sum of the products of perpendicular diameters within 25% above or below the nadir value) maintained for at least 3 months without evidence of PD or further response.
Progressive disease (PD)	PD for subjects in CR required at least one of the following: • Reappearance of serum or urinary M-paraprotein on immunofixation or electrophoresis on 2 consecutive occasions at least 1 week apart. • Increase in the percentage of plasma cells in bone marrow aspirate or biopsy to ≥5%. • Development of at least one new lytic bone lesion or soft tissue plasmacytoma. • Clear increase in size of residual bone lesions (the

Outcome	Criteria for Classification [a]
	development of a bone fracture, including a vertebral compression fracture, did not, in of itself, constitute PD). • Development of hypercalcemia (serum calcium level, corrected for albumin concentration, >11.5 mg/dL [2.8 mmol/L]) not attributable to any other cause.
Progressive disease (PD)	PD for subjects not in CR required at least one of the following: • Compared with the nadir value, a >25% increase in the level of serum M-paraprotein, which represented an absolute increase of ≥500 mg/dL (5 g/L), on 2 consecutive occasions at least 1 week apart. • Compared with the nadir value, a >25% increase in the level of the 24-hour light chain excretion, which represented an absolute increase of ≥200 mg/dL/24 hours, on 2 consecutive occasions at least 1 week apart. • Compared with the lowest marrow plasma cell percentage achieved during study treatment, a >25% increase in plasma cells in bone marrow aspirate or biopsy, which represented an absolute increase of ≥10%. • Development of at least one new lytic bone lesion or soft tissue plasmacytoma. • Clear increase in size of existing bone lesions (the development of a bone fracture, including a vertebral compression fracture, did not, in itself, constitute PD). • Compared with the nadir value achieved, a >25% increase in the sum of the products of existing measurable soft tissue plasmacytomas. • Clear PD of evaluable soft tissue plasmacytomas or non-evaluable disease. • Development of hypercalcemia (serum calcium level, corrected for albumin concentration, >11.5 mg/dL [2.8 mmol/L]) not attributable to any other cause.

[a] Response criteria for both serum and urine myeloma paraprotein (M-paraprotein) must be met in subjects in whom both are present.
[b] Measurable soft tissue plasmacytomas have defined borders and have perpendicular diameters that measure ≥1 cm x ≥1 cm.
[c] Evaluable soft tissue plasmacytomas have poorly defined borders or are measurable in only one dimension.
[d] Non-evaluable disease comprises malignant pleural

3. Functioning and quality of life

Other secondary endpoints included the time to first skeletal-related event (SRE) and time to first decrease in ECOG performance status. These are unpublished data available in the clinical study reports (60;61). Both of these are measures of patient quality of life and functioning which may not be captured through response or survival rates.

The time to first worsening of the ECOG performance status was calculated as the time from randomization to the date of the first worsening compared with the last ECOG evaluation obtained prior to randomization. Data were censored at the last date that the subject was known to be unchanged or improved from before randomization for the subjects who had not worsened at the time of the analysis and for the subjects who were lost to follow-up before worsening in the ECOG performance status was documented.

Adverse events

The severity of adverse events and laboratory abnormalities was graded according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 2.0 (57). The interpretation of these data is not confounded by the conduct of the studies, and similar results can realistically be expected to occur on a patient-by-patient basis, with comparable exposure to the study medications in clinical practice.

5.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

The study objectives and sample calculations for both Study MM-009 and Study MM-010 were identical and are presented below.

Primary objective

To compare the efficacy of oral lenalidomide in combination with oral pulse high-dose Dex with that of placebo and oral pulse high-dose Dex as treatment for subjects with relapsed or refractory multiple myeloma who have received at least one prior therapy.

Secondary objective

To compare the safety of oral lenalidomide in combination with oral pulse high-dose Dex with that of placebo and oral pulse high-dose Dex as treatment for subjects with relapsed or refractory multiple myeloma who have received at least one prior therapy.

Statistical analyses

All primary analyses and OS were based on the intention-to-treat population (ITT), and subgroup analyses were pre-planned on the basis of stratification variables (level of B2-microglobulin (<2.5 mg/L vs. ≥2.5 mg/L; previous stem-cell transplantation (none vs. ≥1); number of previous antimyeloma therapies (1 vs. ≥2)). An unstratified log-rank test was used to compare the time-to-event variables between the two study groups. Both the TTP and OS were estimated by Kaplan–Meier methods. OS was censored at the last date that the patient was known to be alive for patients alive at the time of analysis and for patients who were lost to follow-up before death was documented. Exact tests were used to compare rates of response.

Formal statistical hypothesis tests of the superiority of Len/Dex relative to Dex were conducted at the 2-sided, 0.05 level of significance.

Sample size calculation

The number of patients was calculated so that a one-sided log-rank test at the 0.025 level, allowing for one interim analysis, would have a statistical power of 85% to detect a difference between the TTP for each group with a constant hazard ratio of 1.5, reflecting an increase of 50% in the median TTP. The number of events required was 222. On the basis of the planned accrual rate, a log-rank test of OS that was performed 18 months after the last patient had been enrolled, when 194 deaths were expected, would have a power of 80% to detect a hazard ratio for death of 0.67. In the case of OS, the studies were unblinded before 194 deaths occurred.

Sensitivity analyses of primary outcome

A series of sensitivity analyses were also performed, which included progression-free survival (PFS), TTP based on an FDA definition (TTPFDA) and time-to-treatment failure (TTF). These sensitivity analyses were designed to explore the effect of the different ways to handle early dropouts from the studies. The results are reported as additional information in **Appendix 4**.

Interim analysis

An interim analysis to evaluate safety and efficacy was planned when 111 patients had disease progression; if the predetermined O'Brien–Fleming boundary for the superiority of Len/Dex over Dex was crossed, the study would be unblinded and patients would be allowed to cross over to open-label administration of lenalidomide at progression or at the investigator's discretion. Because the O'Brien–Fleming boundary for the superiority of Len/Dex over Dex was crossed at the interim analysis, the Independent Data Monitoring Committee (IDMC) recommended that the study be unblinded. Patients who had been enrolled on the Dex arm were given the option of also receiving lenalidomide, while remaining assigned to the Dex arm and being analysed as such. Patients enrolled in the Dex arm were also given this option in the event that they had developed disease progression prior to study unblinding.

Procedures for handling dropouts or missing data

No imputation of values for missing data was performed. Various sensitivity analyses were performed to explore different ways of handling early dropouts. One sensitivity analysis requested by the FDA included counting subjects who withdrew from the study for any reason or who received antimyeloma therapy during the treatment period as having events on the last assessment day prior to withdrawal from the

study or to receiving antimyeloma medication. All sensitivity analyses confirmed the significant superiority of Len/Dex relative to Dex. The frequency of missing or out-of-window assessments was comparable between the 2 treatment arms, thereby having no effect on the validity of the analysis results.

Censoring

Censored data was handled in the same way for both studies MM-009 and MM-010:

- **TTP**: Censored at the date of the last response assessment for subjects who (1) had not progressed at the time of the analysis, (2) withdrew from the treatment phase before documented progression, including those who died of causes not related to MM, or (3) were given another antimyeloma therapy with documented progression or experienced intolerable adverse events (for these patients, the date of their last response assessment prior to taking antimyeloma therapy was used as the censor date).

- **OS**: Censored at the last date that the patient was known to be alive for patients alive at the time of analysis and for patients who were lost to follow-up before death was documented.

Sub-group analyses

Subgroup analyses were conducted for TTP, overall survival, and the rate of response in both the MM-009 and MM-010 studies. Subgroups were analyzed on the basis of pre-specified stratification variables including age, gender and the following: the level of β_2-microglobulin (<2.5 mg/L vs. ≥2.5 mg/L), previous stem-cell transplantation (none vs. ≥1), and the number of previous antimyeloma therapies (1 vs. ≥2).

Additional unspecified subgroup analyses were conducted from a pooled analysis of the MM-009 and MM-010 study data. These analyses investigated study outcomes in the following:

- Patients with impaired renal function (as defined by creatinine clearance levels of <30 mL/min and <50 mL/min)

- Patients with pre-existing peripheral neuropathy (unpublished data provided in confidence by Celgene)

- Eastern Cooperative Oncology Group (ECOG) performance status scores (ECOG= 0 vs. ECOG> 0)

- Patients with IgA multiple myeloma

- Patients with a complete or near complete response

- Patients receiving low-dose Dex in combination with lenalidomide

- Patients receiving prior thalidomide therapy

- Patients receiving prior bortezomib therapy

These sub-groups were selected on the basis that they represent important prognostic markers for treatment response in terms of safety and efficacy.

5.3.6 Critical appraisal of relevant RCTs

Each RCT should be critically appraised. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- *How was allocation concealed?*
- *What randomisation technique was used?*
- *Was a justification of the sample size provided?*
- *Was follow-up adequate?*
- *Were the individuals undertaking the outcomes assessment aware of allocation?*
- *Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.*
- *Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?*
- *How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.*
- *For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?*
- *Were the study groups comparable?*
- *Were the statistical analyses used appropriate?*

- *Was an intention-to-treat analysis undertaken?*

- Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

Question	Response
How was allocation concealed?	MM-009 and MM-010 were double-blind studies. The lenalidomide and placebo capsules were identical in appearance, and the subjects, investigators, other study site personnel, and Celgene personnel who were responsible for the study were blinded to each subject's treatment assignment until the study was unblinded. An Interactive Voice Response System (IVRS) was used and all medication allotments were assigned by the IVRS. The clinical sites enrolled the patients and did so by accessing the central IVRS.
What randomisation technique was used?	A stratified randomization list was independently generated before the study was initiated, which randomized the subjects in a 1:1 ratio to either the Len/Dex group or the Dex group. Randomization was done centrally using an IVRS. Randomization was centralized and stratified by three factors: baseline serum β2-microglobulin, prior treatment with high-dose chemotherapy or SCT or no prior treatment, and number of prior anti-myeloma regimens.
Was a justification of the sample size provided?	The sample size was based on 85% power to detect a hazard ratio of 1.5 for TTP between the two arms (an increase of 6 to 9 months) and 80% power to detect a hazard ratio of 1.5 for OS (an increase of 12-18 months).
Was follow-up adequate?	All patients were followed in the active phase of the study until disease progression or treatment was discontinued for any other reason. Subjects are contacted every 6 months during the follow-up phase.
Were the individuals undertaking the outcomes assessment aware of allocation?	No, all review of outcomes by the adjudication committee were conducted in blinded fashion.

Question	Response
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.	It was a parallel-group design. Patients in the Dex group were only allowed to roll over to receive lenolidomide after disease progression, or cross over to receive Len/Dex after the IDMC had declared the studies could be unblinded. Carry-over effect is not applicable in these two trials.
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	MM-009 took place in the USA and Canada, while MM-010 took place in Europe, Israel and Australia. Specifically, MM-010 included sites in The study is being conducted in Australia (6 sites), Austria (1 site), Belgium (2 sites), France (5 sites), Germany (6 sites), Greece (1 site), Ireland (1 site), Israel (3 sites), Italy (6 sites), Poland (3 sites), Spain (6 sites), Switzerland (2 sites), Ukraine (5 sites), and the United Kingdom (3 sites; 2 in London and 1 in Bristol). A total of 15 patients across three UK sites were enrolled into MM-010.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, and setting.	There is no reason to suspect that the trial patient characteristics and outcomes would differ significantly from those seen in UK practice. However, since MM-009 and MM-010 were initiated, thalidomide and bortezomib have been licensed in Europe for first and second-line treatment respectively. Therefore the proportion of patients in the UK receiving either of these drugs as prior therapies may be greater in clinical practice than was seen in the trials. In MM-009, 41.8% and 10.7% of patients in the Len/Dex arm had, respectively, received prior treatment with thalidomide and bortezomib. In MM-010, the respective proportions of patients previously treated with these agents were 30.1% and 4.5% in the Len/Dex arm (5;6). The patients enrolled in the trials are slightly younger and have a better status at baseline than those that might be seen in UK clinical practice. However, the trial data shows Len/Dex significantly improves outcomes over Dex regardless of age and performance status (39;45).
For pharmaceuticals, what dosage regimens were used in the RCT?	Dosage regimens were the same as those detailed in the Summary of Product Characteristics.

Question	Response
Were the study groups comparable?	Yes, the demographic and baseline characteristics of the study groups are comparable.
Were the statistical analyses used appropriate?	Yes the statistical analyses used are considered appropriate. The protocol for both studies, including the statistical methods section, went through a Special Protocol Assessment by FDA and was agreed upon by the agency.
Was an intention-to-treat analysis undertaken?	Yes
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	In the MM-009 and MM-010 trials, patients in the Dex group were allowed to cross-over to the Len/Dex arm when there was a documented progression or at unblinding by the IDMC. This cross-over confounded the measurement of OS in favour of the Dex group in general, and is likely to explain the decreasing difference in OS between the study groups over time. TTP in the Dex arms is relatively unaffected by the treatment crossover, because most patients had developed progressive disease (PD) when the studies were unblinded – 75.0% in MM-009 and 81.1% in MM-010.

5.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

- *The unit of measurement.*
- *The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate)*

differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.

- *A 95% confidence interval.*
- *The number of patients included in the analysis.*
- *The median follow-up time of analysis*
- *State whether intention-to-treat was used for the analysis and how data were imputed if necessary.*
- *Discuss and justify definitions of any clinically important differences.*
- *Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustment should be described to cater for the interim nature of the data.*
- *If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.*
- *Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.*

The data from MM-009 and MM-010 presented here are derived from multiple sources. The majority of the analyses are available from the published sources outline in Table 11. However, to supply the full data requested above it was necessary to use additional sources including the clinical study reports (CSRs) and documents submitted as part of the marketing authorisation application for lenalidomide. In addition for certain outcomes it was necessary to consult the cleaned statistical tables. Table 11 below contains the sources and dates of the various data-cuts.

Table 11: Sources of data utilised for presentation of comparative efficacy.

Information	Source	Data cut off/date presented
Trial methodology (60;61)	CSRs MM-009 MM-010	 15 July 2004 15 September 2004
Subject disposition (63)	MAA Section 2.5 MM-009 MM-010	 15 July 2004 15 September 2004
Demographic data (63)	MAA Section 2.5 MM-009 MM-010	 15 July 2004 15 September 2004
Primary outcome		
Interim analysis of TTP (23;23)	EPAR MM-009 MM-010	 15 July 2004 15 September 2004
Analysis of TTP at unblinding (5;6)	EPAR/Primary publications MM-009 MM-010	 28 June 2005 03 August 2005

Information	Source	Data cut off/date presented
Sensitivity analyses of TTP		
Progression-free survival (63)	MAA Section 2.5	
	MM-009	15 July 2004
	MM-010	15 September 2004
Time-to-progression-FDA (63)	MAA Section 2.5	
	MM-009	15 July 2004
	MM-010	15 September 2004
Time to treatment failure (60;61)	CSRs	
	MM-009	15 July 2004
	MM-010	15 September 2004
Secondary analysis of primary outcome		
Lines of prior therapy	ASH 2006 (41)	
	MM-009	Presented December 2006
	MM-010	
Prior stem-cell transplant	ASH 2006 (40)	
	MM-009	Presented December 2006
	MM-010	
β2-microglobulin level	EPAR (23)	
	MM-009	28 June 2005
	MM-010	03 August 2005
Secondary outcomes		
Myeloma response rates	EPAR (23)	
	MM-009	28 June 2005
	MM-010	03 August 2005
Time to first worsening of ECOG PS	EPAR (23)	
	MM-009	28 June 2005
	MM-010	03 August 2005
Overall survival	MAA Section 2.5 (63)	
	MM-009	15 July 2004
	MM-010	15 September 2004
	EPAR	
	MM-009	28 June 2005
	MM-010	03 August 2005
	ASH 2006 (47)	
	MM-009	Presented December 2006
	MM-010	
	IMW 2007 (36)	
	MM-009	Presented June 2007
	MM-010	Presented June 2007
	ASH 2007 (35)	
	Pooled analysis (MM-009, MM-010)	Presented December 2007

CSRs=Clinical study reports MAA= Marketing authorization application EPAR = European Public Assessment Report; ASH 2006 = American Society of Haematology meeting 2006; IMW 2007 = International Myeloma Workshop 2007.

Interim analysis, study duration and unblinding

Because the O'Brien–Fleming boundary for the superiority of Len/Dex over Dex was crossed at the interim analysis, the IDMC recommended that the study be unblinded.

In MM-009, patients were enrolled from 27 February 2003, and the study was unblinded on 28 June 2005. In MM-010, patients were enrolled from 22 September 2003, and the study was unblinded on 3 August 2005.

Primary and secondary efficacy analyses were conducted on data from all patients (i.e., ITT population) randomised in study MM-009 (N=353) and study MM-010 (N=351). The O'Brien-Fleming boundary for the superiority of lenalidomide over placebo was crossed at the interim analysis in both studies.

TTP results

Interim TTP

The preplanned interim analyses of both Studies MM-009 and MM-010 occurred when half of the specified disease progressions had occurred i.e. studies were to end when 80% of the patients progressed; therefore, the interim analyses occurred when 40% of the total patients had progressed. The results of TTP at the interim phase are presented in Table 12.

Sensitivity analyses of this outcome – progression-free survival (PFS), TTP based on an FDA definition (TTPFDA) and time-to-treatment failure (TTF) – were also conducted with the same data cut-off dates (see **Appendix 4**).

Table 12: Protocol-defined interim analysis (intent-to-treat [ITT] population) of the primary outcome – TTP – from MM-009 and MM-010 (EMEA application)

Statistics		Study MM-009*		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
TTP	N	170	171	176	175
Progressed	n (%)	44 (25.9)	98 (57.3)	39 (22.2)	99 (56.6)
Censored	n (%)	126 (74.1)	73 (42.7)	137 (77.8)	76 (43.4)
	Median (weeks) [95% CI]	41.1 [30.3, NE]	20.1 [16.7, 24.1]	NE [36.1, NE]	20.1 [20.0, 22.1]
Hazard Ratio [95% CI]		3.073 [2.149, 4.395]		3.246 [2.239, 4.708]	
Log-rank test *P*-value		< 0.001		< 0.001	

NE, not estimable

*Data from 12 subjects at investigative site #142 were not reviewed or included in the analysis due to sequestering of the case report forms (CRFs) by this institution. The institution decided to temporarily put a halt to all clinical trial activities of one investigator for unspecified reasons. At the time, the original case report forms were therefore unavailable, and only uncertified copies were obtained – as validity of these copies was unclear, the CRFs for these 12 patients were excluded from the original analysis. Subsequently, the institution released the CRFs, which were included in later analyses of the trial data.

Data source: Table 6, page 20, scientific discussion – European Public Assessment Report. Data cut-off dates: 15 July 2004 for Study MM-009 and 15 September 2004 for study MM-010.Median follow up: 5.3 months for MM-009 (n=161), 5.6 months for MM-010 (n=179), 5.4 months for combined (n=340).(23)

TTP at unbinding

The TTP outcomes at study unblinding are presented in Table 13. Len/Dex was associated with a significantly longer median time to progression (11.1 months) compared to Dex (4.7 months) (hazard ratio= 2.82; 95% CI: 2.146, 3.701; P<0.001) (Figure 4). Results for TTP are based on data obtained prior to unblinding upon reaching the O'Brien-Fleming boundary.

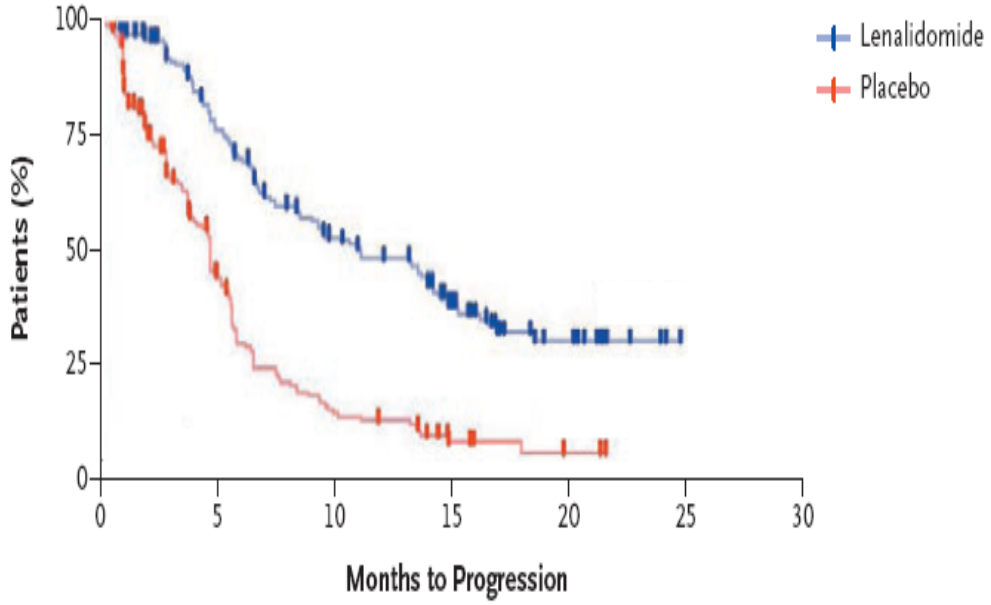
In study MM-010, Len/Dex was associated with a significantly longer median time to progression (11.3 months) compared to Dex (4.7 months) (hazard ratio= 2.85; 95% CI: 2.16-3.76; P<0.001).

Table 13: Analysis of the primary outcome – time-to-progression (TTP) – at study unblinding (intent-to-treat population), with data cut off to June (MM-009)/August (MM-010) 2005 (5;6;23)

Statistic		Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
TTP Progressed Censored	N n (%) n (%)	177 92 (52.0) 85 (48.0)	176 132 (75.0) 44 (25.0)	176 82 (46.6) 94 (53.4)	175 142 (81.1) 33 (18.9)
Overall TTP (weeks)	Median [95% CI] [a]	48.1 [36.9, 61.4]	20.1 [16.7, 23.1]	48.7 [40.9, 72.1]	20.1 [18.1, 20.7]
Hazard Ratio [95% CI] [b]		2.822 [2.146, 3.701]		2.850 [2.159, 3.762]	
Log-rank Test p-Value [c]		< 0.001		< 0.001	

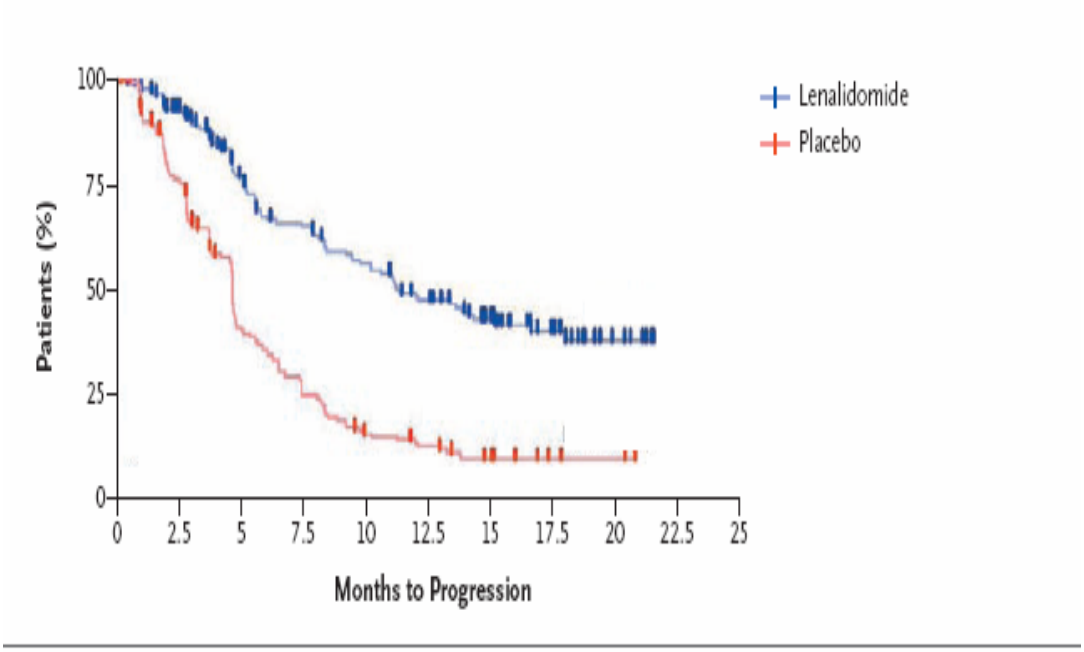
Notes: CI=Confidence interval. Percentages are based on the number of treated subjects. The median in this table is based on Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring.
[a] 95% confidence intervals about the median overall time to progression.
[b] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (Len/Dex:/Dex)
[c] The p-value is based on the a one-tailed unstratified log rank test of survival curve differences between the treatment groups.
Median follow up: 17.1 months for MM-009 (n=76), 16.7 months for MM-010 (n=74), 16.9 months for combined (n=150).

Figure 4: MM-009: Kaplan–Meier curves for the time to disease progression among all patients (6) at study unblinding



Curves show time to progression for the intention-to-treat population (a median of 11.1 months in the lenalidomide (Len/Dex) group and 4.7 months in the placebo (Dex) group, P<0.001 by the log-rank test).

Figure 5: MM-010: Kaplan–Meier curves for the time to disease progression among all patients(5) at study unblinding



Estimates of the median time to disease progression for the intention-to-treat population (11.3 months in the lenalidomide group and 4.7 months in the placebo group) (P<0.001 by the log-rank test).

OS results

Interim OS

Data presented in the clinical overview submitted in section 2.5 as part of the marketing authorisation application for lenalidomide (63) show that in MM-009, as of the cut off date of 15 July 2004:

- 9.4% (16/170) of the Len/Dex-treated subjects had died
- 8.8% (15/171) of the Dex-treated subjects had died.

In MM-010, data presented up to the cut-off date of 15 September 2004 show that:

- 15.9% (28/176) of the Len/Dex-treated subjects had died
- 16.0% (28/175) of the Dex-treated subjects had died.

Therefore, at this stage of follow up, relatively few deaths occurred in either treatment group in MM-009 or MM-010 and consequently, no significant differences were observed between the Len/Dex and Dex groups with respect to OS.

OS at unblinding

With a greater duration of follow up data presented as part of the scientific discussion in the EPAR, a significant survival advantage for Len/Dex relative to Dex in MM-009 was shown (23). At this time, 37 (20.9%) of the 177 Len/Dex-treated patients, compared with 62 (35.2%) of the 176 Dex-treated patients, had died. At this time, no significant difference in OS had been observed between the Len/Dex and the Dex-treated patients in Study MM-010 (47 and 59 deaths, respectively), due to the shorter study duration of follow up.

Updated OS after study unblinding as of May 2006

The median OS is shown in Table 14, and represents data analysed as of May 2006 for both studies – a time from study initiation of 3 years and 3 months for MM-009 and 2 years and 8 months for MM-010 (47). Kaplan–Meier Curves for OS are shown for MM-009 and MM-010 in Figure 6 and Figure 7 below respectively.

Both studies continued to show significant improvement with Len/Dex compared with Dex with respect to median OS. In MM-009, the estimated median OS in the Len/Dex arm was 29.6 months, versus 20.5 months for Dex (hazard ratio= 0.44; 95% CI: 0.30-0.65; P<0.001). These data represent a 9-month increment in median OS for patients in the Len/Dex versus the Dex arm.

Median OS for study MM-010 was not estimable at this time in the Len/Dex combination group and was 20.6 months among those who received Dex. Although OS was not estimable for Len/Dex, it was still significantly higher than for Dex (hazard ratio =0.66; 95% CI: 0.45-0.96; P=0.03).

Table 14: Median OS following treatment with Len/Dex or Dex in the MM-009 and MM-010 trials among patients treated with one prior therapy – ITT population (5;6)

Characteristic	MM-009		MM-010	
	Len/Dex	Dex	Len/Dex	Dex
Died, n (%)	49 (27.7)	63 (35.8)	47 (26.7)	60 (34.3)
Median OS (months)	29.6	20.2	NE	20.6
Hazard ratio	0.44		0.66	
95% CI	0.30–0.65		0.45–0.96	
p	<0.001		0.03	

OS = overall survival; NE = not estimable; CI = confidence interval. Data analysed as of May 2006 for both studies – a time from study initiation of 3 years and 3 months for MM-009 and 2 years and 8 months for MM-010. Median follow-up at this time-point is 17.1 months for MM-009 and 16.5 months for MM-010.

Figure 6: Kaplan–Meier curves for overall survival for all patients in MM-009 as of May 2006 for the intention-to-treat population (a median of 29.6 months in the lenalidomide group and 20.2 months in the placebo group, P<0.001 by the log-rank test).

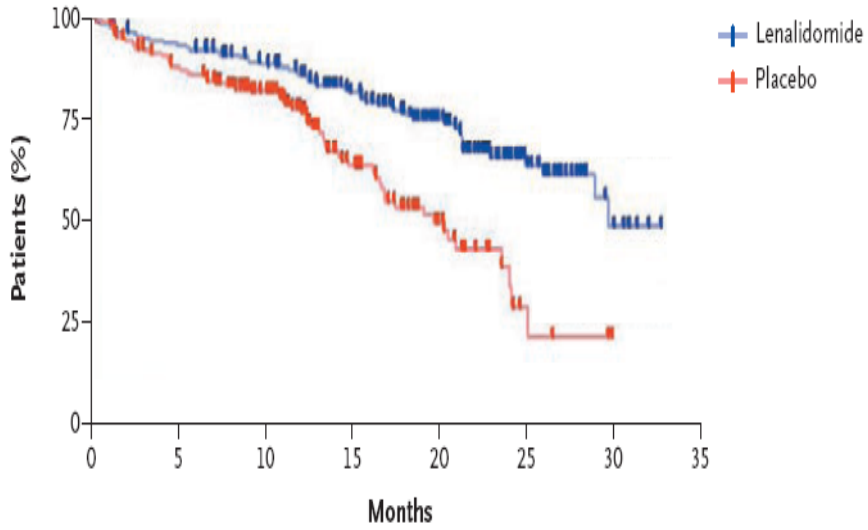
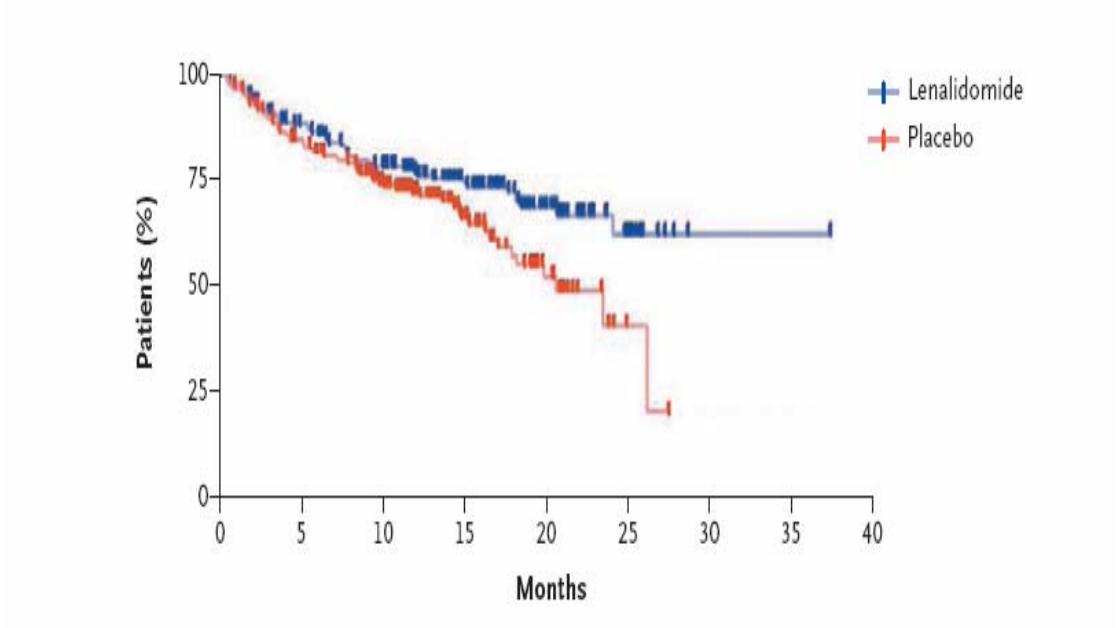


Figure 7: Kaplan–Meier Curves for overall survival among all patients in MM-010 as of May 2006 for the intention-to-treat population (median not yet reached in the lenalidomide group and 20.6 months in the placebo group, P<0.001 by the log-rank test).



Further updated OS analysis is available as a pooled analysis later in this section.

Response to therapy

At study un-blinding

The ITT myeloma response rates of patients treated with Len/Dex versus Dex during studies MM-009 and MM-010 are presented in Table 15. These data are taken from the scientific discussion in the EPAR (23) and are reproduced in the primary publications (5;6). The median follow-up was 17.6 months for MM-009 and 16.4 months for MM-010.

The overall response rate seen in MM-009 (defined as complete, near-complete, or partial response) was significantly higher for Len/Dex patients in comparison to those treated with Dex (61.0% versus 19.9%, P<0.001) - representing a three-fold increase in response for Len/Dex, compared with Dex. There were also more patients who had a complete response in the Len/Dex arm (14.1%) compared to Dex (0.6%) (P<0.001).

The overall response rate for study MM-010 was significantly higher for Len/Dex patients in comparison to those treated with Dex alone (60.2% versus 24.0%, P<0.001). There were also more patients who had a complete response in the Len/Dex arm (15.9%) compared to Dex alone (3.4%) (P<0.001).

Table 15: Studies MM-009 and MM-010 – summary of response rates (ITT population) based on best response assessments (5;6)

	Study MM-009		Study MM-010	
	Len/Dex N=177	**Dex N=176**	**Len/Dex N=176**	**Dex N=175**
Response [b]				
CR [c]	25 (14.1%)	1 (0.6%)	28 (15.9%)	6 (3.4%)
nCR	18 (10.2%)	2 (1.1%)	15 (8.5%)	3 (1.7%)
PR	65 (36.7%)	32 (18.2%)	63 (35.8%)	33 (18.9%)
SD	54 (30.5%)	102 (58.0%)	53 (30.1%)	97 (55.4%)
PD	5 (2.8%)	25 (14.2%)	3 (1.7%)	25 (14.3%)
NE [d]	10 (5.6%)	14 (8.0%)	14 (8.0%)	11 (6.3%)
p-value [e]	<0.001		<0.001	
Dichotomised Response				
CR, nCR or PR	108 (61.0%)	35 (19.9%)	106 (60.2%)	42 (24.0%)
SD, PD or NE	69 (39.0%)	141 (80.1%)	70 (39.8%)	133 (76.0%)
p-value [f]	< 0.001		< 0.001	
Odds Ratio [95% CI] [g]	6.31 [3.91, 10.17]		4.80 [3.03, 7.59]	

[a] Response in this table is based on the review of all myeloma assessment data using Blade criteria.
[b] Response is the highest assessment of response during the treatment phase of the study.
[c] Comparison of the CR response rate shows that the CR rate is significantly higher in the CC-5013/Dex group than in the Placebo/Dex
group ($p < 0.003$ continuity corrected Pearson chi square).
[d] Including subjects who did not have any response assessment data at the data cutoff point, or whose only assessment was RESPONSE
NOT EVALUABLE.
[e] Probability from Wilcoxon rank sum test.
[f] Probability from continuity-corrected Pearson chi square test.
[g] CI=Confidence Interval
The median follow-up was 17.6 months for MM-009 and 16.4 months for MM-010.

Pre-specified sub-group analyses

Most of the data presented in this section have been updated, or additional information is included here since initial publication. This section is therefore referenced as data on file.

Prospectively-defined secondary analyses were conducted, according to level of β2-microglobulin (<2.5 mg/L vs. ≥2.5 mg/L), previous stem-cell transplantation (none vs. ≥1), and the number of previous antimyeloma therapies (1 vs. ≥2) (5;6;60;61). These were selected as they represent important prognostic markers for response to therapy. Patients were stratified on these prognostic factors at study enrolment for both MM-009 and MM0-10.

The results of these analyses are reported in Table 16 - Table 21. In both trials, differences in TTP, favouring Len/Dex, were observed irrespective of baseline serum β2-microglobulin level, prior stem cell transplant (SCT) or not, and the number of prior anti-myeloma regimens (5;6;23). The median TTP for patients treated with one prior therapy was approximately double for patients in the Len/Dex arm of MM-009 compared patients in the Dex arm (Table 16) (62) . While median TTP had not been reached for the Len/Dex patients in study MM-010, there was still a significant difference observed between the two groups (p>0.001). Even for patients who had received two prior therapies, patients given Len/Dex in both studies had approximately double the median TTP compared to patients treated with Dex. This was also true with respect to overall response rates (CR, nCR or PR) which were more than doubled for patients treated with Len/Dex compared with Dex across both studies (p>0.001). Similar results were seen in the other pre-specified subgroups (Table 17). While the efficacy of Len/Dex was lower in subgroups with poorer prognosis compared to those with better baseline prognostic variables (i.e. higher number of prior therapies and Beta-2M > 2.5mg/L), this is to be expected and it is important to note that outcomes were significantly worse for patients with poor prognosis treated with Dex compared with Len/Dex for both studies.

Post-hoc sub-group analyses were also presented in the primary publications for patients treated with prior thalidomide or bortezomib, which suggested Len/Dex was significantly superior to Dex regardless of these prior treatments in terms of overall response rate, and evidence for cross-resistance to thalidomide was lacking (5;6). In addition, a number of sub-groups analyses of the pooled MM-009 and MM-010 data have been presented at various conferences and are available in the public domain as abstracts (these will be discussed in more detail in the pooled results section below). These subgroup analyses were conducted to address questions regarding additional prognostic variables and the place of lenalidomide in the treatment pathway. These analyses are considered exploratory, as they were unplanned, unadjusted for multiplicity, and had small sample sizes.

Table 16: Summary of time to progression (per protocol defined TTP) intent-to-treat population: number of prior therapies pre-specified subgroups (62)

Statistics		One prior therapy				>2 prior therapies			
		MM-009		MM-010		MM-009		MM-010	
		Len/Dex	Dex	Len/Dex	Dex	Len/Dex	Dex	Len/Dex	Dex
TTP Progressed Censored	N n (%) n (%)	68 [redacted] [redacted]	67 [redacted] [redacted]	56 [redacted] [redacted]	57 [redacted] [redacted]	109 [redacted] [redacted]	109 [redacted] [redacted]	120 [redacted] [redacted]	118 [redacted] [redacted]
Overall TTP (wk)	Median [95% CI] [a]	61.4 [redacted]	21.1 [redacted]	NE [redacted]	20.1 [redacted]	40.1 [redacted]	19.9 [redacted]	48.1 [redacted]	20.1 [redacted]
	Mean SD Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratio [95% CI] [b]		[redacted]		[redacted]		[redacted]		[redacted]	
Log-rank Test p-Value [c]		<0.001		<0.001		<0.001		<0.001	

Notes: CI=Confidence interval. Percentages are based on the number of treated subjects. The median in this table is based on Kaplan-Meier estimate and the mean is the univariate mean without adjusting for censoring.
[a] 95% confidence intervals about the median overall time to progression.
[b] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (CC-5013/Dex:Placebo/Dex)
[c] The p-value is based on a one-tailed log rank test of survival curve differences between the treatment groups.

Table 17: Summary of myeloma response rates (based on best response assessments[a]) intent-to-treat population: Number prior therapies pre-specified subgroup (62)

Statistics	One prior therapy				>2 prior therapies			
	MM-009		MM-010		MM-009		MM-010	
	Len/Dex N (%)	Dex N (%)	Len/Dex N (%)	Dex N (%)	Len/Dex N (%)	Dex N (%)	Len/Dex N (%)	Dex N (%)
Number of subjects	68	67	56	57	109	109	120	118
Response [b]								
CR[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NE[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value [e]	[redacted]		[redacted]		[redacted]		[redacted]	
Dichotomised Response								
CR, nCR or PR	44(64.7)	15(22.4)	37 (66.1)	17 (29.8)	64 (58.7)	20 (18.3)	69 (57.5)	25 (21.2)
SD, PD or NE	24 (35.3)	52(77.6)	19 (33.9)	40 (70.2)	45 (41.3)	89 (81.7)	51 (42.5)	93 (78.8)
p-value [f]	<0.001		<0.001		<0.001		<0.001	
Odds Ratio (Len/Dex:Dex) [95% CI][g]	[redacted]		[redacted]		[redacted]		[redacted]	

Notes – These results have been published by Stadtmauer et al. 2006, however those results have been updated here.
- Complete response (CR) Near CR (nCR) Partial Response (PR) Stable Disease (SD) Progressive Disease (PD) Response Not Evaluable (NE).
[a] Response in this table is based on the review of all myeloma assessment data using EBMT criteria.
[b] Response is the highest assessment of response during the treatment phase of the study.
[c] Comparison of the CR response rate shows that the CR rate is significantly higher in the CC-5013/Dex group than in the Placebo/Dex group ($p < 0.003$ continuity corrected Pearson chi square).
[d] Including subjects who did not have any response assessment data at the data cutoff point, or whose only assessment was RESPONSE NOT EVALUABLE.
[e] Probability from Wilcoxon rank sum test.
[f] Probability from continuity-corrected Pearson chi square test.
[g] CI=Confidence Interval

Table 18: Summary of time to progression (per protocol defined ttp) intent-to-treat population: Beta-2M pre-specified subgroups (62)

Statistics		Beta-2M <= 2.5mg/L				Beta-2M > 2.5mg/L			
		MM-009		MM-010		MM-009		MM-010	
		Len/Dex	Dex	Len/Dex	Dex	Len/Dex	Dex	Len/Dex	Dex
TTP	N	52	51	51	48	125	125	125	127
Progressed	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall TTP (wk)	Median [95% CI] [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratio [95% CI] [b]		[redacted]		[redacted]		[redacted]		[redacted]	
Log-rank Test p-Value [c]		<0.001		<0.001		<0.001		<0.001	

Notes: CI=Confidence interval. Percentages are based on the number of treated subjects. The median in this table is based on Kaplan-Meier estimate and the mean is the univariate mean without adjusting for censoring.
[a] 95% confidence intervals about the median overall time to progression.
[b] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (Len/Dex:Dex)
[c] The p-value is based on a one-tailed log rank test of survival curve differences between the treatment groups.

Table 19: Summary of myeloma response rates (based on best response assessments[a]) intent-to-treat population: Beta-2M pre-specified subgroup (62)

Statistics	Beta-2M <= 2.5mg/L				Beta-2M > 2.5mg/L			
	MM-009		MM-010		MM-009		MM-010	
	Len/Dex N (%)	Dex N (%)	Len/Dex N (%)	Dex N (%)	Len/Dex N (%)	Dex N (%)	Len/Dex N (%)	Dex N (%)
Number of subjects	52	51	51	48	125	125	125	127
Response [b]								
CR[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NE[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value [e]	[redacted]		[redacted]		[redacted]		[redacted]	
Dichotomised Response								
CR, nCR or PR	39 (75.0)	15 (29.4)	36 (70.6)	18 (37.5)	69 (55.2)	21 (16.8)	70 (56.0)	24 (18.9)
SD, PD or NE	13 (25.0)	36 (70.6)	15 (29.4)	30 (62.5)	56 (44.8)	104 (83.2)	55 (44.0)	103 (81.1)
p-value [f]	<0.001		<0.001		<0.001		<0.001	
Odds Ratio (Len/Dex:Dex) [95% CI] [g]	[redacted]		[redacted]		[redacted]		[redacted]	

Notes - Complete response (CR) Near CR (nCR) Partial Response (PR) Stable Disease (SD) Progressive Disease (PD) Response Not Evaluable (NE).
[a] Response in this table is based on the review of all myeloma assessment data using EBMT criteria.
[b] Response is the highest assessment of response during the treatment phase of the study.
[c] Comparison of the CR response rate shows that the CR rate is significantly higher in the CC-5013/Dex group than in the Placebo/Dex group ($p < 0.003$ continuity corrected Pearson chi square).
[d] Including subjects who did not have any response assessment data at the data cutoff point, or whose only assessment was RESPONSE NOT EVALUABLE.
[e] Probability from Wilcoxon rank sum test.
[f] Probability from continuity-corrected Pearson chi square test.
[g] CI=Confidence Interval

Table 20: Summary of Time to Progression (Per Protocol Defined TTP) Intent-to-Treat Population: Prior SCT pre-specified subgroups (62)

Statistics		Previously Treated with HDT and SCT				Not Previously Treated with HDT or SCT			
		MM-009		MM-010		MM-009		MM-010	
		Len/Dex	Dex	Len/Dex	Dex	Len/Dex	Dex	Len/Dex	Dex
TTP	N	109	108	97	95	68	68	79	80
Progressed	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall TTP (wk)	Median [95% CI] [a]	[redacted]	[redacted]	48.7 [redacted]	20.1 [redacted]	[redacted]	[redacted]	49.1 [redacted]	20.1 [redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratio [95% CI] [b]		[redacted]		[redacted]		[redacted]		[redacted]	
Log-rank Test p-Value [c]		<0.001		<0.001		<0.001		<0.001	

Notes: CI=Confidence interval. Percentages are based on the number of treated subjects. The median in this table is based on Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring.
[a] 95% confidence intervals about the median overall time to progression.
[b] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (Len/Dex:Dex)
[c] The p-value is based on a one-tailed log rank test of survival curve differences between the treatment groups.

Table 21: Summary of Myeloma Response Rates (Based on Best Response Assessments[a]) Intent-to-Treat Population: Prior SCT pre-specified subgroups (62)

Statistics	Prior SCT				No prior SCT			
	MM-009		MM-010		MM-009		MM-010	
	Len/Dex N (%)	Dex N (%)	Len/Dex N (%)	Dex N (%)	Len/Dex N (%)	Dex N (%)	Len/Dex N (%)	Dex N (%)
Number of subjects	108	103	97	95	69	70	79	80
Response [b]								
CR[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NE[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value [e]	[redacted]		[redacted]		[redacted]		[redacted]	
Dichotomised Response								
CR, nCR or PR	72 (66.7)	20 (19.4)	60 (61.9)	27 (28.4)	36 (52.2)	15 (21.4)	46 (58.2)	15 (18.8)
SD, PD or NE	36 (33.3)	83 (80.6)	37 (38.1)	68 (71.6)	33 (47.8)	55 (78.6)	33 (41.8)	65 (81.3)
p-value [f]	<0.001		<0.001		<0.001		<0.001	
Odds Ratio (Len/Dex:Dex) [95% CI] [g]	[redacted]		[redacted]		[redacted]		[redacted]	

[a] Response in this table is based on the review of all myeloma assessment data using EBMT criteria.
[b] Response is the highest assessment of response during the treatment phase of the study.
[c] Comparison of the CR response rate shows that the CR rate is significantly higher in the CC-5013/Dex group than in the Placebo/Dex group ($p < 0.003$ continuity corrected Pearson chi square).
[d] Including subjects who did not have any response assessment data at the data cutoff point, or whose only assessment was RESPONSE NOT EVALUABLE.
[e] Probability from Wilcoxon rank sum test.
[f] Probability from continuity-corrected Pearson chi square test.
[g] CI=Confidence Interval

Time to first worsening of ECOG PS

Time to first worsening of ECOG PS was analysed as a secondary outcome (Table 22). The median time to first worsening of ECOG PS was significantly greater in the Len/dex arm of MM-009, versus placebo, [redacted] (Table 22).

Table 22: Studies MM-009 and MM-010 – time-to-first worsening of ECOG PS (ITT population)

		Study MM-009		Study MM-010	
	Statistic	Len/Dex N=177	Dex N=176	Len/Dex N=176	Dex N=175
Time to First Worsening	N	171	174	173	172
Worsened	n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Overall Time to First Worsening (wk)	Median [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratio [95% CI]		[redacted]		[redacted]	
Log-rank Test p-Value		[redacted]		[redacted]	

NE, not estimable

[redacted]

[redacted]

Time to first skeletal-related event (SRE)

Regarding the 'time to first skeletal-related event' endpoint, there have been too few events for both studies and no analysis can be done. In fact this does not seem a feasible endpoint so it has been removed from all the new multiple myeloma studies.

Pooled results for MM-009 and MM-010

MM-009 and MM-010 were identically designed trials and it was considered statistically appropriate to pool the patient level data and assess the primary and secondary outcomes in this larger patient population. In addition, a number of post-hoc sub-group analyses have been undertaken on these pooled data to explore the data and better understand the potential impact of a number of important factors. Using this larger data increases the power to detect any significant differences.

Pooled analysis at unblinding

Table 23 shows the pooled results for TTP and response (according to EBMT criteria (58;59)) that were assessed up to unblinding in June 2005 for study MM-009 and in August 2005 for study MM-010, for a median follow-up of 17.5 months (23). Len/Dex was significantly superior to Dex for TTP, OR and CR (p>0.001).

Table 23: Response rates and time-to-progression for pooled MM-009 and MM-010 data. (62)

	Len/Dex (n=353)	Dex (n=351)	Hazard/odds ratio, 95% CI, p-value
Median TTP [weeks]	48.3	20.1	0.35 [0.29, 0.43]
[95% CI]	[41.1, 60.1]	[19.9, 20.7]	p<0.001
OR [n, %]	214 (60.6)	77 (21.9)	0.18 [0.13, 0.25], p < 0.001
CR [n, %]	53 (15.0)	7 (2.0)	0.12 [0.05,0.26], p < 0.001
RR+PR [n, %]	161 (45.6)	70 (19.9)	0.30 [0.21, 0.42], p < 0.001

Response assessed using EBMT criteria. RR=remission response OR=overall response CR=complete response PR=Partial response

OS in the pooled studies at one year was 82% in patients treated with Len/Dex versus 75% in patients treated with Dex, after the start of treatment, with a median follow-up duration of 98.0 weeks (min: 0.3, max: 163.3). Despite 170 out of the 351 patients crossing-over from Dex to Len/Dex after the studies were un-blinded, the pooled analysis of OS demonstrated a statistically significant survival advantage in favour of Len/Dex (hazard/odds ratio: 0.75, 95% CI: [0.59, 0.95], p = 0.015).

The complete results for the pooled OS at unblinding are presented in Table 24.

Table 24: OS for pooled MM-009 and MM-010 data. (62)

		Pooled Study MM-009 and MM-010	
	Statistic	Len/Dex	Dex
Overall survival Died Censored	N n (%) n (%)	353	351
Overall Time to First Worsening (wk)	Median [95% CI] [b]		
	Mean SD Min, Max		
Hazard Ratio [95% CI] [c]			
Log-rank Test p-Value [d]			

Notes: This summary excludes any observations that occurred after 28Jun2005 for MM-009 and after 03Aug2005 for MM-010. The median in this table is based on Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring.
[a] For subjects who died during the follow-up phase and whose death dates are not available, the follow-up visit dates are used as the event date.
[b] 95% confidence intervals about the median survival time.
[c] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (Placebo/Dex:CC-5013/Dex)
[d] The p-value is based on the one-tailed unstratified log rank test of survival curve differences between the treatment groups.

Updated OS analysis: 2007

Data for OS was updated just prior to January 2007 Despite a high rate of patients crossing over to lenalidomide with or without Dex at progression or at the time of unblinding (47%), the OS was significantly improved in patients treated with Len/Dex compared with Dex alone (Table 25).

Table 25: Summary of overall survival intent-to-treat population (MM-009/MM-010 Pooled)

Statistics		Len/Dex	Dex
Overall Survival	N	353	351
Died	n (%)	[redacted]	[redacted]
Censored	n (%)		
Overall survival time since randomization (weeks)[a]	Median	149.7	133.3
	Mean	[redacted]	[redacted]
	StdDev		
	Min,Max		
Hazard Ratio [95% CI] [b]		[redacted]	
Log-rank Test p-Value [c]		0.015	

Notes: This summary excludes any observations that occurred after 28Jun2005 for MM-009 and after 03Aug2005 for MM-010. The median in this table is based on Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring.
[a] For subjects who died during the follow-up phase and whose death dates are not available, the follow-up visit dates are used as the event date.
[b] 95% confidence intervals about the median survival time.
[c] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (Len/Dex: Dex)
[d] The p-value is based on the one-tailed unstratified log rank test of survival curve differences between the treatment groups.

Sub-group analyses of pooled data

The pre-specified data for MM-009 and MM-010 were presented previously. The pooled pre-specified analyses are presented in Appendix 5 and the effect of prior therapy on OS is presented below. A number of post-hoc sub-group analyses were also undertaken on the pooled patient level data and these are also presented in Appendix 5. The purpose of these analyses were to explore the effect of additional prognostic variables in terms of efficacy and safety and to better understand the role of lenalidomide in the multiple myeloma treatment pathway. The results were not adjusted for multiplicity and in many cases the sample sizes were small. However, the results indicate that there is no evidence to suggest that the Len/Dex efficacy relative to Dex differs across the sub-groups including impaired renal function, IgA status, elderly patients, prior thalidomide or bortezomib treatment. The results suggest Len/Dex remains significantly more efficious compared with Dex across these subgroups. In particular, this data does not support any evidence of cross-resistance for patients previously treated with thalidomide, even in patients considered resistant to thalidomide. While the efficacy of Len/Dex was lower for patients previously treated with thalidomide, these patients were more heavily pre-treated with longer disease duration and the reduction in the efficacy of Dex was comparable to the reduction seen in Len/Dex across these groups.

The Cox proportional hazards model was used as an exploratory analysis to determine which demographic and prognostic variables are the strongest predictors of treatment outcome and to adjust the treatment comparisons for these variables. Only those variables that differ at the 0.10 level were included in the multivariate model. A forward selection stepwise procedure was used to identify the subset of

relevant factors. The results are presented in Appendix 5 and show that for these data Len/Dex treatment was the strongest predictor of TTP.

Overall survival with prior therapy

Comparative analysis of OS in the sub-groups of patients previously treated with one or at least two prior therapies was presented at the 49th annual meeting of the American Society of Haematology (64).

In this analysis, treatment with Len/Dex compared with Dex improved median OS both in patients who received only one prior therapy (39.1 versus 33.6 months, [redacted]) and in patients who received at least two prior therapies (33.3 versus 27.3 months, [redacted]). It should be noted that while the differences in OS between Len/Dex and Dex were not statistically significant at the 5% level in either of the number of prior therapies sub-group, there are a number of confounding factors, including statistical power, proportions of patients who died and Dex arm patients receiving treatment with lenalidomide, that should be considered and these are explained in detail below.

Firstly, the studies where not powered to show statistically significant differences in OS in these sub-groups. Therefore, these analyses are underpowered and would likely have demonstrated statistical significant with a larger sample size. Indeed, a p value of <0.10 should be considered both impressive given the sample size and indicative of a strong trend of survival advantage.

Secondly, since median OS was estimated by Kaplan-Meier methods, it is important to consider the proportion of patients who had died at the time of analysis. By definition, a true median OS is only reached when the middle (50th percentile) patient has died. Until such a time is reached when 50% are dead in each sub-group of each arm, it is possible for the estimated median OS to continue to increase. The fewer patients that had died in each arm of each sub-group the more likely that the true (50th percentile) median will increase. Therefore, it is important to note that fewer patients who received only one prior therapy and were treated with Len/dex compared with Dex had died at the time of this OS analysis ([redacted]). Indeed, the proportion dead in the Dex arm ([redacted]) is now close to the 50th percentile and it is unlikely to increase substantially, while the proportion dead in the Len/Dex arm ([redacted]) is some way off the 50th percentile and so the Len/dex OS is more likely to increase further than the Dex OS.

There is a similar pattern in the at least two prior therapies sub-groups, where fewer patients who received treatment with Len/dex compared with Dex had died at the time of this OS analysis ([redacted]). The true median had been reached in the Dex arm, but had not yet been reached in the Len/Dex arm.

Thirdly, and most importantly, 47% of patients from the Dex arm of studies MM-009 and MM-010 received treatment with lenalidomide at progression or at the time of unblinding, but importantly they remained assigned to the Dex arm for analysis. Hence the OS reported for the Dex arm includes a strong lenalidomide effect rather than the pure Dex outcome. In order to capture the correct survival with Dex in the economic model, a factor was added to the survival equation for Dex, calibrated in such a way that modeled Dex median OS matches the median OS predicted from the MRC Myeloma trials (Appendix 8).

Further analysis was performed at time of study unblinding in patients who received only one prior therapy in order to demonstrate both the impact of Dex patients receiving treatment with lenalidomide on comparative OS and the importance of the proportion of patients who had died at the time of analysis (62). At the time of study unblinding in patients who received only one prior therapy, 21 patients had died in the Len/Dex arm compared with 40 in the Dex arm and treatment with Len/Dex compared with Dex statistically significantly improved median OS (median not estimable versus 20.5 months, p=0.002)

Table 26: Summary of overall survival for patients with more than 1 prior therapy intent-to-treat population (MM-009/MM-010 Pooled)(62)

Statistic		One prior therapy		>2 prior therapies	
		Len/Dex	Dex	Len/Dex	Dex
Overall survival Died Censored	N n (%) n (%)	124	124	229	227
Overall survival time since randomization (weeks)[a]	Median [95% CI] [b]	169.1	145.4	144.0	118.0
	Mean SD Min, Max				
Hazard Ratio [95% CI] [c]					
Log-rank Test p-Value [d]					

Notes: The median in this table is based on Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring.
[a] For subjects who died during the follow-up phase and whose death dates are not available, the follow-up visit dates are used as the event date.
[b] 95% confidence intervals about the median survival time.
[c] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (Len/Dex: Dex)
[d] The p-value is based on the one-tailed unstratified log rank test of survival curve differences between the treatment groups.

Perspectives on treatment crossover and overall survival in MM-009 and MM-010

The estimated median OS of patients in the Dex arm has increased with extended follow up of the two trials – as is also the case with the Len/Dex arm. Two factors are likely to have influenced these changes in median OS with continued follow up.

Firstly, the data presented in Table 24 show that, at this duration of follow up (17.1 months for MM-009 and 16.5 months for MM-010), more than 70% of the study subjects remained alive – meaning that the true median OS has not been reached and the values for median OS in Table 30 are only estimated medians.

Secondly, 170 out of 351 patients in the Dex arms opted to receive additional lenalidomide when they developed disease progression prior to or at study

unblinding. These patients remained assigned to the Dex arm and were analysed as such, despite subsequently receiving lenalidomide. It is highly likely the overall survival is prolonged in this group of patients due to the addition of lenalidomide. Indeed, historical retrospective analyses indicate that the median OS of multiple myeloma patients from first relapse is 14–17 months (2;3).

It should be noted that the data for TTP are relatively unaffected by treatment crossover in the Dex group. This is because most patients (>75%) had developed disease progression at study unblinding, and therefore the true median TTP has been reached and has consequently not changed over time – remaining approximately twice as long in the Len/Dex as in the Dex group.

5.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 5.2.3 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis where appropriate.
- Tabulate and/or graphically display the individual and combined results.

We conducted a meta-analysis of the time-to-progression (TTP) and overall survival (OS) outcome from the two pivotal trials MM-009 and MM-010 comparing Dex to Len/Dex based on the NEJM publications, Dimopoulos et al. (5) and Weber et al. (6)

Methods

Treatment success results, as measured by OS and TTP, are presented for the two studies in Table 27 and Table 28. Meta-analytic techniques were used to calculate the difference in OS and TTP between the two treatment strategies.

Table 27: Overall survival for meta-analysis

Study	Treatment	N	Treatment Successes	Deaths
MM-009	Dex	176	113	63
	Len/Dex	177	128	49
MM-010	Dex	175	115	60
	Len/Dex	176	129	47

Source: Dimopoulos et al. (5) and Weber et al. (6)

Table 28: Median TTP for meta-analysis

Study	Treatment	N	Median TTP (weeks)	95% CI
MM-009	Dex	176	20.1	16.7-23.1
	Len/Dex	177	48.1	36.9-61.4
MM-010	Dex	175	20.1	18.1-20.7
	Len/Dex	176	48.7	40.9-72.1

Source: Dimopoulos et al. (5) and Weber et al. (6) and for the 95% CIs Celgene data on file (62)

NOTE: the months in the publications were converted to weeks using the following formula: months=weeks*7/30.25

For the classical meta-analysis, both fixed- and random-effects models (FEM, REM) were calculated. We used the command meta available in the software STATA to calculate fixed and random effects models. The fixed effect model is based on the inverse variance weighted method and the random effects model is based on the DerSimonian and Laird method. A technical description is available from the Stata Statistical Bulletin (STB 38).

All calculations were performed using STATA® software version 9.0.

Results

Pooled overall survival results from the two trials are presented in Table 29.

Table 29: Overall survival results from meta-analysis

	Mean [95% CI]
Odds Ratio Overall Survival	1.44 [1.34, 1.56]

The odds ratio for overall survival for treatment with the combination of Len/Dex relative to Dex monotherapy was 1.44 [95% CI 1.34 - 1.56] in favor of the Len/Dex

intervention. We used Cochrane's Q statistic to investigate possible statistical heterogeneity. There was no evidence of heterogeneity between the two trials (p=0.824).

Pooled overall TTP results from the two trials are presented in Table 30.

Table 30: Difference in median TTP (weeks) from meta-analysis

	Mean [95% CI]
Median difference in TTP (weeks)	28.24 [18.39 - 38.08]

The median difference for TTP for treatment with the combination of Len/Dex compared to DEX monotherapy was 28.24 weeks 95% CI [18.39 – 38.08] in favor of the Len/Dex intervention. We used Cochrane's Q statistic to investigate possible statistical heterogeneity. There was no evidence of heterogeneity between the two trials (p=0.953).

Conclusions

MM-009 and MM-010 were identically designed trials and it was considered statistically appropriate to pool the patient level data and assess the primary and secondary outcomes in this larger patient population. However for comparison and as requested by NICE, a meta-analysis was also performed on the published data.

The meta-analysis results were significantly in favor of Len/Dex compared to Dex both in terms of OS and TTP. In addition, the results are similar to the results of the individual studies, supporting the use of the pooled individual data, which offers more information than the medians and the OS reported in the publications at one time-point.

5.6 Indirect/mixed treatment comparisons

In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest, consideration should be given to using indirect/mixed treatment comparisons. This analysis indirectly compares the proposed technology with the main comparator by comparing one set of RCTs in which participants were randomised to the intervention/common reference with another set of RCTs in which participants were randomised to the main comparator/common reference. The common reference is often placebo, but may be an alternative technology.

Before comparing the proposed technology with the main comparator, the comparability of the two sets of RCTs must be established. If the RCTs have not been described in the previous sections the methodology and results from the RCTs included in the analysis should be summarised using the format described in sections 5.3 and 5.4 Highlight any potential sources of heterogeneity between the RCTs included in the analysis.

Give a full description of the methodology used and provide a justification for the approach.

In the systematic review, no head-to-head trials comparing lenalidomide in combination with high-dose Dex treatment with bortezomib monotherapy were identified. Therefore we undertook an indirect comparison to examine the relative effects on these two treatments in multiple myeloma patients who have received one prior therapy only (given the NICE recommendation for bortezomib for one prior therapy only (21)).

High-dose Dex was chosen as the common comparator and a systematic review was performed to identify relevant RCTs. The search strategies and databases were identical to the Len/Dex clinical searches (see Appendix 2) except the drug terms were substituted for those relating to bortezomib (bortezomib or VELCADE or ps341 OR 'ps 341' or ps-341 or 'proteosome inhibitor' - including MeSH and Emtree) and the search was limited to articles published between 2006 and 2008. This time frame limit was based on the fact a comprehensive systematic review was performed by the manufacturer of bortezomib in February 2006 as part of their NICE STA submission, and only the APEX trial was identified as meeting the inclusion criteria. In their critique and validation of the search strategy, the ERG was satisfied that no other trials relevant to the decision problem were available at that time. Therefore we decided to search for any newly published RCTs or updated analyses of APEX since this date.

Using this systematic review search strategy, we were able to identify an updated analysis of the APEX trial. No new RCTs relevant to the indirect comparison had been published at the time the search was conducted.

The same data extraction strategy detailed in Appendix 2 was applied to the APEX primary publication, updated analysis and any additional data presented in the manufacturer submission to the National Institute for Health and Clinical Evidence (NICE)(21). MM-009, MM010 and APEX were then compared to assess the validity of undertaking an indirect comparison.

APEX study design

The APEX study was an international, randomised, open-label trial, designed to evaluate the efficacy and safety of bortezomib compared with Dex in patients with multiple myeloma receiving 1-3 lines of prior therapy. The study was conducted in the United States, Europe, Canada, and Israel.

APEX was an open-label trial because a blinded study design was not feasible, appropriate or ethical since bortezomib is administered as an IV bolus, while Dex is an oral preparation. To give placebo IV bolus injections was not deemed to be appropriate. Patients were randomly assigned to study treatment in a 1:1 ratio. Treatment arms were balanced with respect to duration of therapy and the frequency of tumour assessments. Randomisation was stratified by (1) number of lines or prior therapy (1 vs. >1), (2) treatment relapse (time to progression after last therapy: ≤ 6 months vs. > 6 months), and (3) baseline serum β2-microglobulin concentration (≤2.5 mg/dL vs. >2.5 mg/dL). This was in contrast with the stratification variables used in studies MM-009 and MM-010 where stratification included the level of serum β2-microglobulin, previous stem cell transplantation, and the number of previous antimyeloma therapies given. Primary study measures (TTP, OS, and disease

response) were assessed at two time points: (1) median follow-up of 8.3 months and (2) 22 months.

APEX interventions

Patients were randomised to receive either:

1. bortezomib 1.3 mg/m2 on days 1,4,8 and 11 of cycles 1 through 8 (21-day cycles) and on days 1,8,15, and 22 of cycles 9 to 11 (35-day cycles), for a maximum treatment period of 273 days.

2. Dexamethasone 40mg on days 1 to 4, 9 to 12, and 17 to 20 of cycles 1 through 4 (35-day cycles), and on days 1 to 4 of cycles 5 through 9 (28-day cycles), for a maximum treatment period of 280 days.

APEX inclusion criteria

The population under study in APEX was similar to studies MM-009 and MM-010 in that patients were required to have progressive multiple myeloma and measurable disease. Specifically, APEX included multiple myeloma patients with a relapse after one to three other therapies. Studies MM-009 and MM-010 were slightly less specific and included patients with progressive multiple myeloma after at least 2 cycles of antimyeloma therapy or to have relapsed with progressive disease after treatment.

Inclusion criteria were as follows:

- At least 18 years of age (similar to MM-009, MM-010),

- Voluntary written informed consent (similar to MM-009, MM-010),

- Women were required to use an acceptable method of contraception for the study duration. Women were also required to be post menopausal, surgically sterilised or to have had a negative pregnancy test (MM-009, MM-010: Women were required to have a negative pregnancy test and to use contraceptive for the duration of the study),

- Karnofsky performance status ≥60% (MM-009, MM-010: required ECOG PS≤2),

- Life-expectancy > 3 months (MM-009, MM-010: no life-expectancy measure),

- Adequate liver function as defined by serum aspartate transaminase or alanine transaminase ≤ 2.5 x upper limit of normal and total serum bilirubin ≤ 1.5 x upper limit of normal (MM-009, MM-010: required serum aspirate transaminiase ≤ 3 x and serum bilirubin ≤ 2 x the upper limit of the normal range),

- Adequate renal function as defined by measured creatinine clearance ≥ 20 mL/min (MM-009, MM-010: required a serum creatinine level < 2.5 mg/dL),

- Platelet count ≥ 50 x 109/L, Hb ≥ 7.5 g/dL and an absolute neutrophil count ≥ 0.75 x 109/L without transfusion or colony stimulating factor support (MM-009,

MM-010: required platelet count ≥ 75,000/mm3 among patients with <50% bone marrow plasma cells and platelet count ≥ 30,000/mm3 among patients with 50% or more bone marrow plasma cells; absolute neutrophil count ≥ 1,000/mm3).

APEX primary efficacy outcome

The primary efficacy variable in the APEX trial was time to disease progression (TTP). Patient responses including disease progression were based on the rigorous European Group for Blood and Marrow (EBMT) criteria. The table below shows how progressive disease (PD) was determined in APEX.

Table 31: Summary of criteria used to determine disease progression

PD (1 of the following)	APEX trial
M Protein	>25% increase, or 5 g/L
Urinary light chain	>25% increase or ≥200 mg/24h
Plasma Cells (PC), marrow	>25% increase in PCs in the bone marrow
Plasmacytoma	New or increase in size
Skeletal disease	New or increase in size
Calcium	Increase

Time to progression was defined as the time from randomization until the date of the first occurrence of progressive disease. Patients were evaluated for disease progression every 3 weeks during treatment.

APEX Secondary efficacy outcome

As in trials MM-009 and MM-010, APEX also measured the rate of response and overall survival as secondary efficacy outcomes.

Response rate

Responses were based on the European Group for Blood and Marrow Transplant (EBMT) criteria. The types of responses and their clinical definition may be compared with trials MM-009 and MM-010 (see section 5.3.6 Assessment of response).

Overall survival

Survival was assessed from the duration in months from randomisation to the date of death. Patients who were lost to follow-up were censored at the date they were last know to be alive. This was identical to how overall survival was assessed in studies MM-009 and MM-010. However, because of the high crossover rate, 62% of Dex

patients received bortezemib in APEX (13) it is difficult to determine the precise difference in terms of survival advantage for bortezemib compared to Dex.

Primary objective

The primary efficacy objective was to determine whether bortezomib provided benefit to patients with relapsed multiple myeloma in comparison to treatment with HDD, as assessed by a significant prolonging of the time to disease progression (TTP).

Secondary objectives

Secondary efficacy objectives were as follows:

Determine whether treatment with bortezomib prolongs overall survival (OS) time and 1 year survival compared with treatment with HDD.

Assess the superiority of bortezomib relative to HDD, as determined by the rates of CR and PR to treatment.

ITT analyses

The intention-to-treat (ITT) population included all subjects randomized to treatment. All primary analyses of TTP and overall survival were assessed according to the treatment that patients were randomised to. Patients who had inadequate data post-baseline to assess efficacy according to the criteria for response were considered treatment failures for the analysis of the rates of response. This was in contrast with studies MM-009 and MM-010 in which the assessment of the rate of response was conducted using the ITT population.

Formal statistical hypothesis tests of the superiority of bortezomib relative to Dex were conducted at the 2-sided, 0.05 level of significance.

Procedures for handling missing data

All available efficacy and safety data were included in all analyses. No imputation of values for missing information was performed for primary and secondary outcomes measures.

Censoring

Censored data was handled similarly in the APEX trial in comparison to both MM-009 and MM-010 trials:

- **TTP**: Patients who started alternate therapy, were lost to follow-up or died before documentation of PD were censored at the last documented visit date at which the study assessment was performed

- **OS**: Patients who were lost to follow-up or were censored at the date that they were last known to be alive.

Methodology and results of the indirect comparison

The methods to obtain data for TTP and trial response rates are described in Appendix 6. For the indirect comparison Bayesian mixed treatment comparison has been employed using the fixed effects assumption.

For the primary efficacy outcome, median time to disease progression (TTP) Len/Dex has a 34 week advantage over bortezomib, with confidence intervals from 95%CI [19.92 – 48.53] to 95%CI [25.81 – 42.53] depending on the assumptions. For the secondary efficacy outcomes, there is no significant difference between Len/Dex and bortezomib for complete response, partial response, and progressive disease using both fixed effects and random effects models. For stable disease, the odds ratio was significant in favour of Len/Dex using the fixed effects model, however not significant using the random effects model.

The validity of these results however is questionable on several grounds.

First, the number of data points is extremely scant (2 trials, 4 data points). There is likely to some instability in the Winbugs model (Windbugs code is in Appendix 6) because of the low number of data points available.

Second, the “placebo” arms in both trials were actually active treatments that included Dex. There were significant responses in the Dex arms in both trials. The indirect comparison accounts for the response in the Dex arms and readjusts the responses in the Lenalidomide/Dex and bortezomib based on this. Given the significance of the role of the active comparator arm, it is essential that the response rates in both trials in both arms be as comparable as possible. A number of differences may in fact be causing significant differences in how response is defined in both trials.

Lastly, the MTC could not be performed on the OS outcome, because both the bortezomib and the Len/Dex studies allowed cross-over at the point of progression, therefore the the validity of the common control arm (Dex) is lost. Because of the uncertainty surrounding the validity of the MTC results, we have not employed the results of the analysis in the economic model.

Len/Dex has two major practical advantages over bortezomib; treatment-induced peripheral neuropathy and the mode of administration (oral versus intravenous). Although peripheral neuropathy has a low baseline incidence in myeloma patients, only a few cases of Grade 3–4 peripheral neuropathy are reported with Len/Dex – e.g. 1.7% in MM-009 (versus 1.1% with Dex) and 0.6% in MM010 (versus 0% with Dex), compared with 8% Grade 3–4 peripheral neuropathy with bortezomib in the APEX pivotal trial (versus <1% with dexamethasone) (5;6;12).

No episodes of Grade 2 peripheral neuropathy were observed in MM-010 trial, while 24% of the patients in the bortezomib arm in the APEX trial suffered from Grade 2 peripheral neuropathy and only 51% of these adverse event resolved or improved (12).(60)

It is also worth noting that, the efficacy results of combination Len/Dex treatment in MM-009 and MM-010 compare favourably with the bortezomib results observed in the APEX trial (56). All three studies enrolled a similar patient population and all three

studies utilised the EBMT response criteria. The response rate in bortezomib-treated subjects was 43%, the median TTP was 6.2 months, and the median survival was 29.8 months (56). In contrast, the response rates were 61% and 60.2%, and the median TTPs were 11.1 and 11.3 months, in the Len/Dex treatment groups in MM-009 and MM-010, respectively (5). In addition, a recent combined analysis showed that the current estimated median overall survival from MM-009 and MM-010 was 35 months (19), compared with a final overall survival of 29.8 months for bortezomib monotherapy in the published APEX pivotal trial (56). The median survival of patients in the MM-009 & 010 trials is expected to prolong further, since at the time of analysis [redacted] of patients remained alive in the Len/Dex arm and the true median has yet to be reached (i.e. < 50% have died).

5.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

Safety from MM-009 and MM-010

The discussion of comparative safety included here is taken from the scientific discussion produced as part of the European Public Assessment Report (EPAR) for lenalidomide, the SmPC and the primary publications (5;6;23;65).

The pooled safety database as of 31 December 2005 includes 703 patients (353 in the Len/Dex group and 350 in the Dex group) and shows the patient exposure as indicated below in Table 32. Median duration of treatment in the Len/Dex arm was 44.0 weeks, with 46.2% of patients completing at least 52 weeks of therapy.

Table 32: Pooled duration of treatment in studies MM-009 and MM-010

	Len/Dex N=353		Dex N=350	
Treatment Phase Duration (Weeks)				
	n	%	n	%
<1 week	1	0.3	2	0.6
1 to < 4 weeks	14	4.0	14	4.0
4 to < 8 weeks	14	4.0	38	10.9
8 to < 12 weeks	27	7.6	42	12.0
12 to < 16 weeks	15	4.2	28	8.0
16 to < 20 weeks	18	5.1	31	8.9
20 to < 24 weeks	16	4.5	23	6.6
24 to < 28 weeks	19	5.4	38	10.9
28 to < 32 weeks	19	5.4	27	7.7
32 to < 36 weeks	10	2.8	12	3.4
36 to < 40 weeks	11	3.1	15	4.3
40 to < 44 weeks	12	3.4	13	3.7
44 to < 48 weeks	8	2.3	8	2.3
48 to < 52 weeks	6	1.7	4	1.1
≥52 weeks	163	46.2	55	15.7
Duration of Exposure (Weeks)				
n	353		350	
Mean	53.9		29.7	
SD	38.76		26.41	
Median	44.0		23.1	
Min, Max	0.1, 161.7		0.3, 124.0	

Table 33 presents the Grade 3–4 adverse events that were reported by the patients or observed by the investigators and recorded in the case report form for studies MM-009 and MM-010.

The primary reason for the discontinuation of treatment in the two groups was disease progression. In MM-009, sixty-eight patients (38.4%) in the Len/Dex group and 126 patients (71.6%) in the Dex group discontinued the study drug because of disease progression (6), in MM-010, disease progression was also the primary reason for discontinuation (5).

Anaemia, neutropenia, thrombocytopenia, constipation, pneumonia, decreased weight, hypocalcaemia, hypocalcaemia, tremor, rash, and deep vein thrombosis (DVT) were reported significantly more frequently in the Len/dex group than in the Dex group. Neutropenia and thrombocytopenia were the primary reasons for dose reductions in the Len/Dex group (5;6). The frequency of discontinuation was low – for Study MM-009, neutropenia (2.4%; 4/170) and thrombocytopenia (0.6%; 1/170) and for Study MM-010, neutropenia or thrombocytopenia (0.6% and 0.6%, respectively).

Table 33: Grade 3–4 adverse events reported in the safety population of studies MM-009 and MM-010

Event, n (%)	MM-009				MM-010			
	Len/Dex		Dex		Len/Dex		Dex	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Haematological								
Neutropenia	62 (35.0)	11 (6.3)	6 (3.4)	2 (1.1)	44 (25.0)	8 (4.5)	4 (2.3)	0
Anaemia	19 (35.0)	4 (2.3)	6 (3.4)	3 (1.7)	14 (8.0)	1 (0.6)	12 (6.9)	0
Thrombocytopenia	24 (13.6)	2 (1.1)	12 (6.9)	0	17 (9.7)	3 (1.7)	7 (4.0)	3 (1.7)
Febrile neutropenia	5 (2.8)	1 (0.6)	0	0	5 (2.8)	1 (0.6)	0	0
Gastrointestinal								
Diarrhoea	6 (3.4)	0	0	0	5 (2.8)	0	4 (2.3)	0
Constipation	5 (2.8)	0	0	0	3 (1.7)	0	2 (1.1)	0
Nausea	5 (2.8)	0	2 (1.1)	0	2 (1.1)	0	0	0
Dyspepsia	1 (0.6)	0	1 (0.6)	0	–	–	–	–
General								
Fatigue	11 (6.2)	0	11 (6.3)	0	11 (6.2)	1 (0.6)	6 (3.4)	0
Peripheral oedema	4 (2.3)	0	1 (0.6)	0	2 (1.1)	0	3 (1.7)	0
Pyrexia	4 (2.3)	0	6 (3.4)	0	1 (0.6)	0	6 (3.4)	0
Asthenia	6 (3.4)	0	6 (3.4	0	11 (6.2)	0	10 (5.7)	0
Infection or infestation								
Any infection/other infection†	33 (18.6)	5 (2.8)	16 (9.1)	5 (2.9)	15 (8.5)	2 (1.1)	9 (5.1)	2 (1.1)
Upper respiratory infection†	2 (1.1)	0	2 (1.1)	0	3 (1.7)	0	0	0
Pneumonia	19 (10.7)	3 (1.7)	10 (5.7)	3 (1.7)	–	–	–	–
Metabolism or nutrition								
Hyperglycaemia	15 (8.5)	4 (2.3)	10 (5.7)	5 (2.0)	–	–	–	–
Hypocalcaemia	10 (5.6)	1 (0.6)	2 (1.1)	0	–	–	–	–
Anorexia	1 (0.6)	0	3 (1.7)	0	–	–	–	–
Weight loss	–	–	–	–	3 (1.7)	0	1 (0.6)	0
Musculoskeletal or connective tissue								
Muscle cramp	2 (1.1)	0	1 (0.6)	0	1 (0.6)	0	0	0
Back pain	2 (1.1)	0	3 (1.7)	0	4 (2.3)	0	3 (1.7)	0
Arthralgia	1 (0.6)	0	4 (2.3)	0	1 (0.6)	0	3 (1.7)	0
Muscle weakness	7 (4.0)	0	3 (1.7)	(0)	13 (7.4)	0	8 (4.6)	0
Bone pain	–	–	–	–	5 (2.8)	0	3 (1.7)	0
Nervous system								
Headache	2 (1.1)	0	0	0	1 (0.6)	0	1 (0.6)	0
Dizziness	6 (3.4)	0	2 (1.1)	0	1 (0.6)	0	1 (0.6)	0
Tremour	0	0	2 (1.1)	0	2 (1.1)	0	2 (1.1)	0
Parasthesia	–	–	–	–	1 (0.6)	0	0	0
Peripheral neuropathy	3 (1.7)	0	2 (1.1)	0	–	–	–	–
Psychiatric disorder								
Insomnia	2 (1.1)	0	0	0	2 (1.1)	0	1 (0.6)	0
Anxiety	4 (2.3)	0	0	0	–	–	–	–

Event, n (%)	MM-009				MM-010			
	Len/Dex		Dex		Len/Dex		Dex	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Respiratory, thoracic or mediastinal								
Cough	–	–	–	–	2 (1.1)	0	1 (0.6)	0
Nasopharyngitis	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Dyspnoea	2 (1.1)	3 (1.7)	7 (4.0)	0	4 (2.3)	1 (0.6)	2 (1.1)	1 (0.6)
Vascular								
Deep-vein thrombosis	21 (11.9)	0	6 (3.4)	0	6 (3.4)	1 (0.6)	5 (2.9)	1 (0.6)
Pulmonary embolism	1 (0.6)	5 (2.8)	0	1 (0.6)	2 (1.1)	6 (3.4)	1 (0.6)	1 (0.6)
Venous thromboembolism‡	21 (11.9)	5 (2.8)	5	1 (0.6)	13 (7.4)	7 (4.0)	6 (3.4)	2 (1.1)

* Listed are data that were available on December 31, 2005.

† This condition was also described in the following terms: infections not otherwise specified, pneumonia, upper respiratory tract infection, upper respiratory viral infection, sepsis, bacterial infection, urinary tract infection, pharyngitis, nasopharyngitis, febrile neutropenia, oral candidiasis, oral fungal infection, primary atypical pneumonia, fungal sinusitis, herpes simplex, herpes zoster, herpes encephalitis, herpes viral infection, cytomegalovirus pneumonia, and viral infection. Data for MM-010 are for all infections other than pneumonia or upper respiratory tract.

‡ This condition was also described in the following terms: deep-vein thrombosis, pulmonary embolism, pulmonary infarction, thrombosis, phlebothrombosis, thrombophlebitis, superficial thrombophlebitis, venous thrombosis, thromboembolism, splenic-vein

A multivariate regression analysis of pooled MM-009 and MM-010 patient level data identified Len/Dex and erythropoietin (Epo) use as independent predictors of venous thromboembolism VTE (46). Concomitant erythropoietin use was found to be associated with a significantly increased risk for thrombosis in the North American trial (MM-009), but not in the European trial (MM-010). Erythropoietin was more commonly utilised in MM-009 than in MM-010 (160 [45%] subjects versus 72 [21%] subjects, respectively) and this might explain the lack of association. In clinical practice in England and Wales (where concomitant erythropoietin use is minimal) this may mean that the risks of thrombosis are lower than those seen in the pooled safety analysis of MM-009 and MM-010, but caution should be exercised when treating any patient concomitantly with erythropoietin and Len/Dex. The European SmPC provides recommendations regarding minimising risk of thrombosis, and use of prophylactic anti-thrombotic therapy (65).

In common with many chemotherapeutic agents used in haematological malignancies and with which specialist haematologists and oncologists are familiar, neutropenia was reversed by interruption of treatment, a reduction in dose or use of granulocyte-colony stimulating factor (G-CSF) (5;6). The frequency of complications of neutropenia such as febrile neutropenia were low at 2.8% illustrating that it can be effectively managed with monitoring and appropriate intervention, including dose reduction and dose interruption. Additional analyses undertaken on data from MM-009 and MM-010 suggest that the incidence of AEs decays over time (see **Appendix 9**).

As of 31 December 2005, 107 (30.3%) deaths had been reported among the 353 Len/Dex-treated patients and 142 (40.5%) deaths had been reported among the 351 Dex-treated patients. The primary cause of death in both treatment groups was disease progression (70/107 in the Len/Dex group and 101/142 in the Dex group).

Of the 107 deaths in the Len/Dex group, 24 were suspected by the investigators to be related to the study medication. Of the 142 deaths in the Dex group, 24 were suspected by the investigator to be related to the study medication.

Owing to the structural similarities between lenalidomide and thalidomide, a risk management programme has been put place to reduce the risk of foetal exposure to lenalidomide. This is a simple process that requires the physician and pharmacists to sign a prescription authorisation form to follow the recommended monitoring procedure (RMP). Given the average age at multiple myeloma diagnosis for female patients, in practice, very few pregnancy tests are required (8).

Expanded Access Program (EAP)

In 2005, Celgene established an expanded access program to make Len/Dex available to subjects with relapsed or refractory multiple myeloma while the treatment was awaiting approval (53). This was in response to a request by the FDA in association with myeloma patient advocacy groups and a main objective was to collect additional safety data. Subjects in the US and Canada with relapsed or refractory multiple myeloma that received at least 1 prior therapy were eligible for the study. Participants were given 25 mg Len/Dex in 4-week cycles until disease progression was documented or the study drug was discontinued. Preliminary results of the EAP were presented at ASH 2006 at which point 746 subjects had been enrolled with a median age of 63 years, 60% were male, 66.5% had Stage III disease and median time on study was 7.1 weeks (0.1-24.4). The results were similar to

those seen in trials MM-009 and MM-010. At least one Grade 3 or 4 adverse event was reported in 261 (35%) of the 746 subjects. The most commonly reported Grade 3-4 events are presented in Table 34.

Table 34: Frequency of adverse event in North American expanded access program for Len/Dex (53)

Adverse event	Poster data
Neutropenia	14.9%
Thrombocytopenia	11.1%
Fatigue	6.4%
Anemia	6.2%
Pneumonia	5.4%
Hyperglycaemia	3.6%

Relevant toxicities which were reported in a low incidence were febrile neutropenia 0.9% and neuropathy 2.4% Patients recruited into the Canadian EAP who had been treated with Len/Dex with or without corticosteroids were evaluated to assess the effect of abnormal serum creatinine levels on outcomes (52). A significantly higher number of patients with abnormal serum creatinine levels experienced grade 3-4 thrombocytopenia compared to those with normal levels and required at least one platelet transfusion (52% vs. 17%; p=0.003). The preliminary efficacy results are summarised in Table 35 and appear to be similar between the two groups.

Table 35: Preliminary efficacy results from the North American EAP

Serum creatinine	N	nCR/PR	PFS	95% CI	OS	95% CI
Elevated	23	61%	30%	11-52%	72%	46-86%
Normal	46	54%	50%	31-67%	76%	55-88%

These results suggest that it is safe to administer Len/Dex with or without corticosteroid to patients with elevated serum creatinine, however, caution is required to monitor for reductions in platelet counts in patients with renal insufficiency. The preliminary efficacy results appear to be similar between the two groups.

Of relevance to renal dosing, a single arm study of lenalidomide in 30 subjects with renal impairment (due to non/malignant conditions) demonstrated increasing serum lenalidomide concentrations with advancing renal insufficiency. The authors recommend starting dose reductions in patients with creatinine clearance <50ml/min (66). Reductions in starting dose of lenalidomide in renal patients are recommended in the lenalidomide SmPC.

Although the EAP was primarily undertaken to assess safety, a small sub-set of patients were examined (n=36) in 2006 to assess any variation in Len/Dex efficacy in patients who had a deletion of chromosome 13 (del13) and t(4;14). In multiple myeloma, these deletions predict poor response and shortened survival. The overall

response RR (CR+PR) to Len/Dex was 90% for the no del13 group and 75% in the del13 group (P=NS). The RR (CR+PR) for t(4;14) and non t(4;14) groups were also similar (71.5% and 86% respectively). Event free survival was not significantly different for del13 and t(4;14) compared to patients without the deletions (p=0.61 and p=0.66 respectively). This study had limited power to detect significant differences and further research is needed to confirm the findings that Len/Dex may overcome the poor prognosis conferred by these deletions.

5.8 Non-RCT evidence

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The level of detail provided should be the same as for RCTs and where possible more than one independent source of data should be examined to explore the validity of any conclusions. Inferences about relative treatment effects drawn from observational evidence will necessarily be more circumspect from those from RCTs.

5.8.1 Summary of methodology of relevant non-RCTs

5.8.2 Critical appraisal of relevant non-RCTs

5.8.3 Results of the relevant non- RCTs

5.9 Interpretation of clinical evidence

5.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

With a prevalence of between 1 per 50,000 and 5 per 10,000, multiple myeloma is a rare form of cancer that is almost uniformly fatal. Overall survival from diagnosis typically ranges from 3–5 years, and overall survival following relapse of first line treatment is estimated to be between 14 and 17 months (2;3).

Lenalidomide has been granted orphan drug status for the treatment of multiple myeloma in the US, Europe, Australia and Switzerland. Clinical efficacy data from two large Phase III RCTs supports the use of Len/Dex combination for the treatment of patients who had progressive disease following one prior therapy. The evidence is based on results in 692 patients – representing a significant body of evidence, particularly given the orphan status of lenalidomide in the US and Europe. The design of the comparator arm and selection of outcome measures for MM-009 and MM-010 were robust and appropriate for the hypothesis under investigation, given the regulatory landscape and availability of approved comparators at the time the studies were initiated. Neither bortezomib nor thalidomide was approved regulatory

standards of care when MM-009 and MM-010 were initiated. Moreover, while thalidomide has recently been granted marketing authorisation for the first-line treatment of untreated multiple myeloma, it is not licensed for use in previously treated multiple myeloma. Furthermore, a marketing authorization application for thalidomide in relapsing or refractory multiple myeloma was withdrawn [redacted]

Significant improvements for patients treated with Len/Dex compared with Dex were seen for primary and secondary outcomes. In MM-009 the overall response rate was almost three time higher for Len/Dex-treated patients (61.0% vs. 19.9%, P<0.001), and median TTP had more than doubled (11.1 months vs. 4.7 months, P<0.001). Similar results were seen in MM-010 for overall response (60.2% vs. 24%, P<0.001)) and for TTP (11.3 months vs. 4.7 months, P<0.001). In studies MM-009 and MM-010, the response to therapy was assessed using the myeloma response determination criteria developed by EBMT (58;59). These criteria provide an international standard for the assessment of treatment response in multiple myeloma. An important feature of these criteria is the use of variables in addition to M-protein levels to define clinical response. Consequently, the measures used to assess the response to Len/Dex are directly applicable to clinical practice and provide a reliable means of assessing the response to therapy among patients. For the same reasons, the duration of remission observed in MM-009 and MM-010 – as measured by median TTP – is transferable to routine practice.

At the time of MM-009 trial un-blinding, median OS was significantly extended by approximately 9 months in patients treated with Len/Dex compared with patients treated with Dex (29.6 months vs. 20.2 months, P <.001) (5;6). Although median overall survival was not yet estimable for patients treated with Len/Dex in the MM-010 trial, a similar significant improvement was observed (5). Despite the extensive crossover from Dex to lenalidomide treatment that occurred following un-blinding (47%), a pooled analysis demonstrated that OS remained significantly longer for patient's originally assigned Len/Dex treatment following median follow-up of 31.3 months.

Len/Dex has a manageable tolerability profile; the most common adverse events ascribed to lenalidomide treatment are haematological in nature – principally neutropenia and thrombocytopenia. Adverse events of this nature are familiar to, and well managed by, haemato-oncologists – serious complications arising from myelosuppression were uncommon in clinical trials.

Len/Dex provides superior myeloma control when compared with Dex across all important sub-groups including age, gender, number and type of prior therapies, renal insufficiency, ECOG performance status, suggesting that the data derived from the two trials are both robust and likely to be reproducible outside of the clinical trial setting. Of note, a substantial proportion of the overall patient population had received at least two prior therapies – likewise, a substantial proportion had been exposed to thalidomide and/or had received prior stem-cell transplantation.

As the MM-009 and MM-010 trials progressed, bortezomib became more widely available, both through a clinical trial setting and commercially. This led to a post-hoc analysis of patients previously exposed to bortezomib. Data from MM-009 show that

the superiority of Len/Dex over Dex was maintained in this group of patients – an important finding, given the recent NICE guidance on bortezomib(21).

5.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

The MM-010 clinical study included 41 sites across Europe, and therefore, the results achieved in the broad European population included should be reflective of those to be expected in the population of multiple myeloma patients in England and Wales. There is no reason to believe that the efficacy from these two trials would not be replicated in UK multiple myeloma patients who have progressed following at least one prior therapy. The strict inclusion and exclusion criteria meant that the range of patients were slightly younger and of higher performance status than might be seen in clinical practice. To examine these particular aspects a number of sub-group analyses were undertaken. They demonstrated that Len/Dex remained superior in efficacy to Dex regardless of age, performance status and all other variables investigated.

The dose used in the trials is the same as that detailed in the Summary of Product Characteristics (65). Patients received a starting dose of 25mg of daily oral lenalidomide or placebo on days 1–21 of each 28-day cycle. All patients also received 40mg of daily oral Dex on days 1–4, 9–12, and 17–20. After the fourth cycle, 40mg of Dex was administered only on days 1–4. Treatment was continued until the occurrence of disease progression or unacceptable toxic effects.

Recommended treatment duration for lenalidomide in the MM-009 and MM-010 trials was until progression, or unacceptable toxic events (5;6). The efficacy demonstrated in the MM-009 and MM-010 trial patients included those who experienced treatment interruptions and dosage reductions.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3.

A systematic review was conducted to identify published economic studies that assessed the cost-effectiveness of Len/Dex in the treatment of multiple myeloma

patients. The databases searched together with dates and initial results are summarised below.

Database	Service provider	Date of search	Initial hits
Embase	Embase.com	17/03/2008	54
Medline including (R) In-Process and Old Medline	SilverPlatter WebSPIRS®	17/03/2008	84
Centre for Reviews and Dissemination (HTA and NHS EED)	CRD website (http://www.york.ac.uk/inst/crd/)	18/03/2008	1
Company literature	Not applicable	13/05/08	2
ISPOR	ISPOR website (http://www.ispor.org/)	18/03/2008	34

A complete search strategy is provided in Appendix 3, section 9.3.

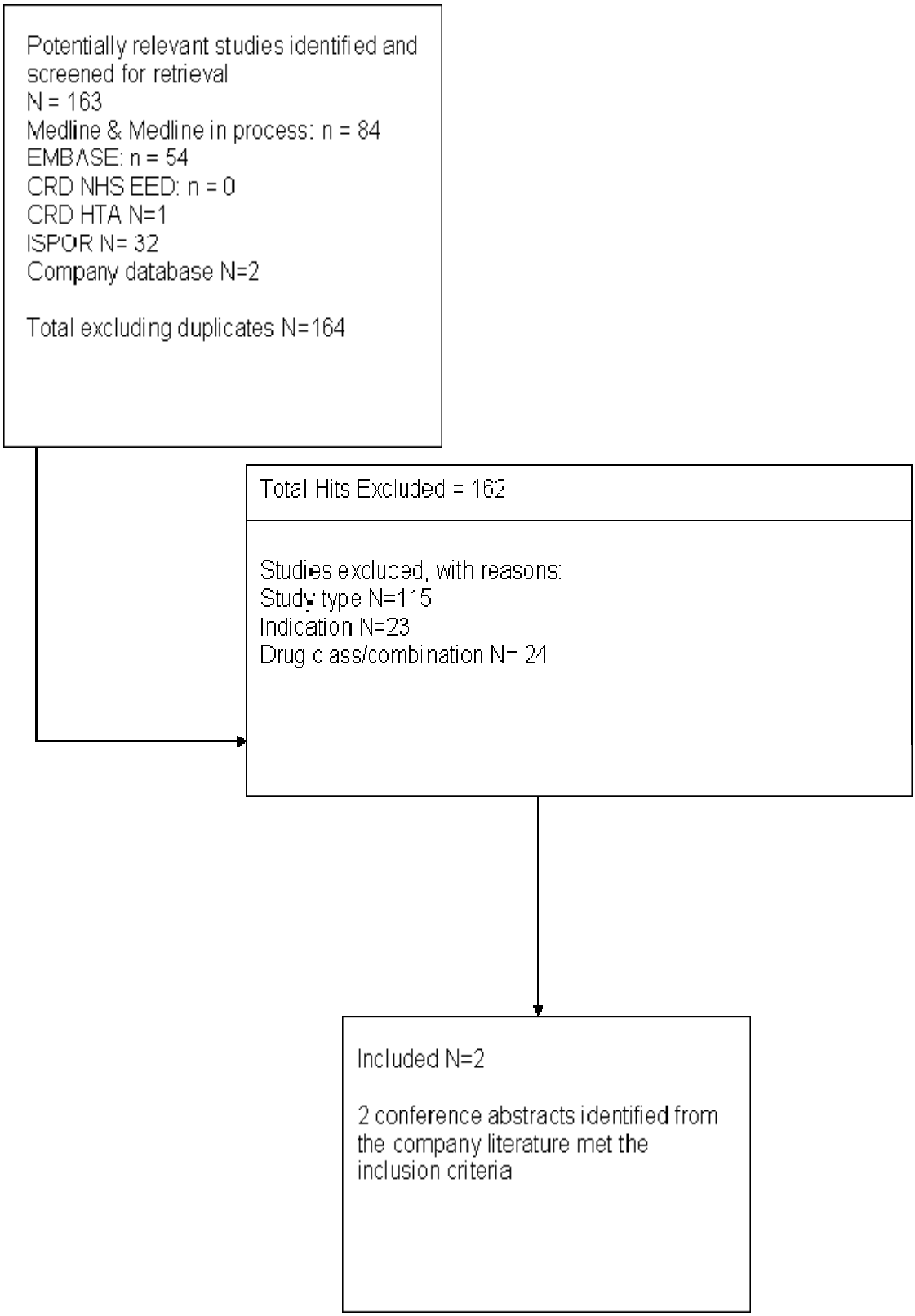
Studies that met the following criteria were included:

- The cost-effectiveness or costing studies of Len/Dex were considered
- Patients considered are those with multiple myeloma

Studies were excluded if any of the following applied:

- Editorials, news reports, comments, reviews, guidelines
- Studies were not cost-effectiveness evaluations or costing studies
- Target patients did not have multiple myeloma
- The combination therapy was not Len/Dex

The above criteria were applied to each of the studies identified by the search strategies. Two studies were identified that met with the criteria and were relevant to the decision problem. Both studies were available in abstract form and were identified from the company database.



6.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

Deniz et al (67) evaluated the long-term health and cost consequences of Lenalidomide in combination with dexamethasone (Len/Dex) versus dexamethasone (Dex) alone in Scottish patients with multiple myeloma who had received one prior therapy only. The authors developed a discrete event simulation model which predicts a patient's disease course following a second-line treatment decision. Clinical inputs for the model were derived from the data collected in the MM-009 and MM-010 trials. The median overall survival for Dex was estimated using data from the UK Medical Research Council (MRC) multiple myeloma trials. Disease management costs reflected clinical practice in Scotland. The results showed that treatment with Len/Dex provides substantial clinical benefits compared to Dex alone (modeled median time to progression was 13.5 months with Len/Dex compared to 4.7 months with Dex). This translated to QALY gains of 3.19 against 1.39, with an incremental cost-effectiveness ratio of £28,980 per QALY. The authors concluded that Len/Dex does provide significant improvements in survival, with an incremental cost per QALY falling within an acceptable cost-effectiveness range.

In another study the same discrete event simulation model was adapted to a Welsh setting (68).In this study two subgroups were evaluated: 1) patients who had received one prior therapy only and 2) those with two or more prior therapies. Efficacy data were obtained from the pivotal MM-009 and MM-010 trials. In the one prior therapy group Dex overall survival was estimated using data from the UK Medical Research Council (MRC) Myeloma trials, however for those with two or more prior therapies the Mayo Clinic prospective database study was used. For patients who had received one prior therapy and were unsuitable for treatment with bortezomib results showed an average incremental outcome gain of 2.54 life years (LYs) (4.54 versus 2.00) and 1.81 additional quality-adjusted life-years (QALYs) per patient (3.20 versus 1.39). Similarly for those patients who received at least two prior therapies the gain in incremental life year was 2.20 with an additional 1.50 QALYs gained. The incremental cost per QALY gained for one prior therapy and at least two prior therapies were £28,943 and £28,184 respectively. The incremental cost per LY gained was £20,617 and £19,218. The results showed that regardless of the number of prior therapies, Len/Dex still yielded a favourable incremental cost per QALY.

Since these two studies were published the Medical Research Council (MRC) Myeloma trial (2) data has been re analysed to include those patients who received more than one prior therapy, consequently data from the Mayo Clinic prospective database study (3) is not used in this submission. MRC Myeloma trials not only provide long term follow-up data, reflect a large patient population, are multi-centre and consider treatment options (Melphalan, ABCM, VAD and Cyclophosphamide) comparable to dexamethasone but are also UK specific. Furthermore it would not be

appropriate to use Mayo clinic data because the median age of patients at diagnosis is older than in the MM-009 and MM-010 study patients and this could influence their prognosis.

6.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Attribute	Reference case	Section in 'Guide to the methods of technology appraisal'
Comparator(s)	The comparator that has been specified in the decision problem	5.3.2
Perspective costs	NHS and Personal Social Services	5.3.3
Perspective benefits	All health effects on individuals	5.3.3
Form of economic evaluation	Cost-effectiveness analysis	5.3.4
Time horizon	Sufficient to capture differences in costs and outcomes	5.3.5
Synthesis of evidence	Systematic review	5.4.1
Outcome measure	Quality-adjusted life years (QALYs)	5.5
Health states for QALY measurement	Described using a standardised and validated instrument	5.5
Benefit valuation	Time trade-off or standard gamble	5.5
Source of preference data	Sample of public	5.5
Discount rate	Health benefits and costs – both 3.5%	5.7.2
Equity	No additional weighting to QALYs	5.9.7
Sensitivity analysis	Probabilistic sensitivity analysis	5.9.3

6.2.1 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

Lenalidomide is a new immunomodulatory agent indicated, in combination with dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy, as defined in the inclusion criteria of the MM-009 and MM-010 trials “had progressive multiple myeloma after at least 2 cycles of antimyeloma treatment or to have relapsed with progressive disease after treatment”. The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of ongoing 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 of every subsequent every 28- day cycles. Dosing is continued or modified based upon clinical and laboratory findings. Dose adjustments are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

In the MM-009 and MM-010 trials treatment with lenalidomide was recommended to continue until the occurrence of either disease progression or unacceptable side effects were experienced. The efficacy data from the trials therefore reflects treatment interruptions and dosage reductions. In order to accurately capture actual dosing and treatment duration data for the economic modelling, the trial data were analysed for unplanned treatment interruptions and dose reductions, as summarised in

Figure 8. Since the effect of dose reductions and treatment interruptions are already implicitly reflected in the clinical outcome results, the economic model considers medication costs resulting from the corresponding doses and treatment durations observed in the MM-009 and MM-010 trials (see **Appendix 12** for more details).

Figure 8: Dose reductions and treatment interruptions observed in the MM-009 and MM-010 clinical trials(62)

6.2.2 Patients

6.2.2.1 *What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?*

Consistent with the NICE scope for this technology appraisal, the economic evaluation considers the role of lenalidomide in combination with high-dose dexamethasone in people with multiple myeloma who have received at least one prior therapy. To evaluate the cost effectiveness of lenalidomide given existing NICE recommendations and different treatment alternatives, the base case analysis considers three populations:

1) Patients with multiple myeloma who have received one prior therapy only. This group is subdivided into (I) all those who have had 1 prior therapy and (II) those with pre-existing peripheral neuropathy

2) Patients with multiple myeloma who have received at least two prior therapies.

3) Patients with multiple myeloma who have previously been treated with thalidomide (by number of prior therapies)

The populations included in the model are sampled directly from the MM-009 and MM-010 trials. The patient baseline characteristics are summarised in section 5.3.2 Table 8 and Table 9. It is assumed that the multiple myeloma population in England and Wales is similar to the population enrolled in the MM-009 and MM-010 trials as discussed earlier in the submission.

6.2.2.2 *Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?*

Other than those included in section 6.2.2.1 no additional patient subgroups are considered.

6.2.2.3 *Were any obvious subgroups not considered? If so, which ones, and why were they not considered?*

We limited consideration of sub-groups or patient populations to those that reflect the potential use of lenalidomide in combination with high-dose dexamethasone given existing NICE guidance in this indication.

6.2.2.4 *At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?*

For all analyses, patients enter the evaluation at the time of treatment initiation, either having received 1 prior therapy or at least 2 prior therapies and treatment is assumed to continue while patients respond to or remain stable on their treatment. Patients discontinue treatment when their disease progresses or they experience unacceptable side effects but continue to be modelled until they finally exit the evaluation due to death.

6.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

Len/Dex is compared in patients who have received one prior therapy to bortezomib monotherapy. For the subset of patients who have pre-existing peripheral neuropathy, Len/Dex is compared to Dex alone; and in patients who have received at least two prior therapies, to Dex alone.

Although bortezomib in combination with Dex may be used in clinical practice in England and Wales we do not consider this to be an appropriate comparator for this economic evaluation because it is an unlicensed combination. Efficacy data for this combination therapy are only available from Phase II studies and even then the trial was not designed as a combination study since all patients were initially treated with bortezomib monotherapy and were only given Dex if they did not respond to monotherapy (69;70). Moreover, in their recent appraisal of bortezomib NICE refused to consider this combination (21).

Another product which is used in patients with multiple myeloma is thalidomide. Thalidomide is not included as a comparator because it is licensed only for newly-diagnosed multiple myeloma. A marketing authorisation application for thalidomide in relapsing or refractory multiple myeloma was withdrawn [redacted]

[redacted] The thalidomide trials also use different clinical end points and none use the response criteria in accordance with the stringent EMBT criteria used in the lenalidomide studies. Most thalidomide studies use M-protein which alone is not a valid surrogate of outcome (18-20). Therefore, comparable data do not exist for thalidomide to enable a meaningful analysis.

Lastly repeat initial chemotherapy, including regimens based on mephalan, vincristine, cyclophosphamide and doxorubicin, is not included because none are superior to Dex in terms of disease control and tolerability. In addition, there are no well conducted studies using these treatments in previously treated patients upon which to base a comparison. Although the BCSH guidelines (4) recommend the use of repeat initial chemotherapy in patients with relapsing or refractory multiple myeloma, these guidelines are now old and are currently being updated. Finally, the NICE recommendation for bortezomib monotherapy (21) makes these options less relevant now compared to when the guidelines were drafted.

6.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The analysis was undertaken from the perspective of the UK NHS and Personal Social Services and is reflective of the NICE reference case. Only direct medical costs are included and indirect costs due to potential productivity losses of patients or carers are not considered. Cost effectiveness analyses use QALYs as the measure of effectiveness and no equity weights are applied.

6.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

A lifetime horizon was adopted for the analysis. As survival after 30 years of initiating treatment is negligible (less than 3% of patients are still alive after 3 decades) the time horizon is set at 30 years. Although data for patients receiving lenalidomide are only available for a median combined follow-up of 31.3 months (median follow up of 32.1 months for MM-009 (n=184) and 28.7 months for MM-010 (n=200), the full health economic impact of treatment with lenalidomide can be calculated by simulating outcomes in the longer term. This is consistent with the scope for this appraisal.

6.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

The evaluation uses a model based upon clinical trial data extrapolated to a lifetime. Thus, to an extent, both recommended sections apply.

a) Model-based evaluations

6.2.6.1 *Please provide the following.*

- *A description of the model type.*

The model is constructed as a discrete-event simulation that utilizes patient-level information, rather than using an aggregated cohort approach. The model predicts a patient's disease course following a treatment decision in patients who have received at least one prior therapy. In the model, a population of individuals is created using the data from real patients enrolled in the MM-009 and MM-010 trials. The model population (e.g. 1,000 simulated patients) is generated by bootstrap sampling with replacement (72) from the actual patient records. As the number of patients to be simulated (in this case 1,000 patients per treatment) is higher than the number of real patients obtained from MM-009 and MM-010, real patients may be used several times in the model. In this process, the selection is random to avoid any bias.

All the characteristics (i.e., age, gender, number of prior treatments, etc.) in the profile are assigned to the simulated patient. Thus, the model uses the course of the disease of each patient as observed in the trial. This automatically implements observed correlations between parameters. This is described in more detail in **Appendix 7**.

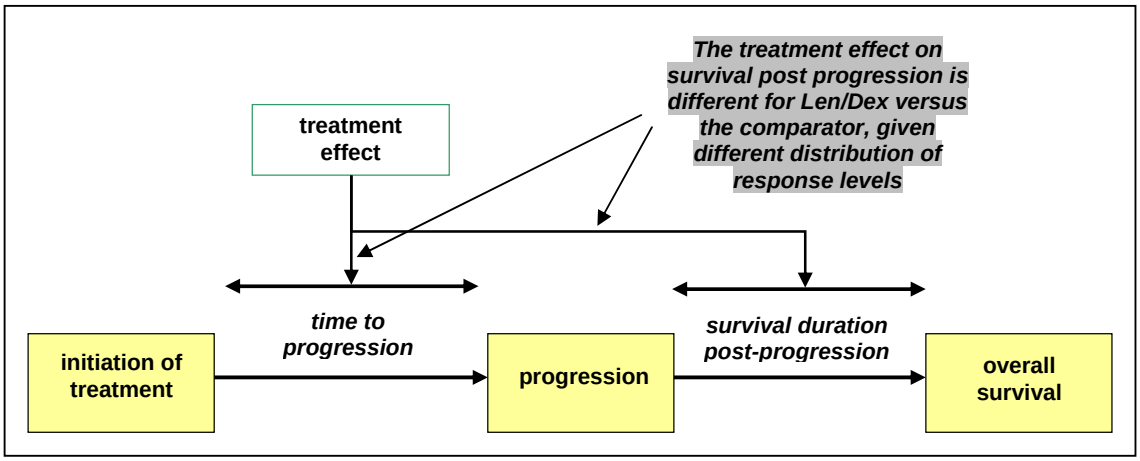
In the model, overall survival is not estimated directly but rather as a combination for each individual of:

1) time to progression, estimated from initiation of treatment and

2) time to death after progression, estimated from time of progression.

This is done to ensure that progression is properly captured and also because time to progression is a predictor of overall survival (Figure 9). Of course, a patient may die before progression was diagnosed, and in line with the trial protocols, these deaths are considered to be progression-related (i.e., time of progression and time of death are identical).

Figure 9: Modelled treatment effect



The model considers four best response levels (Table 36) based on the International Uniform Response Criteria, or EBMT Criteria (59). Best response attained affects both time to progression and post progression survival.

Table 36: Model response levels

International Uniform Response Criteria (59)	Model Criteria
Complete Response	Complete Response (CR)
Remission Response	Partial Response (PR)
Partial Response	
Stable Disease (Neither progressive nor response as defined above)	Stable Disease (SD)
Progressive Disease	Progressive Disease (PD)

Separate prediction equations are employed for time to progression and post-progression survival. The time-to-progression equation includes treatment as a factor, determined directly from the pooled MM-009 and MM-010 clinical trial data. The post-progression survival equation, also derived from the pooled trial data, does not include a treatment effect because 47% of patients randomized to dexamethasone crossed-over to treatment with lenalidomide either at progression or after un-blinding by the independent data monitoring committee. Thus, the observed post-progression survival for the dexamethasone group in the trials includes a strong lenalidomide effect.

To correctly reflect post-progression survival with dexamethasone, a factor was added to the equation by calibrating estimated dexamethasone overall survival to that observed in the UK Medical Research Council (MRC) myeloma trials IV, V, VI, and VIII (2).

Our use of the MRC trial data represent a significant improvement on previous attempts to adjust for cross over from dexamethasone to bortezomib in the APEX trial (21), which used published data from the Mayo clinic in the US (3), for a number of significant reasons. Firstly, the MRC trials represent a large UK specific multiple myeloma patient population. Secondly, the MRC trials represent the outcomes experienced in the UK by patients that could be expected to be achieved with dexamethasone treatment. Specifically, there was no statistically significant difference in survival for patients on regimens involving dexamethasone compared with non-dexamethasone containing regimens. Thirdly, one potential concern with the MRC trial data is that they were initiated between 1 to 3 decades ago and it could be argued that more recent treatment protocols, with different supportive care, may have resulted in improved survival with traditional treatments such as dexamethasone when administered today. However, analysis comparing overall survival from start of first-line treatment or diagnosis for patients in the MRC trials, by year in which treatment was initiated has shown no such improvement in survival over time. This replicates data presented in a recent publication from the Mayo clinic (14).

Together these analyses support the use of these historical data as a robust indicator of the survival likely to be achieved today with traditional therapies. Finally,

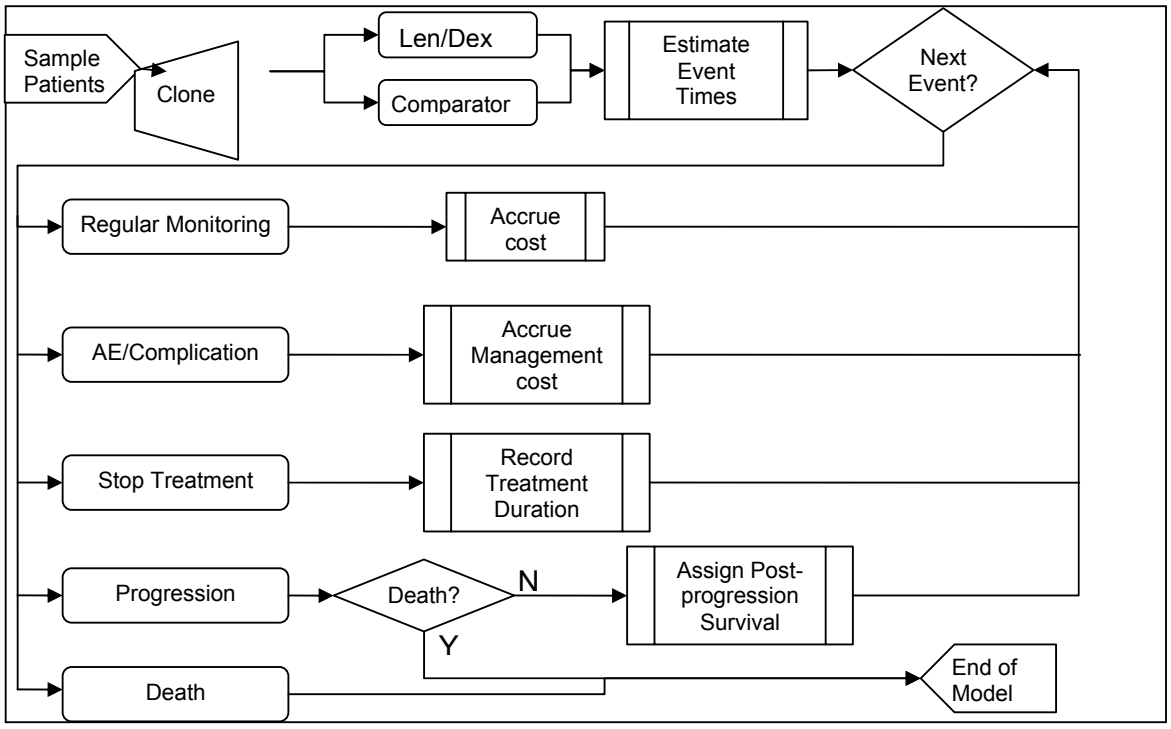
differences between patient profiles in the MRC trials and MM-009 and MM-010 were controlled for by setting the predictors in the MRC trial derived survival equations to the mean values in the MM-009 and MM-010 trials. This approach resulted in a higher (more conservative) estimated median survival for the MM-009 and MM-010 Dex patients than was observed in the MRC trials [redacted] for patients with one or multiple prior therapies respectively.

In the model, the mean and median survival, quality-adjusted life years (QALYs), and TTP are estimated for each treatment, as are the proportion of patients who progress and proportion of patients achieving each level of best response (CR, PR, SD, PD). Adverse events associated with the various treatments and regular monitoring were counted and all direct medical costs were estimated. Cost-effectiveness ratios were calculated as the net costs of lenalidomide plus dexamethasone versus dexamethasone alone divided by the net QALYs gained.

The simulation is implemented in Microsoft® Excel 2003.

- *A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.*

Figure 10: Schematic representation of lenalidomide model for multiple myeloma



- A list of all variables that includes their value, range (distribution) and source.

Variable	Value			Source
Response rate one prior therapy	Len/Dex	Dex	Bortezomib	
Complete Response	23 (19.3%)	3 (2.6%)	13 (10.8%)	MM-009(61) MM-010 (60) APEX (12)
Partial Response	58 (48.8%)	29 (25.0%)	50 (40.7%)	MM-009(61) MM-010 (60) APEX (12)
Stable Disease	33 (27.7%)	68 (58.6%)	52 (42.3%)	MM-009(61) MM-010 (60) APEX (12)
Progressive Disease	5 (4.2%)	16 (13.8%)	8 (6.2%)	MM-009(61) MM-010 (60) APEX (12)
Response rate at least 2 prior therapies			-	
Complete Response	30 (14.3%)	4 (1.9%)	-	MM-009(61) MM-010 (60)
Partial Response	103 (49.0%)	41 (19.5%)	-	MM-009(61) MM-010 (60)
Stable Disease	74 (35.2%)	131 (62.4 %)	-	MM-009(61) MM-010 (60)
Progressive Disease	3 (1.4%)	34 (16.2%)	-	MM-009(61) MM-010 (60)
Utility Values				
Complete Response (first 2years)	0.81			(73)
Partial Response (first 2 years)	0.81			(73)
Stable Disease (first 2 years)	0.81			(73)
Progressive Disease	0.64			(73)
Drug Costs				
Lenalidomide, 25mg, 21 capsules	£4,368			(74)
Lenalidomide, 15mg, 21 capsules	£3,969			(74)
Lenalidomide, 10mg, 21 capsules	£3,780			(74)
Lenalidomide, 5mg, 21 capsules	£3,570			(74)
Dexamethasone, 2 mg, 20 tablets	£2.39			(74)
Bortezomib, 1 3.5-mg vial	£762.38			(74)
Bortezomib administration costs	£1,632 per cycle			(75)

A separate list of all assumptions and a justification for each assumption is provided below.

- In the calculation of quality-adjusted life years, no difference is modelled between response levels (CR, PR and SD) in terms of utility, although it could be argued that better response is associated with higher quality of life. In the current setting, this assumption favours Dex since there were more complete and partial responders with Len/dex and a longer duration of response.

- In the model, only Grade 3 and Grade 4 adverse events observed in the clinical trials are considered assuming that these will have the greater impact on resource use profiles, and therefore overall management costs.

- For this economic evaluation, the patients from trials MM-009 and MM-010 were pooled, regardless of trial or treatment assignment to create single starting population. This population was then subdivided into four datasets, one for each best response category (CR, PR, SD, PD) again irrespective of treatment. This implies that treatment has no effect beyond the best response. In other words, within each response level, the course is not further influenced by whether the response was obtained with Len/dex or Dex. This assumption is conservative for lenalidomide since it is understood that dexamethasone has no disease modifying effect.

- In the MM-009 and MM-010 trials patients in the Dex group were allowed to cross-over to treatment with Lenalidomide either when progression was observed or after unblinding by the IDMC. Thus, the observed post-progression survival for the Dex group in the trials includes a strong lenalidomide effect rather than the pure Dex therapy outcomes. The Medical Research Council (MRC) Myeloma trials (2) were selected to calibrate the post-progression survival predictions derived from the MM-009 and MM-010 trials for the one prior and two or more prior therapy Dex groups in order to estimate the post-progression survival in the absence of cross-over to treatment with lenalidomide (details of the calibration analysis are given in Appendix 8) as the MRC trials provide long term follow-up, reflect a large UK patient population, are multi-centre and only include treatment options comparable to Dex. These data represent an important improvement over the Mayo data used in previous evaluations in multiple myeloma to estimate survival in routine practice (See Appendix 8).

6.2.6.2 Why was this particular type of model used?

Although models today often adopt the cohort technique, where the whole patient population is defined by the mean values in terms of characteristics, health effects and costs, this approach does not have the flexibility to capture the variation in efficacy among individuals. The available data, including data from the clinical trials, however, clearly suggest that the course of the disease differs for individuals, even under the same treatment.This variation depends on many factors, such as patients' characteristics and disease history. Using the patient-level information in the model is important to best reflect the health outcomes observed.

With the patient-level simulation, milestones of disease course are defined as events (e.g., response to treatment, progression of disease, death, adverse events), which are not mutually exclusive (patient can respond and also have an adverse event at the same time). The model considers the impact of these events (e.g. disease progression) on patients' health and on other components of the system, such as resource consumption. This approach was chosen because it permits the development of a more realistic model that avoids the over-simplification required by a cohort Markov model:

- There is no need to have a "memory-less assumption", which would mean ignoring the clinical history of individual patients. Clinical history is very important in multiple myeloma because it has an effect on the course of the

disease and its management (e.g. previous treatments affect the choice of future ones),

- No fixed cycle times and, thus, no need for half cycle corrections. The management and the course of disease is represented with higher accuracy in terms of the events of interest whose appropriate effects can be implemented at the time of the event, avoiding any artificial assumptions on the timing of the events and their consequences.

- Events can follow each other in appropriate sequences and timing. For example, disease progression and death can occur on the same day.

- Patients can be in multiple states at once. Thus, a patient can be on treatment, have a chronic complication, and have stable disease all at the same time, as would occur in real life.

- Proper handling of competing risks is straightforward because there is no limitation of “one transition per cycle”.

6.2.6.3 *What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.*

Using actual patient profiles allows modelling of the disease and treatment effects with higher accuracy and fewer assumptions than would be necessary with mean descriptors of the population. All the characteristics and treatment-related information (e.g. time to best response, time to progression) in the profile are assigned to the simulated patient. Thus, the model uses the course of the disease of each patient as observed in the trial. This automatically implements observed correlations between parameters.

The model considers the experience of a large (e.g. 1,000) hypothetical population consisting of specific individuals with characteristics and clinical histories of the MM-009 and MM-010 trial populations; the course of each one is considered under various treatment options. The model runs many times (replications) and reports the average of these replications as the results of that scenario to reduce the effect of randomisation on the model results that may be created in sampling the random numbers in the simulation process.

Because the disease course for each individual patient with multiple myeloma differs even under the same treatment regimen we believe there are very few alternative structures that might fit the data and the dynamics of this disease. As such we believe the current structure to be the most appropriate.

6.2.6.4 *What were the sources of information used to develop and inform the structure of the model?*

The MM-009 and MM-010 trials and routine clinical practice in patients who have received at least one prior therapy for multiple myeloma were the key sources of information used to develop and inform the structure of the model.

6.2.6.5 *Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?*

The model conceptualises the disease by its clinical milestones such as disease progression and death following progression, which are the most important outcomes in the MM-009 and MM-010 trials. The best response rates achieved by the patients (i.e. CR, PR, SD and PD) represent the treatment effect in the model. These response rates have an impact on the time of disease progression. The model takes into account the effect that best response will have on the time of progression and time of death during the course of the disease.

The model reports the clinical outcomes that are also reported in the clinical trials, such as median time to progression, proportion of patients progressed and the total number of patients who die within the specified model time horizon. In addition the cost related to monitoring these patients and the resources used to manage adverse events are also reported.

6.2.6.6 *For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?*

In a patient level simulation model there is no fixed cycle.

6.2.6.7 *Was a half-cycle correction used in the model? If not, why not?*

Since events can happen at any time in the model and the consequences are modelled at the time of the event there is no need for half cycle corrections.

6.2.6.8 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?*

Cost and outcomes are extrapolated beyond the follow-up period of the MM-009 and MM-010 trials. The post-progression survival among patients randomised to dexamethasone in the trials includes a strong lenalidomide effect. Therefore, to reflect the correct post-progression survival with dexamethasone, a factor was added to the equation for dexamethasone, calibrated in such a way that modelled median overall survival matches the median overall survival derived from Medical Research Council (MRC) Myeloma trials IV, V, VI, and VIII (2).

The MRC Myeloma trials were selected to calibrate the equations because they provide long term follow-up (minimum 7.5 years), are UK specific, reflect a large patient population (1,372 patients were considered in overall survival analyses), are multi-centre and consider treatment options (Melphalan, ABCM, VAD and Cyclophosphamide) comparable to dexamethasone (no significant difference in overall survival between treatment options was found in the MRC trials).

Parametric survival analysis was carried out to derive a prediction equation for time to death, based on the subset of patients in the MRC trials starting on second-line treatment. Age, performance status, M-protein level, Beta-2M level and time to progression with first-line treatment were predictors in this equation. The values of these predictors were then set to the corresponding mean values in the dexamethasone arm of the MM-009 and MM-010 trials to derive the expected median survival for these patients under MRC conditions. The post-progression survival equation derived from the MM-009 and MM-010 trials was then calibrated, by iteratively varying a term added to the equation until the predicted median matched the one obtained from the MRC equation. The full details of the time to progression and post progression survival prediction equations are given in **Appendix 7** and details of the calibration to MRC derived median survival are given in **Appendix 8**.

b) Non-model-based economic evaluations

6.2.6.9 *Was the evaluation based on patient-level economic data from a clinical trial or trials?*

Patient-level data from the MM-009 and MM-010 trials were used to populate the simulation (see section 5.3.8)

6.2.6.10 *Provide details of the clinical trial, including the rationale for its selection.*

Details are provided in the preceding section 5.3.8. Trials MM-009 and MM-010 were selected because they are the only studies within the licensed patient populations.

6.2.6.11 *Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?*

In the MM-009 and MM-010 trials, patients who were missing an element required to determine whether they met response criteria were categorised as Non-Evaluable (NE). Among patients with one-prior therapy, 4% (5/124) of those in the Len/dex group were classified as NE and 6.5% (8/124) in the Dex group. Among those with at least two prior therapies, it was 8% (19/229) and 7% (17/227), respectively. These patients were excluded and the distributions of responses were re-weighted accordingly (Table 39 -Table 43). This approach was taken as there was no evidence regarding the course of these patients. A scenario, which considers NE as equivalent to Stable Disease (SD) is presented as a sensitivity analysis.

6.2.6.12 *Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?*

Resource use data were derived from expert opinion (see section 6.2.9) and utility values from the published literature (see section 6.2.8). All other data were obtained from the MM-009 and MM-010 trials.

6.2.6.13 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this*

extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

See previous section 6.2.6.8.

6.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

6.2.7.1 *How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.*

The clinical trial data from MM-009 and MM-010 were used to estimate the risk of disease progression. For the comparison with bortezomib analysis, the published median TTP for the bortezomib group has been used to adjust the derived disease progression curve, in such a way that the median of the adjusted curve matches the published median time for bortezomib while keeping the shape of the curve the same (12).

6.2.7.2 *How were the relative risks of disease progression estimated?*

Relative risks of disease progression are not used in the model because the course of disease is determined using equations derived from the clinical trial data, and for indirect comparison, by calibrating to the published median TTP.

6.2.7.3 *Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?*

There are no intermediate outcome measures. Survival time is estimated directly.

6.2.7.4 *Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?*

Adverse event rates for Len/Dex and Dex were derived from the MM-009 and MM-010 clinical trial data according to time since initiating treatment. Adverse events were defined as any sign, symptom, illness, or diagnosis that appeared or worsened during the course of the study. The severity of adverse events was classified according to the NCI CTC (version 2.0) (57). Since treatment related adverse events usually occur early in the course of a treatment the clinical trial data were analysed over successive short time intervals (3 months). This enabled the accurate characterisation of the variation of adverse events over time. This approach not only captures the timing of the adverse events more accurately, but also the timing of the modelled resource use consumption due to these events. Only Grade 3 and 4 adverse events were used in the model since these are most relevant with regards to resource use and health outcomes. For bortezomib, published APEX trial outcomes were used to derive the 3-month event rates for grade 3 and 4 adverse events. In order to derive the 3-month rates, constant adverse event risk was assumed during the time period in which the adverse events were reported (i.e. 10 months), and 3

month rates were derived with this assumption. The model, conservatively, does not project the adverse event occurrences beyond the time point that they have been reported (i.e. 10 months). Therefore between 9 and 12 months, to account for one month (i.e. the time between months 9 and 10), one third of the 3-month rate is applied. The adverse event rates used in the model are given in Table 37 and Table 38 (62) (a more detailed explanation is provided in **Appendix 11**).

Table 37: Grade 3 adverse events and complications (62)

Adverse event/ complication		Event rate (%) over time (months)							
	Treatment	0-3	3-6	6-9	9-12	12-15	15-18	18-21	21-24
Anaemia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	2.83	5.57	8.24	9.10	9.10	9.10	9.10	9.10
Thrombocytopenia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	9.03	17.24	24.70	26.97	26.97	26.97	26.97	26.97
Neutropenia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	3.83	7.50	11.04	12.18	12.18	12.18	12.18	12.18
Hypercalcaemia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Diarrhoea	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	2.18	4.30	6.38	7.06	7.06	7.06	7.06	7.06
Constipation	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.60	1.20	1.79	1.99	1.99	1.99	1.99	1.99
Pneumonia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Peripheral Neuropathy	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse event/ complication		Event rate (%) over time (months)							
	Treatment	0-3	3-6	6-9	9-12	12-15	15-18	18-21	21-24
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	2.18	4.30	6.38	7.06	7.06	7.06	7.06	7.06
Deep-vein Thrombosis	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Table 38: Grade 4 adverse events and complications (62)

Adverse event / complication		Event rate over time (months)							
	Treatment	0-3	3-6	6-9	9-12	12-15	15-18	18-21	21-24
Anaemia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.30	0.60	0.90	1.00	1.00	1.00	1.00	1.00
Thrombocytopenia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	1.20	2.39	3.56	3.94	3.94	3.94	3.94	3.94
Neutropenia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.60	1.20	1.79	1.99	1.99	1.99	1.99	1.99
Hypercalcaemia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Diarrhoea	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Constipation	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Pneumonia	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Peripheral Neuropathy	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.30	0.60	0.90	1.00	1.00	1.00	1.00	1.00
Deep-vein Thrombosis	Len/dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bortezomib	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

6.2.7.5 *Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?*

Expert opinion was not used to estimate clinical parameters.

6.2.7.6 *What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?*

See previous section 6.2.6.1.

6.2.8 Measurement and valuation of health effects

6.2.8.1 *Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.*

The health effects include time to progression, overall survival, response rates and adverse event rates. Clinical inputs for Len/Dex were derived from the data collected in the MM-009 and MM-010 trials. The tables below present the treatment efficacy input for the model for Len/Dex and Dex for the different patient populations.

Table 39: Treatment efficacy in the trial population and patients with only one prior therapy (62) (See table 5, in Appendix 5)

Best Response	Combined MM-009 and MM-010 populations		One prior therapy			
			All**		Not evaluable removed	
	Len/dex	Dex	Len/Dex	Dex	Len/Dex	Dex only
Complete	53 (15.0%)	7 (2.0%)	[redacted]	[redacted]	[redacted]	[redacted]
Partial*	161 (45.7%)	70 (19.9%)	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease	107 (30.3%)	199 (56.7%)	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	8 (2.3%)	50 (14.3%)	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable	24 (6.8%)	25 (7.1%)	[redacted]	[redacted]	Removed	Removed

* Remission response was grouped with partial response (see Table 36).
****** Response rates are those reported in Section 5.4 Table 17 applied to model response levels detailed in Table 36.

Table 40: Treatment efficacy in the trial population and patients with at least two prior therapies (62) (See table 5, in Appendix 5)

Best Response	Combined MM-009 and MM-010 populations		At least two prior therapies			
			All**		Not evaluable removed	
	Len/dex	Dex	Len/Dex	Dex	Len/Dex	Dex only
Complete	53 (15.0%)	7 (2.0%)	[redacted]	[redacted]	[redacted]	[redacted]
Partial*	161 (45.7%)	70 (19.9%)	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease	107 (30.3%)	199 (56.7%)	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	8 (2.3%)	50 (14.3%)	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable	24 (6.8%)	25 (7.1%)	[redacted]	[redacted]	Removed	Removed

* Remission response was grouped with partial response (see Table 36).

** Response rates are those reported in Section 5.4 Table 17 applied to model response levels detailed in Table 36.

Table 41: Treatment efficacy in the trial population and patients with only one prior therapy prior thalidomide (62) (See table 11, in Appendix 5)

	One prior therapy			
	All		Not evaluable removed	
Complete	Len/Dex	Dex only	Len/Dex	Dex only
Partial*	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]

* Remission response was grouped with partial response (see Table 36).

Table 42: Treatment efficacy in the trial population and patients with at least two prior therapies prior thalidomide use (62) (See table 11, in Appendix 5)

	One prior therapy			
	All		Not evaluable removed	
Complete	Len/Dex	Dex only	Len/Dex	Dex only
Partial*	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]

* Remission response was grouped with partial response (see Table 36).

Health effects for bortezomib were obtained from the APEX study (refer to Appendix 6, section 6.1.1.1 for further explanation).

Table 43: Treatment efficacy in the bortezomib trial population receiving one prior therapy

Best Response	Overall populations	One prior therapy only	
		All	Not evaluable removed
	Bortezomib	Bortezomib	Bortezomib
Complete	27 (9%)	13 (10.5%)	13 (10.8%)
Partial*	108 (34%)	50 (39.5%)	50 (40.7%)
Stable Disease	148 (47%)	52 (41.1%)	52 (42.3%)
Progressive Disease	22 (7%)	8 (6.1%)	8 (6.2%)
Not Evaluable	10 (3%)	4 (2.8%)	Removed

* Remission response was grouped with partial response (see Table 36).

6.2.8.2 *Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?*

A systematic literature review was undertaken to identify relevant randomised controlled trials of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy. All health effects were obtained from these studies.

6.2.8.3 *Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?*

The utility values used in the analysis are based on a study by The Dutch-Belgian Haemato-Oncology Cooperative Study Group (HOVON). They conducted a prospective multi-centre randomised phase III study to evaluate the efficacy of intensive chemotherapy followed by myeloablative therapy with autologous stem cell rescue as compared to intensive chemotherapy. Quality of life information was collected using the EQ-5D questionnaire. A cost-utility analysis (73) was conducted on the data from this study to provide information on the quality of life in patients with multiple myeloma. The study estimated the utility value for patients who did not respond to treatment (e.g. those patients who were still suffering from the effects of their disease) to be 0.64. The value for those who responded was based on the utility value of the general public at an age value corresponding to that of the patients in the study (0.81).

In the simulation, we assumed the value 0.64 for progressive disease and 0.81 for all other response levels (see Table 44). As in the published study from which these values are derived, a utility value of 0.77 at 24 months is also presented for those who respond to treatment with intensive chemotherapy (73) a utility score of 0.77 after two years is used for those who haven't progressed at the end of two years

Table 44: Utility scores by response level (73)

Response levels	Utility score
Complete Response	0.81
Partial Response	0.81
Stable Disease	0.81
Progressive Disease	0.64

Utility decrements for adverse events and complications were not incorporated into the model due to lack of available published data.

6.2.8.4 *Were any health effects excluded from the analysis? If so, why were they excluded?*

Grade 1 and 2 adverse events had no resource use consequences, as they were mostly treated with 'watchful waiting', dose interruptions or reductions; they were therefore excluded from the analysis.

6.2.8.5 *If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?*

Health effects are expressed in QALYs.

6.2.9 Resource identification, measurement and valuation

6.2.9.1 *What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)*

The following tables provide the resource use inputs for the model. These include adverse events by location of care (percentage and number of visits), routine management profiles in the outpatient setting, and frequency of lab tests and services for disease monitoring.

Resource use profiles for management of relapsed/refractory multiple myeloma (including tests to monitor therapy response and disease state) were collected separately by disease status. Specifically, resource use profiles were collected for patients during relapse and/or on treatment, and for patients in remission/plateau and either on maintenance therapy or off therapy. The "during relapse and/or on treatment" resource use profiles were applied to patients in the model whom had initiated treatment, but had not yet achieved a response. Once patients achieved a response, the resource use profiles associated with "in remission/plateau and on maintenance therapy" were applied while patients remained in remission on maintenance therapy. Resource use profiles associated with "in remission/plateau and off therapy" were applied to those patients whom discontinued therapy prior to disease progression. Following disease progression and subsequent relapse the "during relapse and/or on treatment" resource use profiles were applied.

Arithmetic means of the disease monitoring tests (Table 45) and ranges of the values are reported in **Appendix 10**. Details of the sources for the costs of each specific test to monitor therapy response and disease state are included in Table 49.

Table 45: Mean number of regular outpatient consultations and disease monitoring tests

	Cost (£)	Source	Frequency (mean # of assessments/yr)		
			During relapse/on treatment§	In remission / plateau*	
				Maintenance therapy	Off therapy†
Outpatient	97	(76)	12	12	6
Tests to monitor therapy response and disease status					
Routine Blood Counts (FBC)	2.93	(77)	20.1	10.7	7.1
Clotting	2.93	(77)	3.9	1.1	0.4
INR	2.93	(77)	2.6	2.9	0.4
Biochemistry (U&Es)	1.59	(78)	17.3	9.7	6.6
Liver function tests (LFTs)	1.59	(78)	14.6	7.6	5.1
Erythrocyte sedimentation rate (ESR)	2.93	(77)	2.6	1.4	0.9
Plasma Viscosity	1.59	(78)	1.6	0.3	0.3
Uric Acid (Urate)	1.59	(78)	2.7	1.4	0.9
Immunoglobulin (IGs)	1.59	(78)	9.7	6.4	4.9
Paraprotein Measurements (PP)	1.59	(78)	11.1	7.6	6.1
Protein Electrophoresis	1.59	(78)	9.6	6.7	5.1
Serum β2 microglobulin	1.59	(78)	5.0	3.0	2.0
C-reactive protein	1.59	(78)	3.3	1.6	1.3
Serum erythropoietin level	1.59	(78)	0.5	0.1	0.1
Immunofixation (SIF)	1.59	(78)	4.8	3.4	2.9
Creatinine-clearance (CRCL)	1.59	(78)	2.3	0.7	0.4
Glomerular filtration rate (GFR)	1.59	(78)	7.1	3.3	2.7
Serum Free Light Chains (SFLC)	1.59	(78)	4.1	2.9	1.7
Routine urinalysis	1.59	(78)	4.4	1.7	1.0
24-hour urine measurement (24hr UR)	1.59	(78)	3.0	1.3	1.0
24-hour urine for creatinine (24hr UrCr)	1.59	(78)	1.4	0.6	0.1
Total Urine Protein (24hr TUP)	1.59	(78)	3.2	1.4	0.4
Urine protein electrophoresis/ light chains	1.59	(78)	4.9	2.7	2.1
Urine Immunofixation	18.56	(79)	2.1	1.0	1.0
Skeletal Survey by X-Ray (SS)	18.56	(79)	1.6	0.1	0.0
Skeletal Survey by X-Ray Individual Sites	2.93	(77)	1.6	0.1	0.1
MRI	312.95	(80)	0.9	0.0	0.0
Bone Densitometry (BMD)	6.35	(81)	0.1	0.0	0.0
Bone Marrow Aspirate (BMA)	1.59	(77)	2.1	0.2	0.1
Bone Marrow Trephine Biopsy (BMT)	1.59	(77)	2.0	0.2	0.1
Neuropathy (please specify)	2.93	(77)	0.1	0.1	0.1
Bacterial investigation	6.35	(78)	1.6	0.4	0.3

§ Induction or re-induction treatment
* Remission defined per EBMT criteria. Plateau defined as stable disease following response to induction/reinduction treatment and now on maintenance therapy or off therapy (without maintenance)
† Off therapy would include patients on bisphosphonate treatment alone

Resource use profiles for the management of disease complications and treatment-related adverse events were collected separately for Grade 3 and 4 toxicities as defined by the National Cancer Institute (NCI) Common Toxicity Criteria (CTC)

Version 2.0 (57), in order to ensure consistency with the pivotal phase III trials of lenalidomide (MM-009 and MM-010).

Table 46: National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 2.0 Grade 3–4 classifications of disease complications and treatment related adverse events (57)

	Grade 3	Grade 4
Disease-related complications		
Renal failure	Requiring dialysis, but reversible	Requiring dialysis and irreversible
Anaemia (Haemoglobin (Hb))	6.5 - < 8.0 g/dL	< 6.5 g/dL
Hypercalcaemia	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Pneumonia (pneumonitis / pulmonary infiltrates)	Radiographic changes and requiring oxygen	Radiographic changes and requiring assisted ventilation
Treatment-related adverse events		
Thrombocytopenia (platelets)	≥ 10.0 - < 50.0 x 10^9L	< 10.0 x 10^9L
Neutropenia (neutrophils)	≥ 0.5 - < 1.0 x 10^9L	< 0.5 x 10^9L
Diarrhoea	Increase of ≥ 7 stools/day or incontinence; or need for a parenteral support for dehydration	Physiologic consequences requiring intensive care; or haemodynamic collapse
Constipation	Obstipation requiring manual evacuation or enema	Obstruction or toxic megacolon
Neuropathy (sensory)	Sensory loss or paresthesia interfering with activities of daily living	Permanent sensory loss that interferes with function
DVT (thrombosis/embolism)	DVT requiring anticoagulant therapy	Embolic event including pulmonary embolism

For each specific disease-related complication and treatment-related adverse events incorporated into the model, information on the proportion of patients who would receive treatment, the location where treatment would be administered, up to three most frequently administered treatments/interventions and if treated with a medication, the formulation, average dosage, duration of therapy and any additional laboratory tests was collected. Arithmetic means of both the proportion of patients whom would receive treatment for each of the complications/adverse events and the location where treatment would be administered were used in the model (Table 47), ranges of the values are reported in **Appendix 10**. For those complications or adverse events treated as a day case, outpatient, primary care or community care, the mean numbers of visits were used in the model (Table 49), ranges of the values are reported in **Appendix 10**.

In order to accurately estimate the unit cost of inpatient and day case treatment for multiple myeloma disease-related complications and treatment-related adverse events, patient level CHKS data (which contains routine data from approximately 90% of trusts in the UK and reports in the same structure as Health Episodes Statistics (HES)) were combined with NHS Reference Costs (82). Specifically,

patients with a first diagnosis (index admission) of multiple myeloma recorded between January 2000 and June 2006 were selected. Patients were identified with a diagnosis of multiple myeloma recorded using the ICD-10 classification C90.0 in one of thirteen diagnostic fields. All hospital activity for these patients was analysed and flagged if it related to a relevant complication occurring either during or after the index admission. Each complication was identified where an admission had a primary diagnosis (ICD-10 (83) &/or OPCS-4 (84)) (Table 49). All complication related admissions were grouped into day cases, elective admissions and emergency admissions. Costs per admission were attributed according to the NHS Reference Costs for 2005 (82). Health Related Groups (HRGs) were attributed to each admission using HRG grouper (V 3.5) software (National Casemix Office, Winchester, UK). Unit costs for inpatient and day case treatment for multiple myeloma disease-related complications and treatment-related adverse events were calculated as the average HRG cost of all identified admissions for each complication / adverse event (Table 50). This enabled unit cost estimates to reflect multiple myeloma specific complications. Details of the identified admissions and associated HRG costs used in derivation of average inpatient and day case unit costs for each complication / adverse events are reported in **Appendix 11**.

The cost of outpatient treatment for disease-related complications and treatment-related adverse events were taken from NHS Reference Costs by appropriate specialty (82) (Table 50). The cost of those treatments/interventions which would be administered during an inpatient or day case hospitalisation were assumed to be included in the hospitalisation cost. Those treatments/interventions which would either continue to be administered following hospital discharge or be administered in a community setting were included separately (see additional costs section in **Appendix 11**).

Table 47: Average proportion of patients receiving treatment and location of treatment for each of the complications/adverse events

	Grade	% whom receive treatment	Location of care (%)				
			In-patient	Day case	Out-patient	Primary-care	Community care
Disease-related complications							
Anaemia	3	91.86%	5.71%	73.21%	15.36%	0.00%	5.71%
	4	100.00%	19.62%	69.62%	5.38%	0.00%	5.38%
Hypercalcaemia	3	100.00%	50.36%	27.50%	22.14%	0.00%	0.00%
	4	100.00%	77.50%	11.79%	10.71%	0.00%	0.00%
Pneumonia	3	100.00%	98.57%	1.43%	0.00%	0.00%	0.00%
	4	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%
Treatment-related adverse events							
Thrombocytopenia	3	28.85%	6.15%	81.54%	12.31%	0.00%	0.00%
	4	96.43%	17.14%	80.00%	2.14%	0.00%	0.71%
Neutropenia	3	44.11%	5.00%	55.56%	39.44%	0.00%	0.00%
	4	70.71%	12.31%	40.38%	43.46%	0.00%	3.85%
Diarrhoea	3	95.71%	57.50%	12.50%	28.57%	1.43%	0.00%
	4	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%
Constipation	3	100.00%	37.50%	21.43%	35.36%	3.57%	2.14%
	4	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%
Peripheral neuropathy	3	79.29%	0.00%	4.62%	94.62%	0.00%	0.77%
	4	83.85%	9.09%	15.45%	71.82%	3.64%	0.00%
Deep-vein	3	100.00%	12.86%	16.07%	68.93%	2.14%	0.00%

Thrombosis	4	100.00%	81.15%	3.46%	15.38%	0.00%	0.00%

Table 48: Average number of visits for treatment of complications/adverse events

	Grade	Visits per month			
		Day case	Outpatient	Primary care	Community care
Disease-related complications					
Anaemia	3	1	1	NA	4
	4	1	2	NA	4
Hypercalcaemia	3	2	3	NA	NA
	4	4	3	NA	NA
Pneumonia	3	2	1	NA	NA
	4	NA	NA	NA	NA
Treatment-related adverse events					
Thrombocytopenia	3	1	3	NA	NA
	4	2	4	NA	NA
Neutropenia	3	1	3	NA	NA
	4	1	3	NA	2
Diarrhoea	3	2	2	1	NA
	4	NA	NA	NA	NA
Constipation	3	1	2	1	3
	4	NA	NA	NA	NA
Peripheral Neuropathy	3	1	2	NA	2
	4	2	2	1	NA
Deep-vein Thrombosis	3	5	3	3	NA
	4	8	2	NA	NA

Table 49: Unit costs

	Grade	Cost per visit £		
		Inpatient	Day case	Outpatient
Disease-related complications				
Anaemia	3	1,228.45†	430.53†	97#
	4	1,228.45†	430.53†	-
Hypercalcaemia	3	1,493.06†	420.58†	97#
	4	1,493.06†	420.58†	-
Pneumonia	3	1,670.98†	506.80†	-
	4	1,670.98†	506.80†	-
Treatment-related adverse events				
Thrombocytopenia	3	1,559.56†	547.89†	97#
	4	1,559.56†	547.89†	97#
Neutropenia	3	1,796.67†	470.00†¥	97#
	4	1,796.67†	470.00†¥	97#
Diarrhoea	3	1,302.90†	477.84†	-
	4	1,302.90†	477.84†	-
Constipation	3	1,685.26†	445.77†	-
	4	3,953.50†	445.77†Φ	-
Peripheral Neuropathy	3	1,631.57†	523.80†	97#
	4	1,631.57†	523.80†	97#
Deep-vein Thrombosis	3	1,197.83†	311.28†	199§ / 111ℓ
	4	1,869.50†	282.00†	199§ / 111ℓ

NHS reference costs 2005 - TOPS FUA - Specialty code: 303 - Clinical Haematology (76)
§ NHS reference costs 2005 - TOPS FAA - Specialty code: 300 - General medicine (85)
ℓ NHS reference costs 2005 - TOPS FUA - Specialty code: 300 - General medicine (86)
† NHS reference costs 2005 (82) combined with CHKS data see **Appendix 11**
Φ No day case admissions were identified for grade 4 constipation. Therefore, grade 3 constipation average costs per visit were used,
¥ No day case admissions were identified for neutropenia. Therefore, the average of the identified HRG costs was used.

6.2.9.2 *How were the resources measured?*

Data on the NHS resources used to treat relapsed/refractory multiple myeloma were obtained by interviewing with a structured questionnaire fifteen haematologists whom specialise in the treatment of multiple myeloma (87). These specialists were selected to provide a broadly representative geographic spread across England and Wales in order to incorporate any regional variation. NHS resources covered in the questionnaire included type and frequency of laboratory and disease monitoring, and treatment of disease-specific complications and treatment-related adverse events.

6.2.9.3 *Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?*

No, resource use was measured in separate study as described above.

6.2.9.4 *Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)?*

Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Based on expert clinical opinion it was assumed that both "during relapse and/or on treatment" and "in remission/plateau and on maintenance therapy" patients would make one outpatient visit per month and while "in remission/plateau and off therapy" patients would make one outpatient visit every second month. The cost of a haematology outpatient consultation was taken from NHS Reference Costs (76)

The lenalidomide summary of product characteristics states that a "complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias" (65). The responses provided by the haematologists to the frequency of routine blood counts performed on patients during relapse and/or on treatment indicates that the recommendation on the frequency of blood counts during treatment with lenalidomide would result in only a negligible additional resource use compared current clinical practice in England and Wales.

6.2.9.5 *What source(s) of information were used to value the resources?*

See Table 49.

6.2.9.6 *What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?*

The unit costs for the medications used in the analyses are summarised below:

Table 50: Medication costs

Medication	Cost	Source
Multiple myeloma treatment		
Lenalidomide, 25mg x 21 capsules	£4,368	(74)
Lenalidomide, 15mg x 21 capsules	£3,969	(74)
Lenalidomide, 10mg x 21 capsules	£3,780	(74)
Lenalidomide, 5mg x 21 capsules	£3,570	(74)
Dexamethasone, 40mg*	£29	(74)
Bortezomib, 3.5-mg vial	£762.38	(74)

* 20x2mg tablets £2.41.

6.2.9.7 *Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?*

Resources are measured and valued in a manner consistent with the reference case.

6.2.9.8 *Were resource values indexed to the current price year?*

All unit costs are indexed to 2005, although drug treatment costs are current (2008) costs.

6.2.9.9 *Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.*

No additional assumptions were made.

6.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Future costs and benefits were discounted at 3.5% as specified in the NICE reference case.

6.2.11 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.2.11.1 *Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?*

Univariate and multivariate sensitivity analyses were conducted for all patient groups considered and results are presented in

Table 58 to Table 63. The sensitivity analyses were selected based upon those variables where there was more uncertainty. A table with the sensitivity analyses and their ranges is presented below.

Table 51: Parameters for the univariate sensitivity analyses

Parameter	Range or alternative
Resource use associated with AEs	± 100%
Resource use associated with disease monitoring (i.e. tests)	± 100%
All Costs (except medication cost)	± 100%
Lenalidomide Costs	-5%
Best Response Achieved	Includes NE patients in SD group
Utility Scores	± 10%
Separate utility scores by response rate	RR = 0.75 SD =0.70
Median overall survival used for calibration	95%CI , ± 1 month

For the multivariate analysis the following scenarios were run.

Table 52: Parameters for the multivariate sensitivity analyses

	Parameter to change		
	Len/Dex cost reduction	**Utility score**	**Median overall survival**
Scenario 1	0%	10% decrease	+ 1 month
Scenario 2	5%	10% increase	- 1 month

6.2.11.2 *Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.*

Probabilistic sensitivity analyses of the key model parameters (time to progression prediction equations, post progression survival prediction equations, utility scores and management costs) were performed by sampling point estimates from the appropriate distributions. A detailed description of the methodology used for probabilistic sensitivity analysis is provided in **Appendix 14**.

6.2.11.3 *Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?*

The various sensitivity analyses have explored the main areas of uncertainty contained within the model. Elements of structural uncertainty have not been specifically explored.

6.2.12 Statistical analysis

6.2.12.1 *How were rates or probabilities based on intervals transformed into (transition) probabilities?*

Transition probabilities are not used in this model.

6.2.12.2 *Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.*

Not applicable.

6.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The face validity was examined by presenting the influence diagram, data sources, assumptions and other design aspects to clinical and modeling experts. The technical validity of the model was tested internally to ensure that calculations were correct and that the results were logical and consistent with published results from the data sources (the APEX trial (12) and MM-009 & MM-010 trials) that are used to populate the model. This was conducted by several analysts, by examining formulae and conducting one and two-way sensitivity analyses.

6.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- *costs, QALYs and incremental cost per QALY*
- *disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment*
- *a statement as to whether the results are based on a probabilistic sensitivity analysis*
- *cost-effectiveness acceptability curves*
- *scatterplots on cost-effectiveness quadrants.*

6.3.1 Base-case analysis

6.3.1.1 *What were the results of the base-case analysis?*

The base case analyses are presented in Table 53 to Table 57. The model outcomes include clinical results, survival, costs and cost-effectiveness. All the costs, projected life years and quality adjusted life years are reported as both discounted and undiscounted values.

Patients with multiple myeloma who have received one prior therapy only

This analysis compares patients receiving Len/Dex to patients receiving bortezomib monotherapy. The model predicted median time-to-progression (TTP) for bortezomib is 6.75 months compared to 7 months observed in the clinical trial (12). For the Len/Dex group, the model predicted median TTP is 14.08 compared to 14.3 months in the clinical trials (62).

The estimated discounted cost of medication, monitoring and adverse event management with Len/Dex treatment was estimated at [redacted] per patient compared to [redacted] with bortezomib alone. In the Len/Dex group, the largest contributor to the cost is treatment medication. Although costs are higher, patients treated with Len/dex have better clinical outcomes in terms of best response achieved, time to progression and overall survival.

These improved clinical outcomes result in estimated discounted QALYs of [redacted] for Len/Dex versus [redacted] for bortezomib, a gain of [redacted] QALYs. As a result, the incremental cost-effectiveness ratio is [redacted] per QALY for Len/Dex versus bortezomib. The estimated life years gained were [redacted] for Len/Dex versus [redacted] for bortezomib resulting in an incremental cost per life year gained of [redacted].

The results of this analysis need to be considered as exploratory only. The existing NICE recommendation for bortezomib is based on the implementation of the Velcade Response Scheme and aims to ensure that only patients who respond to treatment with bortezomib continue to receive treatment beyond 4 cycles of therapy.

However, at this time, published audit data of the scheme are not available. It is therefore not possible to estimate the true cost of bortezomib to the NHS, or its efficacy in routine practice, because it is not clear whether the expected levels of response to bortezomib are accurate. A more accurate estimate of the cost effectiveness of Len/Dex relative to bortezomib can therefore only be developed when audit data for the Velcade Response Scheme are published.

Table 53: Results for patients with multiple myeloma who have received one prior therapy only

	Undiscounted		Discounted	
	Len/dex	**Velcade**	**Len/dex**	**Velcade**
Summary of Clinical Outcomes				
Achieved Best Response (%)				
Complete Response	19%	11%	19%	11%
Partial Response	49%	41%	49%	41%
Stable Disease	28%	42%	28%	42%
Progressive Disease	4%	6%	4%	6%
Patients Progressed (%)	100%	100%	100%	100%
Median Time to Progression (months)	14.08	6.75	14.08	6.75
Deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]
Quality Adjusted Life Years (QALYs)	[redacted]	[redacted]	[redacted]	[redacted]
Life Years (median)	[redacted]	[redacted]	[redacted]	[redacted]
Total Life Years (mean)	[redacted]	[redacted]	[redacted]	[redacted]
Average Cost (per patient)				
Medication	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event-Complication	[redacted]	[redacted]	[redacted]	[redacted]
Cost-Effectiveness Outcomes				
Incremental cost per QALY Gained	[redacted]		[redacted]	
Incremental cost per Life Year Gained	[redacted]		[redacted]	

Patients with multiple myeloma who have received one prior therapy only and have pre-existing peripheral neuropathy

This analysis compares patients receiving Len/Dex to patients receiving Dex alone. The rationale for this comparison is that for some patients it may not be appropriate to consider a therapy which is likely to induce peripheral neuropathy and this may discount consideration of bortezomib as a treatment option. The analysis utilises the same efficacy data for the Len/Dex treated patients as for the previous comparison because post-hoc analysis suggests the same outcomes can be expected for patients with pre-existing peripheral neuropathy (see Appendix 4, section 5.1.7.1).

The model predicted median time-to-progression (TTP) for Dex is 4.63 months compared to 4.7 months observed in the clinical trials MM-009 and MM-010 (62).

The estimated discounted cost of medication, monitoring and adverse event management with Len/Dex treatment was estimated at £106,344 per patient compared to £1,366 with Dex alone. In the Len/Dex group, the largest contributor to the cost is treatment medication. Although costs are higher, patients treated with Len/Dex have significantly better clinical outcomes in terms of best response achieved, time to progression and overall survival.

These improved clinical outcomes result in estimated discounted QALYs of 3.77 for Len/Dex versus 1.53 for Dex, a gain of 2.24 QALYs. As a result, the incremental cost-effectiveness ratio is £46,865 per QALY for Len/Dex versus Dex. The estimated life years gained were 5.43 for Len/Dex versus 2.20 for Dex resulting in an incremental cost per life year gained of £32,501.

Table 54: Results for patients with multiple myeloma who have received one prior therapy only and have pre-existing peripheral neuropathy

	Undiscounted		Discounted	
	Len/dex	**Dex**	**Len/dex**	**Dex**
Summary of Clinical Outcomes				
Achieved Best Response (%)				
Complete Response	19%	3%	19%	3%
Partial Response	49%	25%	49%	25%
Stable Disease	28%	59%	28%	59%
Progressive Disease	4%	14%	4%	14%
Patients Progressed (%)	100%	100%	100%	100%
Median Time to Progression (months)	14.08	4.63	14.08	4.63
Deaths (%)	97%	100%	97%	100%
Quality Adjusted Life Years (QALYs)	4.65	1.67	3.77	1.53
Life Years (median)	4.20	1.65	4.20	1.65
Total Life Years (mean)	6.76	2.41	5.43	2.20
Average Cost (per patient)				
Medication	113,242	110	103,063	109
Monitoring	3,284	1,197	2,535	1,072
Adverse Event-Complication	749	187	746	185
Cost-Effectiveness Outcomes				
Incremental cost per QALY Gained	38,853		46,865	
Incremental cost per Life Year Gained	26,616		32,501	

Patients with multiple myeloma who have received at least two prior therapies

This analysis compares patients receiving Len/Dex to Dex alone. The model predicted median time-to-progression (TTP) for Dex is 4.63 months compared to 4.7

months observed in the clinical trials MM-009 and MM-010. For the Len/Dex group, the model predicted median TTP is 9.54 compared to 10.2 months in the clinical trials (62).

The estimated discounted cost of medication, monitoring and adverse event management with Len/Dex treatment was estimated at £61,171 per patient compared to £694 with Dex alone. Similarly to the one prior therapy analysis the largest contributor to the cost in the Len/Dex group is treatment medication. Although costs are higher, patients treated with Len/Dex have significantly better clinical outcomes in terms of best response achieved, time to progression and overall survival.

These improved clinical outcomes result in estimated discounted QALYs of 3.23 for Len/Dex versus 0.77 for Dex, a gain of 2.46 QALYs. As a result, the incremental cost-effectiveness ratio is £24,584 per QALY for Len/Dex versus Dex. The estimated life years gained were 4.76 for Len/dex versus 1.05 for Dex resulting in an incremental cost per life year gained of £16,301.

Table 55: Results for patients with multiple myeloma who have received at least two prior therapies

	Undiscounted		Discounted	
	Len/dex	**Dex**	**Len/dex**	**Dex**
Summary of Clinical Outcomes				
Achieved Best Response (%)				
Complete Response	14%	2%	14%	2%
Partial Response	49%	20%	49%	20%
Stable Disease	35%	62%	35%	62%
Progressive Disease	1%	16%	1%	16%
Patients Progressed (%)	100%	100%	100%	100%
Median Time to Progression (months)	9.54	4.63	9.54	4.63
Deaths (%)	97%	100%	97%	100%
Quality Adjusted Life Years (QALYs)	3.98	0.79	3.23	0.77
Life Years (median)	3.39	1.11	3.39	1.11
Total Life Years (mean)	5.92	1.08	4.76	1.05
Average Cost (per patient)				
Medication	59,843	110	57,921	109
Monitoring	3,216	415	2,504	404
Adverse Event-Complication	750	182	746	181
Cost-Effectiveness Outcomes				
Incremental cost per QALY Gained	19,781		24,584	
Incremental cost per Life Year Gained	13,038		16,301	

Patients with multiple myeloma who have previously been treated with thalidomide (1 prior therapy)

This analysis again compares patients receiving Len/Dex to Dex alone and for patients who have previously received treatment with thalidomide.

The estimated discounted cost of medication, monitoring and adverse event management with Len/Dex treatment was estimated at £119,676 per patient compared to £1,311 with Dex alone. In the Len/Dex group, the largest contributor to the cost is treatment medication. Although costs are higher, patients treated with Len/Dex have significantly better clinical outcomes in terms of best response achieved, time to progression and overall survival.

These improved clinical outcomes result in estimated discounted QALYs of 4.49 for Len/Dex versus 1.43 for Dex, a gain of 1.84 QALYs. As a result, the incremental cost-effectiveness ratio is £38,861 per QALY for Len/Dex versus Dex. The estimated life years gained were 6.58 for Len/Dex versus 2.10 for Dex resulting in an incremental cost per life year gained of £26,421.

Table 56: Results for patients with multiple myeloma who have previously been treated with thalidomide (1 prior therapy)

	Undiscounted		Discounted	
	Len/dex	**Dex**	**Len/dex**	**Dex**
Summary of Clinical Outcomes				
Achieved Best Response (%)				
Complete Response	18%	6%	18%	6%
Partial Response	73%	11%	73%	11%
Stable Disease	9%	72%	9%	72%
Progressive Disease	0%	11%	0%	11%
Patients Progressed (%)	100%	100%	100%	100%
Median Time to Progression (months)	18.82	2.84	18.82	2.84
Deaths (%)	97%	100%	97%	100%
Quality Adjusted Life Years (QALYs)	5.63	1.57	4.49	1.43
Life Years (median)	5.83	1.56	5.83	1.56
Total Life Years (mean)	8.33	2.31	6.58	2.10
Average Cost (per patient)				
Medication	126,073	107	115,775	107
Monitoring	4,162	1,135	3,149	1,017
Adverse Event-Complication	755	188	752	187
Cost-Effectiveness Outcomes				
Incremental cost per QALY Gained	31,911		38,861	
Incremental cost per Life Year Gained	21,522		26,421	

NOTE: The response rates do not exactly match those reported in Section 5, due to rounding.

Patients with multiple myeloma who have previously been treated with thalidomide (at least two prior therapies)

For this comparison, the model predicted median time-to-progression (TTP) for Dex is 4.11 months compared to 4.7 months observed in the clinical trials MM-009 and MM-010 (62).

The estimated discounted cost of medication, monitoring and adverse event management with Len/Dex treatment was estimated at £51,745 per patient compared to £694 with Dex alone. In the Len/Dex group, the largest contributor to the cost is treatment medication. Although costs are higher, patients treated with Len/Dex have significantly better clinical outcomes in terms of best response achieved, time to progression and overall survival.

These improved clinical outcomes result in estimated discounted QALYs of 2.96 for Len/Dex versus 0.70 for Dex, a gain of 2.26 QALYs. As a result, the incremental cost-effectiveness ratio is £22,589 per QALY for Len/Dex versus Dex. The estimated life years gained were 4.43 for Len/Dex versus 1.01 for Dex resulting in an incremental cost per life year gained of £14,927.

Table 57: Results for patients with multiple myeloma who have previously been treated with thalidomide (at least two prior therapies)

	Undiscounted		Discounted	
	Len/dex	**Dex**	**Len/dex**	**Dex**
Summary of Clinical Outcomes				
Achieved Best Response (%)				
Complete Response	8%	1%	8%	1%
Partial Response	48%	15%	48%	15%
Stable Disease	43%	67%	43%	67%
Progressive Disease	1%	18%	1%	18%
Patients Progressed (%)	100%	100%	100%	100%
Median Time to Progression (months)	7.86	4.11	7.86	4.11
Deaths (%)	98%	100%	98%	100%
Quality Adjusted Life Years (QALYs)	3.60	0.72	2.96	0.70
Life Years (median)	3.14	1.08	3.14	1.08
Total Life Years (mean)	5.42	1.03	4.43	1.01
Average Cost (per patient)				
Medication	49,981	106	48,622	106
Monitoring	2,989	423	2,377	412
Adverse Event-Complication	749	177	746	176
Cost-Effectiveness Outcomes				
Incremental cost per QALY Gained	18,407		22,589	
Incremental cost per Life Year Gained	9,727		14,927	

NOTE: The response rates do not exactly match those reported in Section 5, due to rounding.

6.3.2 Subgroup analysis

6.3.2.1 *What were the results of the subgroup analysis/analyses if conducted?*

No subgroup analyses were conducted.

6.3.3 Sensitivity analyses

6.3.3.1 *What were the main findings of the sensitivity analyses?*

(a) Resource use

Because resource utilisation for patients with multiple myeloma in England and Wales was estimated by experts, sensitivity analyses were conducted to explore the uncertainty surrounding the haematologist's responses. Using lower and upper ranges (± 100%) had no major impact on the incremental cost per QALY or per life year gained.

(b) Cost changes

Costs of specific tests to monitor multiple myeloma were obtained from the NHS Reference Costs (82). In the NHS Reference Costs laboratory tests are grouped by appropriate specialty and are not reported as individual items. Thus, the reported costs represent the average cost of all laboratory tests for that specialty. Sensitivity analyses were therefore conducted where these costs were increased or decreased by 100%. Changing these costs had no major impact on the cost per QALY or per life year gained. Likewise varying all costs by ± 100% did not have an impact of the ICERs.

(c) Lenalidomide Costs

Should the current suggestion from the Department of Health for the PPRS, for (88) a 5% saving in the cost of drugs sold to the NHS, become effective, the cost of all drugs would be reduced. Thus the scenario was explored where the cost of lenalidomide was first discounted by 5%. As expected this resulted in a lower incremental cost per QALY or per life year gained.

(d) Best responses, including the NE group in the SD category

Since excluding non-responders appears to favour Len/Dex more than Dex in terms of proportions of best responses, we have included non-evaluable patients in the stable disease group. The result is a decrease in total costs but also a decrease in benefits with a slight increase in the ICER compared to the base case.

(e) Utility scores

The utility scores associated with response levels were obtained from published literature (73). Since there is limited information regarding both point estimates of the health utility information and the variation of the point estimates, sensitivity analyses were performed on utility scores assuming ±10% (

Table 58) variation on the point estimates used for the base case analysis. Increasing utility scores by 10% improved the estimated ICER as the Len/Dex group is associated with better clinical outcomes compared to Dex group. Similarly, reducing the utility scores by 10% resulted in a marginally higher ICER. In a separate analysis we assumed utility scores of 0.75 for PR and 0.70 for SD. This had a minimal impact on the ICER.

Table 58: Utility Scores by Response Rate Used in Sensitivity Analysis

	Sensitivity		
Response	Linear relation between response rates	-10%	+10%
CR	0.81	0.73	0.89
PR	0.75	0.73	0.89
SD	0.70	0.73	0.89
PD	0.64	0.58	0.71

(f) Median overall survival used for calibrating Dex group post progression survival equation.

In the base case analysis, the post progression survival equation was adjusted to reflect the correct post-progression survival with Dex (as explained in **Appendix 8**) using data from MRC trials. To investigate the effect of this calibration of overall survival in the Dex group on the ICER, sensitivity analyses around the median overall survival used for calibration was performed first by varying the adjustment factor (see **Appendix 8**) in such a way to lead to a ±1 month of variation in the median overall survival estimate for the Dex group and then using the 95% CI obtained from the MRC data analysis.

The 95% CI's are created from the MRC analysis, by using the overall population for the MM trials by prior therapies. When subgroups of patients are considered from the overall population, as their characteristics will be different to the overall patient population characteristics, 95%CI's will vary as well. Since we do not know the correct 95% CI's for these subgroups, we varied by +-1 month the OS modification for the SA's. The sensitivity analyses showed that the ICER is sensitive to the calibration factor used in the analyses as it directly affects the life year estimate for the Dex group.

Table 59: Results of univariate sensitivity analyses for patients with multiple myeloma who have received one prior therapy only – discounted results

Analyses description	Incremental cost (£)	Incremental life years	Incremental QALYs	Cost/ QALY (£)	Cost/ LYG (£)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use associated with AEs					
+100% increase in costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-100% decrease in costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use associated with disease monitoring (i.e. tests)					
Upper (+100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower (-100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All Costs (except medication cost)					
+100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide Costs					
5% discount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Response Achieved (includes NE patients in SD group)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility Scores					
+10% increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-10% decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Separate utility scores by response rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: No median overall survival adjustments are considered for the bortezomib comparisons because median overall survival calibration is only performed in the Dexamethasone analyses.

Table 60: Results of univariate sensitivity analyses for patients with multiple myeloma who have received one prior therapy only and have pre-existing peripheral neuropathy – discounted results

Analyses description	Incremental cost (£)	Incremental life years	Incremental QALYs	Cost/ QALY (£)	Cost/ LYG (£)
Base case	104,978	3.23	2.24	46,865	32,501
Resource use associated with AEs					
+100% increase in costs	105,539	3.23	2.24	47,116	32,675
-100% decrease in costs	104,417	3.23	2.24	46,615	32,327
Resource use associated with disease monitoring (i.e. tests)					
Upper (+100%)	106,441	3.23	2.24	47,518	32,954
Lower (-100%)	103,515	3.23	2.24	46,212	32,048
All Costs (except medication cost)					
+100%	107,002	3.23	2.24	47,769	33,128
-100%	102,954	3.23	2.24	45,962	31,874
Lenalidomide Costs	99,894	3.24	2.25	44,397	30,831
5% discount					
Best Response Achieved (includes NE patients in SD group)	102,138	3.16	2.19	46,638	32,322
Utility Scores					
+10% increase	105,076	3.23	2.47	42,241	32,531
-10% decrease	105,163	3.24	2.02	52,061	32,458
Separate utility scores by response rate	104,943	3.24	2.23	47,060	32,390
Median overall survival used for calibration					
-1 month	105,182	3.42	2.36	44,569	30,755
+1 month	105,032	2.99	2.08	50,496	35,128
95% lower CI (16.6 months)	105,807	4.02	2.75	38,475	26,230
95% upper CI (22.9 months)	104,543	2.47	1.75	59,739	42,325

Table 61: Results of univariate sensitivity analyses for patients with multiple myeloma who have received at least two prior therapies – discounted results

Analyses description	Incremental cost (£)	Incremental life years	Incremental QALYs	Cost/ QALY (£)	Cost/ LYG (£)
Base case	60,477	3.71	2.46	24,584	16,301
Resource use associated with AEs					
+100% increase in costs	61,042	3.71	2.46	24,814	16,453
-100% decrease in costs	59,912	3.71	2.46	24,354	16,149
Resource use associated with disease monitoring (i.e. tests)					
Upper (+100%)	62,577	3.71	2.46	25,438	16,867
Lower (-100%)	58,377	3.71	2.46	23,730	15,735
All Costs (except medication cost)					
+100%	63,142	3.71	2.46	25,667	17,019
-100%	57,812	3.71	2.46	23,501	15,583
Lenalidomide Costs					
5% discount	57,550	3.69	2.45	23,490	15,596
Best Response Achieved (includes NE patients in SD group)	58,035	3.66	2.42	23,981	15,857
Utility Scores					
+10% increase	60,488	3.69	2.70	22,403	16,392
-10% decrease	60,660	3.70	2.21	27,448	16,395
Separate utility scores by response rate	60,560	3.69	2.43	24,992	16,412
Median overall survival used for calibration					
-1 month *	60,718	4.03	2.67	22,741	15,067
+1 month	60,041	3.15	2.10	28,591	19,061
95% lower CI (9.5 months)	-	-	--	-	-
95% upper CI (14.2 months)	59,775	2.56	1.71	34,956	23,350

Table 62: Results of univariate sensitivity analyses for patients with multiple myeloma who have previously been treated with thalidomide (1 prior therapy) – discounted results

Analyses description	Incremental cost (£)	Incremental life years	Incremental QALYs	Cost/ QALY (£)	Cost/ LYG (£)
Base case	118,365	4.48	3.06	38,681	26,421
Resource use associated with AEs					
+100% increase in costs	118,930	4.48	3.06	38,866	26,547
-100% decrease in costs	117,800	4.48	3.06	38,497	26,295
Resource use associated with disease monitoring (i.e. tests)					
Upper (+100%)	120,497	4.48	3.06	39,378	26,897
Lower (-100%)	116,233	4.48	3.06	37,985	25,945
All Costs (except medication cost)					
+100%	121,062	4.48	3.06	39,563	27,023
-100%	115,668	4.48	3.06	37,800	25,819
Lenalidomide Costs					
5% discount	112,536	4.49	3.07	36,657	25,064
Utility Scores					
+10% increase	118,204	4.47	3.37	35,075	26,444
-10% decrease	118,325	4.49	2.75	43,027	26,353
Separate utility scores by response rate	118,263	4.48	3.03	39,031	26,398
Median overall survival used for calibration					
-1 month	118,283	4.65	3.16	37,431	25,437
+1 month	117,896	4.23	2.90	40,654	27,871

Table 63: Results of univariate sensitivity analyses for patients with multiple myeloma who have previously been treated with thalidomide (at least two prior therapies) – discounted results

Analyses description	Incremental cost (£)	Incremental life years	Incremental QALYs	Cost/ QALY (£)	Cost/ LYG (£)
Base case	51,051	3.42	2.26	22,589	14,927
Resource use associated with AEs					
+100% increase in costs	51,621	3.42	2.26	22,841	15,094
-100% decrease in costs	50,481	3.42	2.26	22,337	14,761
Resource use associated with disease monitoring (i.e. tests)					
Upper (+100%)	53,016	3.42	2.26	23,458	15,502
Lower (-100%)	49,086	3.42	2.26	21,719	14,353
All Costs (except medication cost)					
+100%	53,586	3.42	2.26	23,711	15,668
-100%	48,516	3.42	2.26	21,467	14,186
Lenalidomide Costs					
5% discount	48,747	3.45	2.27	21,474	14,130
Utilities					
+10% increase	51,008	3.44	2.50	20,403	14,828
-10% decrease	51,012	3.44	2.04	25,006	14,829
Separate utility scores by response rate	51,036	3.44	2.25	22,683	14,836
Median overall survival used for calibration					
-1 month *	51,350	3.89	2.56	20,059	13,201
+1 month	50,643	2.78	1.84	27,523	18,217

The parameters considered and results for the multivariate sensitivity analyses are included below in Table 64 and Table 65.

Table 64: Parameters for the multivariate sensitivity analyses

	Parameter to Change		
	Lenalidomide Cost Reduction	Utility Score	Median Overall Survival
Scenario 1	0%	10% decrease	+ 1 month
Scenario 2	5%	10% increase	- 1 month

Table 65: Results of the multivariate sensitivity analysis – discounted

Analyses description	Incremental cost (£)	Incremental life years	Incremental QALYs	Cost/ QALY (£)	Cost/ LYG (£)
1 Prior vs. Dex					
Scenario 1	104,915	3.00	1.88	55,806	34,972
Scenario 2	100,145	3.40	2.59	38,666	29,454
2+ Prior vs. Dex					
Scenario 1	60,164	3.16	1.89	31,833	19,039
Scenario 2	57,821	4.03	2.94	19,667	14,348
1 Prior (Thalidomide) vs. Dex					
Scenario 1	118,273	4.23	2.61	45,315	27,961
Scenario 2	112,350	4.66	3.49	32,192	24,109
2+ Prior (Thalidomide) vs. Dex					
Scenario 1	48,675	2.80	1.67	29,147	17,384
Scenario 2	48,957	3.89	2.81	17,422	12,585
1 Prior vs. Bortezomib					
Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: No median overall survival adjustments are considered for the bortezomib comparisons

Probabilistic sensitivity analyses for one prior therapy analysis Len/Dex vs bortezomib

Results of the probabilistic sensitivity analyses for the one prior therapy base case analysis are presented in Table 66. The cost-effectiveness acceptability curve and cost-effectiveness plane are shown in

Figure 11 and Figure 12 respectively. Probabilistic sensitivity analyses around time to progression and post progression survival prediction equations, utility scores and costs showed that the model results are consistent. The analyses produced ICERs that were between [redacted]QALY and [redacted]/QALY (min/max).

Table 66: Probabilistic sensitivity analysis for one prior therapy analysis Len/Dex vs bortezomib

Statistics:	Incremental Cost (£)	Incremental QALY	Incremental cost per QALY (£)
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]	[redacted]
Range Minimum	[redacted]	[redacted]	[redacted]
Range Maximum	[redacted]	[redacted]	[redacted]
Mean Std. Error	[redacted]	[redacted]	[redacted]
2.5% Percentile	[redacted]	[redacted]	[redacted]
97.5% Percentile	[redacted]	[redacted]	[redacted]

Costs and benefits discounted 3.5%

Figure 11: Cost-effectiveness acceptability curve – one prior therapy vs bortezomib

Figure 12: Cost-effectiveness plane – one prior therapy vs bortezomib

Probabilistic sensitivity analyses for patients with one prior therapy and pre-existing peripheral neuropathy

Results of the probabilistic sensitivity analyses for the one prior therapy base case analysis, Len/Dex vs Dex are presented in Table 67. The cost-effectiveness acceptability curve and cost-effectiveness plane are shown in Figure 13 and Figure 14 respectively. Analyses produced ICERs that were between £23,602 and £89,848/QALY

Table 67: Probabilistic sensitivity analysis for patients with one prior therapy and pre-existing peripheral neuropathy

	Incremental Cost (£)	Incremental QALY	Incremental cost per QALY (£)
Mean	£107,645	2.29	£48,138
Median	£105,714	2.27	£47,148
Standard Deviation	£15,084	0.43	-
Range Minimum	£72,596	1.06	£23,602
Range Maximum	£181,471	4.06	£89,848
Mean Std. Error	£275	0.01	-
2.5% Percentile	£84,186	1.54	£33,616
97.5% Percentile	£142,308	3.19	£68,291

Costs and benefits discounted 3.5%

Figure 13: Cost-effectiveness acceptability curve – Probabilistic sensitivity analysis for patients with one prior therapy and pre-existing peripheral neuropathy

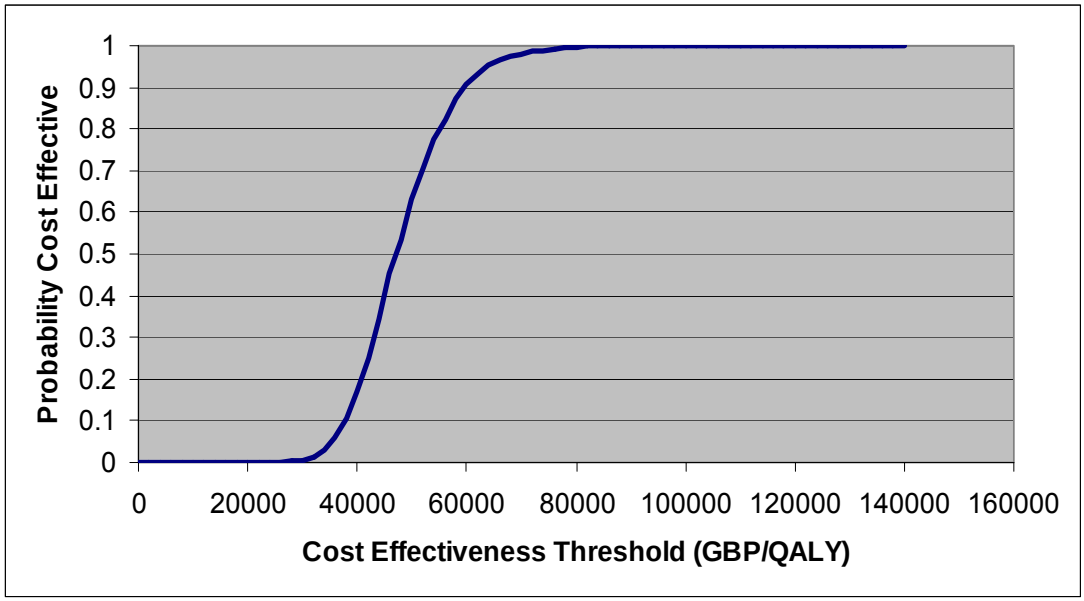
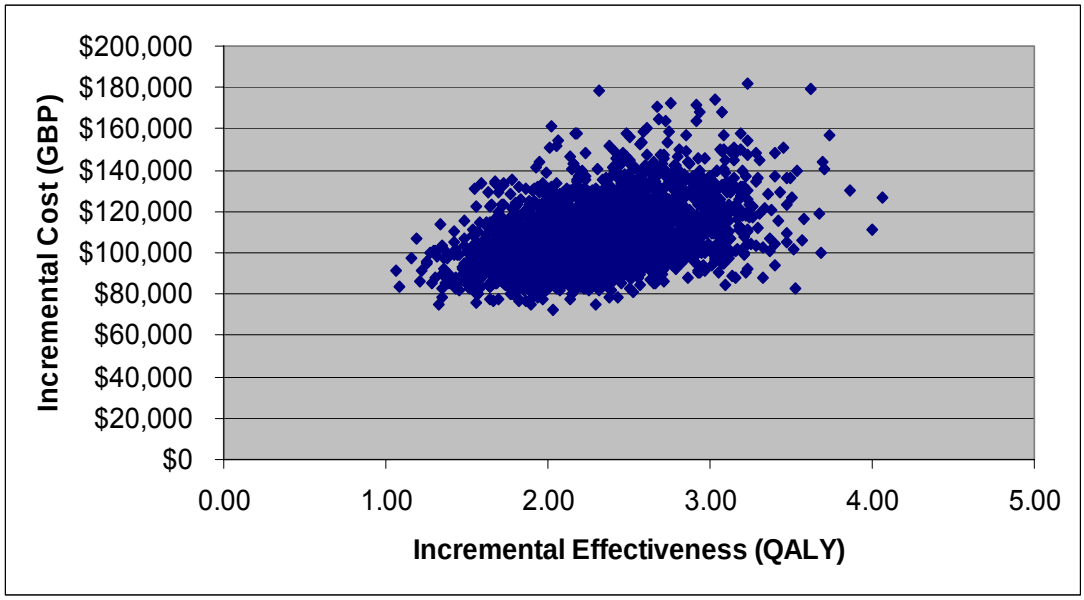


Figure 14: Cost-effectiveness plane – Probabilistic sensitivity analysis for patients with one prior therapy and pre-existing peripheral neuropathy



Probabilistic sensitivity analyses for at least two prior therapies

Results of the probabilistic sensitivity analyses for the one prior therapy base case analysis, Len/Dex vs Dex are presented in Table 68. The cost-effectiveness acceptability curve and cost-effectiveness plane are shown in Figure 15 and Figure 16 respectively. While analyses produced ICERs that were between £15,724/QALY and £49,654/QALY (min/max), approximately 45% of the runs produced ICERs below £24,000/QALY.

Table 68: Probabilistic sensitivity analysis for two prior therapies

	Incremental Cost (£)	Incremental QALY	Incremental cost per QALY (£)
Mean	£60,567	2.49	£24,899
Median	£60,574	2.47	£24,521
Standard Deviation	£1,051	0.38	-
Range Minimum	£56,948	1.24	£15,724
Range Maximum	£63,957	3.98	£49,654
Mean Std. Error	£19	0.01	-
2.5% Percentile	£58,547	1.79	£18,480
97.5% Percentile	£62,700	3.31	£33,668

Costs and benefits discounted 3.5%

Figure 15: Cost-effectiveness acceptability curve – at least two prior therapies

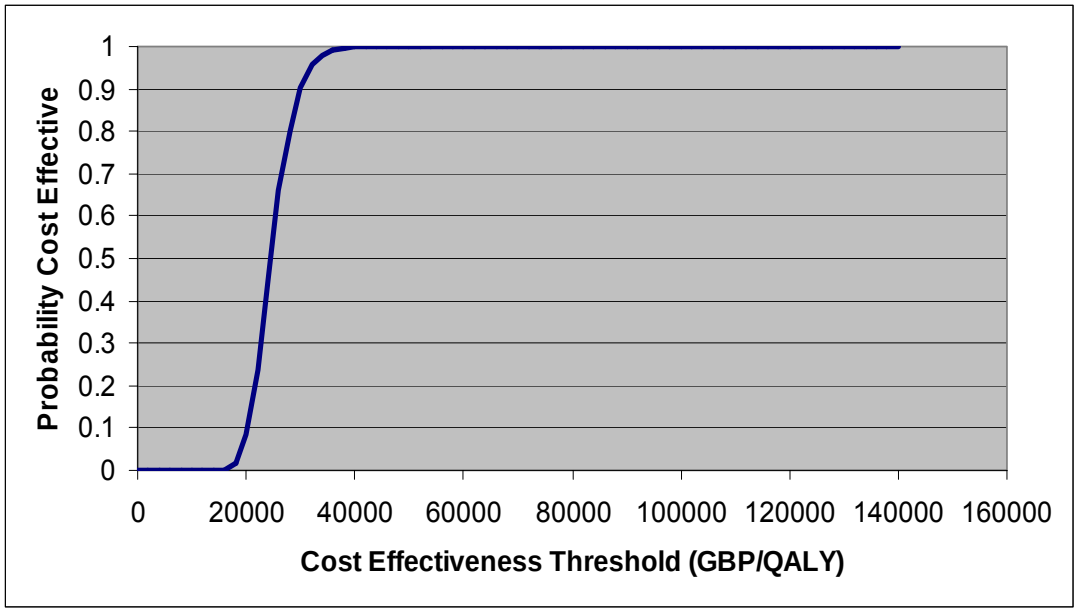
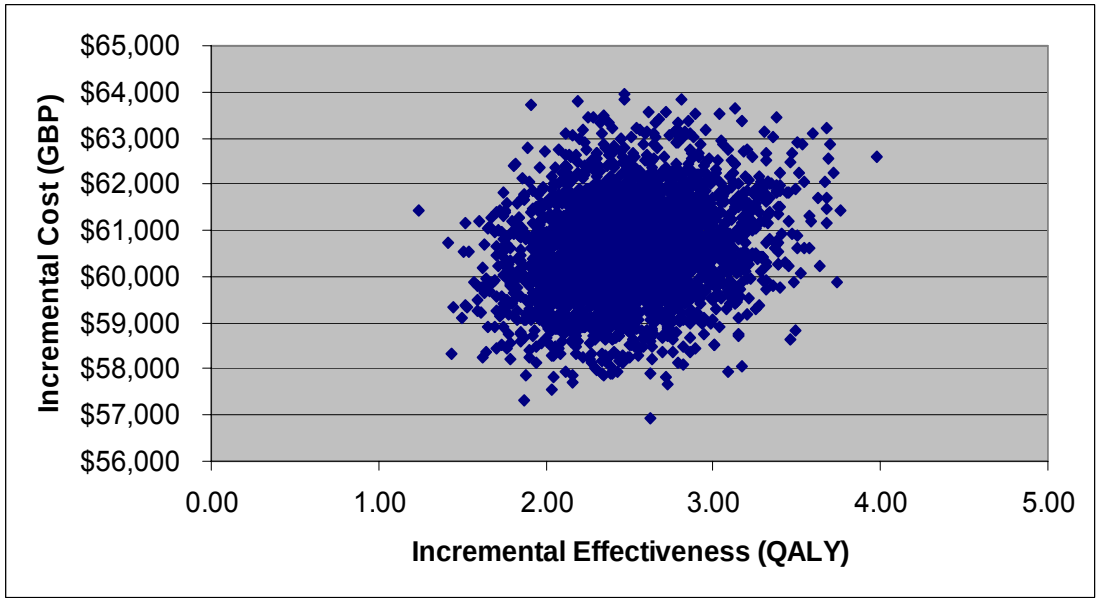


Figure 16: Cost-effectiveness plane – at least two prior therapies



Probabilistic sensitivity analyses for patients with multiple myeloma who have previously been treated with thalidomide (1 prior therapy)

Results of the probabilistic sensitivity analyses for this analysis are presented in Table 69. The cost-effectiveness acceptability curve and cost-effectiveness plane are shown in Figure 17 and Figure 18 respectively. While analyses produced ICERs that were between £20,951 and £72,860/QALY (min/max).

Table 69: Probabilistic sensitivity analysis for one prior therapy with thalidomide

	Incremental Cost (£)	Incremental QALY	Incremental cost per QALY (£)
Mean	£120,483	3.09	£39,874
Median	£119,053	3.08	£39,074
Standard Deviation	£14,360	0.52	-
Range Minimum	£85,414	1.56	£20,951
Range Maximum	£184,790	5.09	£72,860
Mean Std. Error	£262	0.01	-
2.5% Percentile	£96,844	2.10	£28,098
97.5% Percentile	£153,151	4.14	£56,220

Costs and benefits discounted 3.5%

Figure 17: Cost-effectiveness acceptability curve – one prior therapy with thalidomide

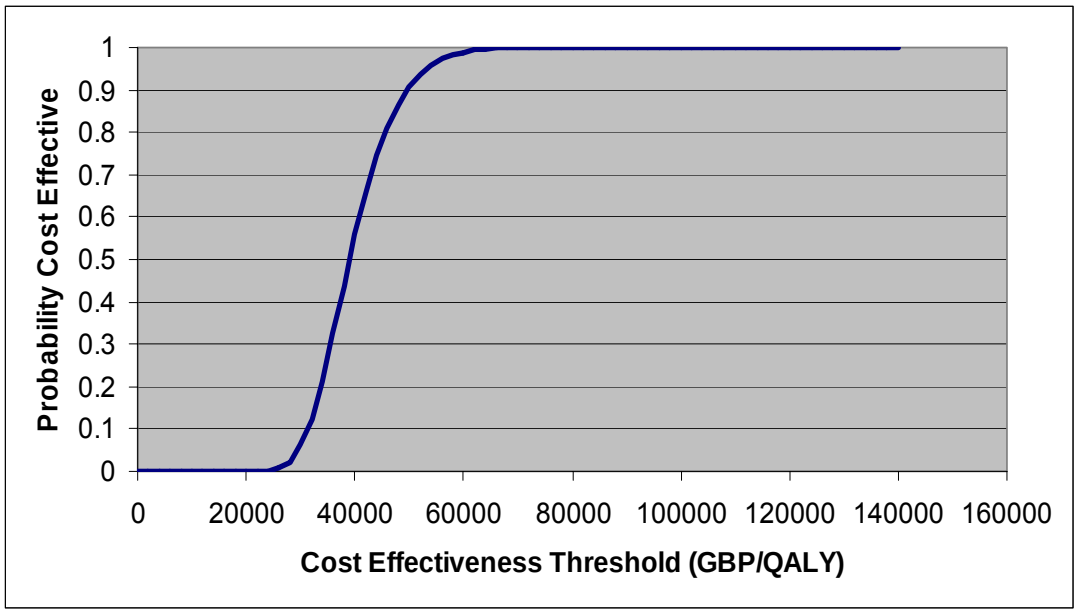
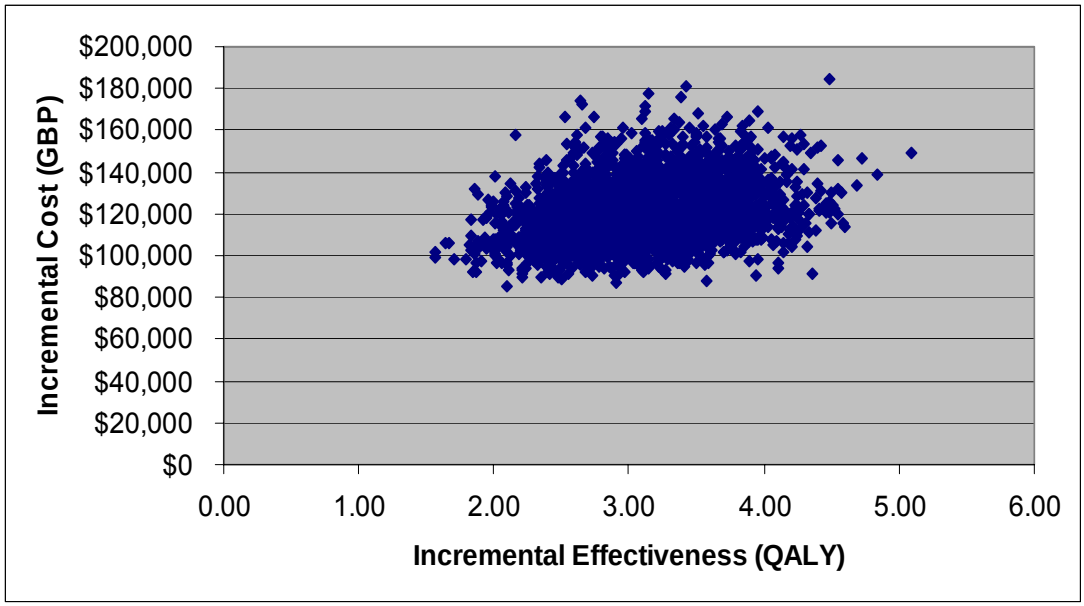


Figure 18: Cost-effectiveness plane – one prior therapy with thalidomide



Probabilistic sensitivity analyses for for patients with multiple myeloma who have previously been treated with thalidomide (at least two prior therapies)

Results of the probabilistic sensitivity analyses for the one prior therapy base case analysis are presented in Table 70**.** The cost-effectiveness acceptability curve and cost-effectiveness plane are shown in Figure 19 and Figure 20 respectively. While analyses produced ICERs that were between £15,402/QALY and £32,847/QALY (min/max), approximately 73% of the runs produced ICERs below £24,000/QALY.

Table 70: Probabilistic sensitivity analysis for at least two prior therapies including thalidomide

	Incremental Cost (£)	Incremental QALY	Incremental cost per QALY (£)
Mean	£51,167	2.29	£22,592
Median	£51,168	2.28	£22,392
Standard Deviation	£843	0.26	-
Range Minimum	£48,484	1.51	£15,402
Range Maximum	£54,566	3.38	£32,847
Mean Std. Error	£15	0.00	-
2.5% Percentile	£49,492	1.81	£18,351
97.5% Percentile	£52,820	2.81	£28,204

Costs and benefits discounted 3.5%

Figure 19: Cost-effectiveness acceptability curve – at least two prior therapies including thalidomide

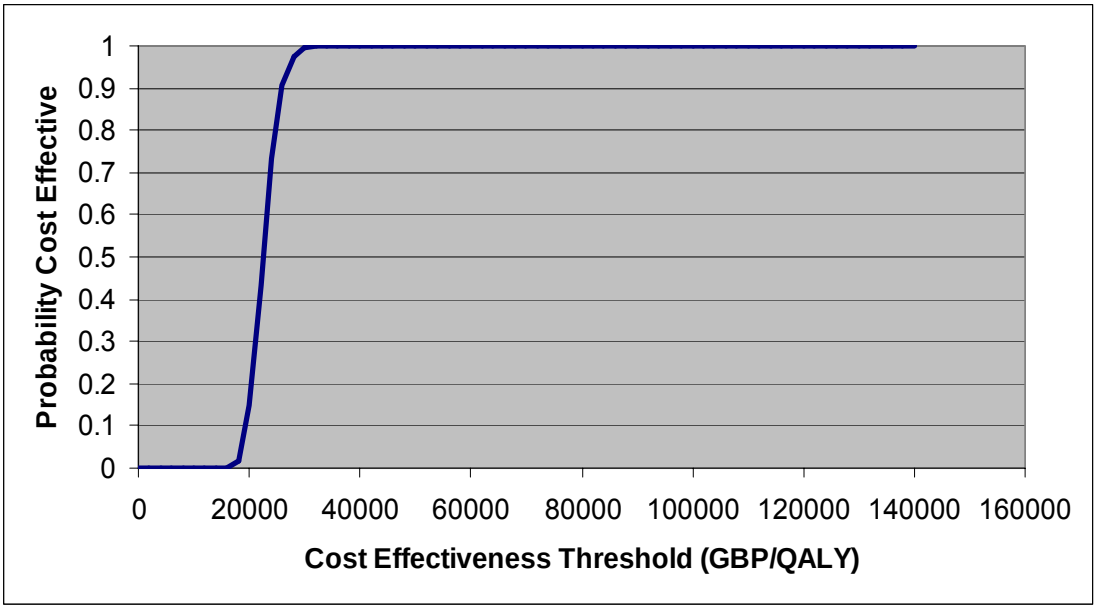
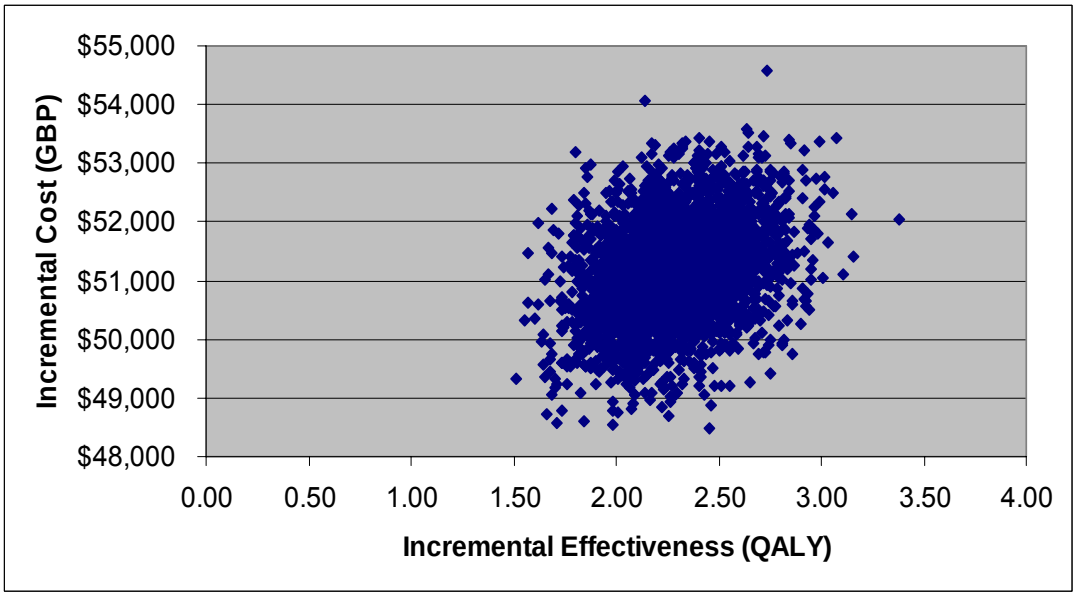


Figure 20: Cost-effectiveness plane – at least two prior therapies including thalidomide



6.3.4 Interpretation of economic evidence

6.3.4.1 *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this*

evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results of this economic evaluation will vary from those previously published (67;68) because the analysis presented here uses a model that has been built to run in MS Excel as recommended by NICE, it considers different treatment comparisons to reflect the scope of the appraisal from the Institute, and importantly, the model updates a number of key data inputs, for example, data from the MRC Myeloma Trials to provide accurate estimates of overall survival for patients receiving both one prior and two prior therapies. A number of other elements and adaptations have been made to this model, to ensure adherence to the NICE reference case, for example, the use of a lifetime time horizon for analysis.

6.3.4.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology?*

The evaluation assesses outcomes in several different patient populations that are consistent with the patients we would expect to be considered for lenalidomide treatment. These patient groups have been included to try and reflect the breadth of the scope for this appraisal and to take into account existing NICE recommendations for bortezomib.

6.3.4.3 *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

The main strengths of this economic evaluation are:

- The use of the latest and most relevant clinical data for modelling the course of disease history at the point of disease progression. The model utilises data from patients studied in the myeloma IV, V, VI, and VIII trials enrolled between 1980 and 1997 and conducted by the UK Medical Research Council (MRC). The MRC data include information on patients from multi-centre trials on a total of 2,528 patients starting first-line treatment. Average follow-up of these data exceeds 7.5 years. A specific analysis of the data was undertaken in collaboration with the MRC in order to derive a survival equation that could be applied to the Dex patients in the MM-009 and MM-010 trials to estimate what their overall survival would have been had they not crossed over to lenalidomide. Our use of the MRC trial data represent a significant improvement on previous attempts to adjust for cross over from dexamethasone to bortezomib in the APEX trial (21) which used published data from the Mayo clinic in the US (3).

- The analysis pools the two pivotal trials which combined considers a patient population of 692 individuals. This represents a significant and robust body of evidence for a relatively rare disease and a medication which has orphan status.

- The modelling approach uses patient-level simulation in preference to a cohort approach and this is important to include the flexibility required to properly model response, duration of response, and survival among individual patients with multiple myeloma. To achieve a more accurate reflection of the decision problem, the model was implemented as a discrete event simulation (DES). This modelling technique conceptualizes the course of disease and its management in terms of events rather than states. The simulation considers the impact of these events (e.g. disease progression) on patients' health and

on other components of the system, such as resource consumption. DES is a well-established approach to modelling complex processes over time.

The model is not without its limitations, and the most important ones are related to the availability of data for the analyses:

- Direct clinical trial data comparing Len/Dex to treatment with bortezomib are not available, meaning comparisons had to be made using indirect methods. While the trials for the different therapies had similar designs and the patients enrolled had similar characteristics, there are undoubtedly differences in the trials that cannot be controlled for and this was highlighted in the results of the indirect comparison. The analysis showed results which favoured Len/Dex treatment when comparing the primary endpoint of TTP and the secondary endpoints of partial response, stable disease & progressive disease and spuriously appeared to favour bortezomib treatment when comparing complete response, even though more complete responses were observed for Len/Dex. Most importantly because of the cross-over from control to experimental treatment in both the lenalidomide studies (MM-009 and MM-010) and the bortezomib APEX study, the studies did not have a common comparator making such indirect comparison techniques inappropriate for the overall survival endpoint. The inconsistent results of the indirect comparison are not surprising given these issues and the limited number of data points available.

- All clinical effectiveness estimates in the model are based on clinical trial data. The extent to which these benefits will hold in routine practice is always uncertain, however, sub-group analysis has shown that Len/Dex is effective in many groups of patients

- Treatment for patients with this disease is evolving rapidly with the recent approval and introduction of new therapies. A true or adequately representative base case for comparison may therefore be difficult to establish for multiple myeloma treatment. The treatment regimens used and modelled in this evaluation are most appropriate as a baseline for comparison but they are not exhaustive of the treatment scenarios in which Len/Dex could be considered for use.

- The cost effectiveness of existing treatment options is unknown and this makes judging the cost effectiveness of Len/Dex in comparison particularly difficult. For instance, the NICE recommendation for bortezomib was informed by an economic evaluation which used survival data not representative of the survival experience of patients in the UK. The evaluation presented here uses more UK relevant and up to date data to assess survival than was used in the earlier evaluation and furthermore, the bortezomib recommendation by NICE is founded on the Velcade Response Scheme. Data for this scheme are not currently published and it is therefore not possible to evaluate the expected cost and efficacy of bortezomib in routine practice for comparative purposes.

6.3.4.4 *What further analyses could be undertaken to enhance the robustness/completeness of the results?*

Confidence in the results of the economic evaluation comparing Len/Dex to bortezomib could be improved considerably if head-to-head clinical trial data were available comparing the agents. The indirect evidence is inconclusive, reflecting the

limited comparable trial data currently available. In the absence of clinical trial data, published data about the Velcade Response Scheme would help to assess the true cost effectiveness of bortezomib to the NHS and therefore the relative cost effectiveness of Len/Dex.

Additional patient reported outcome data would also be useful to better assess the outcomes presented here. Direct evidence of the health status for patients in the clinical trials and the impact of treatment on quality of life are not available but are important elements within the evaluation. Given the known efficacy of Len/Dex it would be unethical to undertake an additional clinical trial compared with standard care in this setting, but additional quality of life data may be considered and collected outside of the trial setting.

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

7.1 *What is the estimated annual budget impact for the NHS in England and Wales?*

We have estimated the first year budget impact for the NHS in England and Wales following the introduction of Len/Dex to be between £7.8 million for patients with one prior therapy and pre-existing peripheral neuropathy and £46.3 million for patients with two prior therapies. This rises to £17.9 million and £66.4 million in the fifth year depending on the patient population. Table 71 to Table 75 below present the total budget impact according to the current status quo, according to an increasing market share for Len/Dex over time, and the net difference.

Table 71: Budget impact for patient with one prior therapy

Patient starts treatment in:	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact with status quo					
Len/Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact with projected market shares					
Len/Dex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 72: Budget impact for patients with one prior therapy and preexisting peripheral neuropathy

Patient starts treatment in:	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact with status quo					
Len/Dex	£0	£0	£0	£0	£0
Dex	£188,581	£185,066	£196,258	£209,053	£220,256
Total	£188,581	£185,066	£196,258	£209,053	£220,256
Budget impact with projected market shares					
Len/Dex	£7,952,859	£8,938,819	£10,577,853	£12,570,194	£18,082,202
Dex	£75,432	£64,094	£53,513	£40,090	£23,264
Total	£8,028,291	£9,002,914	£10,631,366	£12,610,284	£18,105,466
Net budget impact	**£7,839,710**	**£8,817,848**	**£10,435,108**	**£12,401,231**	**£17,885,210**

Table 73: Budget impact for patients with two prior therapies

Patient starts treatment in:	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact with status quo					
Len/Dex	£0	£0	£0	£0	£0
Dex	£1,182,276	£857,452	£786,233	£795,772	£826,484
Total	£1,182,276	£857,452	£786,233	£795,772	£826,484
Budget impact with projected market shares					
Len/Dex	£46,981,427	£46,699,839	£51,482,418	£58,598,055	£67,225,273
Dex	£472,910	£280,715	£173,768	£93,265	£16,399
Total	£47,454,337	£46,980,554	£51,656,186	£58,691,320	£67,241,672
Net budget impact	**£46,272,061**	**£46,123,101**	**£50,869,953**	**£57,895,548**	**£66,415,188**

Table 74: Budget impact for patients with one prior therapy with thalidomide

Patient starts treatment in:	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact with status quo					
Len/Dex	£0	£0	£0	£0	£0
Dex	£251,267	£245,227	£259,114	£276,485	£291,844
Total	£251,267	£245,227	£259,114	£276,485	£291,844
Budget impact with projected market shares					
Len/Dex	£12,026,817	£14,208,745	£17,003,883	£20,088,437	£23,479,220
Dex	£100,507	£84,858	£70,420	£52,827	£30,778
Total	£12,127,323	£14,293,602	£17,074,302	£20,141,264	£23,509,999
Net budget impact	**£11,876,056**	**£14,048,375**	**£16,815,189**	**£19,864,779**	**£23,218,155**

Table 75: Budget impact for patient with two prior therapies, including thalidomide

Patient starts treatment in:	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact with status quo					
Len/Dex	£0	£0	£0	£0	£0
Dex	£462,815	£340,672	£307,132	£311,707	£324,933
Total	£462,815	£340,672	£307,132	£311,707	£324,933
Budget impact with projected market shares					
Len/Dex	£17,057,754	£16,050,718	£17,203,664	£19,596,148	£22,483,185
Dex	£185,126	£111,894	£67,500	£36,216	£6,536
Total	£17,242,880	£16,162,612	£17,271,165	£19,632,364	£22,489,721
Net budget impact	**£16,780,065**	**£15,821,941**	**£16,964,033**	**£19,320,657**	**£22,164,788**

The yearly figures are calculated from the cost of the patients starting in that year and the cost of the patients started in previous years, but continuing to accrue treatment costs. Therefore, for example, the cost of Len/Dex in year 2 is estimated from the following:

- Cost of patients starting in year 2

  number of eligible patients in year 2 X predicted market share of Len/Dex in year 2 X cost of patients starting treatment = £17,451,950

- Cost of patients who started in year 1, but still accruing costs in year 2

  number of eligible patients in year 1 X predicted market share of Len/Dex in year 1 X cost of patients in their second year of treatment = £14,472,404

Table 76: Calculation method for patients with one prior therapy

Len/Dex	Year		Year 1	Year 2	Year 3	Year 4	Year 5
	Starting treatment in year	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2		[redacted]	[redacted]	[redacted]	[redacted]
		3			[redacted]	[redacted]	[redacted]
		4				[redacted]	[redacted]
		5					[redacted]
	Total		£28,403,068	£31,924,354	£37,778,046	£44,893,551	£52,887,209
Bortezomib	**Year**		**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
	Starting treatment in year	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2		[redacted]	[redacted]	[redacted]	[redacted]
		3			[redacted]	[redacted]	[redacted]
		4				[redacted]	[redacted]
		5					[redacted]
	Total		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.2 *What number of patients were assumed to be eligible? How was this figure derived?*

The tables below provided a step by step explanation of how the eligible patient population was derived.

Step 1: Raw data

The International Agency for Research on Cancer (9) reports data for multiple myeloma and malignant plasma cell neoplasms (ICD-10 C90.0 – C90.2). As data from the Office for National Statistics (10) does not provide both prevalence and incidence figures, numbers of cases were derived from the GLOBOCAN database from the International Agency for Research on Cancer (9) .

Table 77: Globocan 2002 data (9)

Globocan 2002	Country/ Region	Incidence			Mortality			Prevalence	
		Cases	Crude Rate	ASR(W)	Deaths	Crude Rate	ASR(W)	1-year	5-year
Males	United Kingdom	2,087	7.1	4.3	1,283	4.4	2.5	1,483	4,087
Females	United Kingdom	1,946	6.4	3.1	1,209	4	1.8	1,369	3,806
Total	United Kingdom	4,033			2,492				7,893

Table 78: Population of UK (89)

	Population 2006	Percentage of the population
England	50,762,900	83.8%
Wales	2,965,900	4.9%
England and Wales		*88.7%*
Scotland	5,116,900	8.4%
Northern Ireland	1,741,600	2.9%
Total	60,587,300	100.0%

Step 2: Conversion of data to England and Wales

We obtained data for the population of the UK by region from the Office for National Statistics (89) (Table 78) permitting the conversion of the GLOBOCAN data (9) into the relevant data for England and Wales (Table 79)

With the help of the population data from the Office for National Statistics (89) (Table 78) the number of case for the UK were multiplied by the percentage of the population living in England and Wales resulting in an incidence of 3,575 patients and a 5-year prevalence of 7,000.

Table 79: Estimation from Globocan 2002 for England and Wales

Globocan 2002	Country/Region	Incidence	Prevalence
		Cases	5-year
Males	England and Wales	1,851	3,624
Females	England and Wales	1,726	3,375
Total	England and Wales	3,576	7,000

Step 3: Increase of incidence

Given that the GLOBOCAN data are not the most recent (9), and the data for England from the Office for National Statistics (10) shows a yearly increase in incidence in multiple myeloma and malignant plasma cell neoplasms (Table 80), the incidence and prevalence data probably underestimate the true current figures. Assuming a constant increase in the future for England and Wales, we used the average increase in incidence for both females and males in England over the past five years to calculate the trend associated with the increase in the multiple myeloma and malignant plasma cell neoplasms population (Table 80).

Table 80: Increase of incidence (10)

Year	Incidence		Increase	
	Males	Females	Males	Females
2001	1,528	1,331	NA	NA
2002	1,567	1,361	0.0249	0.0220
2003	1,657	1,404	0.0543	0.0306
2004	1,691	1,394	0.0201	-0.0072
2005	1,739	1,504	0.0276	0.0731
average increase rate			0.0317	0.0297

Step 4: Forecast with increasing incidence/prevalence

Table 81: Forecast with increasing incidence

Forecast incidence	Males	Females	Total
2002	1,851	1,726	3,576
2003	1,951	1,779	3,730
2004	1,991	1,766	3,756
2005	2,045	1,895	3,940
2006	2,110	1,951	4,062
2007	2,177	2,009	4,186
2008	2,246	2,069	4,315
2009	2,318	2,130	4,448
2010	2,391	2,193	4,584
2011	2,467	2,258	4,725
2012	2,545	2,325	4,870
2013	2,626	2,394	5,020

Table 82: Forecast with increasing prevalence

Forecast prevalence	Males	Females	Total
2002	3,624	3,375	7,000
2003	3,821	3,479	7,300
2004	3,898	3,454	7,352
2005	4,006	3,706	7,712
2006	4,133	3,816	7,949
2007	4,264	3,929	8,193
2008	4,399	4,046	8,445
2009	4,539	4,166	8,704

Step 5: Estimating incidence and prevalence for multiple myeloma only

The ICD-10 C90.0 – C90.2 codes used by GLOBOCAN includes malignant plasma cell neoplasms as well as multiple myeloma. Thus the proportion of patients suffering from multiple myeloma (94.5%) within the ICD-10 codes C90.0 – C90.2 was calculated based on the inpatient data (90). Of these 39% has relapsing-remitting multiple myeloma (91).

Table 83: Number of patients in England and Wales with relapsing-remitting multiple myeloma

	Males	Females	Total
Forecast incidence			
2009	854	785	1,639
2010	881	808	1,689
2011	909	832	1,741
2012	938	857	1,795
2013	968	882	1,850
Forecast prevalence			
2009	1,673	1,535	3,208

Step 6: Estimation of the eligible patient population

- To estimate the proportion of patients who would receive one or two or more prior therapies, the percentage of each enrolled in the MM-009 and MM-010 trials (35.23% and 64.67% respectively) was used (5;6) as a proxy.
- 28% of patients were assumed unsuitable for bortezomib (92) due to their pre-existing peripheral neuropathy.
- To estimate the proportion of patients who would have received prior thalidomide treatment, the percentage of those enrolled in the MM-009 and MM-010 trials (39%) was used as a proxy (5;6). Thus the numbers of patient with one and two or more prior therapies were multiplied by 39%.
- 100% of patients were assumed to have received prior thalidomide for the prior thalidomide specific analyses

The patient numbers for each patient population are presented below in Table 84 to Table 88.

Table 84: Number of eligible patients with one prior therapy

	Males	Females	Total
Forecast incidence			
2009	301	277	577
2010	310	285	595
2011	320	293	613
2012	330	302	632
2013	341	311	652
Forecast prevalence			
2009	589	541	1,130

Table 85: Number of eligible patients with two prior therapies

	Males	Females	Total
Forecast incidence			
2009	553	508	1,062
2010	571	524	1,094
2011	589	539	1,128
2012	608	555	1,163
2013	627	571	1,198
Forecast prevalence			
2009	1083	994	2,078

Table 86: Number of eligible patients with one prior therapy unsuitable for bortezomib

	Males	Females	Total
Forecast incidence			
2009	84	77	162
2010	87	80	167
2011	90	82	172
2012	93	85	177
2013	95	87	182
Forecast prevalence			
2009	165	151	316

Table 87: Number of eligible patients with one prior thalidomide therapy

	Males	Females	Total
Forecast incidence			
2009	117	107	224
2010	121	111	231
2011	125	114	238
2012	128	117	246
2013	133	121	253
Forecast prevalence			
2009	229	210	439

Table 88: Number of eligible patients with two prior therapies including thalidomide

	Males	Females	Total
Forecast incidence			
2009	215	198	413
2010	222	204	425
2011	229	210	438
2012	236	216	452
2013	244	222	466
Forecast prevalence			
2009	421	387	808

7.3 *What assumption(s) were made about current treatment options and uptake of technologies?*

Table 89: The uptake of lenolidamide in the next five years

Year	% Treated with lenalidomide
1	60%
2	70%
3	80%
4	90%
5	100%

We have assumed a rapid uptake of lenalidomide following positive NICE recommendations.

7.4 *What assumption(s) were made about market share (where relevant)?*

In the patient population with one prior therapy based on the previous NICE recommendation, all patients that are eligible for treatment with Len/Dex are assumed to currently receive bortezomib.

7.5 *What unit costs were assumed? How were these calculated?*

The unit costs were taken directly from the economic model as presented in section 6 of the report and are detailed in **Appendix 11**.

7.6 *In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?*

The drug costs were taken directly from the economic model as presented in section 6 and **Appendix 11** of the report.

The detailed annual costs for each patient population from the cost-effectiveness model are presented in the table below.

Table 90: Direct annual costs associated with the treatment

		1 prior therapy			2 prior therapies		1 prior thalidomide therapy		2 prior therapies inc. thalidomide	
		Len/Dex	Dex	Bortezomib	Len/Dex	Dex	Len/Dex	Dex	Len/Dex	Dex
1st year	**Medication**	£40,902	£109	[redacted]	£36,668	£109	£44,655	£107	£34,163	£106
	Monitoring and AE Management Complication	£989	£487	[redacted]	£1,017	£460	£976	£465	£1,035	£467
	Total	£41,891	£596	[redacted]	£37,685	£569	£45,631	£572	£35,198	£573
2nd year	**Medication**	£21,019	£0	[redacted]	£13,951	£0	£25,552	£0	£11,125	£0
	Monitoring and AE Management Complication	£326	£271	[redacted]	£353	£113	£320	£257	£368	£120
	Total	£21,345	£271	[redacted]	£14,304	£113	£25,872	£257	£11,493	£120
3rd year	**Medication**	£11,988	£0	[redacted]	£4,913	£0	£15,263	£0	£2,642	£0
	Monitoring and AE Management Complication	£294	£154	[redacted]	£317	£10	£327	£144	£319	£6
	Total	£12,282	£154	[redacted]	£5,230	£10	£15,590	£144	£2,961	£6
4th year	**Medication**	£7,806	£0	[redacted]	£1,554	£0	£9,313	£0	£513	£0
	Monitoring and AE-Complication Management	£251	£99	[redacted]	£253	-£2	£301	£94	£243	-£3
	Total	£8,057	£99	[redacted]	£1,807	-£2	£9,614	£94	£756	-£3
5th year	**Medication**	£5,778	£0	[redacted]	£597	£0	£6,055	£0	£114	£0

		1 prior therapy			2 prior therapies		1 prior thalidomide therapy		2 prior therapies inc. thalidomide	
		Len/Dex	Dex	Bortezomib	Len/Dex	Dex	Len/Dex	Dex	Len/Dex	Dex
	AE-Complication Management	£202	£65	[redacted]	£201	£2	£260	£63	£192	£3
	Total	£5,980	£65	[redacted]	£798	£2	£6,315	£63	£306	£3

NOTE: The results for the different years are from different simulation runs that are run stochastically, thus negative numbers might appear in the breakdown of the costs.

7.7 *Were there any estimates of resource savings? If so, what were they?*

No direct resource or cost savings are anticipated.

7.8 *Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?*

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