NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation

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List of abbreviations

Table 1: Table of abbreviations

Acronym	Definition
AE	Adverse event
ASCT	Auto stem cell transplant
Allo-SCT	Allogenic stem cell transplant
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
BNF	British National Formulary
BCNU	Bis-chloroethylnitrosourea
BCSH	British Committee for Standards in Haematology
CAD	Cyclophosphamide, Adriamycin® (doxorubicin) and dexamethasone
CD	Cyclophosphamide and dexamethasone
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CrI	Credible Intervals
CRF	Case report form
CSR	Clinical study report
CTD	Cyclophosphamide, thalidomide, and dexamethasone
CVAD	Cyclophosphamide, vincristine, Adriamycin® (doxorubicin) and dexamethasone
d	days
DCEP	Dexamethasone combined with cyclophosphamide, etoposide or etoposide phosphate, and cisplatinum
Del	Deletion
Dex	Dexamethasone
DIC	Deviance information criterion
DOCR	Duration of complete response
DSU	Decision Support Unit
DVT	Deep vein thrombosis
EBMT	European Group for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EHA	European Hematology Association
ERG	Evidence Review Group
EORTC	European organisation for research and treatment of cancer
EQ5D	Euro-QoL 5D
FBC	Full blood count
FE	Fixed-effect
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
HDC	High-dose chemotherapy
HDM	High-dose melphalan
HDT	High-dose therapy
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HRG	Health Related Groups
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IDM	Intermediate dose melphalan
IFM	Intergroupe Francophone du Myelome
IG	Immunoglobulin
IK	Interleukin
IMW	International Myeloma Workshop
INR	International normalised ratio
ISS	International Staging System
ITT	Intention-to-treat
IV	Intravenous
kg	kilograms
KM	Kaplan Meier
LDH	Lactate dehydrogenase
LYG	Life years gained
m	Metres
Max	Maximum
MCMC	Markov chain Monte Carlo

MRC	Medical Research Council
mg	Milligrams
MGUS	Monoclonal gammopathy of undetermined significance
min	Minute
Min	Minimum
ml	Millilitre
MIX	Myeloma IX
MM	Multiple myeloma
MP	Melphalan
MR	Minimal response
MRC	Medical Research Council
MTC	Mixed treatment comparison
MU	Million units
n	Sample size
N	Group size
N/A	Not applicable
NC	No change
nCR	Near complete response
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMA	Nonmyeloablative
NOK	Norwegian Kroner
NR	Not reported
NR	Non responders (in economic section 7)
OPATT	Outpatient Attendance
OR	Overall Response
ORR	Overall Response Rate
OS	Overall survival
PAD	Velcade® (bortezomib), Adriamycin® (doxorubicin), and dexamethasone
PBSC	Peripheral Blood Stem Cells
PBR	Payment by Results
PE	Pulmonary embolism
PFS	Progression-free survival
PN	Peripheral neuropathy
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjusted Life Year
q2w	Once every 2 weeks
q28d	Every 28 days
RCT	Randomised Controlled Trial
RD	Revlimid® (lenalidomide), dexamethasone
RE	Random-effect
RR	Relative risk
SCT	Stem cell transplantation
SD	Standard deviation
SFLC	Serum free light chains
SMC	Scottish Medicines Consortium
SMM	Smouldering multiple myeloma
STA	Single Technology Appraisal
SWOG	Southwest Oncology Group
TAD	Thalidomide, Adriamycin® (doxorubicin) and dexamethasone
TD	Thalidomide and dexamethasone
TE	Thrombosis
TTP	Time to progression
TTR	Time To Response
Tx	Treatment
µg	Micrograms
ULN	Upper limit of normal
UK	United Kingdom of Great Britain and Northern Ireland
VAD	Vincristine, Adriamycin® (doxorubicin) and dexamethasone
VAT	Value added tax
VBAD	Vincristine, carmustine, Adriamycin® (doxorubicin) and dexamethasone
VBMCP	Vincristine, carmustine, melphalan, cyclophosphamide, and prednisone
V	Velcade® (bortezomib)
VCD	Velcade® (bortezomib), cyclophosphamide, and dexamethasone
VCDR	Velcade® (bortezomib), cyclophosphamide, dexamethasone and lenalidomide
VCTD	Velcade® (bortezomib), cyclophosphamide, thalidomide, and dexamethasone

VT	Velcade® (bortezomib), thalidomide
VCR	Vincristine, Cyclophosphamide and Revlimid® lenalidomide
VD	Velcade® (bortezomib) and dexamethasone
VDR	Velcade® (bortezomib), dexamethasone, and Revlimid® (lenalidomide)
VGPR	Very good partial response
VTD	Velcade® (bortezomib), thalidomide and dexamethasone
VTE	Venous thromboembolism
WHO	World Health Organisation

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (Sections 9.1 to 9.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason 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'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

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

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

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 that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for 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 clinical-effectiveness 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 by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126]' rather than 'One trial[126]').

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see 'Related procedures for evidence submission', Appendix 10.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Disease background and treatment pathway

- Multiple myeloma (MM) is an incurable malignant disorder in which plasma cells accumulate in the bone marrow.(1) It usually manifests as one or more lytic bone lesions, monoclonal protein in the blood or urine, and disease in the bone marrow. Disease advancement is often associated with worsening of symptoms and organ dysfunction, such as anaemia, bone lesion-related symptoms, renal function impairment, and susceptibility to infections.
- MM is associated with significant mortality. In the UK there were more than 2,600 deaths directly attributable to MM in 2010.(2) In England during 2005-2009, approximately 70% of patients were expected to survive their disease for at least one year, falling to 37% surviving five years or more.(3) In the past decade, median overall survival has improved from approximately 36 months to 50-55 months with the use of autologous stem-cell transplantation either at the time of the initial diagnosis or at progression.(4)
- At the time of diagnosis, patients can be classified into two categories: those non-eligible for a transplant following a non-intensive pathway and those eligible for transplant (the population relevant to this submission) following the intensive pathway. Eligibility for a transplant is based upon the biological fitness of the patient, which may be related to age, performance status and comorbidities. For patients eligible for a transplant, induction with chemotherapy followed by high dose therapy-stem cell transplant (HDT-SCT) is considered the standard of care in the UK.
- The choice of induction therapy is important in order to maximise the response to treatment. Many studies in the transplant setting have demonstrated a link between the maximal response attained and long-term outcome after initial therapy. For example, increasing the complete remission rate after transplant has shown to result in prolonged progression free survival (PFS) and overall survival (OS).(5;6) The induction therapy VAD (vincristine, doxorubicin and dexamethasone) was the standard of care until the introduction of bortezomib and thalidomide-based induction therapies, which are now recommended in UK clinical guidelines as they have demonstrated higher response rates than VAD. There remains a need however, for induction regimens that elicit higher post-induction complete response rates in the highest possible number of patients, to increase the number of MM patients proceeding to transplant.

Bortezomib

- Bortezomib (Velcade®) is a first-in-class dipeptidyl boronic acid that works by reversible inhibition of the proteasome, a multienzyme complex present in all cells that selectively degrades intracellular proteins.
- Bortezomib is anticipated to be indicated in combination with dexamethasone, or with dexamethasone and doxorubicin, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated MM, eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
- Bortezomib 1.3 mg/m^2 is a subcutaneous formulation. Four injections are administered per cycle, on days 1, 4, 8 and 11 of each cycle in combination with:
    - *Dexamethasone* 40mg, oral (on days 1-4 and days 9-12 of the bortezomib treatment cycle during cycles 1-2, and on days 1-4 during cycles 3-4). Four cycles of 21 days are recommended. This is the **VD** combination.

- *Doxorubicin* 9 mg/m², intravenous (on days 1-4 of the bortezomib treatment cycle and after the bortezomib injection) and *dexamethasone* 40mg, oral (on days 1-4, 9-12, 17-20 of the bortezomib treatment cycle). Three cycles of 28 days are recommended. This is the **PAD** combination.
- *Thalidomide* 50 mg daily, oral (on days 1-14 and if tolerated the dose is increased to 100 mg on days 15-28, and thereafter 200 mg daily) and *dexamethasone* 40mg, oral (on days 1-4 and days 8-11 of the bortezomib treatment cycle). Six cycles of 28 days are recommended. This is the **VTD** combination.

Comparators

- There is currently no licensed induction regimen for use in MM patients eligible for HDT-SCT. Cyclophosphamide, thalidomide, dexamethasone (CTD) is the combination for which there is the most clinical experience in the UK, despite the lack of randomised or observational clinical trials. (7) As there are no head-to-head trials comparing bortezomib-based regimens with the most relevant comparator for the UK (CTD), a mixed treatment comparison (MTC) was undertaken. However due to the considerable uncertainty underlying the MTC as well as the relative immaturity of the OS data from the pivotal trials presented in section 6, only the comparison of VTD vs. TD was evaluated in the economic model. No comparison vs. CTD was performed as it was assumed to be equivalent to TD by UK clinicians. (Appendix 14)
- The Pethema trial includes the most effective bortezomib-based regimen that was evaluated, i.e. the combination of two novel agents (bortezomib and thalidomide) with dexamethasone (VTD). The other combinations evaluated only include bortezomib as a novel regimen, and as such, did not elicit as strong as a response as VTD. The two other trials evaluating bortezomib-based regimens, Hovon and IFM, comparing PAD to VAD and VD to VAD, respectively, will also be explored.

Clinical evidence

- The efficacy of bortezomib-based induction therapies was demonstrated in four large, adequately powered, independently conducted randomised clinical trials. Both the Pethema and Gimema trials compared **VTD** (bortezomib, thalidomide, dexamethasone) to TD.(8;9) The Hovon trial compared **PAD** (bortezomib, adriamycin, dexamethasone) to VAD.(10) The IFM trial compared **VD** (bortezomib, dexamethasone) to VAD.(11)
- VTD, PAD and VD showed higher post-induction complete response (CR) rate than their comparator (VTD=35.4% vs. TD=14.2% in Pethema; VTD=18.6% vs. TD=4.6% in Gimema; PAD=11% vs. VAD=2.9% in Hovon; VD=5.4% vs. VAD=1.2% in IFM). These complete response rates were further increased post-transplant. VTD, PAD and VD showed higher post-transplant CR rate than their comparator (VTD=46.9% vs. TD=23.6% in Pethema; VTD=37.7% vs. TD=22.7% in Gimema; PAD=22.5% vs. VAD=12.3% in Hovon; VD=18.3% vs. VAD=10.3% in IFM).
- Across all trials a higher percentage of patients underwent a transplant following induction therapy with a bortezomib-based regimen vs. comparators (VTD=80.8% vs. TD=61.4% in Pethema, VTD=90.8% vs. TD=81.3% in Gimema, PAD=84.9% vs. 83.7% in Hovon, VD=86.7% vs. 81.8% in IFM).
- These superior post-induction and post-transplant complete response rates and higher percentages of patients receiving a transplant were translated into a

significantly better progression free survival (PFS) for VTD and PAD vs. TD and VAD respectively (HR=0.65 (0.45-0.92) for VTD vs. TD in Pethema; HR=0.63 (0.45-0.88) for VTD vs. TD in Gimema; HR=0.82 (0.69-0.98) for PAD vs. VAD in Hovon; HR=0.88 (0.70-1.11) for VD vs. VAD in IFM).

- There was no statistically significant difference between any of the bortezomib-based regimens and their comparators for overall survival. However, OS was not the primary endpoint in the studies and thus, these studies were not powered to detect a statistically significant difference in OS. In addition, the trials were of insufficient duration to show a difference in median OS between the treatment groups.
- Treatment-related AE rates were similar in both treatment arms across trials. However, a significantly greater number of total treatment-related AEs were reported at induction in the VTD treatment arm compared to TD in the Pethema trial (RR=1.42; 95% CI: 1.17-1.73). The two most common treatment AEs in the Pethema trial, pneumonia and peripheral neuropathy occurred more frequently in the VTD arm compared to the TD arm. No other bortezomib-relevant statistically significant differences in treatment-related AEs was reported at induction. The most commonly reported AEs following bortezomib-based treatment are in line with the established safety profile of bortezomib. It is important to note that in the four transplant induction studies, bortezomib was given through the intravenous route. With the recently approved subcutaneous route of administration, the incidence of peripheral neuropathy is expected to decrease with no change in efficacy.

Economic evaluation

- This submission addresses the cost-effectiveness of three bortezomib-based induction regimens as follows: VTD compared to the comparator relevant to the scope, TD (assuming clinical equivalence to CTD), PAD compared to VAD, and VD compared to VAD.
- The base case of the VTD regimen focuses on the population from the PETHEMA trial which includes the most relevant comparison to UK clinical practice – 6 cycles of VTD vs. TD (considered to be equivalent to CTD by UK clinicians). The Gimema trial is used in the sensitivity analysis.
- A state transition model was developed in Microsoft Excel to evaluate the cost-effectiveness of bortezomib-based regimens for induction of newly diagnosed MM compared to alternative induction regimens. This type of model was chosen as it provides a structure which is representative of the clinical pathway of care for transplant-eligible MM patients, enabling consideration of the very distinct phases of treatment, from induction prior to SCT, SCT and post-SCT. Patients enter the model at the start of the induction therapy (randomly assigned to either VTD or TD, PAD or VAD, and VD or VAD). Post-induction, patients enter one of three health states: complete response (CR), partial response (PR), or non responders (NR) defined as minimal response, stable disease and progressive disease. Patients subsequently proceed to HDT-SCT (SCT group) or post-induction PFS health state (non-SCT group) depending upon their post-induction response rate. The post-induction response rate also defines the patient's OS.
- The duration of the clinical trials investigating the bortezomib-based induction regimens prior to SCT is of insufficient duration to demonstrate an OS advantage, and therefore post-induction response rate was used as the main measure of efficacy in the model. Long-term OS rates have been linked to the post-induction response rate via long-term follow-up data from the UK-based MRC VII trial (12) segmented by post-induction response categories. It is accepted that response rates, depth of response, and PFS as surrogate outcomes are appropriate markers for overall survival, which is the final outcome

relevant to patients. On this basis, current decision making has established three-drug combinations such as VTD as the standard of care prior to transplantation.(13)

- The base case analysis of VTD vs. TD resulted in an ICER of £24,683/QALY, of £11,041/QALY for PAD vs. VAD, and £14,446/QALY for VD vs. VAD, as reported in Table 2. Sensitivity analyses consistently resulted in ICERs between approximately £20,000/QALY and £30,000.

Table 2. Base-case Cost-effectiveness results

	VTD	TD
Cost Components (£)		
Drug	£28, 034	£8, 865
Other costs	£44, 781	£40,549
TOTAL COSTS	£72,815	£49, 414
Health Outcomes		
LYG	5.95	4.57
LYG DIFFERENCE	-	1.38
QALYs	4.00	3.06
QALY DIFFERENCE	-	0.95
ICER		**£24,683**
	PAD	**VAD**
Cost Components (£)		
Drug	£11,356	£2,331
Other costs		
TOTAL COSTS	£59,632	£49,359
Health Outcomes		
LYG	5.72	4.41
LYG DIFFERENCE	-	1.31
QALYs	3.84	2.91
QALY DIFFERENCE	-	0.93
ICER		**£11,041**
	VD	**VAD**
Cost Components (£)		
Drug	£14,158	£2,783
Other costs		
TOTAL COSTS	£62,874	£50,163
Health Outcomes		
LYG	5.64	4.42
LYG DIFFERENCE	-	1.22
QALYs	3.79	2.91
QALY DIFFERENCE	-	0.88
ICER		**£14,446**

LYG, life years gained; QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios

Table 3. Incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) incre-mental (QALYs)
VTD	£72,815	5.95	4.00	+£23,401	+1.38	+0.95	£24,683
TD	£49,414	4.57	3.06				
PAD	£59,632	5.72	3.84	+£10,274	+1.31	+0.93	£11,041
VAD (Hovon)	£49,359	4.41	2.91				
VD	£62,874	5.64	3.79	+£12,710	+1.22	+0.88	£14,446
VAD (IFM)	£50,163	4.42	2.91				

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

Conclusion

- The prognosis of MM patients is poor; despite significant advances in treatments available to these patients, MM remains an incurable disease and almost all patients will eventually relapse and die from their illness. Bortezomib-based regimens offer an important licensed addition to the therapeutic interventions currently on offer, demonstrating higher post-induction response rates versus non bortezomib-based regimens.
- The economic evaluation showed a base case ICER of £24,683 for the comparison of VTD vs TD, £11,041 for the comparison of PAD vs VAD, and £14,446 for VD vs VAD. The model was robust across the range of sensitivity analyses tested and demonstrated a highly convincing level of external validity.

Section A – Decision problem

1 Description of technology under assessment

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

Brand name: VELCADE®

Approved name: Bortezomib
Therapeutic Class: Antineoplastic agent

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

Bortezomib (Velcade®) is a first-in-class dipeptidyl boronic acid that works by reversible inhibition of the proteasome, a multienzyme complex present in all cells that selectively degrades intracellular proteins.(14) Several proteins which play a critical role in cell growth and differentiation have been shown to be processed for degradation through the proteasome including oncogenes, the tumour suppressor p53, cell-cycle regulators, and transcription factor inhibitors (including IκBa).(15)

Cancer cells generally have higher levels of proteasome activity compared with normal cells and, moreover, are more sensitive to the proapoptotic effects of proteasome inhibition than normal cells,(16) making the proteasome a rational therapeutic target in oncology.(16;17)

The anti-tumour effect of bortezomib as a proteasome inhibitor is mediated through a cascade of events leading to cell-cycle arrest and apoptosis. It is believed that this occurs predominantly through blocking NFkB activation resulting among other things in a reduction in the levels of IL-6, a cytokine that plays an important role in the pathophysiology of multiple myeloma (MM). It has been shown that myeloma cells are more sensitive to the action of proteasome inhibitors than normal cells(15).

As well as exerting direct actions on MM cells, bortezomib alters the tumour microenvironment by interfering with interactions between MM cells and bone-marrow stromal cells and by inhibiting the production of growth and survival factors.(14)

When bortezomib is used in combination with other agents there is evidence of chemosensitisation and synergy.(8-11;18-20)

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

The opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected in [redacted]. The marketing authorisation is expected to be granted in [redacted].

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The European Medicines Agency has not produced a draft EPAR at this stage.

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

Bortezomib is anticipated to be indicated in combination with dexamethasone (VD), or with dexamethasone and doxorubicin (PAD), or with dexamethasone and thalidomide (VTD), for the induction treatment of adult patients with previously untreated multiple myeloma, eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

No additional evidence from completed or ongoing studies is expected in the next 12 months for the indication appraised in this submission.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Not applicable.

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

For the indication that is the focus of this submission, the technology does not have regulatory approval outside the UK.

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

Janssen anticipates submitting to the SMC in [redacted] with a decision expected in [redacted].

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 4: Unit costs of technology being appraised

Pharmaceutical formulation	Bortezomib (as a mannitol boronic ester).
Acquisition cost (excluding VAT)	Bortezomib 3.5mg vial: £762.38, in combination with: - Dexamethasone: 40mg: £2.62 (price for 100 tablets=£13.09) - Doxorubicin (Adriamycin) 10mg: £18.72 - Thalidomide 50mg: £10.66 (price for 28 capsules=£298.48)
Method of administration	Subcutaneous bortezomib in combination with: - Oral dexamethasone - Intravenous doxorubicin and oral dexamethasone - Oral thalidomide and oral dexamethasone
Doses of	The recommended dose of bortezomib is 1.3 mg/m^2, in combination with: - Dexamethasone 40mg - Doxorubicin 9 mg/m² and dexamethasone 40mg, or - Thalidomide: 50mg (up to 200mg) and dexamethasone 40mg
Dosing frequency	Four injections of bortezomib are administered per cycle, on days 1, 4, 8 and 11 of each cycle in combination with: *Dexamethasone (*on days 1-4 and days 9-12 of the bortezomib treatment cycle during cycles 1-2, and on days 1-4 during cycles 3-4). *Doxorubicin (*on days 1-4 of the bortezomib treatment cycle and after the bortezomib injection) *and dexamethasone (*on days 1-4, 9-12, 17-20 of the bortezomib treatment cycle). *Thalidomide* 50 mg daily (on days 1-14 and if tolerated the dose is increased to 100 mg on days 15-28, and thereafter 200 mg daily) *and dexamethasone (*on days 1-4 and days 8-11 of the bortezomib treatment cycle).
Average length of a course of treatment	As indicated in the draft SmPC (Appendix 1), the length of a course of treatment is as follows: *In combination with dexamethasone:* 4 cycles of 21 days *In combination with doxorubicin and dexamethasone :* 3 cycles of 28 days *In combination with dexamethasone and thalidomide:* 6 cycles of 28 days
Average cost of a course of treatment	*Combination therapy with dexamethasone (VD regimen):* the median number of cycles observed in the trial is 4, resulting in a median treatment cost of £12,260.91 *Combination therapy with doxorubicin and dexamethasone (PAD):* the median number of cycles observed in the trial is 3, resulting in a median treatment cost of £ 9,692.09 *Combination therapy with thalidomide and dexamethasone (VTD):* the median number of cycles observed in the trial is 6, resulting in a median treatment cost of £24,840.10

Anticipated average interval between courses of treatments	The bortezomib-based regimens are administered for one course of treatment only.
Anticipated number of repeat courses of treatments	Upon clinical disease progression, patients will receive the next line of treatment.
Dose adjustments	Bortezomib treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy. Once the symptoms of the toxicity have resolved, bortezomib treatment may be re-initiated at a 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk. *Neuropathic pain and/or peripheral neuropathy:* Patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy are to be managed as per section 4.4 of the Summary of Product Characteristics (SmPC) (Appendix 1). Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

There is no additional test or investigation needed for selection or particular administration requirements for bortezomib-based regimens.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

There is no need to monitor patients over and above usual clinical practice for bortezomib-based regimens.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

- *Combination therapy with dexamethasone (VD):* dexamethasone is administered orally at 40 mg on days 1-4 and days 9-12 of the bortezomib treatment cycle during cycles 1-2, and on days 1-4 during cycles 3-4.
- *Combination therapy with dexamethasone and doxorubicin (PAD):* dexamethasone is administered orally at 40 mg on days 1-4, 9-12, 17-20 of the bortezomib treatment cycle. Doxorubicin is administered at 9 mg/m² on days 1-4 of the bortezomib treatment cycle as an intravenous infusion administered after the bortezomib injection.
- *Combination therapy with dexamethasone and thalidomide (VTD):* dexamethasone is administered orally at 40 mg on days 1-4 and days 8-11 of the bortezomib treatment cycle. Thalidomide is administered orally at 50 mg daily on days 1-14 and if tolerated the dose is increased to 100 mg on days 15-28, and thereafter 200 mg daily.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

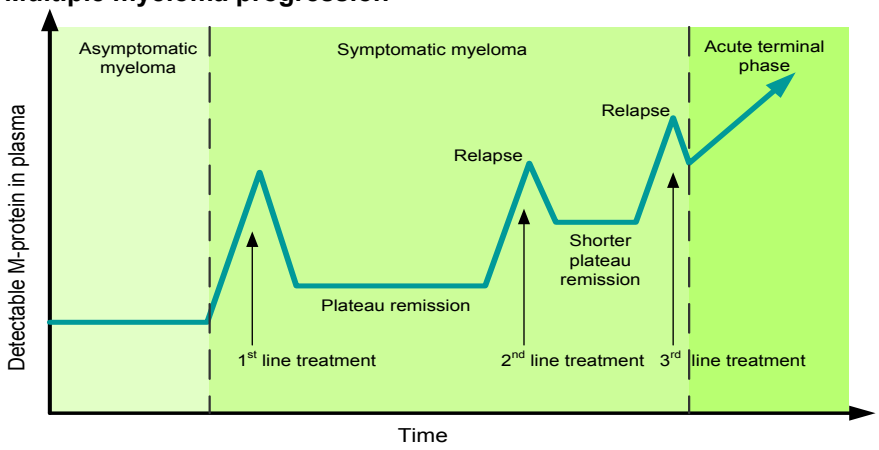
Multiple myeloma (MM) is an incurable malignant disorder in which plasma cells accumulate in the bone marrow.(1) It usually manifests as one or more lytic bone lesions, monoclonal protein in the blood or urine, and disease in the bone marrow. Disease advancement is often associated with worsening of symptoms and organ dysfunction, such as anaemia, bone lesion-related symptoms, renal function impairment, and susceptibility to infections.

The natural disease course of MM is illustrated in Figure 1 below.

The presentation of MM can range from asymptomatic to severly symptomatic with complications requiring immediate treatment. Once a patient becomes symptomatic, they become eligible for 1st line treatment, which is the focus of this submission, and will be described in detail under section 2.5 below.

Following their first line treatment, patients typically experience a period of remission defined as no sign of active disease in the body. Inevitably, subsequent relapses and remissions will occur, necessitating further lines of treatment, including various chemotherapeutic regimens. Remission stages typically become shorter as MM progresses. Despite significant advances in treatment during the past decade, MM remains an incurable disease and almost all patients will eventually relapse and die from their illness.

Figure 1: Multiple myeloma progression



Measure of response

Changes in the M-protein level are the principal indicators used for response and progression evaluation in multiple myeloma. Several categories of response are defined according to the level of serum M protein. The exact definition of each response category varies slightly depending upon the criteria used. The European Group of Blood and Bone Marrow Transplant (EBMT) criteria and the International Myeloma Working Group uniform criteria are two commonly used set of response criteria(21;22). Details of these two sets of criteria are presented in Table 5 and Table 6.

Table 5: Overview of the EBMT response criteria

Complete response (CR) requires all of the following:	
1.	Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
2.	< 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed. If absence of monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
3.	No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).
4.	Disappearance of soft tissue plasmacytomas.
Patients in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.	
Partial response (PR) requires all of the following:	
1.	≥50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks.
2.	Reduction in 24 h urinary light chain excretion either by ≥90% or to <200 mg, maintained for a minimum of 6 weeks.
3.	For patients with non-secretory myeloma only, ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine biopy, if biopsy is performed, maintained for a minimum of 6 weeks.
4.	≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
5.	No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).
Patients in whom some, but not all, the criteria for PR are fulfilled are classified as MR, provided the remaining criteria satisfy the requirements for MR.	
Minimal response (MR) requires all of the following:	
1.	25–49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 weeks.
2.	50–89% reduction in 24 h urinary light chain excretion, which still exceeds 200 mg/24 h, maintained for a minimum of 6 weeks.
3.	For patients with non-secretorymyeloma only, 25–49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.
4.	25–49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
5.	No increase in the size or number of lytic bone lesions lesions (development of a compression fracture does not exclude response).
MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.	
No change (NC)	
1.	Not meeting the criteria of either minimal response or progressive disease.

Plateau	
1.	Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.
Time point for assessing response	
1.	Response to the transplant procedure will be assessed by comparison with results immediately prior to conditioning.
2.	If transplant is part of a treatment programme response to the whole treatment programme will be assessed by comparison with the results at the start of the programme.
Relapse from CR requires at least one of the following:	
1.	Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
2.	≥5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
3.	Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
4.	Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.
Progressive disease (for patients not in CR) requires one or more of the following:	
1.	>25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/l and confirmed by at least one repeated investigation.
2.	>25% increase in the 24 h urinary light chain excretion excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed by at least one repeated investigation.
3.	>25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
4.	Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
5.	Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
6.	Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.

Table adapted from Blade, J. (1998). British Journal of Haematology, 102:1115–1123(21)

Table 6: Overview of the International Myeloma Working Group uniform criteria

CR*	Stringent complete response (sCR)†	VGPR*	PR	SD	PD†
Negative immunofixation of serum and urine, *and*	CR as defined, *plus*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or*	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours	Not meeting criteria for CR, VGPR, PR, or PD	Increase of 25% from lowest response value in any of the following:
Disappearance of any soft tissue plasmacytomas, *and*	Normal FLC ratio *and*	≥ 90% reduction in serum M component plus urine M-component < 100 mg/24 h	If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria		Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or*
<5% PCs in bone marrow	Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry	If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was _≥30%			Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or*
		In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required			Only in patients without measurable serum and urine M-protein levels: the difference between involved and ninvolved FLC levels (absolute increase must be >10 mg/dL)
					Only in patients without measurable serum and urine

CR*	Stringent complete response (sCR)†	VGPR*	PR	SD	PD†
					M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%)
					Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
					Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is _ 5 g/dL.
PCs indicate plasma cells.
*Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a _ 90% decrease in the difference between involved and uninvolved FLC levels.
†Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; “25% increase” refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the “lowest response value” does not need to be a confirmed value.

Table adapted from: Rajkumar, S.V., Harousseau, J-L., Durie, B. et al.. Blood 2001; 117:18: 5691-5695(22)

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

For the proposed indication, it is estimated that 661 newly diagnosed MM patients will be eligible for high dose therapy with stem cell transplant (HDT-SCT) in England and Wales in 2013. Of these, Janssen anticipates that approximately 33% of patients will receive a bortezomib-based induction regimen. This estimation is based upon:

- the projected population of interest i.e. adults, and those 20 years and older in England and Wales as MM is predominantly a disease of older people, with no reported cases in these countries in the age group <20 years between 2007 and 2010.(3;23;24)
- the age standardized incidence rate for men and women in 2010 (8.5 per 100,000 and 6.6 per 100,000 in England; 9 per 100,000 and 8.6 per 100,000 in Wales).(25;26)
- NICE estimating that approximately 20% of newly diagnosed myeloma patients are eligible for HDT-SCT.(27)

For other therapeutic indications, in 2011NICE estimated that 435 newly diagnosed MM patients for which HDT-SCT is considered inappropriate would be eligible to receive bortezomib in combination with an alkylating agent and a steroid.(28) Similarly, in 2007, NICE estimated that approximately 2794 MM patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation would be eligible to receive bortezomib.(29)

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Multiple myeloma is associated with significant mortality. In the UK there were more than 2,600 deaths directly attributable to MM in 2010.(2) In England during 2005-2009, approximately 70% of patients were expected to survive their disease for at least one year, falling to 37% surviving five years or more.(3)

In the first British Medical Research Council (MRC) trial (comparing cyclophosphamide versus melphalan), the median survival for all patients was 18 months, and the estimated four-year survival was 20% in 1971.(30)

For more than three decades, a combination of oral melphalan and prednisone has been the standard treatment for multiple myeloma, and more complex combination chemotherapy regimens have not significantly improved survival. With this approach, complete remissions are rare (occurring in less than 5% of patients), and all patients ultimately relapse. Nearly 25 years ago, a key therapeutic advance was the introduction of high-dose melphalan therapy supported by autologous hematopoietic stem-cell transplantation. The Intergroupe Francophone du Myelome (IFM) was the first to conduct a randomised trial showing the superiority of this approach, as compared with conventional chemotherapy, in terms of the response rate, event-free survival, and overall survival. These results were confirmed 7 years later by the British Medical Research Council.(4)

An important finding from these studies was a significant increase in the rate of complete remission or very good partial remission with autologous stem-cell transplantation, results that were significantly correlated with prolonged progression-free survival and overall survival.(4) Several randomised clinical studies have demonstrated a clear correlation between depth of response and survival.(5;31) The importance of achieving a complete response (CR) post-induction and post-transplant has been highlighted in a meta-analysis conducted in myeloma patients treated with HDT-SCT.(6) These studies indicated highly significant associations between the maximal response (complete response/near complete response/very good partial response) achieved post-induction and long-term outcomes such as OS and PFS.

Overall, transplantation has improved the response rate, the rate of complete or very good partial remission and progression-free survival. The use of autologous SCT either at the time of the initial diagnosis or at progression has improved the median overall survival from approximately 36 months to 50 to 55 months.(4)

The different components of therapy have changed dramatically in the past decade, however this approach based upon SCT eligibility has remained the backbone of treatment.(32)

Several factors continue to be associated with a poorer prognosis: older age, high serum levels of β_2-microglobulin, C-reactive protein, low serum levels of albumin, renal impairment, infection and vertebral fractures all independently correlate with poorer survival (33-35). Furthermore, gene-expression profiling has shown that cytogenetic abnormalities are also associated with a poorer prognosis, particularly deletion of chromosomes 17 or 13 and t(4;14), t(14;16) translocations. (36-38)

2.4 **Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed**.

NICE has produced three guidance documents for MM. None of these submissions to date have considered the use of therapeutic strategies for induction prior to an SCT:

- Bortezomib and thalidomide for the first-line treatment of multiple myeloma. TA 228. July 2011.(28) Patients considered in this guidance are those newly diagnosed for whom HDT-SCT is considered inappropriate. NICE recommended the use of bortezomib in combination with an alkylating agent and a corticosteroid in patients unable to tolerate or having contraindications to thalidomide.

- Bortezomib monotherapy for relapsed multiple myeloma. TA 129. October 2007. In this guidance NICE recommended the use of bortezomib in the subgroup of patients with one prior therapy only.(39)

- Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. TA171. July 2009.(40) In this guidance NICE recommended the use of lenalidomide in MM patients with progressive disease who have received at least two prior therapies.

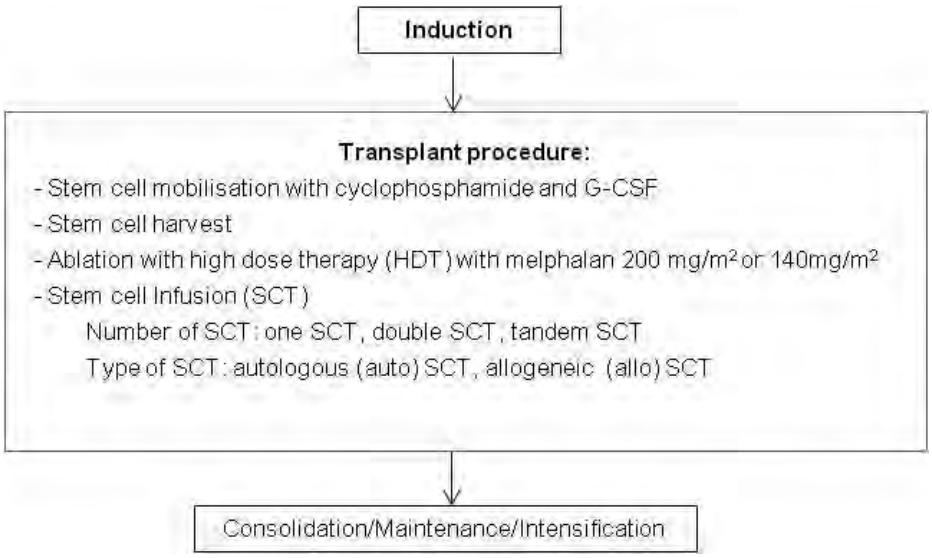
2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a

relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

At the time of diagnosis, patients can be divided into two categories: those non-eligible for a transplant following a non-intensive pathway and **those eligible for transplant (the population relevant to this submission) following the intensive pathway**. Eligibility for a transplant is based upon the biological fitness of the patient, which may be related to age, performance status and comorbidities.

For patients eligible for a transplant, **induction with chemotherapy followed by HDT-SCT** is considered the standard first line treatment in the UK. (Figure 2)

Figure 2: First line treatment pathway for patients eligible for a transplant



Adapted from Ludwig et al.Oncologist 2011;16(4): 388-403 (41)

Induction with chemotherapy

The focus of this submission is to assess the clinical and cost-effectiveness of bortezomib-based regimens as induction therapy prior to HDT-SCT. In contrast to previous MM appraisals that have been conducted by NICE, rather than focusing on the use of novel agents to manage the disease, the focus of this appraisal is the use of novel agents to maximise outcomes from SCT.

For patients who are eligible for SCT, the aim of induction therapy is to induce high remission rates rapidly and with minimal toxicity and to preserve haemopoietic stem cell function to ensure successful mobilisation of the peripheral blood stem cells.(7) An effective induction regimen is therefore one which gives the patient the highest possible chance of meeting the eligibility criteria for the SCT and which maximise the benefits to the patient upon receiving it. In particular, treatment strategies which include the use of induction regimens that are associated with high rates of complete response are a priority, as this is associated with an improved long term(42).

Therefore, the choice of induction regimen is critically important to the clinical course of the disease, because the **depth of response** to treatment, and especially the rate of complete response is a significant predictor of PFS and OS following SCT. Many studies both in the transplant and non-transplant settings have suggested a link

between the maximal response attained and long-term outcome after initial therapy. For example, increasing the complete remission rate after transplant has shown to result in prolonged progression-free survival (PFS) and overall survival (OS).(5;43)

Historically, the **VAD** regimen (vincristine, doxorubicin and dexamethasone) has been the standard of care with modest post-induction complete response rates of between 5% to 7%, increasing to between 20% and 25% post-transplant(44). However, induction therapies containing at least one novel agent such as thalidomide or bortezomib are now recommended in UK clinical guidelines as they have demonstrated higher responses rate than VAD. For example, the induction regimen **TD** (thalidomide, dexamethasone) has demonstrated post-induction complete response rates of 11%, increasing to 31% post-transplant.(8) **CTD** (cyclophosphamide, thalidomide, dexamethasone) is the combination for which there is the most clinical experience in the UK, despite the lack of randomised or observational clinical trials. It is important to emphasise that none of these currently used regimens are specifically licensed for use in induction of MM by the regulatory authorities. The forthcoming license for bortezomib-based regimens is an important development in this respect, which will provide patients and clinicians with the first licensed combination for use in induction prior to SCT in MM.

Although the use of regimens such as VAD have proven effective, there remains a pressing need for novel induction regimens that elicit higher post-induction response rates in the highest possible number of patients, in order to increase the number of patients receiving a transplant and to optimise long term outcomes in patients who receive one. Bortezomib-based regimens are an example of such recent developments in this respect. A synergistic effect upon adding an immunomodulatory drug like thalidomide to bortezomib has been demonstrated in preclinical studies.(45) Importantly, clinical studies have showed that better response rates are achieved with **VTD** (bortezomib, dexamethasone, and thalidomide) vs. thalidomide-dexamethasone (**TD**) or bortezomib-dexamethasone (**VD**).(46-48)

Given that HDT-SCT is considered the standard of care in frontline therapy of MM due to its beneficial impact on survival(49), **the ultimate goal of therapy remains getting a patient to transplant**, in order to optimise the long term survival.

High dose therapy-stem cell transplant (HDT-SCT)

Following induction with chemotherapy, patients then undergo stem cell transplantation (SCT). SCT is a procedure in which a patient's haematopoetic and immune system is completely or partially destroyed by chemotherapy and/or radiotherapy (known as high dose therapy, or HDT), and is then replaced by either haematopoetic stem cells donated by another individual (known as allogeneic SCT), or a previously harvested portion of the patient's own haematopoetic stem cells (known as autologous SCT).

Modern autolgous SCT involves transplanting stem cells from the peripheral blood; however, only a small number of haematopoetic stem cells actually circulate in the peripheral blood. As a result, growth factors such as granulocyte colony-stimulating factor (G-CSF) are now administered in order to increase the number of stem cells in the peripheral blood. This is known as 'mobilisation' of stem cells. The administration of G-CSF usually begins 4-6 days prior to the collection of stem cells by apheresis, a procedure that involves pumping blood through a machine that collects stem cells and returns the remaining blood to the patient.(50) After mobilisation and harvesting of the stem cells, the patient then receives high dose therapy (HDT), prior to re-

infusion of their own stem cells. High dose melphalan (200 mg/m^2) is the standard HDT used.

It is important to note that in the UK, only one autologous SCT is standard practice. The strategy is to collect sufficient stem cells to support two SCT but to defer the second one until the time of relapse. Tandem (or double) transplant are still experimental procedures and not routine clinical practice in the UK.

Lastly, included in Figure 2 are the various experimental strategies such as intensification, consolidation and/or maintenance that can sometimes follow HDT-SCT. These techniques, however, remain exploratory, are not common clinical practice in the UK (outside of clinical trials) and are therefore not relevant to induction nor to the decision problem. The evidence base in MM is still evolving, but what remains relevant is the choice of induction therapy leading to HDT-SCT.

Clinical aims of induction with chemotherapy

The clinical aims of induction therapy, are to achieve a high response rate rapidly with minimal toxicity, preserve haemopoietic stem cell function to ensure successful mobilisation of peripheral blood stem cells, and bring patients to transplant.(7) **Maximising response rate post-induction** is important as meta-analyses have shown a clear correlation between the maximal response achieved and long-term outcomes such as progression-free survival and overall survival.(6)

Of note, for those patients not eligible for transplant (outside of the scope of this submission), NICE recommends thalidomide in combination with an alkylating agent and a corticosteroid as a treatment option and bortezomib in combination with an alkylating agent and a corticosteroid when patients are unable to tolerate or are contraindicated to thalidomide.(51) Once MM has progressed, NICE recommends bortezomib as an option for the treatment of patients having received one prior therapy(39) and lenalidomide for patients having received two or more prior therapies(40).

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice

There are currently no licensed induction regimens for use in MM patients eligible for HDT-SCT.

Clinical guidelines recommend induction regimens with at least one novel agent such as cyclophosphamide, thalidomide, dexamethasone (CTD), thalidomide, adriamycin, dexamethasone (TAD), bortezomib/dexamethasone and bortezomib, adriamycin, dexamethasone (PAD).(7)

In UK clinical practice, cyclophosphomide, thalidomide, dexamethasone (CTD) is the most commonly used induction regimen. Other thalidomide-based regimens are not commonly used in the UK, even though they are standard practice in many other countries.(7) (Appendices 14 and 16). UK clinical practice is different in this respect, in part for historical reasons, as cyclophosphomide has been extensively studied in the numerous UK-based Medical Research Council (MRC) trials since 1964.(52) As indicated in Table 7 cyclophosphamide has been studied in eight MRC trials out of the nine completed to date and is also used in two ongoing MRC trials. Additional details on these MRC trials are available in Appendix 15.

Table 7: Overview of the use of cyclophosphamide in the MRC trials.

MRC Myeloma Trial Number	Treatment regimen studied	Patient Population	References
1	• Melphalan (oral) • **Cyclophosphamide (oral)**	Patients who are untreated and suffering from myelomatosis who had not received chemotherapy.	(30)
2	• **Cyclophosphamide (oral)** • Intermittent melphalan (oral) • Melphalan with prednisone (oral)	Patients with who had not received chemotherapy. Patients with myelomatosis were not considered unless abnormal plasma cells had been identified in marrow films or sections and, in addition, characteristic skeletal lesions had been demonstrated radiologically, and/or characteristic protein changes had been found in the serum or urine. Patients who had previously received urethane or cytotoxic therapy were ineligible.	(53)
3	• **Cyclophosphamide (i.v.)** • Melphalan and prednisone (oral) • **Cyclophosphamide (i.v.)** • (Cyclophosphamide (oral); Melphalan (oral); Prednisone (oral); CCNU.	Newly diagnosed patients with myelomatosis	(54)
4	• MVP (melphalan (oral), vincristine (i..), prednisolone (oral)) • PM (prednisolone (oral) and melphalan (oral)) • If there was any haematological toxicity encountered and the interval between each course had to be extended to more than 6 weeks due to haematological toxicity, the treatment was changed to **cyclophosphamide** every 21 days.	Patients with myelomatosis that had not received previous cytotoxic therapy or radiotherapy except to localised lesions were included in the trial.	(55)
5	• ABCM (adriamycin (i.v.), (carmustine) BCNU (i.v.), **cyclophosphamide (oral)** and melphalan (oral)) • Melphalan (oral)	Newly diagnosed multiple myeloma patients	(56)
6	• ABCM (adriamycin (i.v.), (carmustine) BCNU (i.v.), **cyclophosphamide (oral)** and melphalan (oral)) • High Dose Melphalan (HDM)(i.v.)	Newly diagnosed multiple myeloma patients, who had no previous cytotoxic chemotherapy, other than minimum dose of radiotherapy were included in the trial	(56)

MRC Myeloma Trial Number	Treatment regimen studied	Patient Population	References
7	• Doxorubicin (i.v.), carmustine (i.v.), **cyclophosphamide (oral)** and melphalan (oral) • Doxorubicin (i.v.), Vincristine (i.v.), methylprednisolone (i.v. or oral), **cyclophosphamide** (i.v.). High dose melphalan (i.v.) reinfusion of peripheral blood stem cells.	Previously untreated multiple myeloma patients who were suitable for high dose therapy.	(12)
8	• ABCM (adriamycin (i.v.), (carmustine) BCNU (i.v.), **cyclophosphamide (oral)** and melphalan (oral)) • **Cyclophosphamide** weekly (oral)	Previously untreated multiple myeloma patients	(57)
9	• Intensive pathways: • (CVAD-**cyclophosphamide (oral)**, vincristine (i.v.), doxorubicin (i.v.), and dexamethasone (i.v.) or • Oral CTD-**cyclophosphamide**, thalidomide, and dexamethasone). • Non-intensive pathways: • Oral melphalan and prednisolone or • Attenuated oral CTD (**cyclophosphamide**, thalidomide and dexamethasone).	Newly diagnosed multiple myeloma patients eligible for a transplant Newly diagnosed multiple myeloma patients non-eligible for a transplant	(58;59)
10	• PAD (bortezomib (i.v.), doxorubicin (i.v.) and dexamethasone (oral)). • PBSC mobilisation and harvest (**Cyclophosphamide** (i.v.) + G-CSF • HDM (High Dose Melphalan (i.v.) + ASCT • **Cyclophosphamide- weekly** (oral)	Patients with multiple myeloma previously treated with standard chemotherapy and autologous stem cell transplant.	(60)
11	• **Cyclophosphamide**-lenalidomide-dexamethasone (RCD) • **Cyclophosphamide**-thalidomide-dexamethasone (CTD)	Newly diagnosed patients with symptomatic myeloma, where intensive high dose therapy with stem cell support is appropriate.	(61)

Consequently, the use of CTD in the induction setting has only been studied in the UK-based MRC Myeloma IX trial. As this induction therapy is not used in other countries, it is highly unlikely that any international randomised clinical trial will be conducted using CTD as a comparator in the future. As a result of this, there are

currently no head-to-head data comparing the use of bortezomib-based induction regimens versus CTD, an issue that will be explored in section 6.7.

2.7 Please identify the main comparator(s) and justify their selection.

- CTD (cyclophosphamide, thalidomide, dexamethasone) was idenitified as the main comparator in the decision scope for this submission as it is the most widely used induction regimen and for which there is the most clinical experience in UK practice.(7) (Appendices 14 and 15). Hence the following comparisons were included in the mixed treatment comparison section 6.7: VTD vs. CTD, PAD vs. CTD, VD vs. CTD. However, in the absence of head-to-head trials comparing the bortezomib-based regimens with CTD, the relative immaturity of the OS data from the pivotal trials presented in section 6.5.3.2 as well as the considerable uncertainty underlying the mixed treatment comparison (details in section 6.7) as it was assumed to be equivalent to TD by UK clinicians (appendix 14), an economic evaluation comparing the cost-effectiveness of bortezomib-based regimens vs. CTD was not performed. Only the comparison of VTD vs. TD was carried out in the economic model. Thalidomide, dexamethasone (TD) is the comparator used in two of the RCTs relevant to the decision problem (8;9) although this regimen is not as commonly used in UK clinical practice as CTD. (7) (Appendices 14)

- The VAD (vincristine, doxorubicin, dexamethasone) regimen was considered a standard induction regimen at the time that the studies were originally designed. (10;11) However, since the introduction of novel agents such as thalidomide and bortezomib, it is no longer used in UK clinical practice and as a result is not considered a relevant comparator. The comparisons of PAD vs. VAD based on the Hovon trial and VD vs. VAD based on the IFM trial are included in the submission, however, in order to align with the decision problem. In addition, comparisons of PAD vs. CTD and VD vs. CTD are difficult to perform, due to the lack of trial data connecting these regimens. This issue will be explored further in section 6.7.

- TAD (thalidomide, adriamycin, dexamethasone) is not used in UK clinical practice, and is therefore not a relevant comparator.(7) (Appendices 14 and 15). Comparisons vs. TAD are not presented in this submission.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

In patients receiving bortezomib as part of their induction regimen (e.g. VD, PAD, VTD) acyclovir is administered as prophylaxis for varicella zoster infection.

In patients receiving thalidomide as part of their induction regimen (VTD, CTD) dalteparin or aspirin is administered as prophylaxis for thromboembolic events.(62)

No specific therapy is administered for thalidomide or bortezomib-related neuropathic pain and/or peripheral neuropathy. These adverse events should be managed according to the dose modifications stated in the SmPC.(62;63)

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Bortezomib is administered in a hospital setting. Treatment must be initiated under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents. Bortezomib must be reconstituted by a healthcare professional. It is anticipated that it will be administered predominantly subcutaneously, as the license for this route of administration was granted on 20 September 2012.

The costs associated with administration of the induction regimen, and with the monitoring and testing of patients, are presented in **Error! Reference source not found.** and Table 9 below. The items listed for monitoring and frequency are based upon the NICE submission for lenalidomide in the relapse setting(64).

Table 8: Costs associated with bortezomib administration

Regimen	Frequency	Unit cost	Administration code and description	Reference
VTD	1	£203	SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case)	(65)
	5	£284	SB15Z - Deliver subsequent elements of a Chemotherapy cycle (Day case)	
PAD	1	£203	SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case)	
	2	£284	SB15Z - Deliver subsequent elements of a Chemotherapy cycle (Day case)	
VD	1	£203	SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case)	
	3	£284	SB15Z - Deliver subsequent elements of a Chemotherapy cycle (Day case)	

Table 9: Costs associated with bortezomib and patients' monitoring and testing

Item	Frequency per year	Unit Cost	Administration code and description	Reference
Hospital / clinic appointment with consultant	6	£152	Outpatient Service code 303 - Clinical Haematology. Consultant Led Follow up Attendance Non-Admitted Face-to-Face	(66)
Biochemistry e.g. U&E	6.6	£1	Other Currencies Data. DAP841. Biochemistry	
Urine protein electrophoresis / light chains	2.1	£1	Other Currencies Data. DAP841. Biochemistry	
Neuropathy	0.1	£3	Other Currencies Data. DAP841. Biochemistry	
Bone marrow trephine biopsy	0.1	£1	Other Currencies Data. DAP841. Biochemistry	
Paraprotein	6.1	£1	Other Currencies Data. DAP841. Biochemistry	
Serum B2 microglobulin	2	£1	Other Currencies Data. DAP841. Biochemistry	
Protein electrophoresis	5.1	£1	Other Currencies Data. DAP841. Biochemistry	
Immunofixaton	2.9	£1	Other Currencies Data. DAP841. Biochemistry	
Immunoglobulin	4.9	£1	Other Currencies Data. DAP841. Biochemistry	
Serum free light chains	1.7	£1	Other Currencies Data. DAP841. Biochemistry	
Liver function test	5.1	£1	Other Currencies Data. DAP841. Biochemistry	
24-hour urine measurement	1	£1	Other Currencies Data. DAP841. Biochemistry	
Renal function test (GFR)	2.7	£1	Other Currencies Data. DAP841. Biochemistry	
Urine immunofixation	1	£7	-	(67)
Blood count e.g. FBC	7.1	£3	Other Currencies Data. DAP823.Haematology [Excluding Anti-Coagulant Services]	(66)
Clotting*	0.4	£3	Other Currencies Data. DAP823.Haematology [Excluding Anti-Coagulant Services]	
INR*	0.4	£3	Other Currencies Data. DAP823.Haematology [Excluding Anti-Coagulant Services]	

*for thalidomide-containing regimen only i.e.(bortezomib, thalidomide, dexamethasone (VTD), thalidomide, dexamethasone (TD) and cyclophosphamide, thalidomide, dexamethasone (CTD))

2.10 Does the technology require additional infrastructure to be put in place?

Not applicable.

3 Equality

3.1 Identification of equality issues

3.1.1 **Please let us know if you think that this appraisal:**

3.1.2 **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**

3.1.3 **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**

3.1.4 **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

3.1.5 **Please provide us with any evidence that would enable the Committee to identify and consider such impacts.**

Not applicable

3.1.6 **How has the analysis addressed these issues?**

Not applicable

4 Innovation

4.1.1 **Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.**

Not applicable

4.1.2 **Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.**

Not applicable

4.1.3 **Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.**

Not applicable

5 Statement of the decision problem

	Final scope issued by NICE(68)	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with newly diagnosed multiple myeloma for whom induction therapy is considered appropriate prior to high dose chemotherapy and autologous stem cell transplantation	The submission will address the clinical and cost-effectiveness of bortezomib within its licensed indication.	N/A
Intervention	Bortezomib in combination with other chemotherapy regimens for induction therapy	- Bortezomib in combination with dexamethasone (VD) for 4 cycles of 21 days each - Bortezomib in combination with doxorubicin and dexamethasone (PAD) for 3 cycles of 28 days each - Bortezomib in combination with thalidomide and dexamethasone (VTD) for 6 cycles of 28 days each – (based on the Pethema RCT)	Bortezomib in combination with VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, prednisone) and VBAD (Vincristine, carmustine, Adriamycin® (doxorubicin) and dexamethasone) will not be reported in the submission as this combination will not be licensed.
Comparator(s)	Chemotherapy regimens containing thalidomide	- The clinical and cost-effectiveness of VTD will be assessed vs. TD as per the Pethema and Gimema trials. - The clinical and cost-effectiveness of PAD will be assessed vs. VAD as per the Hovon trial, - The clinical and cost-effectiveness of VD will be assessed vs. VAD as per the IFM trial. - The clinical effectiveness of bortezomib-based regimens (VD, PAD, VTD) will be assessed vs. CTD, the most commonly used induction regimen in UK clinical practice, via a mixed treatment comparison of the PFS, TTP and OS endpoints.	Section 2.6 - CTD was the main comparator in the decision scope given its widespread experience in UK clinical practice.(7) (Appendices 14 and 15). - In the absence of head-to-head trials comparing the bortezomib-based regimens with CTD, the relative immaturity of the OS data from the pivotal trials presented in section 6.5.3.2 as well as the considerable uncertainty underlying the mixed treatment comparison (details in section 6.7) as CTD was assumed to be equivalent to TD by UK clinicians (appendix 14), an economic evaluation comparing the cost-effectiveness of bortezomib-based regimens vs. CTD was not performed. - Thalidomide, dexamethasone (TD) is the comparator used in two of the RCTs relevant to the decision problem (8;9) although this regimen is not as commonly used in UK clinical practice as CTD. (7) (Appendices 14)
Outcomes	-Response rate -Proportion of	In this submission, the following outcomes	The response rate post-induction is used as the primary measure

	Final scope issued by NICE(68)	Decision problem addressed in the submission	Rationale if different from the scope
	people undergoing high dose chemotherapy and autologous stem cell transplantation -Progression-free survival -Overall survival -Adverse effects of treatment -Health-related quality of life	measures will be used to compare the clinical and cost-effectiveness of bortezomib-based regimens to the comparators. These are as follows: - **Response rate post-induction (primary endpoints in most RCTs)** - Response rate post-transplant - Progression-free survival and time to progression - **Proportion of people undergoing high dose chemotherapy and autologous stem cell transplantation (HDT-SCT)** - Overall survival - Adverse events related to the induction treatment - Health-related quality of life was not assessed during the RCTs and therefore data from the published literature is used in the economic model	of efficacy in the economic model.

	Final scope issued by NICE(68)	Decision problem addressed in the submission	Rationale if different from the scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The cost-effectiveness model is a state transition model that compares the bortezomib-based regimen VTD to TD (assuming equivalence to CTD based on clinical experts' input – Appendix 14) based upon the Pethema trial, PAD to VAD based upon the Hovon trial, and VD to VAD based upon the IFM trial. The incremental cost per QALY gained has been generated using historical survival data in this patient population. A life time horizon has been applied to ensure that all relevant costs and effects were captured. Costs are considered from the NHS and Personal Social Services perspective.	
Subgroups to be considered	If the evidence allows, a subgroup of people with myeloma cell genetic abnormalities should be considered. Guidance will only be issued in accordance with the marketing authorisation	The efficacy of bortezomib-based regimens is reported for the subgroup of patients with high risk cytogenetics. However, no cost-effectiveness analysis was undertaken for this subgroup.	Cytogenetic testing performed to identify patients with high risk cytogenetics is not routine clinical practice nor routinely funded in the UK. This lack of funding prevents the test from being performed in some areas, and thus clinicians do not generally determine whether a patient is high risk until they progress. Therefore the cost-effectiveness analysis of bortezomib-based regimens in this subgroup of patients is not relevant to UK clinical practice.
Special considerations, including issues related to equity or equality	N/A	N/A	N/A

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 Identification of studies

6.1.1 **Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be 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 Section 10.2, appendix 2.**

A systematic review was conducted to identify all studies related to the following study question:

- What are the efficacy, safety, and tolerability of induction therapies, including licensed bortezomib-based therapies and CTD, used prior to SCT for the treatment of adult patients with newly diagnosed MM, as determined from RCTs?

The study question aimed to address the decision problem as discussed in Section 5.

A full protocol for the systematic review was prepared *a priori* detailing the patient population, interventions, and study designs to be included, as described in the following sections.

Information sources and search strategy

The search strategy for the systematic review consisted of three components: a search of electronic literature databases, a bibliographic search of the identified publications, and a search of conference abstracts. In addition, clinical study reports (CSRs) were available to Janssen from three randomised control trials (RCTs) evaluating bortezomib against other induction therapies in the treatment of MM: HOVON-65/GMMG-HD4, IFM 2005-01, and Pethema trials. For the electronic database search, four databases were searched from the start of each database to 7th September 2012 (full search strings detailed in Appendix 2.4):

- Embase®
- MEDLINE®
- MEDLINE In-Process®
- Cochrane® CENTRAL

Conference abstracts were hand-searched to retrieve the latest studies, awaiting publication in peer-reviewed journals, or to supplement results of previously published studies. Abstracts from four conference proceedings were searched for this reason (7th September 2012). These include:

- American Society of Hematology (ASH, searched 2008-2011; the 2012 conference had not taken place at the time of the review)
- European Hematology Association (EHA, searched 2008-2012)
- International Myeloma Workshop (IMW, searched 2009 and 2011 [conference not held in 2008, 2010, and 2012])
- American Society of Clinical Oncology (ASCO, searched 2008-2012)

To be included in the review, trials had to meet pre-defined eligibility criteria (Section 6.2). The inclusion criteria allowed the capture of studies which examined the efficacy, safety, and tolerability of bortezomib- or thalidomide-based regimens as induction therapies used prior to HDT-SCT for treatment of patients with newly diagnosed MM. In addition, studies which evaluated other conventional or novel induction regimens were captured as these had the potential to contribute to a mixed treatment comparison (MTC).

Implementation of the systematic review followed the recommendations and standards required by NICE and the preferred reporting method for systematic reviews and meta-analyses (PRISMA statement:(69)).

Abstracts of all citations identified by the literature searches were initially reviewed for inclusion, based upon the title and abstract alone (first screen). Full-text copies of the studies, which potentially met the inclusion criteria, were obtained. In instances where it was not possible to determine whether studies met the inclusion criteria based on their title and abstract alone, the full texts were obtained for further assessment. Following receipt of full texts, the inclusion criteria were applied (second screen), and publications were included or excluded accordingly. At this stage, only studies explicitly meeting the inclusion criteria were included. In all cases (first and second screen), assessment of inclusion was performed by two reviewers independently. Any discrepancies in inclusion decisions between reviewers were reconciled by a third independent reviewer. Two reviewers undertook data extraction of the included studies and any discrepancy in extracted data was resolved by a third reviewer. The extraction grid used to capture data is displayed in Appendix 2.6.

A further search was conducted, within the bibliographies listed in the publications identified during the review process, to identify additional publications not yet included. Any cited sources were also screened using the same screening method as described above.

Data from the three clinical study reports (CSRs) were included in the review.(70-72) These three CSRs reported data from three pivotal Phase III bortezomib trials: the HOVON-65/GMMG-HD4 trial, the IFM 2005-01 trial, and the Pethema trial. An additional fourth RCT (the Gimema trial) has been performed and was known to the sponsor. However, due to legal restrictions on access to patient data in Italy, a CSR was not available for this fourth study; published reports regarding this trial were obtained during the literature search.

There are some data discrepancies between the CSRs and publically available data with respect to the HOVON-65/GMMG-HD4, IFM 2005-01, and Pethema trials; minor differences exist in the number of patients randomised to treatment, and safety and efficacy results. These differences are slight and data trends remain similar. Data reported in this submission are primarily taken from the CSRs as the CSRs contain a more complete data set and allow a consistent and full presentation of clinical trial results. In addition, this data set is used within the economic model reported in Section 7.[1] Additional data was extracted from the publications, if not present in the CSR.

6.2 Study selection

6.2.1 **Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.**

To be included in the review, trials had to meet the eligibility criteria specified in the systematic review protocol and have a full-text English publication available (criteria described in Table 10 and Table 11).

The systematic review collected non-RCT studies (i.e. single arm trials or non-experimental studies) that did not assign treatments, in the event that the review did not return evidence from RCTs (Appendix 6). The efficacy and safety data from non-RCT studies are not presented in detail in this submission.

[1] Those outcomes for which equivalent data are reported in articles published in publically available literature are not marked as being‘commercial data in confidence’; the CSR data are presented in these instances

Table 10: Inclusion criteria used during study screening

Inclusion criteria		Rationale
Population	Age: Adults (≥18 years)* Gender: Any Race: Any Disease: Patients with MM including symptomatic MM (also known as Kahler's disease, and myelomatosis) (Studies, which enrolled a mixed population of MM and monoclonal gammopathy of undetermined significance (MGUS)/smouldering MM (SMM)/other diseases, were included only if there was a subgroup analysis of the MM patient population)	The patient population was restricted to match the MM population stated in the decision problem in Section 5
Interventions	Pharmacological treatments evaluated as induction therapy prior to SCT for newly-diagnosed MM (first line therapy): bortezomib (including Velcade®, LDP341, PS341) thalidomide (including Thalomid®) vincristine (including Oncovin®, Leurocristine, VCR), cyclophosphamide (including Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®) Interventions may be given as monotherapy or in combination with other interventions (including treatments not in the list of included interventions). Inclusion was not restricted to the licensed dose of the therapy. Studies, which enrolled a mixed population of patients receiving induction and later lines of therapy, were only included if there was a sub-group analysis reported for the induction therapy, or if the results were presented stratified by line of treatment	The therapy under submission is bortezomib CTD is the main comparator for first line induction treatment. Studies which involved other regimens (e.g. TD, TAD, and VAD) were also included in order to contribute to the MTC analysis
Study designs	RCTs (parallel group and crossover), non-randomised controlled clinical trials, cohort studies/longitudinal studies (prospective), case control study, cross sectional study, single arm studies (uncontrolled trials) RCTs were included regardless of the blinding of participants, investigators, or assessors With respect to non-RCTs, only full journal publications with a sample size of >30 patients were included. Non-RCTs, which were reported only in conference abstract form, enrolled 30 or fewer patients, did not assess or report the safety or efficacy of the therapy, or were retrospective reports, were all excluded	The review included RCTs, as they are the gold standard of clinical evidence, minimise the risk of confounding and allow the comparison of the relative efficacy of interventions Non-RCT studies were included in the search in the event that the review failed to return sufficient evidence from RCTs to address the decision problem
Outcomes	There were no inclusion criteria based around outcomes measures	The inclusion of studies was not restricted by outcomes, so as to include all studies which reported relevant data

*MM is rarely diagnosed in patients aged <35 years, therefore, if age was unclear, studies were included

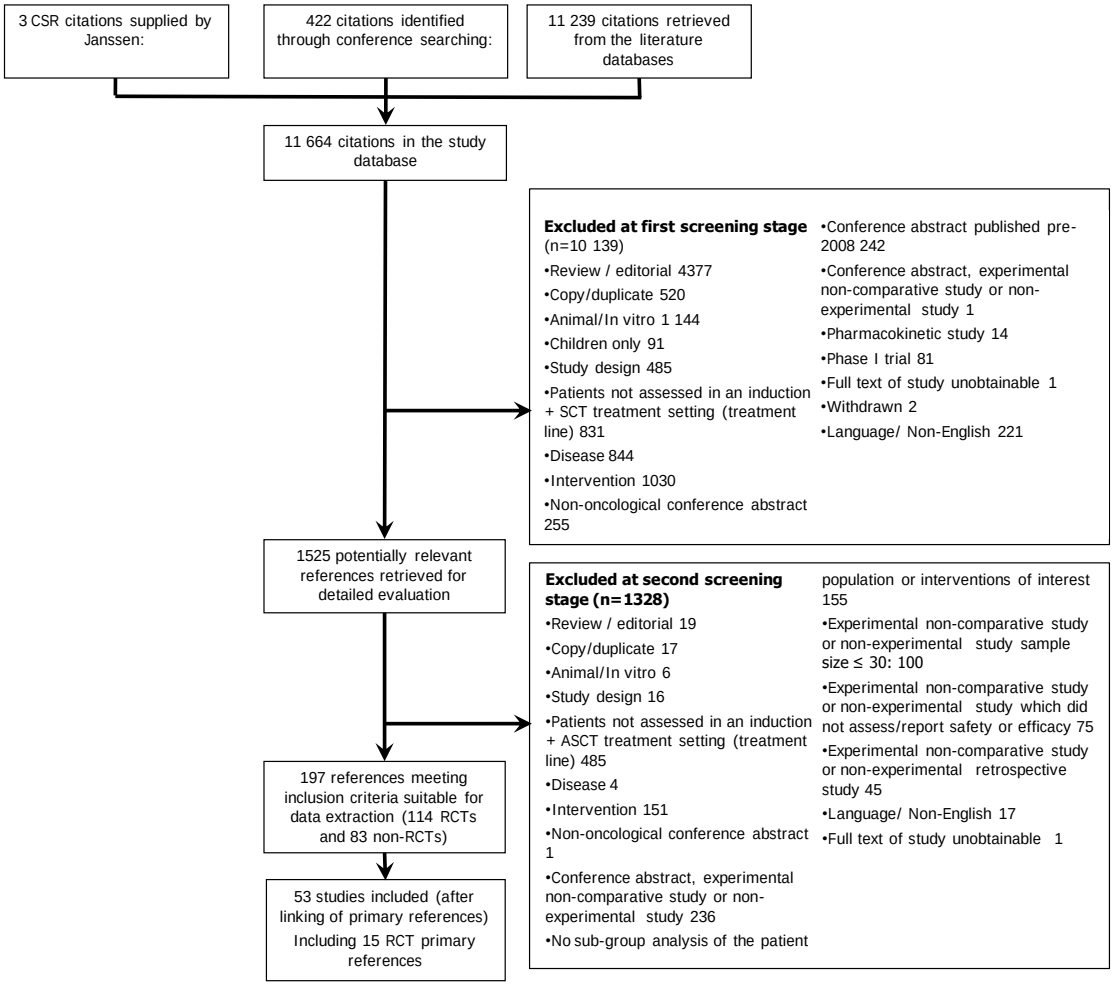
Table 11: Exclusion criteria used during study screening

Exclusion criteria		Rationale
Population	Age: children or adolescents (<18 years) Studies that do not provide subgroup data for the population of interest Studies in animals Disease: Patients with smouldering MM (SMM), monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma, extramedullary plasmacytoma, multiple solitary plasmacytoma (recurrent), primary systemic amyloidosis, plasma cell leukaemia	Excluded studies report no subgroup data for the population of interest (adult patients with MM) within the indication identified in Section 5
Interventions	Studies investigating the role of radiotherapy, surgery, or SCT Studies evaluating only the efficacy or safety of ineligible transplant settings, or post-transplant maintenance/ consolidation therapy Interventions used only to control the symptoms of the disease, e.g., bisphosphonates to treat bone disease, erythropoietin to treat anaemia, antibiotics to treat infections, and various types of pain medication Studies assessing patients who had previously received second or further line treatment for MM	The named interventions are not included as they do not reflect the indication of the submission (induction therapy), as detailed in Section 5
Comparators	There was no exclusion on the basis of trial comparator	The search was not restricted by trial comparator, so as to include all comparators reported
Study designs	Analysis of hospital records/database, case reports, case series, pharmacokinetic studies, Phase I studies	These studies are generally smaller, non-comparative studies, which are at a higher risk of bias compared to other study designs
Outcomes	There was no exclusion on the basis of outcomes	The search was not restricted by outcomes, so as to include all outcomes measures reported
Language restrictions	Publications were excluded if there was no full text available in the English language	It is unlikely that studies relevant to the decision problem will be published in languages other than English

6.2.2 **A flow diagram of the number of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram. (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.**

11 664 reports were identified using the search strategies detailed in Section 6.1.1. The flow of citations through the inclusion screening process is described in **Error! Reference source not found.**.

Figure 3: The flow of citations through the review screening process



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

The 15 RCTs returned by the review are reported with their associated references (Table 12). Of the 15 trials listed in Table 12, six trials are excluded from further consideration in this submission as they do not assess treatments relevant to the decision problem; the HOVON-50/GMMG-HD3 trial(73), Total therapy II trial(74), and trials reported by Bjorkstrand 2003(75), Mellqvist 2008(76), Rajkumar 2006(77), and Mounier 2009(78), are excluded in this manner. These trials did not report bortezomib-based induction regimens in either treatment arm.

Table 12: The 15 RCTs returned by the review, and linked citation reports

Study name	Primary reference	Additional/ linked references
HOVON-65/GMMG-HD4 trial	(10)	(70;79-95)
IFM 2005-01 trial	(11)	(31;72;96-101)
PETHEMA/GEM trial	(9)	(71;102-105)
GIMEMA trial	(8)	(106-117)
MRC Myeloma IX trial	(58)	(118-138)
Bjorkstrand 2003*	(75)	-
HOVON-50/GMMG-HD3 trial*	(73)	(139-145)
Mellqvist 2008*	(76)	-
Total therapy II trial*	(74)	(76;146-168)
Rajkumar 2006*	(77)	(169)
IFM2007-02 study	(170)	(171-173)
Mounier 2009*	(78)	-
Ludwig 2010	(174)	(175)
EVOLUTION study	(176)	-
GMMG MM5 trial	(177)	-

*Excluded from further discussion; these trials did not present evidence relevant to the decision problem

Complete list of relevant RCTs

6.2.4 **Provide details 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 Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.**

Table 13 displays nine RCTs retrieved during the systematic review which assess the efficacy or safety of bortezomib- or thalidomide-based regimens as induction therapy in patients with MM. Amongst these RCTs were the three pivotal bortezomib-based Phase III trials, the HOVON-65/GMMG-HD4 trial (hereafter referred to as 'Hovon'), the IFM 2005-01 trial (hereafter referred to as 'IFM'), and the PETHEMA/GEM trial (hereafter referred to as 'Pethema'), and also another bortezomib-based RCT: the Gimema trial.

The MRC Myeloma IX trial (hereafter referred to as 'MRC MIX') does not assess a bortezomib-based regimen, but it is relevant to the MTC presented in Section 6.7, and so is considered alongside these bortezomib-based RCTs throughout the remainder of the submission.

Full details of dosing schedules are detailed in Appendix 7.2.

Table 13: RCTs included in the clinical systematic review which evaluate the safety or efficacy of bortezomib-, thalidomide-based induction regimens for the treatment of newly-diagnosed patients with MM (bolded text indicates relevance to the decision problem)

Study name	Induction regimen	N randomised	Population
Hovon	**PAD**	833	Newly-diagnosed, previously untreated MM Patients diagnosed with non-secretory MM, were excluded
	VAD		
IFM	**VD**	482	Newly-diagnosed, previously untreated symptomatic MM with measurable disease
	VAD		
Pethema	**VTD**	386	Newly-diagnosed, previously untreated symptomatic MM, and measurable disease, eligible for autologous transplantation. Patients diagnosed with non-secretory MM, or who had a known hypersensitivity to bortezomib, boric acid, mannitol, or thalidomide were excluded
	TD		
	VBMCP/VBAD/bortezomib		
Gimema	**VTD**	480	Newly-diagnosed, previously untreated symptomatic MM with measurable disease
	TD		
MRC MIX	**CVAD**	1111	Patients with newly-diagnosed symptomatic myeloma
	CTD		
IFM2007-02 study	VD	199	Newly-diagnosed, previously untreated symptomatic MM with measurable disease
	VTD		
Ludwig 2010	VTD	98	Newly-diagnosed, previously untreated MM with measurable disease requiring systematic therapy and eligible for high dose therapy and SCT
	VCTD		
GMMG MM5 trial	VCD	150	Newly diagnosed MM
	PAD		
EVOLUTION study	VCD	140	Newly-diagnosed, previously untreated symptomatic MM with measurable disease
	VCD*		
	VDR		
	VCDR		

CD: Cyclophosphamide and dexamethasone; CTD: Cyclophosphamide, thalidomide, and dexamethasone; CVAD: Cyclophosphamide, vincristine, Adriamycin® (doxorubicin) and dexamethasone; Dex: Dexamethasone; PAD: Velcade® (bortezomib), Adriamycin® (doxorubicin), and dexamethasone; TAD: Thalidomide, Adriamycin® (doxorubicin) and dexamethasone; TD: Thalidomide and dexamethasone; VAD: Vincristine, Adriamycin® (doxorubicin) and dexamethasone; VBAD: Vincristine, carmustine, Adriamycin® (doxorubicin) and dexamethasone; VBMCP: Vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VCD: Velcade® (bortezomib), cyclophosphamide, and dexamethasone; VCDR: Velcade® (bortezomib), cyclophosphamide, dexamethasone and lenalidomide; VCTD: Velcade® (bortezomib), cyclophosphamide, thalidomide, and dexamethasone; VDR: Velcade® (bortezomib), dexamethasone, and lenalidomide; VD: Velcade® (bortezomib) and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone.

*modified with additional cyclophosphamide dose on day 15

References for all the clinical trials listed here are presented in Table 12

6.2.5 **Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.**

No clinical trial has directly compared bortezomib-based regimens against CTD as induction therapy for patients with MM (reasons outlined in Section 2.5 above). Only the MRC MIX trial was identified as assessing the effectiveness of the cyclophosphamide, thalidomide, dexamethasone (CTD) combination in this review.

Table 14 presents the abbreviations used to describe treatment regimens evaluated in the main RCTs relevant to the decision problem.

Table 14: Abbreviations of treatment regimens for the relevant RCTs reported

Acronym	Definition
CTD	Cyclophosphamide, thalidomide, and dexamethasone
CVAD	Cyclophosphamide, vincristine, Adriamycin® (doxorubicin) and dexamethasone
PAD	Velcade® (bortezomib), Adriamycin® (doxorubicin), and dexamethasone **Of note: in this regimen, Velcade® (bortezomib) is designated by P, as opposed to V. This regimen is unique in this regard.**
TD	Thalidomide and dexamethasone
VAD	Vincristine, Adriamycin® (doxorubicin) and dexamethasone
VD	Velcade® (bortezomib) and dexamethasone
VTD	Velcade® (bortezomib), thalidomide and dexamethasone

6.2.6 **When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.**

RCTs displayed in Table 15 which do not contain sufficient data relevant to the decision problem or do not have a treatment regimen relevant to the decision problem are not discussed further within this submission. The rationale for exclusion of these studies is displayed in Table 15. Furthermore, as these studies are not relevant to the decision problem, they are not included within the MTC (described in Section 6.7).

Table 15: Excluded studies and rationale for exclusion

Study name	Reason for exclusion
IFM2007-02 study	Both treatment arms contain bortezomib The study aimed to demonstrate that a reduced dose of bortezomib is superior to TD. This dosing regimen is therefore not in line with that stated within this submission
Ludwig 2010	All treatment arms contain bortezomib, and therefore are not suitable to determine the efficacy of bortezomib relative to current standard of care, i.e. non-bortezomib containing regimens
GMMG MM5 trial	
EVOLUTION study	

List of relevant non-RCTs

6.2.7 **Please provide details of any non-RCTs (for example experimental and non-experimental (observational) data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.**

Non-RCT studies (i.e. single arm trials or non-experimental studies that did not assign treatments) were also identified during the systematic review in the event that RCT evidence was not identified. However, RCTs were returned by the review and hence the efficacy and safety data from non-RCT studies are not presented in this submission (see Section 6.2.6). A full list of non-RCT studies identified is reported in Appendix 6.7.

6.3 Summary of methodology of relevant RCTs

6.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (**www.consort-statement.org**). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.**

The focus of this submission are four randomised controlled trials which evaluated the safety and efficacy of bortezomib-based regimens compared to other commonly used induction treatments, and one randomised controlled trial which evaluated the safety and efficacy of two non-bortezomib based regimens.

All four bortezomib-based trials were independently conducted and were not sponsored by the manufacturer. Three of these trials (Hovon, IFM, and Pethema), formed the evidence base for the regulatory submission. A fourth randomised trial (Gimema) is also included in this submission. Two of these four studies used a VAD-based induction regimen as the comparator, which was considered standard induction treatment at the time. The other two studies, which were conducted later, used a TD-based induction regimen as comparator.

These four studies represent the only relevant, randomised, controlled studies designed to compare the efficacy and safety of bortezomib-based induction regimens for the treatment of patients with newly diagnosed MM eligible for SCT to other induction regimens; they contribute to the MTC analysis in Section 6.7.

As shown in Table 16, there is considerable heterogeneity in terms of the design of the studies. Key differences between the studies include the number of cycles of induction therapy recommended in the trial protocol, the therapeutic agents to which bortezomib is added and the management of patients following SCT. This heterogeneity is further discussed in Sections 6.3.2.

The MRC MIX trial is the only trial assessing the efficacy of CTD, which is considered the main comparator of importance in terms of current UK clinical practice. It is considered relevant to the decision problem as it is the only potential evidence that permits any form of comparison to be made between bortezomib-based regimens and CTD. This synthesis of evidence is undertaken through a MTC analysis (described in Section 6.7).

A summary of the design of the RCTs included is presented in Table 16. CONSORT flow diagrams of patient numbers are presented for each RCT in Section 6.3.8.

6.3.2 **Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.**

Methodology of the pivotal bortezomib-based Phase III trials and other relevant RCTs

Table 16 presents the methods of randomisation, primary and secondary endpoints, and treatment regimens administered during these trials. A discussion of the RCT methods (including a discussion of the open-label nature of the RCTs) as relates to trial quality is reported in section 6.4.

Table 16: Methodology and treatment regimens with respect to the relevant RCTs

		Hovon	IFM	Pethema	Gimema	MRC MIX
Design		RCT	RCT	RCT	RCT	RCT
Location		Multicentre international; Netherlands, Germany, Belgium	Multicentre international; France, Belgium, Switzerland	Multicentre; Spain	Multicentre; Italy	Multicentre; UK
Induction regimens*	**Interventions**	PAD induction (n=417) V: 1.3 mg/m^2 A: 9 mg/m^2 D: 40 mg	VD induction (n=240) V: 1.3 mg/m^2 D: 40 mg	VTD induction (n=130) V: 1.3 mg/m^2 T: 50 mg; if tolerated, increased to 100 mg, then 200 mg D: 40 mg	VTD induction (n=241) V: 1.3 mg/m^2 T: 100 mg, then 200 mg D: 40 mg	CVAD intensive therapy (n=540) C:500mg V: 0.4mg A: 9 mg/m^2 D: 40mg
	Comparators	VAD induction (n=416) V: 0.4 mg A: 9 mg/m^2 D: 40 mg	VAD induction (n=242) V: 0.4 mg A: 9 mg/m^2 D: 40 mg	TD induction (n=127) T: 50 mg; if tolerated, increased to 100 mg, then 200 mg D: 40 mg VBMCP/VBAD/bortezomib induction (n=129)	TD induction (n=239) T: 100 mg, then 200 mg daily D: 40 mg	CTD intensive therapy (n=548) C:500mg T: 100 mg, then 200 mg D: 40 mg
Duration of study		3 cycles of induction treatment Maintenance continued for up to 2 years	4 cycles of induction treatment No maintenance or consolidation following SCT	6 cycles of induction treatment Maintenance continued for up to 3 years	3 cycles of induction treatment Consolidation therapy for 2 cycles, maintenance continued until progression or relapse	Up to 6 cycles until maximum response of induction therapy Maintenance continued until disease progression
Randomisation method		Randomisation in 1:1 ratio. Randomisations were balanced with a biased-coin minimization procedure ensuring balance within each stratum and overall balance. Initially, the minimization was based on study centre, Salmon & Durie Stage (2 versus 3), and LDH level (≤ULN versus >ULN of LDH). After the third protocol amendment, the minimization was based on study centre and ISS stage (I versus II versus III)	Randomisation in 1:1 ratio was performed through a centralised computer system and was stratified on the basis of the initial β2 microglobulin level (> or ≤3 mg/L) and the presence of chromosome 13 abnormalities identified by fluorescence in situ hybridization analysis **	Randomised in 1:1:1 ratio using a computer system. The patient will be assigned an identification number to be used to identify the patient in the CRF. Subsequently, when all data from the screening visit is entered, the electronic CRF itself will randomize the patient to a treatment arm **	Computer generated by study coordinating team and was stratified by international staging ISS disease stage	Computer generated randomisation in a 1:1 ratio; this used a minimisation algorithm stratified by centre, haemoglobin (<115 vs. ≥115 g/L for men, <95 vs. ≥95 g/L for women), serum calcium (<2·6 vs. ≥2·6 mmol/L; corrected for serum albumin), serum creatinine (<140 vs. ≥140 µmol/L), and platelet count (<150×10^9/L or ≥150×10^9/L).
Number of patients randomised		833	482	386	480	1111

	Hovon	IFM	Pethema	Gimema	MRC MIX
Blinding	Open-label	Open-label However, response assessors were blinded	Open-label	Open-label However, response assessors were blinded	Open-label
Primary endpoint (s)	PFS (censored at allo-SCT)	Post-induction CR+nCR rate	Post-induction and post-transplant response rate • CR+nCR+PR • CR/nCR	Post-induction CR+nCR rate	Response rate PFS OS
Secondary endpoint (s)	Response rate OS PFS without censoring at allo-SCT	Post-induction and post-transplant ORR (CR, nCR, VGPR, PR) Post-transplant CR/nCR rate PFS OS	PFS OS TTP[#]	Response rate (CR+nCR) to double SCT and consolidation treatment TTP or time to relapse PFS OS Safety	Toxicity Quality of life (reported separately)
Other endpoint (s)	TTP[#] Duration of CR Proportion of patients who received transplant Safety	TTP[#] Proportion of patients who received transplant Safety	Proportion of patients who received transplant Safety	Proportion of patients who received transplant	
Response assessment[#]	Assessment of response was conducted: • After the third cycle of PAD or VAD (post-induction) • After stem cell collection, • After each course of HDM. (post-transplant) • During maintenance treatment, disease status was evaluated every 2 months.	• At inclusion • Before each cycle of induction treatment • Before the pre- auto-SCT tests carried out 4 weeks after the last cycle of induction treatment (post-induction) • At the time of the auto-SCT(s) (2 weeks after the pre- auto-SCT tests) • 1 to 3 months after the auto-SCT(s) (post-transplant)	• At the end of induction treatment (post-induction) • 3 months after transplantation (post-transplant) • Every 3 months during the maintenance and follow-up periods if there was no evidence of disease progression		
Duration of follow up (median)	42 months	33 months	35.9 months	36 months	47 months

CR: Complete response; CTD: Cyclophosphamide, thalidomide, and dexamethasone; CVAD: Cyclophosphamide, vincristine, Adriamycin® (doxorubicin) and dexamethasone; HDM: High-dose melphalan; nCR: Near complete response; OS: Overall survival; PAD: Velcade® (bortezomib), Adriamycin® (doxorubicin), and dexamethasone; PFS: Progression-free survival; PR: Partial response; RCT: Randomised Controlled Trial; SCT: Stem cell transplantation; TD: Thalidomide and dexamethasone; TTP: Time to progression; VAD: Vincristine, Adriamycin® (doxorubicin) and dexamethasone; VBAD: Vincristine, carmustine, Adriamycin® (doxorubicin) and dexamethasone; VBMCP: Vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VD: Velcade® (bortezomib) and dexamethasone; VGPR: Very good partial response; VTD: Velcade® (bortezomib), thalidomide and dexamethasone

*Doses are provided per induction therapy (see Appendix 7.2)

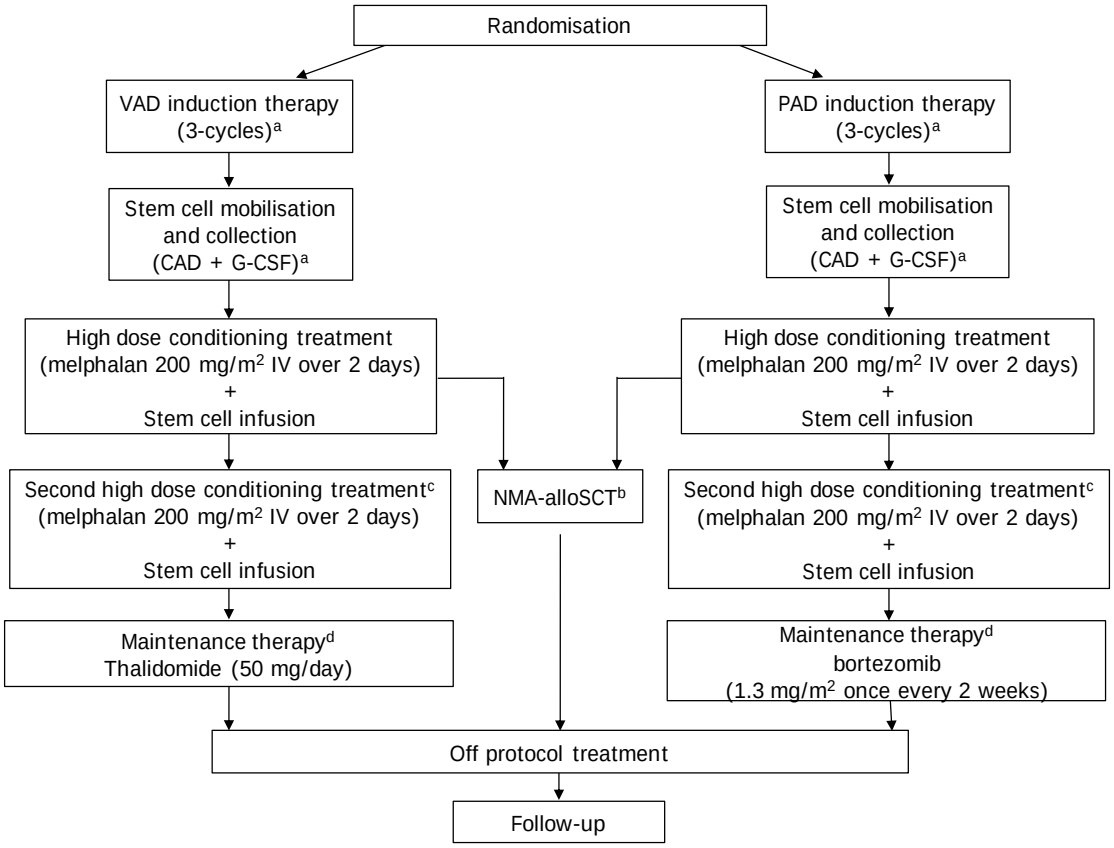
**Further details of randomisation procedures are not reported

[#] Information provided in the clinical study reports of the trials

6.3.2.1 Hovon(10)

The Hovon trial was a randomised, open-label study comparing the efficacy and safety of PAD induction followed by bortezomib maintenance treatment, against VAD induction followed by thalidomide maintenance treatment in MM patients. The study design is displayed in Figure 4. It is important to note that the maintenance therapies following induction therapies may confound the post-induction trial long-term outcomes (time to event data) for PAD vs. VAD as patients were not re-randomised to the maintenance therapies. Neither progression-free survival nor overall survival was adjusted for maintenance.

Figure 4: Hovon study design



CAD; Cyclophosphamide, doxorubicin (Adriamycin®) and dexamethasone was to be started 4 to 6 weeks after the start of the third PAD or VAD cycle

a = Subjects who did not meet the inclusion criteria for CAD or HDM but with a CR, PR, minimal response , or no change might proceed with three more cycles of VAD (Treatment A) or PAD (Treatment B), followed by thalidomide maintenance (Treatment A) or bortezomib maintenance (Treatment B) for 2 years until progression.

b = Subjects with a HLA-identical family donor who met the eligibility criteria proceeded with NMA-alloSCT after the first course of HDM and SCT.

c = For subjects who achieve at least a PR. This was applicable to HOVON centres only. GMMG centres performed a second HDM procedure for all subjects regardless of response after first HDM.

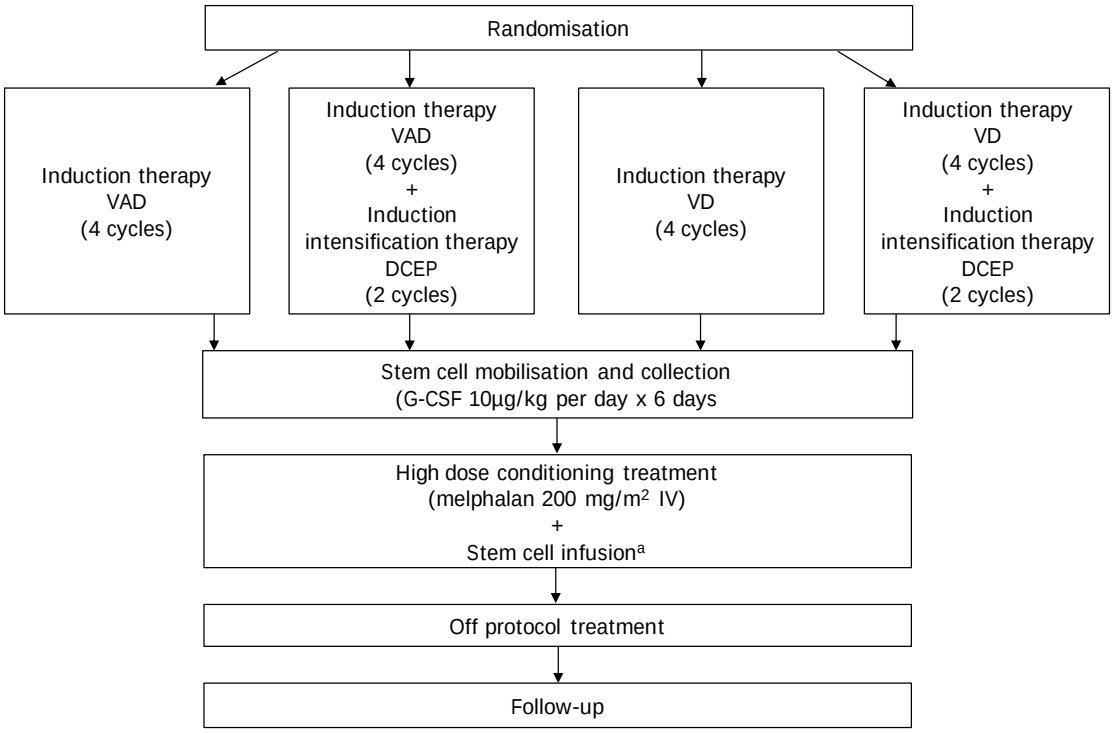
d = Maintenance therapy was given for up to 2 years or until disease progression occurred. Maintenance was discontinued after six months in patients who did not achieve at least a minimal response.

6.3.2.2 IFM(11)

The IFM trial was a randomised, open-label study designed to compare the efficacy and safety of VD (with or without intensification with dexamethasone/ cyclophosphamide/ etoposide or etoposide phosphate/ cis-platinum [DCEP]) against VAD (with or without intensification; a two 4-week cycle with DCEP consolidation therapy) as induction treatment in MM patients. The use of the DCEP intensification treatment is not relevant to the decision problem. (Section 5) Therefore the results of the VD and VAD arms with DCEP are not reported. An outline of the design of the IFM study is presented in Figure 5.

Patients with complete response (CR) or very good partial response (VGPR) after either the first or second SCT were to be recruited to a follow on trial (IFM 2005-02) to evaluate maintenance treatment, since maintenance was not part of the original IFM trial protocol. Consequently, the maintenance therapies may confound the progression-free survival or overall survival observed for VD vs. VAD for patients with CR or VGPR post SCT. Similarly to the Hovon study, neither progression-free survival nor overall survival was adjusted for maintenance.

Figure 5: IFM study design



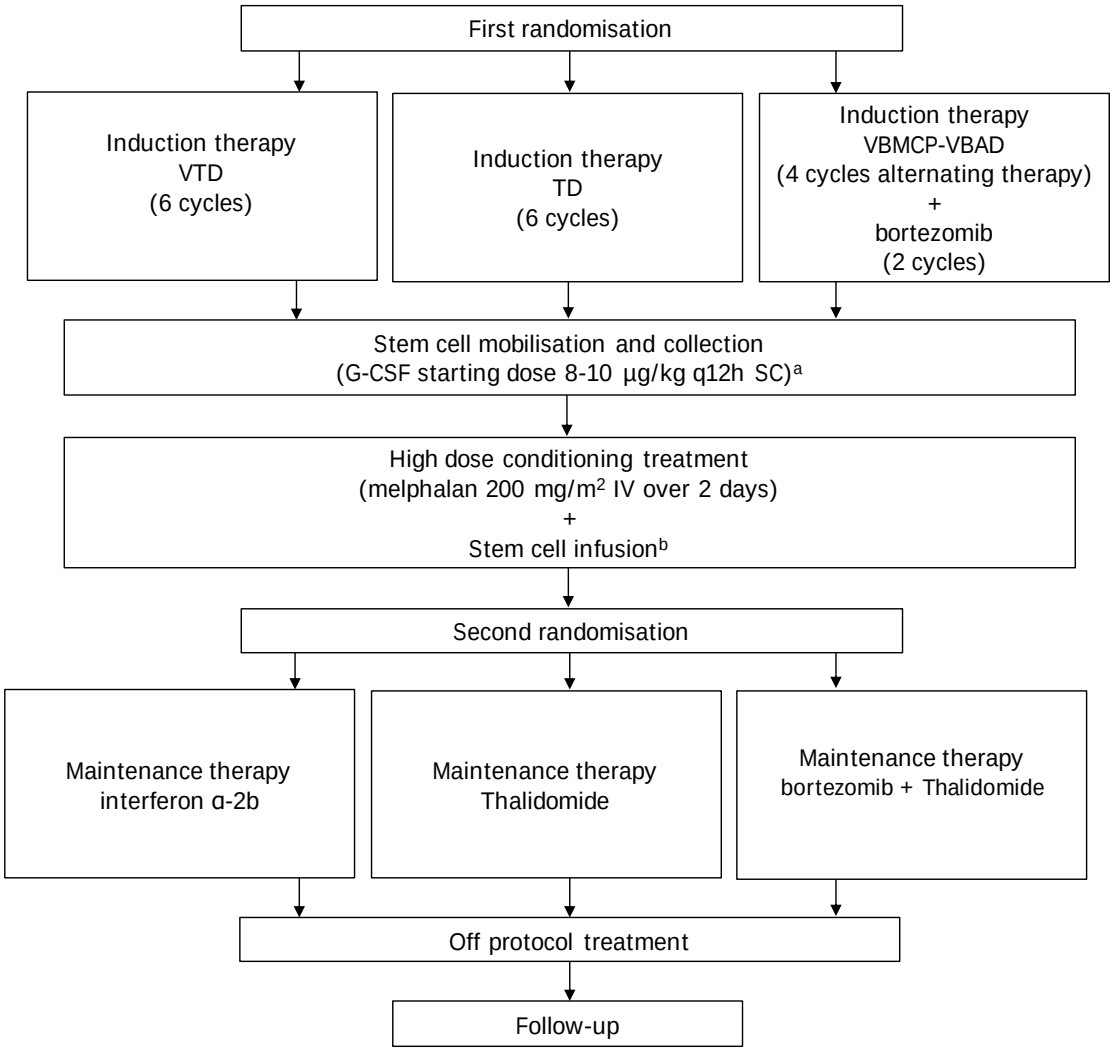
a = Subjects could receive up to two SCTs. Subjects with a less than VGPR 1-3 months after the first SCT were eligible to receive a second SCT. Subjects with less than a PR received a second SCT. Subjects with a PR received a second SCT; unless the subject had a donor with a matching HLA haplotype, in which case, allo-SCT was performed.

6.3.2.3 Pethema(9)

The Pethema trial was a randomised, open-label study to compare the efficacy and safety of three induction regimens as presented in Figure 6. The treatment arm with the induction therapy VBMCP-VBAD is not relevant to the decision problem (section 5) and therefore results with this combination will not be presented throughout the remainder of the submission.

Post-transplantation, patients who continued in the trial were re-randomised to receive one of three maintenance treatments. As a result, in-trial maintenance does not confound the progression-free survival or overall survival of VTD vs. TD.

Figure 6: Pethema study design



a = If stem cell mobilisation failed, a second stem cell mobilisation procedure including the use of high doses of cyclophosphamine followed by normal pegylated G-CSF could have been performed

b = Patients who did not achieve CR following SCT and who had a HLA-identical donor could withdraw from the study to receive allo-SCT

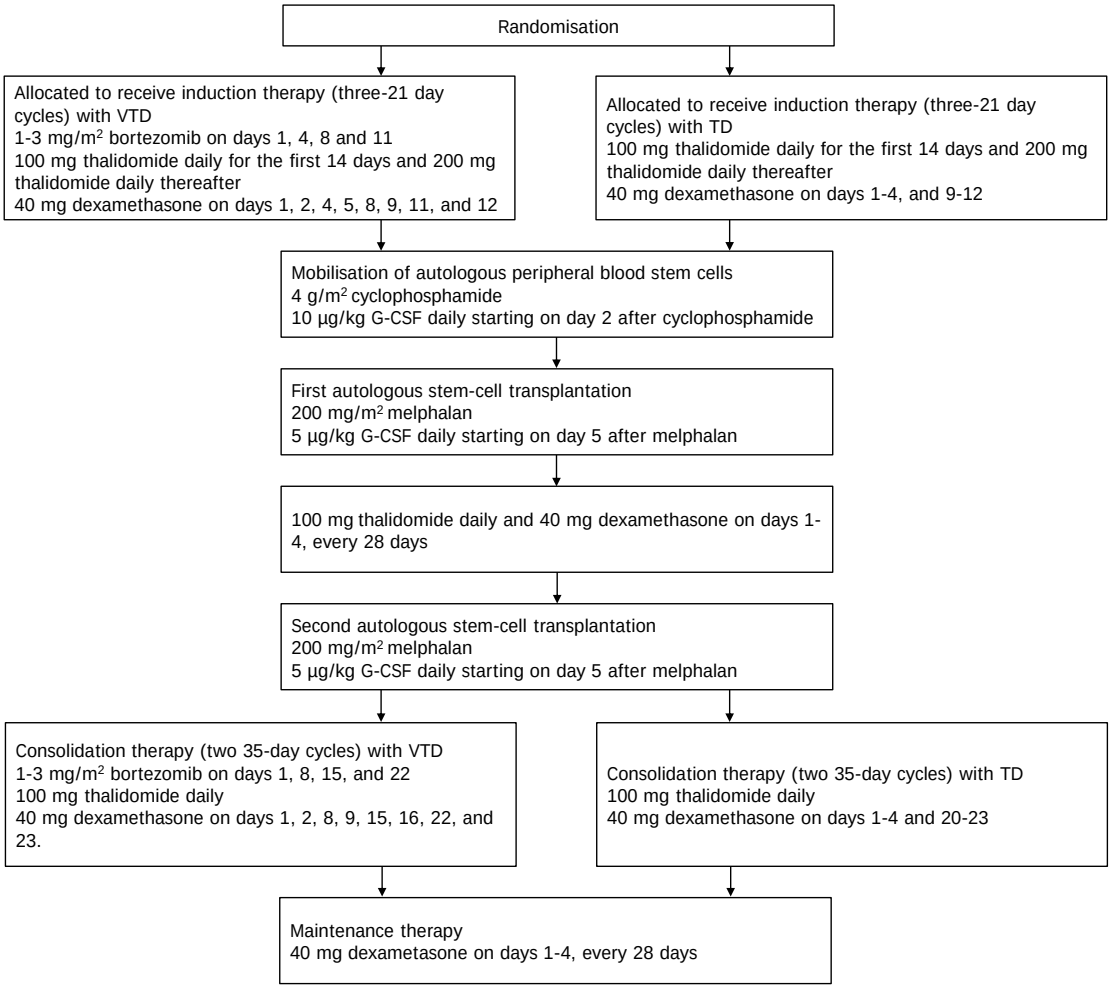
Maintenance therapy was continued for up to 3 years, or until disease progression

6.3.2.4 Gimema(8)

The Gimema trial was a randomised, open-label, Phase III study designed to compare the efficacy and safety of three cycles of TD versus three cycles of VTD as induction treatment prior to SCT and to evaluate consolidation thereafter. The study design is displayed in Figure 7.

Consolidation treatment with VTD in the VTD induction group and TD in the TD induction group may confound the progression free survival and overall survival of VTD vs. TD.

Figure 7: Gimema study design

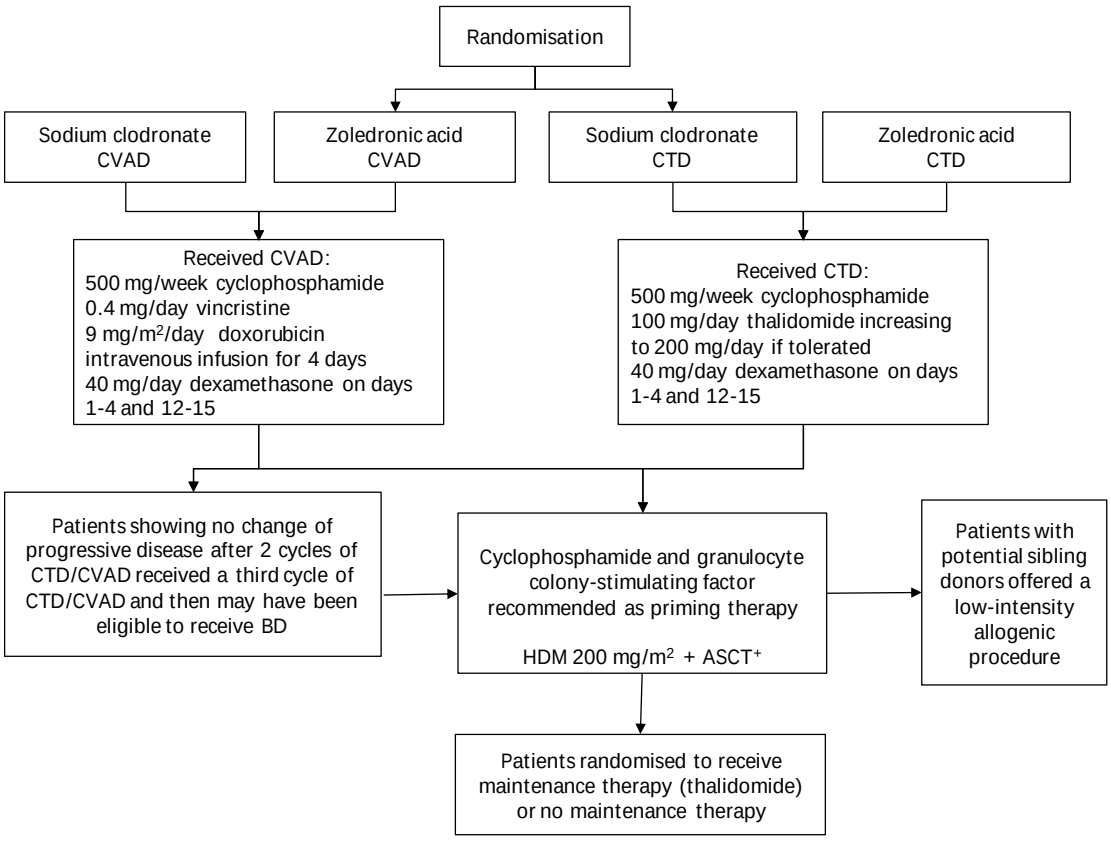


6.3.2.5 MRC MIX Trial(58)

Patients meeting the inclusion criteria for this study were randomised to receive induction chemotherapy following either an intensive or the non-intensive (attenuated treatment) pathway. In line with the scope of this submission and the decision problem, only the intensive pathway of the MRC MIX trial is considered here and is presented in Figure 8.

Response to treatment was assessed after each cycle of induction chemotherapy (before high-dose melphalan and SCT in the intensive pathway) and every three months thereafter, with an assessment at 100 days after transplantation in the intensive pathway. Following transplant, all patients in the trial were re-randomised to receive either maintenance therapy (thalidomide) or no maintenance.

Figure 8: MRC MIX study design – Intensive pathway



Participants

6.3.3 **Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.**

Trial protocols specifically stated that patients were newly diagnosed and previously untreated for MM.

The MRC MIX trial did not have an upper age limit with respect to trial inclusion; any patient over the age of 18 was potentially eligible for inclusion, (although only 1.5% patients were over 70 years of age) whilst the other trials included patients up to the age of 65 years.

MM staging was reported according to the International Staging System (ISS); no trials restricted inclusion by ISS stage. The Hovon trial included patients with a WHO/ECOG performance status ≤3 whilst the other RCTs (which reported the performance status criteria for inclusion in the trial) only included patients with WHO/ECOG performance status ≤2, or a broadly-equivalent Karnofsky status ≥50%. Therefore, it may be the case that the patient population in the Hovon trial had more severe MM than the patient population of the other RCTs. However, all trials excluded patients with the most severe disease performance status (4 or 5) and, therefore, may be considered broadly similar.

Table 17: Main eligibility criteria within the relevant RCTs

Study name	Inclusion criteria	Exclusion criteria
Hovon	• Diagnosis: Newly-diagnosed, previously untreated MM • Age: 18- 65 years • Performance status: WHO 0 - 2, 3 when caused by MM Disease stage: ISS I or II or III; stage II or III according to the • Salmon & Durie criteria • Pregnancy status: negative • Informed consent: in writing	• Patients diagnosed with non-secretory MM • Known intolerance of thalidomide or boron • Previous chemotherapy or radiotherapy except 2 cycles of melphalan/prednisone or local radiotherapy in case of local myeloma progression • History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or Stage 0 cervical carcinoma • Systemic amyloid light-chain amyloidosis • Severe cardiac dysfunction New York Heart Association (NYHA) classification II to IV • Significant hepatic dysfunction (serum bilirubin ≥30 µmol/L or transaminases ≥2.5 times normal level), unless related to myeloma • Neuropathy, common toxicity criteria (CTC) Grade 2 or higher • Known to be HIV-positive • Active, uncontrolled infections • Not willing or capable to use adequate contraception during the therapy (all men, all pre-menopausal women) • Age ≤65 years with an HLA-identical sibling who will undergo NMA-allo-SCT • Lactating women

Study name	Inclusion criteria	Exclusion criteria
IFM	• Diagnosis: Newly-diagnosed, previously untreated symptomatic MM with measurable disease and secretion of a measurable monoclonal spike (>10 g/L in the serum or 0.2 g/24 hour in the urine) • Age: ≤65 years • Performance status: ECOG ≤2, life expectancy ≥2 months • Disease stage: ISS I or II or III; Stage II or III disease according to the Durie and Salmon classification or Stage I disease with symptomatic bone lesion • Prior treatment: None - apart from local radiotherapy in the case of a threatening or • incapacitating lesion, and/or a 4-day block of dexamethasone (40 mg) in an emergency • Pregnancy status: negative • Informed consent: in writing • Active infection: none (apyretic for 48 hours before the start of treatment)	• Stage I indolent myeloma • Known hypersensitivity to bortezomib, boron, or mannitol • Use of an investigational medicinal product during the 30 days prior to inclusion • >65 years of age • Eastern Cooperative Oncology Group (ECOG) performance status >2 • History of cancer (other than basal cell carcinoma or carcinoma of the cervix in situ) • Life expectancy <2 months • Confirmed amyloidosis • Clinical signs of heart failure or coronary heart disease • Bilirubin >3 X normal • Transaminases or gamma glutamyltransferase (GGT) >4 X normal • Platelets <50 x 10^9/L during the 15 days prior to inclusion • Neutrophils <0.75 x 10^9/L during the 15 days prior to inclusion • Renal failure requiring dialysis • Peripheral neuropathy National Cancer Institute (NCI) Grade ≥2 • Known to be HIV positive • Serious psychiatric item in the history • Uncontrolled diabetes, contraindicating the use of corticosteroids

Study name	Inclusion criteria	Exclusion criteria

Pethema	• Diagnosis: Newly-diagnosed, previously untreated symptomatic MM, and measurable disease, eligible for autologous transplantation.
	• Age: ≤65 years
	• Performance status: ECOG ≤2, life expectancy >3 months
	• Disease stage: ISS I or II or III
	• Informed consent: in writing
	• Contraception: agree to use of contraception protocol. Men receiving study treatment (including vasectomized men) agreed to use a barrier contraceptive method while receiving study treatment and for at least 4 weeks after the last dose.
	• Was able to comply with all clinical study requirements in the opinion of the investigator
	• Measurable disease was defined by the presence of quantifiable monoclonal component in serum, or in urine if light-chain excretion was 200 mg/24 hours or higher
	• A subject must have had the following laboratory values before the start of the corresponding induction treatment.
	  ○ Platelet count ≥50,000/mm^3
	  ○ Hemoglobin ≥8 g/dL
	  ○ Absolute Neutrophil Count (ANC) ≥1000/mm^3
	  ○ (Lower haematology values were permitted if they were due to bone marrow infiltration.)
	  ○ Corrected serum calcium ≤14 mg/dL
	  ○ Aspartate aminotransferase ≤2.5 x upper limit of normal (ULN)
	  ○ Alanine aminotransferase ≤2.5 x ULN
	  ○ Total bilirubin ≤1.5 x ULN
	  ○ Serum creatinine ≤2 mg/dL
	• Women of childbearing age agreed to practice total abstinence from intercourse or to use 2 contraceptive methods from 4 weeks before study start, throughout the study, and for at least 4 weeks after the last dose. The 2 contraceptive methods must have included a highly effective method as described in the study protocol. Women of childbearing age must have had a negative serum or urine pregnancy test result 24 hours prior to the start of treatment. Women entering the thalidomide treatment groups were required to undergo a pregnancy test periodically as described in the study protocol. Men receiving study treatment (including vasectomized men) agreed to use a barrier contraceptive method while receiving study treatment and for at least 4 weeks after the last dose.
		• Patients diagnosed with non-secretory MM
		• Known hypersensitivity to bortezomib, boric acid, mannitol, or thalidomide
		• Received previous treatment for MM, except steroid pulses for any emergency before the start of induction treatment, bisphosphonate administration, or radiation therapy
		• Was currently participating in another clinical study or receiving any investigational agent, or received any investigational agent within 30 days of study entry
		• Underwent major surgery within 4 weeks of recruitment
		• Experienced peripheral neuropathy Grade 2 or higher within 14 days of study entry
		• Experienced a myocardial infarction within 6 months of entry into the clinical trial or are in New York Heart Association functional class III or IV; heart failure or presence of clearly identifiable risk factors for such disease, uncontrolled angina, uncontrolled ventricular arrhythmia or acute ischemia detected in the electrocardiogram, or conduction system abnormalities
		• Known carrier of human immunodeficiency virus (HIV)
		• Known carrier of hepatitis B virus surface antigen, or had active infection by hepatitis C virus
		• Was pregnant or nursing

Study name	Inclusion criteria	Exclusion criteria
Gimema*	• Diagnosis: Newly-diagnosed, previously untreated symptomatic MM with measurable disease • Age: 18–65 years • Performance status: Karnofsky≥60% • Disease stage: ISS I or II or III • Pregnancy status: negative • Informed consent: NR	• Cardiac function (uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrolment, New York Heart Association class II–IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis) • Hepatic function (aspartate amino transferase >2.5 times the upper limit of normal, alanine aminotransferase >2.5 times the upper limit of normal, and total bilirubin >1.5 times the upper limit • Peripheral neuropathy of grade 2 or higher according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0) • History of venous thromboembolism • Previous diagnosis of thrombophylic alterations
MRC MIX*	• Diagnosis: Patients with newly-diagnosed symptomatic myeloma • Age: ≥18 years • Performance status: NR • Disease stage: ISS I or II or III • Pregnancy status: negative • Informed consent: NR	• Asymptomatic myeloma • Solitary bone plasmacytoma or extramedullary plasmacytoma • Previous or concurrent active malignancies, or had previously received treatment for myeloma (apart from local radiotherapy, bisphosphonates, or low-dose corticosteroids) • Acute renal failure (serum creatinine >500 µmol/L and unresponsive to 72 h of rehydration, urine output <400 mL/day, or need for dialysis) • Pregnant or lactating

References for all the clinical trials listed here are presented in Table 12

6.3.4 **Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.**

Overall the baseline characteristics of patients are similar across the four bortezomib-based trials.

Only the following minor differences between patient baseline characteristics across the five trials were noted (Table 18):

- Patient age was slightly higher in the MRC MIX trial compared to the RCTs of bortezomib-based therapy (median age=59 vs. 57). The MRC MIX trial was also distinct from the bortezomib-based RCTs in that it included a small number of patients over 65 years of age. These patients typically have a worse prognosis than younger patients; the four relevant bortezomib-based RCTs excluded patients over 65 years of age.

- The MRC MIX trial included fewer patients with ISS stage I MM and a higher proportion of patients at ISS stage III compared to the bortezomib-based RCTs.

- There is a greater proportion of later stage patients in the MRC MIX trial compared to bortezomib-based trials. These patients would be expected to have a worse prognosis than earlier stage patients.

Despite the minor differences in patient characteristics, clinical experts considered the patient populations enrolled in all four bortezomib-based trials and the MRC MIX trial to be broadly similar (Appendix 14).

Table 18: Baseline characteristics of patients included in the five relevant RCTs

Study name	Hovon		IFM		Pethema		Gimema		MRC MIX	
Regimen	**PAD**	**VAD**	**VD**	**VAD**	**VTD**	**TD**	**VTD**	**TD**	**CVAD**	**CTD**
Age (median)	57	57	57	57	57	56	58	58	59	59
Male (%)	62	60	58	52	58	54	58	57	63	62
ISS stage (%)										
N	380	380	240	238	130	127	236	239	556	555
I	38	38	43	42	34	38	45	45	22	27
II	40	34	33	35	44	37	39	39	34	34
III	22	28	25	23	22	25	16	16	33	29
Performance status (% ECOG/WHO)										
N	412	413	220	224	130	127	236	239	556	555
0	47	44	42	44	44	32	NR	NR	NR	NR
1	42	42	44	45	44	55	NR	NR	NR	NR
2	8	11	13	10	12	13	NR	NR	NR	NR
3	4	2	1	1	NR	NR	NR	NR	NR	NR
Immunoglobulin type (%)										
N	415	416	216	208	130	127	236	238	556	555
IG-A	22.4	23.3	21.8	21.6	20	24.4	17.4	22.7	18.7	20
IG-D	1.2	0.7	1.9	1.4	2.3	2.4	NR	NR	1.8	2.2
IG-G	60.5	56.3	59.7	61.5	66.2	58.3	65.3	61.8	55.2	56.2
IG-M	0.2	0.2	0	0.5	NR	NR	NR	NR	0.5	0.4

The proportion of patients with cytogenetic abnormalities (del 13, del 17, t(4;14)) is presented in Table 19.

Table 19: Cytogenetic abnormalities of patients included in the five relevant RCTs

Study name	Induction regimen	N	Del 13 (%)	Del17 (%)	t(4;14) (%)	t(14;16) (%)
Hovon	PAD	417	41.0	8.7	14.0	NR
	VAD	416	44.1	12.8	13.4	
IFM	VD	240	42.1	16.7		NR
	VAD	242	42.6	12.0		NR
Pethema	VTD	130	NR	18		
	TD	127	NR	17		
Gimema	VTD	236	47.2	6.9	19.0	NR
	TD	238	46.2	7.6	20.1	NR
MRC MIX	CVAD	556	42.8	6.8	11.5	NR
	CTD	555	49.2	8.7	13.1	NR

Outcomes

6.3.5 **Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.**

The primary and secondary endpoints assessed during the relevant RCTs are reported in Table 20 below.

Three time points are reported:

- 'Post-induction' and 'post-SCT' for the response rate endpoints
- 'After a median duration of follow-up' for TTP, PFS and OS

None of the bortezomib trials evaluated quality of life. In the MRC MIX trial, quality of life was collected and reported separately. These quality of life data were not considered further in this submission as the data were presented as an aggregate of the whole population in the trial i.e. those that receive a transplant and those that received chemotherapy, with or without maintenance therapy.

Table 20: Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures (time point)	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures (time point)	Reliability/validity/ current use in clinical practice	Other endpoints relevant to decision problem (time point)
Hovon	PFS (median follow-up 42 months)	Response rate (RR), PFS and OS are highly patient-relevant outcomes and key outcomes as determined by clinical experts and NICE (detailed in section 5 and 8.2.9, and citations (178) (179))	• Response rate (post-induction, post-SCT) • OS (median follow-up 42 months) • PFS without censoring at allo-SCT (median follow-up 42 months)	All secondary measures are patient-relevant outcomes and key outcomes as determined by clinical experts and NICE (Section 5) RR: The importance of patient response is confirmed by a recently published meta-analysis which demonstrates that response predicts a patient's PFS and OS. There is a clear correlation between depth of response and long-term outcomes (179). Patients who had CR or VGPR showed OS or PFS benefit compared to patients who had other responses or no responses in many clinical trials, therefore, response could be considered as a proxy measure of survival Proportion of patients who received SCT: As the aim of induction therapy is to prepare patients sufficiently (i.e. achieve response) to become eligible for SCT, and SCT confers a survival benefit (appendix 14), the proportion of patients who undergo SCT is an important outcome	• TTP (median follow-up 42 months) • Proportion of patients who received transplant • Safety
IFM	Response rate CR+nCR rate (post-induction)		• Response rate (post-induction and post-SCT) • PFS (median follow up 33 months) • OS (median follow up 33 months)		• TTP (median follow up 33 months) • Proportion of patients who received transplant • Safety
Pethema	Response rate CR+nCR+PR and CR/nCR (post-induction and post-SCT)		• PFS (median follow up 35.9 months) • TTP (median follow up 35.9 months) • OS(median follow up 35.9 months)		• Proportion of patients who received transplant • Safety
Gimema	Response rate CR+nCR rate (post-induction)		• Response rate (post 1st SCT, post 2nd SCT) • PFS (median follow up 36 months) • TTP (median follow up 36 months) • OS (median follow up 36 months) • Safety		• Proportion of patients who received transplant
MRC MIX	OS (median follow up 47 months) PFS (median follow up 47 months) Response rate (post-induction, post SCT)		• Skeletal-related events • Toxic effects • Quality of life (results not reported)		-

PFS: Progression free survival; CR: Complete response; nCR: near complete response; PR: Partial response; OS: Overall survival; SCT: Stem cell transplant; TTP: Time to progression; RR: Response rate

For the purpose of this submission, the key endpoints of most interest are response to treatment, overall survival, progression-free survival and TTP. **Response to treatment is an especially critical endpoint**, since there is extensive evidence in the literature to demonstrate that patients who achieve robust responses to treatment (and complete response to treatment in particular) have higher rates of overall survival than patients who get lower levels of response (179). For this reason, the rate of response post-induction is of key importance from a clinical perspective.

The results presented in this submission focus on response rates post-induction and post-transplant (post 1st transplant with respect to the Gimema study) i.e. before patients received maintenance/ consolidation, in order to assess the effectiveness of induction and induction plus transplantation, respectively. Post-induction time points are the most comparable across the studies as they are assessed during the randomised phase of the study and because the four clinical trial protocols differed markedly in terms of the management of patients following SCT. As stated in section 6.3.2, patients enrolled in the Hovon, Gimema and MRC MIX trials had the opportunity to receive additional treatment post-SCT that may confound the effect of the induction therapy on PFS, TTP and OS.

Response was reported in terms of:

- Overall response rate (ORR)
- Complete response (CR)
- near CR (nCR)
- Very Good Partial Response (VGPR) (not used during the Pethema trial)
- Partial response (PR)
- Progressive disease

ORR is calculated from these measures combined, as the total proportion of patients who achieve PR or better; ORR=CR+nCR+VGPR+PR. All response rates were evaluated locally using the internationally accepted EMBT criteria(21) and the updated international response criteria(180).

Time to event data are presented using ITT populations, which include patients who went on to receive maintenance or consolidation in some cases. Patients were randomised to induction therapy; differences in the results are therefore due to the relative treatment effects of induction therapy.

Across trials which reported endpoint definitions (with the exception of Gimema), PFS was measured from the date of randomisation to the date of disease progression or death from any cause, whichever occurred first.

TTP was calculated from the date of randomisation to the date of disease progression or death due to disease progression. TTP calculations were not performed by the original study investigators as part of the Hovon, IFM, and Pethema RCTs, but were recalculated using the original patient-level data.

OS was calculated from the date of randomisation to the date of death from any cause for the intention-to-treat (ITT) patient populations.

Statistical analysis and definition of study groups

6.3.6 **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). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.**

A summary of the statistical methods, power, and data management of patients is displayed in Table 21.

Efficacy data were analysed in all studies using the ITT population. Safety was evaluated using a 'safety analysis set', which included patients who had received at least one dose of study drug during induction. Censoring of data occurred for the OS and PFS outcomes. Patients with missing follow-up data were censored at the last date they were known to be alive (OS), or alive without disease progression. The Hovon RCT reported PFS data with and without censoring at the time of allo-SCT for the few patients who underwent allo-SCT.

Table 21: Statistical methods, power calculations, and data management

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management patient withdrawals
Hovon [1]	The null hypothesis is that there is no difference between the 2 treatment arms with regard to the primary efficacy endpoint, PFSC (progression-free survival with censoring at allo-SCT).	• Level of significance: all tests were 2-sided. For the primary efficacy endpoint, the significance level was 0.049, taking into account 1 interim analysis. A significance level of 0.05 was used for other efficacy endpoints. **Primary efficacy endpoint: PFSC** • Primary comparison based on stratified log-rank test. Stratification was to include ISS disease staging (I versus II versus III versus unknown), which was derived using data reported in the case report form (CRF) • The hazard ratio (HR) and its 95% confidence interval (CI) were determined to estimate the treatment effect using the stratified Cox regression analysis **Secondary endpoints:** OS, PFS without censoring at AlloSCT, PFS from HDM: • Analyses for all secondary endpoints were similar to those described for the primary efficacy endpoint, except response rate where comparisons were made using the stratified Cochran-Mantel-Haenszel (CMH) test	A sample size of 800 patients was required, and 356 events had to be observed, in order to detect a HR of 0.74 with a power of 80%. This is based on the assumption that the 3-year PFS was 50% for the control group, and 60% for the experimental group (two-sided significance level = 0.049, because of one planned interim analysis at a significance level = 0.001), and assuming three years of accrual, additional follow-up time of two years, and 10% of subjects would receive allo-SCT	All available efficacy and safety data from all randomised patients who received at least one dose of induction therapy were to be included. (4 ineligible subjects who received study treatment were excluded from the safety population due to unavailability of safety data) Reasons for discontinuation included: • Not eligible for CAD (Cyclophosphamide, doxorubicin (Adriamycin®), and dexamethasone) and stem cell collection, and response is not CR, VGPR, PR, MR, or NC • Not eligible for conditioning with HDM • Not eligible for bortezomib maintenance • Not achieved at least MR for at least 6 months after start of either thalidomide or bortezomib maintenance • Excessive toxicity (including toxic death) • Progression/relapse (after HDM or during maintenance) • NMA-allo-SCT • Intercurrent death • Non compliance of the subject (especially refusal to continue treatment) • Pregnancy (of female subject) • Completion of protocol treatment Patients who discontinued treatment were followed up for disease progression and survival status Patients who were lost to follow-up, or the date of death was unknown, were censored at the date they were last known to be alive

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management patient withdrawals
IFM [1]	For post-induction end points, the null hypothesis is that there is no difference between VAD and VD with regard to these end points. For post-transplant end points, the null hypothesis is that there is no difference between VAD and VD with regard to these end points.	• Level of significance: All tests were 2-sided. For the primary efficacy endpoint, a significance level of 0.0475 was used, taking into account 1 interim analysis. A significance level of 0.05 was used for other efficacy endpoints. • **Primary endpoint (post-induction CR/nCR rate):** Comparison of the post-induction CR/nCR rates was performed using a stratified Cochran-Mantel-Haenzel test. Response rate and its associated 95% confidence interval (CI) were to be provided for each treatment group. **Secondary endpoints:** • Post-induction and post-transplant response rate (CR, nCR, VGPR, PR), post-transplant CR/nCR rate were to be analyzed similarly to the primary endpoint (post-induction CR/nCR rate) • PFS and OS: The Kaplan-Meier method was used to estimate the distribution of PFS/OS for the VAD and VD combination induction treatment groups. The primary treatment comparison was based on a stratified log-rank test. The hazard ratio and its 95% CI were determined to estimate the treatment effect using the stratified Cox regression analysis.	A sample size of 480 were to be enrolled to ensure 440 subjects (220 subjects need to be included per group) were included to provide 80% power to detect a 10% difference in CR+nCR rate. It also provided 80% power (two-sided α = 0.05) to demonstrate a 15% CR/nCR benefit with the addition of DCEP consolidation to VAD (10% to 25%) or bortezomib plus dexamethasone (20% to 35%).	All available efficacy and safety data from all randomised patients who received at least one dose of induction therapy were to be included Reasons for discontinuation included: • Occurrence of a severe adverse event • Decision by the investigator that, for safety reasons , it was in the best interest of the subject • Major protocol violation confirmed by the principal investigator • Withdrawal of consent by the subject • Lack of compliance • Progression of the disease during treatment • Occurrence of non-haematological Grade 3 or 4 toxicity; in the absence of sufficient therapeutic efficacy despite adjustment of the dosage • Intercurrent disease • Pregnancy Patients who discontinued treatment were followed up for end of treatment evaluation Patients who were lost to follow-up, or the date of death was unknown, were censored at the date they were last known to be alive
Pethema[1]	For RR and CR rate, the null hypothesis is that there is no difference between the 3 induction schemes with regard to these end points. For duration of	• **Level of significance**: All tests were 2-sided. For the primary efficacy endpoint, the overall significance level was 0.05. • **Primary efficacy endpoints:** (Response rates post-induction and post-transplant (CR, nCR or PR) and CR/nCR rates post-induction and post-transplant): Comparison of the response rate between the induction treatment groups was made	A sample size of 390 patients was required to provide 80% statistical power (2-sided α = 0.05) to detect a 15% difference in the response rate between treatment groups. The patient recruitment period was 36 months and an analysis was scheduled 12 months after the	All available efficacy and safety data from all randomised patients who received at least one dose of induction therapy were to be included Reasons for discontinuation included: • Refusal to receive treatment or return for follow-up visits • Major protocol violation

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management patient withdrawals
	response, PFS and OS, the null hypotheses are that 1) there is no difference between the 3 induction treatments with regard to these end points; 2) there is no difference between the 3 maintenance treatments with regard to these end points.	using the Cochran-Mantel-Haenszel test. Response rate and the associated 95% confidence interval (CI) were provided for each treatment group. **Secondary endpoints:** (PFS, OS, TTP) : • Estimated and tested separately for the induction stage. The distribution of PFS/OS/TTP will be estimated for each treatment group using the Kaplan-Meier method. The log-rank test will be used to compare the induction treatment groups. , The hazard ratio (HR) and its 95% confidence interval (CI) for each pair of comparison will be estimated by using the Cox regression procedure. • To adjust for confounding of maintenance therapy from two stage randomization, inverse probability weighting (IPW) method may be performed as an exploratory analysis to compare PFS/OS/TTP of different induction therapies followed by the same maintenance therapy.	last patients were recruited. All tests were 2-sided	• Concomitant disease • Subject request • Non-compliance with established visits • Administrative reasons • Specific or general changes in the subjects condition requiring discontinuation of any additional study medication, in the judgment of the investigator • Documented disease progression • Occurrence of any unacceptable adverse effect • Inadequate number of stem cells collected for transplantation For patients who the date of death was unknown, were censored at the date they were last known to be alive

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management patient withdrawals
Gimema	The study objective was to detect a significant increase in the rate of post-induction CR+nCR rate in patients who received bortezomib in addition to TD (VTD) versus TD alone.	• Level of significance: all tests were two-sided with p values of less than 0.05 deemed significant. All statistical analyses were by intention to treat. • **Primary endpoint (response rate CR/nCR post induction) and response rates in secondary endpoints:** Response rates were compared between treatment groups with estimates of 95% CIs using Chi^2 test • **Other secondary endpoints (time to events endpoints)**: Between-group comparisons of time to best CR or nCR (time from start of treatment to complete or near complete response achieved at any time), TTP, PFS, and OS were compared using the log-rank test and times to these outcomes were estimated using the Kaplan-Meier method **Additional analysis** : • In a post-hoc univariate analysis, best overall rates of high-quality response and PFS were compared between groups, within subgroups defined by adverse prognostic factors by use of the Chi^2 test • A multivariate Cox regression analysis was done to identify factors significantly affecting progression free survival, with calculation of HRs and 95% CIs.	A sample size of 450 patients (225 per group) was needed to provide 80% power to detect a significant increase in rate of CR+nCR response from 15% with TD induction therapy to 27% with VTD induction therapy	All available efficacy and safety data from all randomised patients who received at least one dose of induction therapy were to be included Patients who were lost to follow-up, or the date of death was unknown, were censored at the date they were last known to be alive

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management patient withdrawals
MRC MIX	To demonstrate that CTD was non-inferior to CVAD across the primary endpoints OS, PFS, and response rate (post-induction and post-SCT).	• **Level of significance:** all hypothesis tests and CIs are two-sided and at the 5% significance level. • **PFS and OS**: between-group comparisons for OS and PFS were done with Cox regression models group and the minimization factors. • Stratification was by pathway and adjusted for minimisation factors (including treatment centre) and biphosphonate treatment group • **Response rates**: between-group comparisons response rates were assessed with logistic-regression models	The trial was powered with a calculated sample size of 1080 patients (540 per treatment arm), based on an assumed 40% 5-year OS for CVAD, a non-inferiority margin of 7% (i.e. 33% OS for CTD; hazard ratio of 1.2), a one-sided modified log rank test, at 5% significance and 80% power. If 366 patients were entered, the trial would be powered to detect an increase in the number achieving a CR 100 days after ASCT from 50 to 65% (80% power at 5% significance). The planned number would provide more than 80% power.	Available efficacy and safety data from all randomised patients who received at least one dose of induction therapy were to be included Patients who were lost to follow-up, or the date of death was unknown, were censored at the date they were last known to be alive and progression free

[1]Median duration of follow-up was also calculated for all marked trials using the reverse Kaplan-Meier method

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

The Hovon, Pethema and IFM RCTs analysed primary and secondary endpoints, including response rate, PFS, TTP, and OS, categorised according to the following patient subgroups: age, sex, ISS staging, cytogenetic classification, and creatinine clearance (mL/min). The Gimema trial investigated the following patient subgroups: age, ISS disease stage II–III presence of del(13q), LDH, presence of t(4;14) with or without del(17p), and bone marrow plasma cells. All subgroup analyses were pre-specified.

Evaluation of a patients' cytogenetic risk profile is presented here, as this is requested within the NICE decision problem. However, cytogenetic testing is not routine clinical practice, nor routinely funded in the UK (Advisory Board Minutes: Appendix 14).

A high risk cytogenetic profile was defined slightly differently in each study to include the following abnormalities:

- HOVON: deletion 13, deletion 17p, t(14,16), or t(4, 14)
- IFM: deletion 13, deletion 17p, or t(4, 14),
- PETHEMA: t(4,14), or t(14,16)
- Gimema: t(4;14) with or without deletion 17p
- MRC MIX: gain(1q), deletion 17p, del1p32, t(4;14), t(14;16) or t(14;20)

Patient numbers by subgroup are presented in Table 22, and results in section 6.5.3.4.

Cytogenetic testing was performed at the time of diagnosis for many patients. The reason for not performing the test for some patients was not reported in the publication, the protocol or the clinical study report of the trials.

Cytogenetic abnormalities were not stratification criteria for patient's randomisation except in the IFM trial where the presence of chromosome 13 abnormalities identified by fluorescence in situ hybridization analysis was used as a stratification criterion. (Section 6.3.2, Table 16)

Table 22: Subgroups analysed as part of the systematic review analysis

Study name	Regimen	N ITT	Cytogenetic subgroups analysed	
			Cytogenetic risk profile	**N randomised**
Hovon	PAD	417	High risk	181
			Standard risk	198
	VAD	416	High risk	195
			Standard risk	191
IFM	VD	240	High risk	116
			Standard risk	113
	VAD	242	High risk	110
			Standard risk	124
Pethema	VTD	130	High risk	16
			Standard risk	66
	TD	127	High risk	20
			Standard risk	70
Gimema	VTD	236	High risk	53

Study name	Regimen	N ITT	Cytogenetic subgroups analysed	
			Standard risk	165
	TD	238	High risk	57
			Standard risk	166
MRC MIX	CVAD	556	High risk	141
			Standard risk	166
	CTD	555	High risk	152
			Standard risk	167

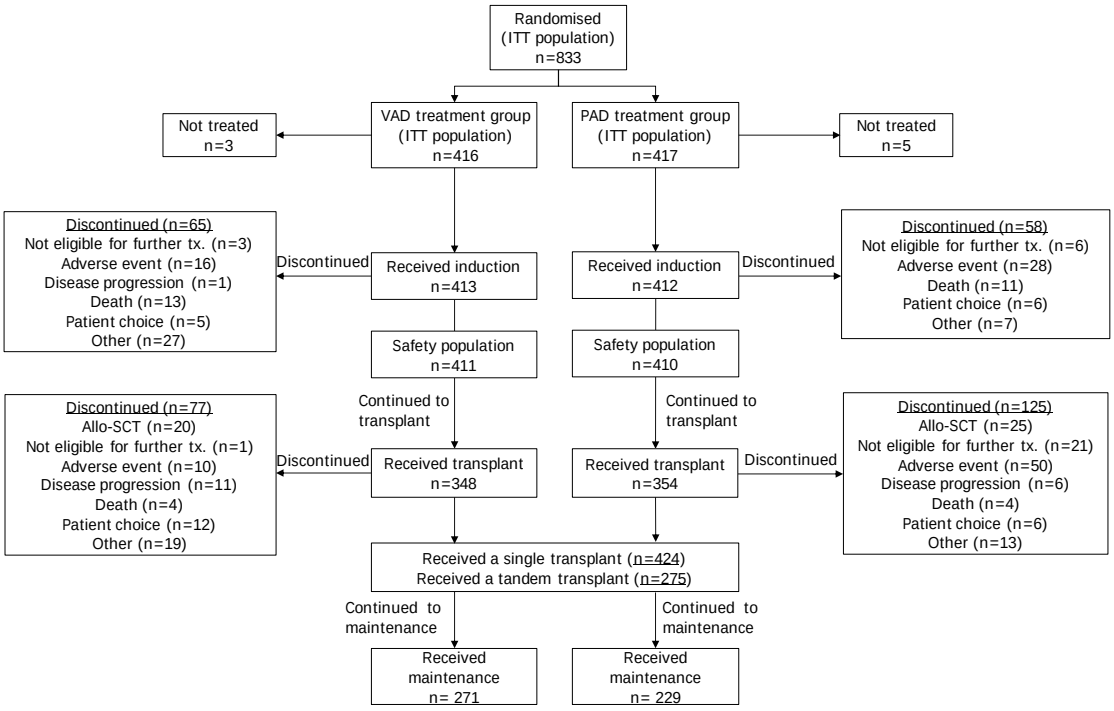
Participant flow

6.3.8 **Provide details of the numbers of patients who were eligible to enter the RCT(s), 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 or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

Patient flow diagrams are presented in Figure 9 to Figure 13.

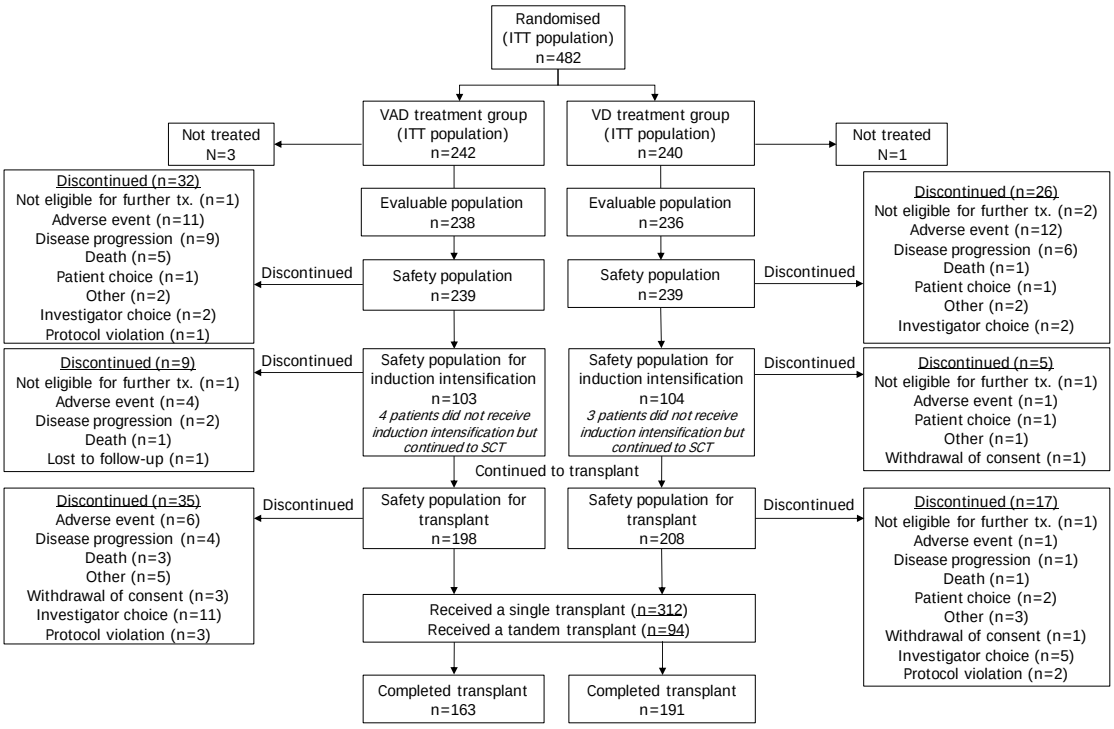
6.3.8.1 Hovon(10)

Figure 9: Patient flow diagram for Hovon



6.3.8.2 IFM(11)

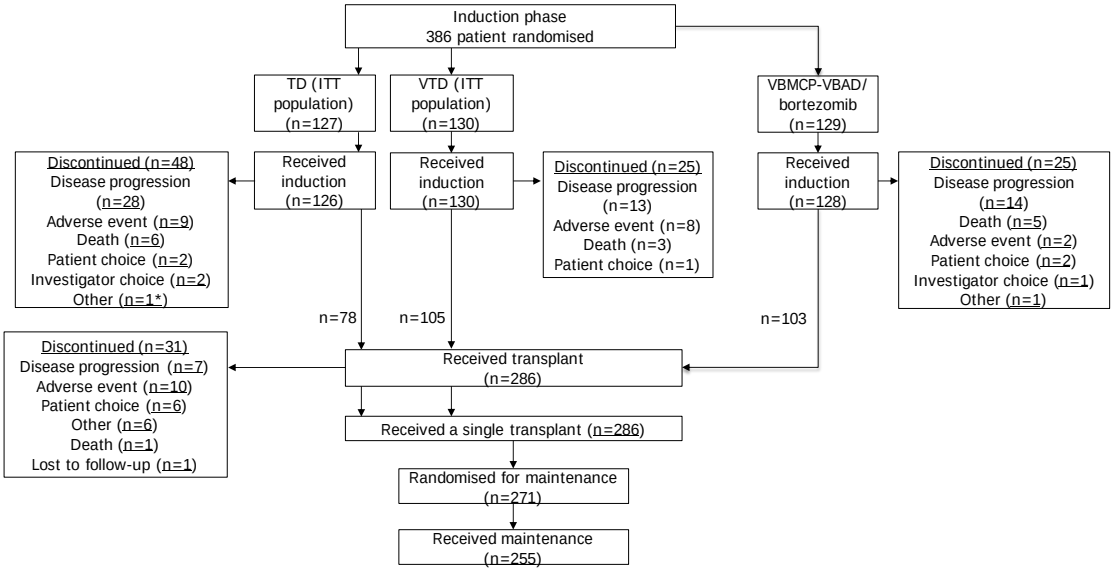
Figure 10: Patient flow diagram for IFM



A1 = VAD only; A2 = VAD plus DCEP; B1 = VD only; B2 = VD plus DCEP.

6.3.8.3 Pethema(9)

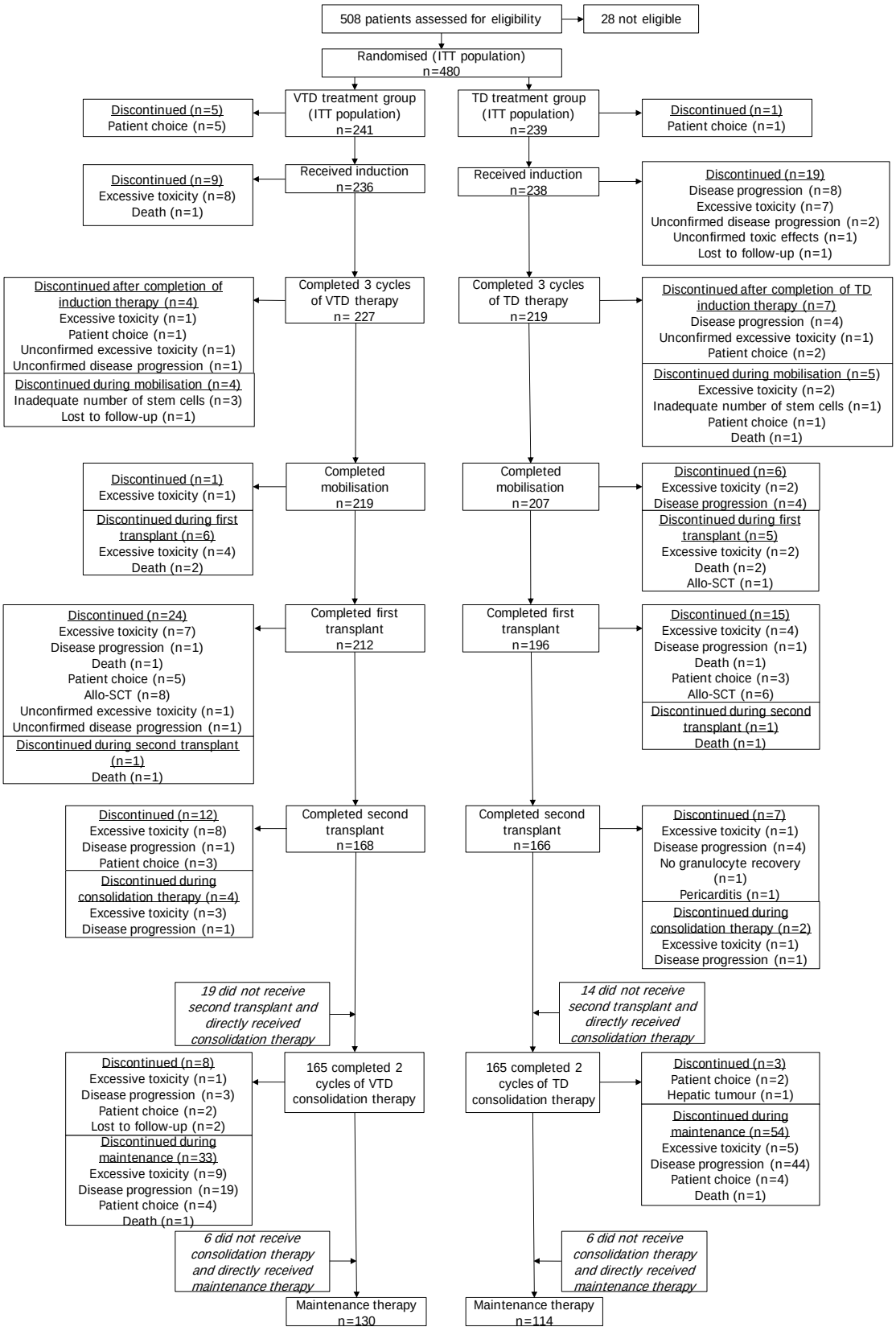
Figure 11: Patient flow diagram for Pethema



*Discontinuations after transplant included those subjects who were randomized to maintenance treatment but may have discontinued before actually receiving maintenance treatment.

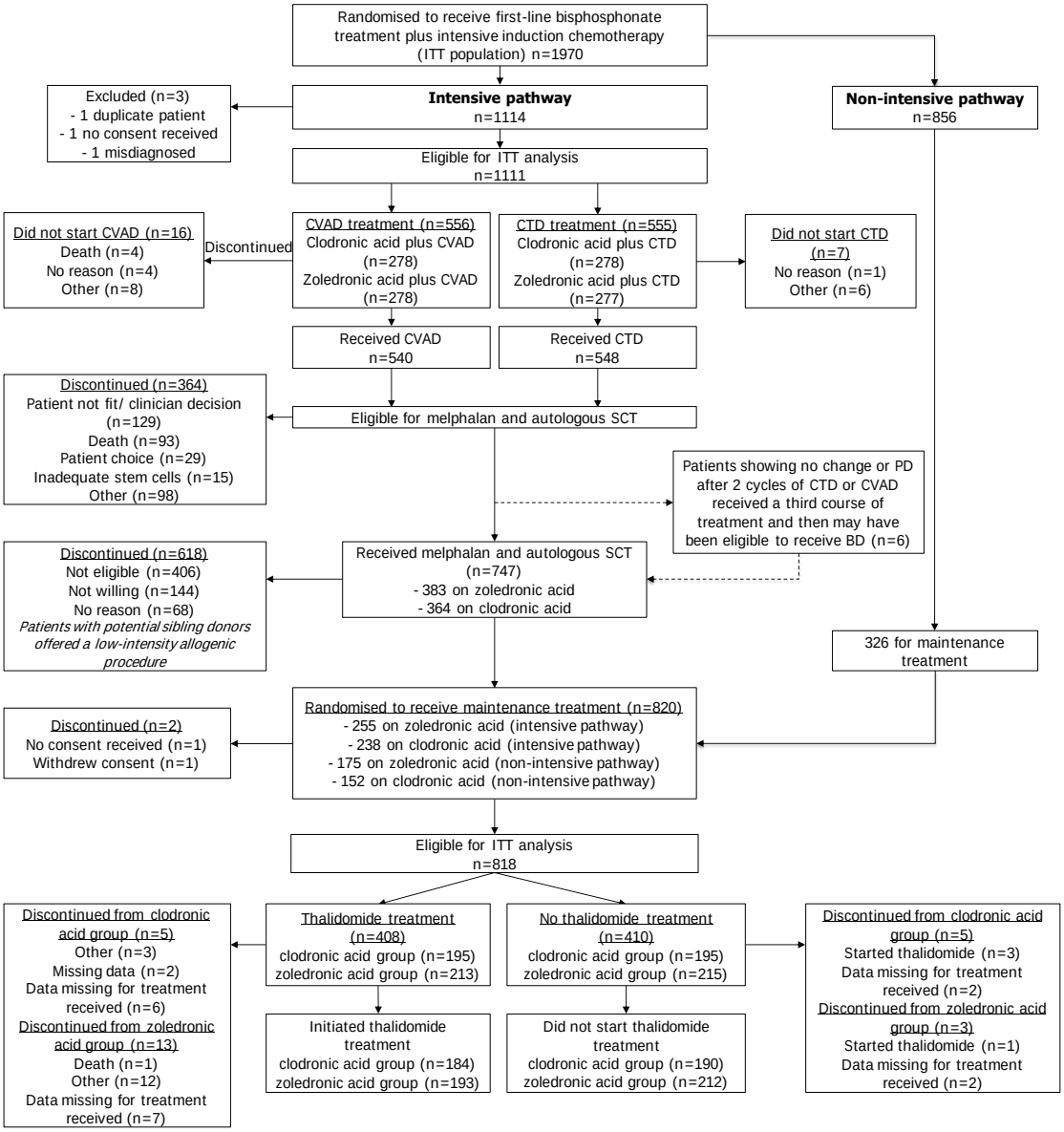
6.3.8.4 Gimema(8)

Figure 12: Patient flow diagram for Gimema



6.3.8.5 MRC MIX(58)

Figure 13: Patient flow diagram for MRC MIX



6.4 Critical appraisal of relevant RCTs

6.4.1 **The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.**

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 **Please provide as an appendix a complete quality assessment for each RCT. See appendix 3 for a suggested format.**

A complete quality assessment of each RCT is presented below in Section 6.4.3, and in the Appendix 3.

6.4.3 **If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.**

A summary of results from the critical appraisal is presented in Table 23 (further details displayed in Appendix 3).

All trials demonstrated high quality with regards to randomisation, patient drop-out, baseline characteristics, prognostic factors, outcome selection and reporting, and use of ITT analysis. The quality of the trials with respect to allocation concealment and blinding was less consistent.

The Gimema and MRC MIX trial specifically stated that patients and investigators were not masked to the allocation of treatment, and hence the quality of the treatment allocation concealment during these trials was rated as poor.

All trials had an open-label design; hence, blinding of patients was not performed. Due to the nature of treatment (i.e., different timing, mode of administration, and number of cycles associated with different induction regimens), it is not possible to blind patients and clinicians to treatment. However, in the IFM trial, response assessments were confirmed by an independent review committee, and during the MRC MIX trial, assessors of response (from laboratory results) were blinded to treatment allocation.

No trials were judged to be of poor quality, and, hence, none of the trials were removed from further investigation.

Table 23: Critical appraisal heat map of studies included in the systematic review (further detail in Appendix 3)

Study name	Allocation	Random-isation	Blinding	Baseline Character-istics	With-drawl	Outcome selection and reporting	Statistical analysis
Hovon							
IFM							
PETHEMA							
Gimema							
MRC MIX							

Key: Green = Low risk, Yellow = Uncertain risk; Red = High risk

6.5 Results of the relevant RCTs

6.5.1 **Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.**

Results presented in the following section have been extracted from the five main RCTs relevant to the decision problem: the Hovon, IFM, Pethema, Gimema, and MRC MIX trials(8;58;70-72)

Subgroup analyses are presented according to cytogenetic risk profile.

6.5.2 **The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.**

For the four bortezomib-based trials, the Kaplan-Meier plots are presented for OS, PFS, and TTP from the Hovon, IFM, and Pethema trials (Section 6.5.3.1 and 6.5.3.2). The Gimema trial reported the KM plots for the TTP or relapse, and PFS; these KM plots are also presented.

6.5.3 **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.
- Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.
- When 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 adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

The results for the endpoints relevant to the decision problem are presented below.

Response rates

Response rates comparing bortezomib-based regimens with other regimens were reported post-induction and post-transplant. ORR, CR, nCR, VGPR, and disease progression were reported in all four relevant bortezomib-based RCTs and the MRC MIX trial (Table 24).

A significantly greater number of patients who received bortezomib-based induction achieved ORR post-induction compared to VAD treated patients ($p<0.001$ in both Hovon and IFM trials). There was also a statistically significant difference with respect to ORR in favour of VTD compared to TD in the Pethema and Gimema trials ($p<0.001$ and $p<0.0001$ respectively).

There were a statistically significantly greater number of patients who achieved CR when treated with bortezomib-based treatment compared to VAD and TD, post-induction, across all trials ($p<0.001$, $p=0.01$, $p<0.001$, and $p<0.0001$ for Hovon, IFM, Pethema, and Gimema trials respectively). These post-induction complete response rates were further increased post-transplant. VTD, PAD and VD showed statistically higher post-transplant complete response (CR) rates than their comparator.

In the IFM trial, similar post-induction or post-transplant response rates were observed in all categories for the VAD and VD induction regimens with or without DCEP, indicating that induction intensification with the addition of DCEP did not result in an improvement of response rates; hence stratified results based upon patient receipt of DCEP are not reported here.

Both the Gimema and Pethema trials reported that a statistically significantly lower proportion of patients experienced disease progression when treated with VTD compared with patients treated with TD induction therapy ($p=0.0005$, and $p=0.0004$ respectively).

Table 24: CR, nCR, VGPR and ORR response rates post-induction and post-transplant

Study name	Induction regimen	% (n/N)	P value	% (n/N)	P value	Reference
		ORR post-induction		**ORR post-transplant**		
Hovon	PAD	**84.2 (351/417)**	**<0.001**	**77.5 (323/417)**	**<0.001**	(70)
	VAD	**61.3 (255/416)**		**65.9 (274/416)**		
IFM	VD	**77.1 (185/240)**	**<0.001**	79.6 (191/240)	0.179	(72)
	VAD	**60.7 (147/242)**		74.4 (180/242)		
Pethema	VTD	**84.6 (110/130)**	**<0.001**	**77.7 (101/130)**	**<0.001**	(71)
	TD	**61.4 (78/127)**		**56.7 (72/127)**		
Gimema	VTD	**93.2** (220/236)	**<0.0001**	**93.2 (220/236)**	**0.0025**	(8)
	TD	**78.6** (187/238)		**84.5 (201/238)**		
MRC MIX	CVAD	**71.2** (396/556)	**<0.0001**	61.3 (341/556)	0.45**	(58)
	CTD	**82.5** (458/555)		61.1 (339/555)		
		CR post-induction		**CR post-transplant**		
Hovon	PAD	**11 (46/417)**	**<0.001**	**22.5 (94/417)**	**<0.001**	(70)
	VAD	**2.9 (12/416)**		**12.3 (51/416)**		
IFM	VD	**5.4 (13/240)**	**0.010**	**18.3 (44/240)**	**0.011**	(72)
	VAD	**1.2 (3/242)**		**10.3 (25/242)**		
Pethema	VTD	**35.4 (46/130)**	**<0.001**	**46.9 (61/130)**	**<0.001**	(71)
	TD	**13.4 (17/127)**		**23.6 (30/127)**		
Gimema	VTD	**18.6 (44/236)**	**<0.0001**	**37.7 (89/236)**	**0.0004**	(8)
	TD	**4.6 (11/238)**		**22.7 (54/238)**		
MRC MIX	CVAD	**8.1 (45/556)**	**0.0083**	**25.4 (141/556)**	**0.00052****	(58)
	CTD	**13.0 (72/555)**		**33.3 (185/555)**		
		Near CR post-induction		**Near CR post-transplant**		
Hovon	PAD	7.2 (30/417)	-	10.1 (42/417)	-	(70)
	VAD	3.4 (14/416)		7.5 (31/416)		
IFM	VD	9.2 (22/240)	-	19.2 (46/240)	-	(72)
	VAD	5 (12/242)		12.8 (31/242)		
Pethema	VTD	13.8 (18/130)	-	8.5 (11/130)	-	(71)
	TD	3.9 (5/127)		11.0 (14/127)		
Gimema	VTD	-	-	-	-	
	TD	-		-		
MRC MIX	CVAD	-	-	-	-	
	CTD	-		-		
		VGPR post-induction		**VGPR post-transplant**		
Hovon	PAD	31.9 (133/417)	-	25.2 (105/417)	-	(70)
	VAD	13.2 (55/416)		19.2 (80/416)		
IFM	VD	22.5 (54/240)	-	25.0 (60/240)	-	(72)
	VAD	8.7 (21/242)		21.9 (53/242)		
Pethema	VTD	25 (33/130)	-	-	-	(9)
	TD	15 (19/127)		-		
Gimema	VTD	-	-	-	-	
	TD	-		-		
MRC MIX	CVAD	**19.4 (108/556)**	**0.00003**	**17.1 (95/556)**	0.73**	(58)
	CTD	**30.3 (168/555)**		**15.9 (88/555)**		
		Partial response post-induction		**Partial response post-transplant**		
Hovon	PAD	34.1 (142/417)	-	19.7 (82/417)	-	(70)
	VAD	41.8 (174/416)		26.9 (112/416)		
IFM	VD	40 (96/240)	-	17.1 (41/240)	-	(72)
	VAD	45.9 (111/242)		29.3 (71/242)		
Pethema	VTD	35.4 (46/130)	-	22.3 (29/130)	-	(71)
	TD	44.1 (56/127)		22.0 (28/127)		
Gimema	VTD	-	-	-	-	
	TD	-		-		
MRC MIX	CVAD	43.7 (243/556)	0.14	**18.9 (105/556)**	**0.0017****	(58)
	CTD	39.3 (218/555)		**11.9 (66/555)**		
		Progressive disease post-induction		**Progressive disease post-transplant**		
Hovon	PAD	1.0 (4/417)	-	1.2 (5/417)	-	(70)

Study	Induction	% (n/N)	P value	% (n/N)	P value	Reference
	VAD	3.6 (15/416)		2.6 (11/416)		
IFM	VD	5.0 (12/240)	-	0.4 (1/240)	-	(72)
	VAD	4.1 (10/242)		0.0 (0/242)		
Pethema	VTD	**6.2 (8/130)**	**0.0004**	1.5 (2/130)	-	(71)
	TD	**23.6 (30/127)**		0.8 (1/127)		
Gimema	VTD	**0.0 (0**/236)	**0.0005**	-	-	(8)
	TD	**5.0 (12**/238)		-		
MRC MIX	CVAD	2.7 (15/556)	0.6	1.6 (9/556)	0.51**	(58)
	CTD	3.2 (18/555)		2.2 (12/555)		

Note: Gimema post transplant data are taken after the first autologous SCT. Note: PETHEMA patient numbers are back calculated from published percentages for response rates, and hence .are only presented to two significant figures

**P values compare the two induction regimes within the study using modified patient N as stated in the publication (number of patients who received transplant rather than ITT N; CVAD N=379 ; CTD N=370) Percentages were back calculated from the raw data using ITT N values

Bold text means that data are statistically significant at 0.05 level; ORR= PR or above

'-' indicates that the information was not reported

6.5.3.1 Progression Free Survival

Unadjusted PFS HRs are reported for each relevant RCT (Table 25). Kaplan-Meier plots of PFS stratified by treatment group were reported for the bortezomib-based RCTs; Hovon, IFM, Pethema, and Gimema trials (Figure 14). The Hovon and IFM trials only reported PFS HR and CI after adjusting for patient characteristics, such as baseline ISS stage. Unadjusted PFS values are reported here so as to allow comparison of consistent PFS results between trials. These unadjusted values were obtained from the Kaplan-Meier curves for Hovon and IFM using graphical reading of the curves and calculation methods as described by Tierney and colleagues(181).

Other PFS values reporting PFS adjusted for baseline characteristics are reported in the CSR or publication linked to each individual trial (adjusted values are noted in Appendix 7.3).

The trials had a median follow-up of 42 months (Hovon), 33 months (IFM), 35.9 months (Pethema), 36 months (Gimema), and 47 months (MRC MIX). PFS was maintained for longer in patients treated with bortezomib-based regimens compared to patients treated with other induction therapies. This difference was statistically significant comparing VTD to TD (p=0.015 and p=0.0061 in the Pethema and Gimema trials, respectively), and as part of the unadjusted Hovon trial analysis (PAD vs. VAD HR=0.82 [95%CI 0.69-0.98]). The comparison of VD vs. VAD in the IFM trial was not statistically significant at the 95% confidence level.

Table 25: Median PFS (months), and HR of PFS (months) for bortezomib induction therapy compared to other treatments

Study name	Induction regimen	ITT N	Median (95% CI; p values NR)	Setting adjustment	HR (95% CI; p value)	Reference
Hovon	PAD	417	35.0 (30.8, 39.2)		-	(70)
	VAD	416	28.1 (24.8, 31.8)			
	PAD	417	34.5 (30.7, 38.3)	Unadjusted with censoring Read from survival curve	**0.82† (0.69, 0.98; p=NR)**	
	VAD	416	28.6 (25.2, 31.8)			
IFM	VD	240	36.1 (32.5, 41.1)	Unadjusted Read from survival curve	0.88† (0.70, 1.11; p=NR)	(72)
	VAD	242	29.7 (26.3, 37.2)			
Pethema	VTD	130	55.5 (31.2, Not reached)	Unadjusted	**0.65 (0.45, 0.92; p=0.015)**	(9;71)
	TD	127	27.9 (19.8, 34.6)			
Gimema	VTD	236	Not reached (Not reached, Not reached)	Unadjusted	**0.63 (0.45, 0.88; p=0.0061)**	(8)
	TD	238	42 (Not reached, Not reached)			
MRC MIX	CTD	555	27** (24, 29)	Unadjusted	0.94 (0.81, 1.09; p=0.56)	(58)
	CVAD	556	25** (23, 26)			

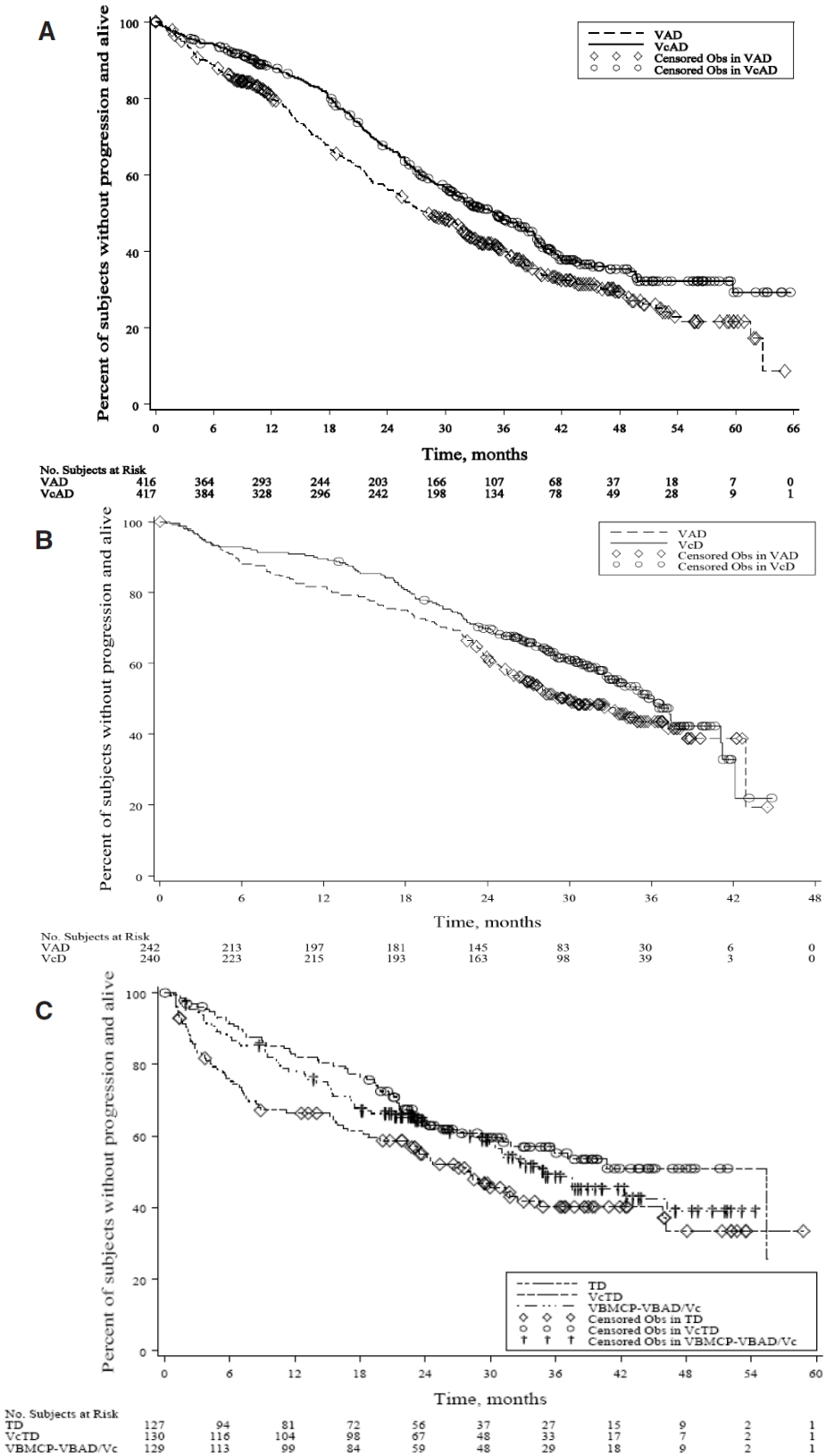
† Data read from PFS Kaplan-Meier plot

PFS values are without SCT censoring unless otherwise stated

** Per protocol analysis

Bold text indicates that data are statistically significant at 95% confidence level

Figure 14: PFS Kaplan-Meier curves reported by the Hovon, IFM, Pethema and Gimema RCTs(70-72), time to progression or relapse as reported by the Gimema RCT(8)



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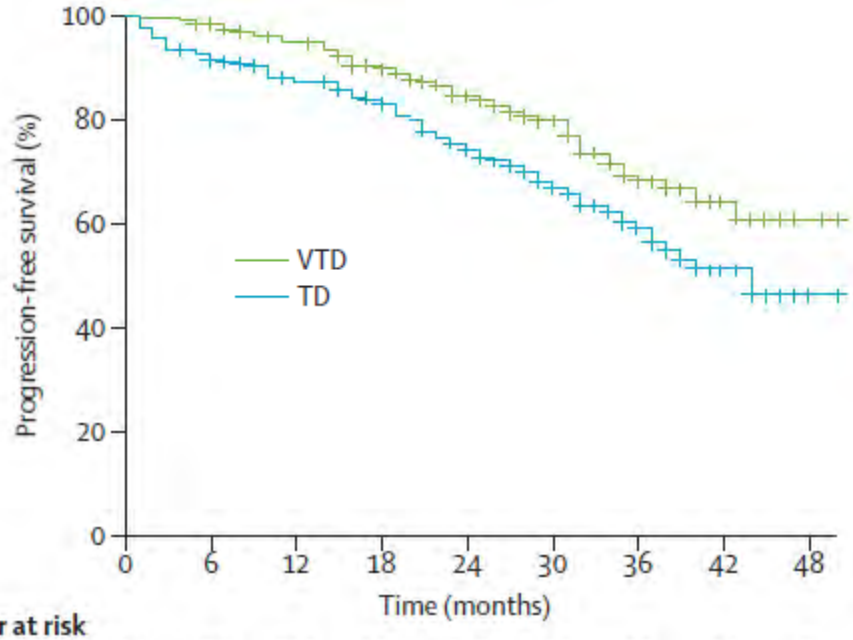


Number at risk

VTD	236	230	212	195	159	111	55	21	2
TD	238	218	200	185	158	99	51	13	2

Time to progression

TTP HRs, as presented in the CSR, are displayed in Table 26 (adjusted values are noted in Appendix 7.3). There was a statistically significant lower hazard of progression in patients treated with PAD, compared to patients treated with VAD (p=0.010), and in patients treated with VTD compared to TD (p=0.017). TTP KM curves for the Hovon, IFM, and Pethema trials, and the TTP or relapse KM curve for the Gimema trial are presented in Figure 15.

The Hovon, IFM, and Pethema trials also reported median TTP (median follow-up of 42 months, 33 months, and 35.9 months, for the Hovon, IFM, and Pethema respectively). No statistically significant difference in median results was reported.

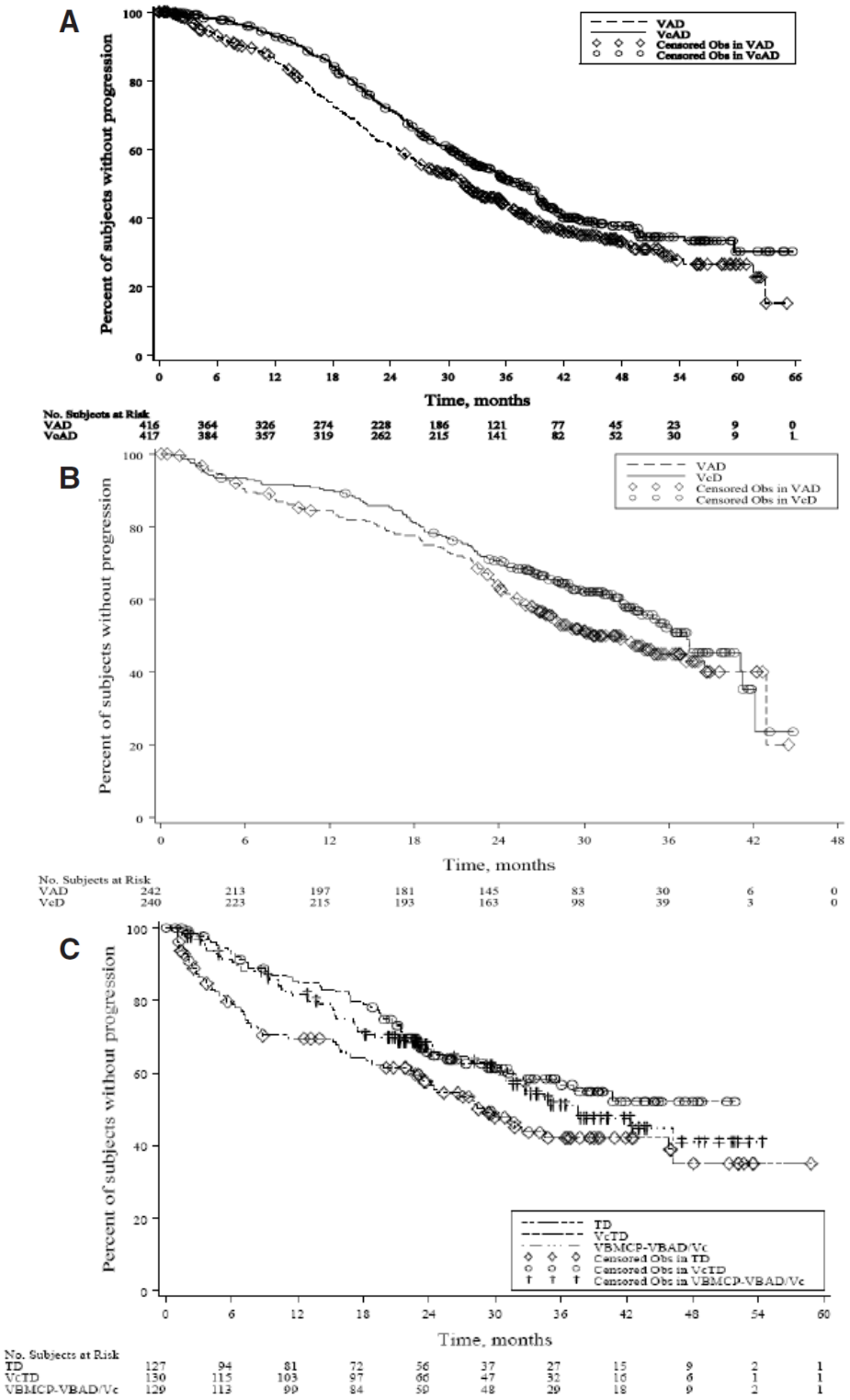
Table 26: Median TTP (months), and HR (hazard of progression; months) for TTP comparing bortezomib induction therapy to other treatments

Study name	Induction regimen	ITT N	Median (95% CI; p values NR)	Setting adjustment	HR (95% CI; p value)	Reference
Hovon	PAD	417	37.4 (33.3, 39.8)	Unadjusted Read from survival curve	**0.79† (0.66, 0.95; p=0.010)**	(10;70)
	VAD	416	31.7 (27.4, 35.4)			
IFM	VD	240	37.3 (33.6, 41.2)	Unadjusted Read from survival curve	0.82† (0.63, 1.06; p=NR)	(11;72)
	VAD	242	30.6 (27.2, 38.5)			
Pethema	VTD	130	Not reached (31.9, Not reached)	Unadjusted	**0.64 (0.44, 0.93; p=0.017)**	(9;71)
	TD	127	29.0 (23.3, 45.9)			
Gimema	VTD	236	Not reported			
	TD	238				
MRC MIX	CTD	555	Not reported			
	CVAD	556				

† Data read from PFS Kaplan-Meier plot

Bold text indicates that data are statistically significant at 95% confidence level

Figure 15: <u>TTP Kaplan-Meier curves reported by the Hovon, IFM, and Pethema RCTs(70-72), and</u> time to progression or relapse as reported by the Gimema RCT(8)



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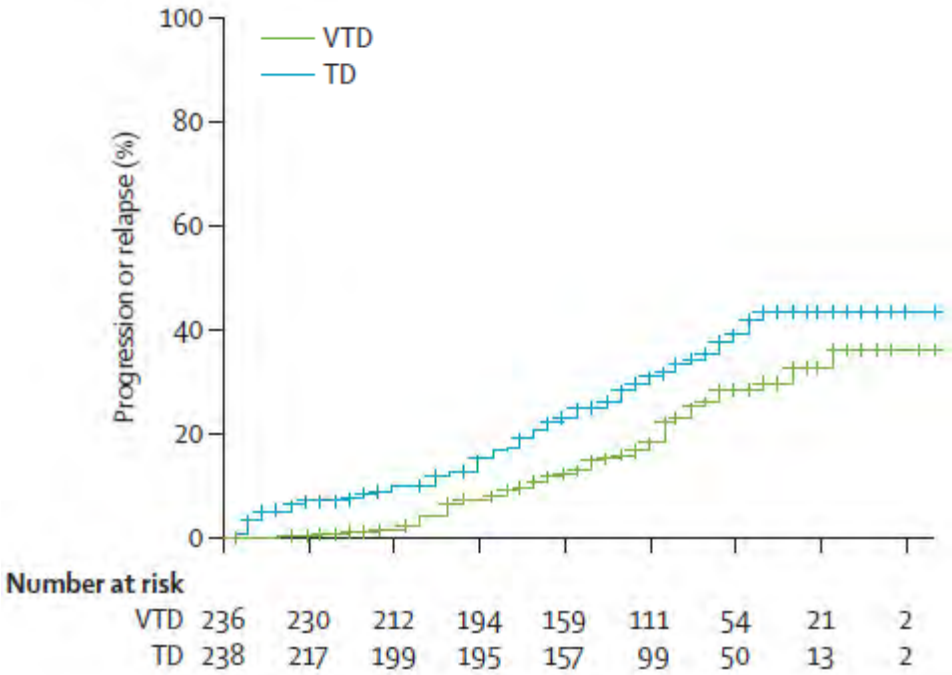


Please note. Curve D, time to progression or relapse as reported with respect to the Gimema trial appears upside down compared to the other KM curves. However each event in the curve represents movement from the progression free state to the progression/relapse state.

6.5.3.2 Overall Survival

OS unadjusted HRs are reported for each relevant RCT. (Table 27) Kaplan-Meier plots of OS stratified by treatment group were reported for three of the bortezomib RCTs (Figure 16). Unadjusted OS data are reported here in order to allow comparison of consistent data between trials; these comparable results were then used as part of the MTC described in Section 6.8. Unadjusted values were obtained from the Kaplan-Meier curves for Hovon and IFM using graphical reading of the curves and calculation methods as described by Tierney and colleagues(181).

After a median follow-up of 42 months (Hovon), 33 months (IFM), 35.9 months (Pethema), and 47 months (MRC MIX), **median OS had not been reached** across the majority of trials and treatment groups (Table 27). Similarly, median OS was not reached at the date of reporting cut-off for patients who received CTD in the MRC MIX RCT.

Clinical experts considered the duration of the RCTs to be too short to allow sufficient difference to be measured in OS/PFS rates between treatment groups, given the relatively long survival post-transplant in this population. Furthermore, the heterogeneity of the trial designs and the post SCT management strategies mean that making firm conclusions on overall survival of the original induction regimen challenging. In these studies, although trends towards a difference in OS were observed, median survival was not reached in many cases (Advisory Board Minutes: Appendix 14).

Table 27: OS HR of death comparing bortezomib to other treatments

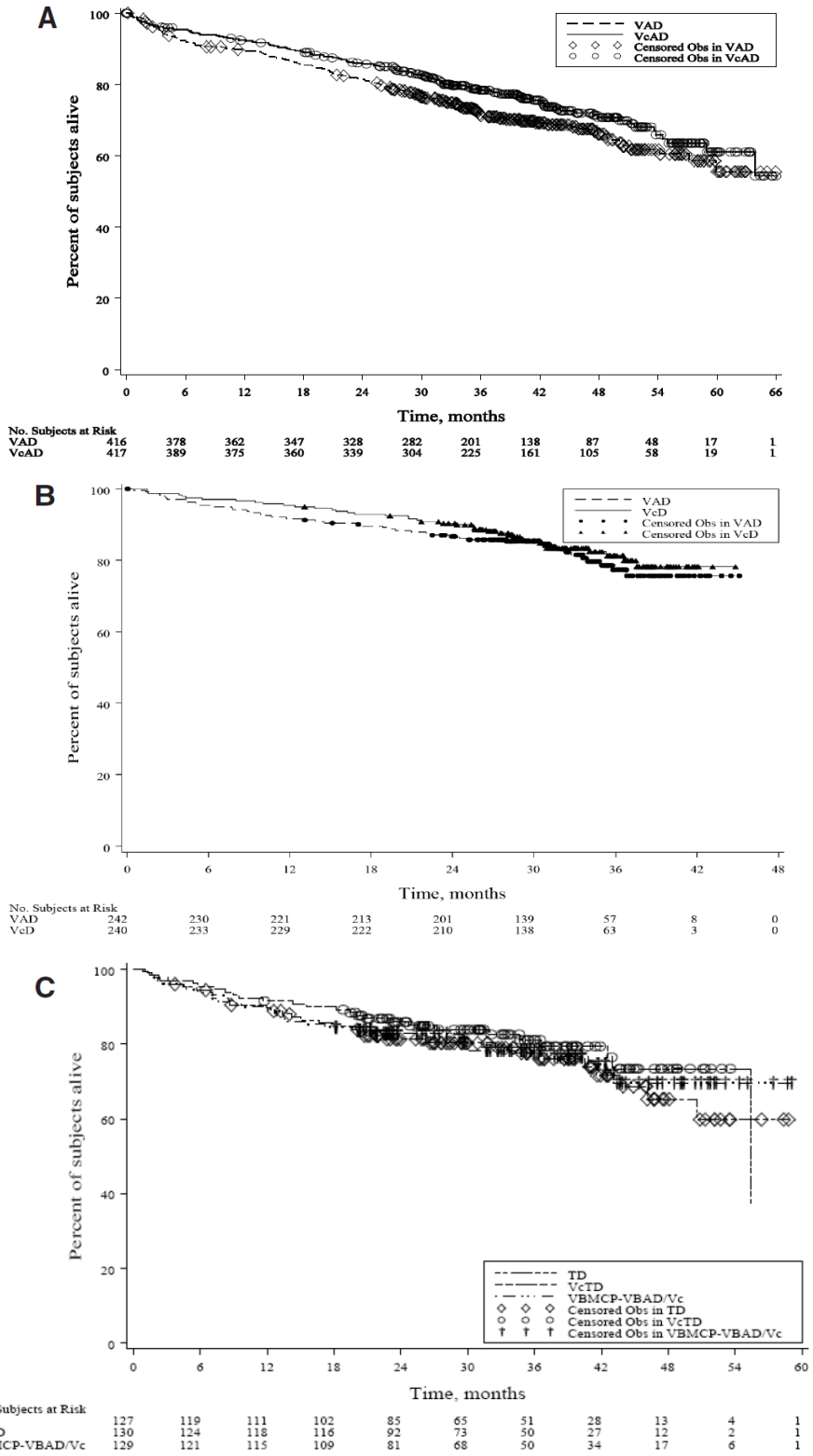
Study name	Induction regimen	ITT N	Median (95% CI)	Setting	HR (95% CI; p value)	Reference
Hovon	PAD	417	Not reached (63.9, not reached)	Unadjusted Read from survival curve	0.8† (0.62, 1.02; p=NR)	(70)
	VAD	416	Not reached (59.9, not reached)			
IFM	VD	240	Not reached	Unadjusted Read from survival curve	0.8† (0.54, 1.19; p=NR)	(72)
	VAD	242	Not reached			
Pethema	VTD	130	55.5 (55.5, not reached)	Unadjusted	0.80 (0.48, 1.34; p=0.393)	(9;71)
	TD	127	Not reached (50.6, not reached)			
Gimema	VTD	236	NR	-	(p=0.30)	(8)
	TD	238				
MRC MIX	CTD	555	Not reached (61, not reached)	Unadjusted	0.92 (0.75, 1.13; p=0.29)*	(58)
	CVAD	556	63* (59, not reached)			

† Data read from PFS Kaplan-Meier plot

* Per protocol analysis

Bold text indicates that data are statistically significant at 95% confidence level

Figure 16: OS Kaplan-Meier curves reported by the Hovon, IFM, and Pethema trials(70-72)



6.5.3.3 Proportion of patients who underwent SCT

Although the studies were not powered on this endpoint, the proportion of patients who, following induction, were actually able to receive a SCT is clearly an important outcome in this setting. Results across the studies are presented in Table 28. In the Pethema trial, a higher percentage of patients underwent SCT following induction therapy with bortezomib, compared to TD. This is due mainly to the high occurrence of disease progression in patients treated with TD: the rate of discontinuation post-induction was 22% with TD vs. 10% with VTD, rendering these patients ineligible for transplant. Other reasons for discontinuation were similar in both treatment groups: adverse events VTD=6%, TD=7%, subject choice VTD=1%, TD=2%, death VTD=2%, TD=5%, investigator choice VTD=0, TD=2%, unknown VTD=0, TD=1%. This suggests that the VTD regimen is more effective at ensuring patients were eligible for transplant than the TD regimen in this study, although no statistical tests were reported. A similar difference was not observed in the Hovon trial, although comparisons between trials are limited by the fact that the dosing regimens were different, with only three cycles of induction being used as opposed to six in Pethema.

A lower percentage of patients received SCT in the MRC MIX trial (both treatment arms) as patients were judged not fit for transplant by the clinicians; more detailed reasons for this are not reported.

Table 28: Proportion of randomised patients who underwent SCT following induction regimens

Study name	Induction regimen	% patients (n/N) *	Reference
Hovon	PAD	84.9 (354/417)	(70)
	VAD	83.7 (348/416)	
IFM	VD	86.7 (208/240)	(72)
	VAD	81.8 (198/242)	
Pethema	VTD	80.8 (105/130)	(71)
	TD	61.4 (78/127)	
Gimema	VTD	88.0 (212/241)	(8)
	TD	82.0 (196/239)	
MRC MIX	CVAD	68.2 (379/556)	(58)
	CTD	66.7 (370/555)	

Percentages have been recalculated from the raw data using ITT N numbers. * No statistical test of comparison was performed.

6.5.3.4 Subgroup analysis (Response rate, PFS, TTP, and OS)

Subgroup analysis of response rate, PFS, TTP and OS across trials were evaluated for subgroups including age, ISS staging, creatinine clearance, and cytogenetic risk. The point estimates of the odds ratios across these subgroups were consistent with the treatment effect observed in the ITT population, in that the treatment effects associated with bortezomib-based induction regimens were consistent across all subgroups. Only the results by cytogenetic risk group are presented in Table 29 and Table 30. Results for other subgroups according to age, ISS and creatinine clearance are presented in Appendix 17.

Table 29: Response rates post-induction and post-transplant for patients with high and standard cytogenetic risk

Study name	Regimen full	Subgroup	CR/nCR Post-induction (number achieving response/number with confirmed risk status)	CR/nCR Post-transplant (number achieving response/number with confirmed risk status)	Reference
Hovon	PAD	High risk	21 (38/181)	35.9 (65/181)	(70)
		Standard risk	14.1 (28/198)	28.8 (57/198)	
	VAD	High risk	5.6 (11/195)	23.1 (45/195)	
		Standard risk	6.8 (13/191)	16.8 (32/191)	
IFM	VD	High risk	20.7 (24/116)	46.6 (54/116)	(72)
		Standard risk	7.1 (8/113)	27.4 (31/113)	
	VAD	High risk	6.4 (7/110)	19.1 (21/110)	
		Standard risk	6.5 (8/124)	25.8 (32/124)	
Pethema	VTD	High risk	56.3 (9/16)	43.8 (7/16)	(71)
		Standard risk	42.4 (28/66)	54.5 (36/66)	
	TD	High risk	5.0 (1/20)	20.0 (4/20)	
		Standard risk	18.6 (13/70)	35.7 (25/70)	
Gimema	VTD	NR			
	TD				
MRC MIX	CVAD	NR			
	CTD				

NR indicates data not reported

Table 30: PFS, TTP and OS (months) HR for patients at different cytogenetic risk levels

Study name	Setting adjustment	Induction regimen	Risk level	HR (95% CI)	Median (months)	Reference
PFS						
Hovon	Unadjusted	PAD vs. VAD	High risk	**0.75 (0.59, 0.96)**	PAD: 28.4 VAD: 22.3	(70)
			Standard risk	0.87 (0.66, 1.14)	PAD: 39.8 VAD: 36.6	
IFM	Unadjusted	VD vs. VAD	High risk	0.90 (0.62, 1.29)	VD: 33.6 VAD: 28.9	(72)
			Standard risk	0.76 (0.52, 1.11)	VD: 37.5 VAD: 38.5	
Pethema	Unadjusted	VTD vs. TD	High risk	0.71 (0.34, 1.48)	VTD: 14.9 TD: 8.0	(71)
			Standard risk	0.87 (0.54, 1.42)	VTD: 35.9 TD: 31.8	
Gimema	Adjusted		High risk	**0.51* (0.29, 0.88)**	NR	(8)
MRC MIX	PFS not reported					
TTP						
Hovon	TTP not reported					
IFM	TTP not reported					
Pethema	Unadjusted	VTD vs. TD	High risk	0.8 (0.36, 1.74)	VTD: 15.5 TD: 8.8	(71)
			Standard risk	0.84 (0.51, 1.4)	VTD: 37.1 TD: 32.5	
Gimema	TTP not reported					
MRC MIX	TTP not reported					
OS						
Hovon	Unadjusted	PAD vs. VAD	High risk	**0.65 (0.46, 0.91)**	PAD:58.9 VAD:48.8	(70)

Study name	Setting adjustment	Induction regimen	Risk level	HR (95% CI)	Median (months)	Reference
			Standard risk	1.22 (0.78, 1.91)	Not reached	
IFM	OS not reported					
Pethema	Unadjusted	VTD vs. TD	High risk	1.19 (0.49, 2.87)	VTD: 27.3 TD: 40.5	(71)
			Standard risk	0.94 (0.37, 2.39)	VTD: Not reached TD: Not reached	
Gimema	OS not reported					
MRC MIX	OS not reported					

†p=0.002; *p=0.0174; **p=0.0003; Bold text indicates that data are statistically significant at 95% confidence level (i.e. the 95% confidence interval does not cross 1)

6.6 Meta-analysis

6.6.1 **The following steps should be used as a minimum when presenting a meta-analysis.**

6.6.2 **If a meta-analysis is not considered appropriate, a 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.**

It was not appropriate to meta-analyse the bortezomib-based trials because of the major differences in the design of the four studies. As has been previously described, these trials were very different in almost all aspects, including the bortezomib combination regimens, the variable duration of induction, comparator arms and the differences in study design.

Another consideration was that some of the studies used induction regimens (such as VAD) that are no longer considered to be standard practice in the UK, which is relevant to the decision-problem. In the UK, CTD is considered to be the current standard of care, despite not being licensed for use in this setting.

The systematic review did not identify any trials that compared bortezomib-based regimens to CTD. It was determined that the only way to synthesise the relevant evidence was therefore to explore the feasibility of undertaking an MTC (section 6.7).

6.6.3 **If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) 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.**

Not applicable

6.7 Indirect and mixed treatment comparisons

6.7.1 **Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. 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 section 9.4, Appendix 4.

Clinical data were derived from the systematic review reported in Section 6.1-6.5; the search strings for this review are reported in Appendix 2.4. In order to ensure that trials evaluating relevant pharmacological induction therapy regimens were not excluded inappropriately, all comparators which could potentially contribute to an MTC were included at the search stage, and only excluded during citation screening.

6.7.2 **Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, and a complete quality assessment for each comparator RCT identified.**

The RCTs included in the MTC have been described and evaluated previously in this submission, Section 6.1-6.5. A complete quality assessment is provided in Section 6.4 and Appendix 3.

6.7.3 **Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.**

Trials used to conduct the indirect comparison and regimens compared in each trial are presented in Table 31.

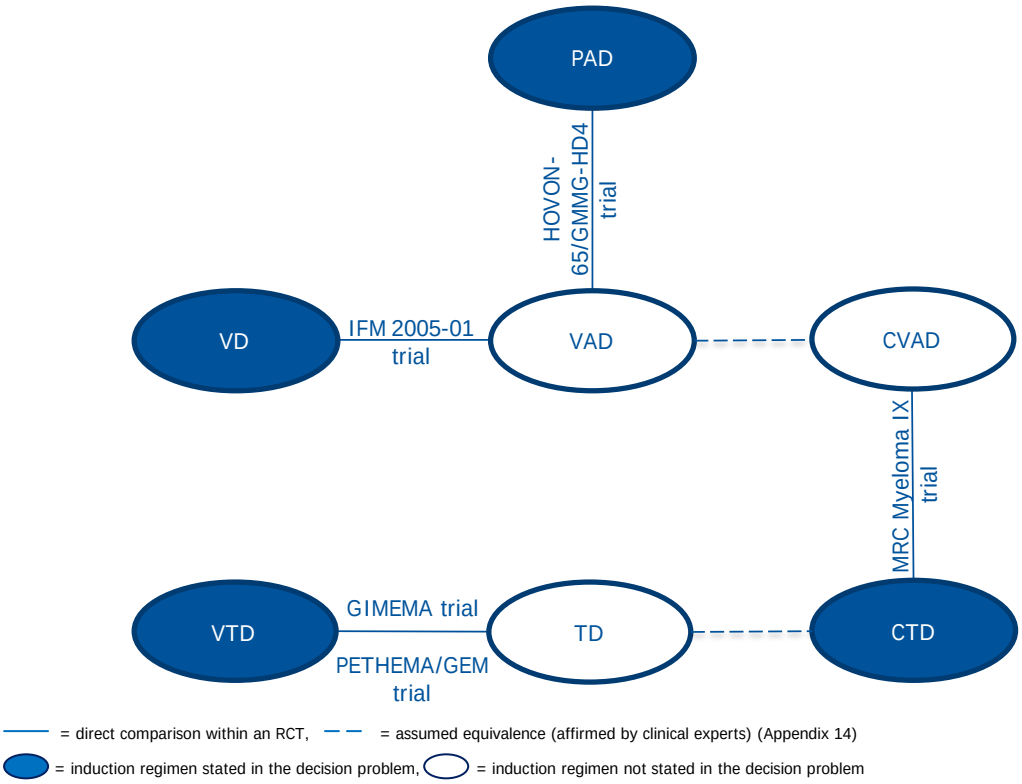
Table 31: Summary of the regimen evaluated during the four bortezomib trials and the MRC MIX trial, used to conduct the MTC

RCT name	Intervention	Comparator
IFM	VD	VAD
HOVON	PAD	VAD
MCR MIX	CTD	CVAD
GIMEMA & PETHEMA	VTD	TD

References for these RCTs are reported in Table 12

The network diagram for the evidence structure comprising the four bortezomib trials and the MRC M IX trial is presented in Figure 17.

Figure 17: Network diagram for the five trials



This work demonstrated that a network is unable to be formed from the available trials. Specifically, the evidence base provides no ability to directly link between bortezomib-based regimens and CTD.

The only possible method that was identified in order to link bortezomib-based regimens to CTD is to make a number of assumptions regarding the relative effectiveness of different treatment regimens. The two assumptions that underpin an MTC in this setting are (1) that CVAD and VAD are clinically equivalent and (2) that TD and CTD are clinically equivalent.

If these assumptions hold, the MTC method allows them to be used simultaneously in a model whilst providing an estimate of internal coherence of the model (an alternative would be to perform two separate models, but this would not allow the internal coherence of the assumptions to be simultaneously evaluated).

The assumption of clinical equivalence between CVAD and VAD adds an element of uncertainty to the analysis. This issue was one that was discussed carefully in consultations with clinical experts. In discussions with Janssen, the consensus from the clinical experts was that this clinical equivalence between CVAD and VAD is indeed plausible. The justification for this is as follows. Firstly, it is considered that cyclophosphamide in CVAD is largely redundant as both cyclophosphamide and doxorubicin (the “A” in CVAD) are alkylating agents, and therefore act via a similar mechanism of action with no additive effect when used together. Secondly, clinical practice in the UK is anomalous compared to other European countries; the frequent addition of cyclophosphamide to induction regimens containing novel agents such as thalidomide and bortezomib in the UK is considered to be a remnant of MRC

cyclophosphamide trials carried out in myeloma since 1964 (Section 2.6), and the addition of cyclophosphamide is habit-driven rather than delivering clinical benefit.

Likewise, the addition of cyclophosphamide to TD is considered to have little or no clinical benefit, and the assumption of clinical equivalence between CTD and TD was felt to be plausible by the clinical experts who were consulted (Appendix 14). It is postulated that the redundant addition of low dose cyclophosphamide (500 mg) to regimens is not evidence-based, and the clinical advice is that there is no additional benefit conferred by adding cyclophosphamide to either VAD or to TD. (Appendix 14).

6.7.4 Whilst these assumptions of similarity were considered plausible by clinical experts at the advisory board, it is recognised that there is considerable uncertainty underlying the mixed treatment comparison conducted to meet the decision problem. This uncertainty, combined with the heterogeneity in the trial designs of bortezomib-based regimens and the acknowledged limitations of MTCs means that these results should be treated with utmost caution. The most robust evidence to rely on in this instance are the results of the individual trials themselves as any form of evidence synthesis is severely limited in this particular instance. Consequently, the economic evaluation presented in section 7 was focused only on the comparison of VTD vs. TD, PAD vs. VAD, and VD vs. VAD. **For the selected trials, provide a summary of the data used in the analysis.**

Results for both the primary and secondary endpoints were presented for the five trials in Section 6.5. The MTC was performed on the following endpoints:

TTP and OS: The MTC of TTP and OS was conducted using time-to-event (HR, 95% CI) data. Where unadjusted HR or CI data were missing or incompletely reported, these were derived from digitalised versions of the Kaplan-Meier survival curves that were presented in the clinical trial reports (as the ratio of hazards between treatment groups). The HR with the 95% CI for OS was not reported in the Gimema trial so this trial was not included in this analysis. As TTP data were not available from the Gimema or the MRC MIX trials, PFS data was used as a proxy. Data included in the MTC are summarised in Table 32.

Table 32: Overview of the data included in the MTC for TTP and OS

Trial comparison	Data used/ assumption	HR	95% lower bound	95% upper bound	Source
TTP					
PAD vs. VAD	TTP	0.79	0.66	0.95	Hovon
VD vs. VAD		0.82	0.63	1.06	IFM
CTD vs. CVAD		0.94†	0.81†	1.09†	MRC MIX
VTD vs. TD		0.64	0.44	0.93	Pethema
VTD vs. TD		0.63†	0.45†	0.88†	Gimema
OS					
PAD vs. VAD	OS	0.8	0.62	1.02	Hovon
VD vs. VAD		0.8	0.54	1.19	IFM
CTD vs. CVAD		0.92	0.75	1.13	MRC MIX
VTD vs. TD		0.8	0.48	1.34	Pethema*

†PFS data used as a proxy, as TTP not available

*OS data not available for Gimema

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Mixed treatment comparison

Evidence networks were produced to identify comparative analyses, which were then performed using an MTC approach. An MTC was undertaken in order to simultaneously rank all the bortezomib-based regimens and CTD, rather than perform a sequence of indirect comparisons (Figure 17).

The network included indirect evidence, which allowed a comparison of treatments that had not been evaluated within individual head-to-head trials, through mediating via a common comparator and direct evidence. Bayesian MTC analyses were used to compare the different treatments.

The MTC model was built in WinBUGS 1.4 and provided HRs for treatment comparisons along with 95% credible intervals (CrL). Models employed Markov chain Monte Carlo (MCMC) simulation, based upon 20 000 iterations after 10 000 burn-in iterations (to ensure the model had converged on the posterior distribution prior to the results being generated by the subsequent updates). A vague prior was assumed for the treatment effects (N(0,10000)). Sampled values were used to estimate the posterior medians, the 95% CrI for the HRs and the probabilities for the HRs to be smaller than 1; treatment efficacy was therefore assessed according to the probability of each treatment having the largest beneficial effect, calculated as the proportion of simulations in which the treatment was ranked as most efficacious.

The analysis was performed for all outcomes on ITT data. The deviance information criterion (DIC), which measures the fit of the model whilst penalising for the number of effective parameters, was used to determine whether a fixed-effect (FE) or a random effect (RE) model best fit the data (Table 33). The FE model had the lowest DIC (best fit), and was therefore selected for reporting results (DIC). A RE model was also carried out as a sensitivity analysis for comparison of the heterogeneity of data, and for transparency (Section 6.7.7).

Table 33: Comparison of DIC from fixed effect and random effect models

Response	Fixed effects	Random effects
OS	0.822	0.833
TTP	-3.604	-2.276

The methods used are consistent with recommendations provided by the NICE Decision Support Unit (DSU)(182). The model codes for the fixed effects and random effects models are tabulated in Appendix 17.

6.7.6 Please present the results of the analysis.

Results are presented in terms of a simultaneous assessment ranking of superiority, pairwise comparisons of superiority, and pairwise assessment of HRs. Superiority is demonstrated by a lower HR (of death).

Table 34 and Table 35 display the MTC analysis results with respect to TTP. VTD had the highest probability of being the most effective treatment (91.0%). Bortezomib-based regimens, in particular VTD and PAD, had probabilities close to 100% of being superior to CTD. Patients treated with VTD had significantly lower hazard of progression or death due to progression compared to CTD treated patients.

Table 34: HR and CrL for all treatments for TTP (fixed effects model)

Comparison	Comparator	Median	95% CrI
PAD	vs.CTD/TD	0.84	0.66, 1.06
VD		0.87	0.65, 1.17
VTD		**0.63**	**0.49, 0.81**
PAD	vs. VAD/CVAD	**0.79**	**0.66, 0.95**
VD		0.82	0.63, 1.06
VTD		**0.60**	**0.45, 0.8**

Table 35: Probability of superiority with respect to TTP for different treatment regimens

Intervention	Probability of being the most efficacious treatment for TTP (%)	Probability of superiority of PFS for different treatment regimens		
Comparators		**PAD (%)**	**VD (%)**	**VTD (%)**
CTD/TD	0.0	92.6	81.5	100.0
VAD/CVAD	0.0	99.4	93.2	100.0
VD	4.5	58.8	-	94.6
VTD	91.0	5.4	5.4	-
PAD	4.4	-	41.2	94.6

Table 36 and Table 37 present these results with respect to the OS outcome. VTD had the highest probability of being the most effective treatment (41.8%), followed by VD (27.7%) and PAD (22.6%), CTD/TD (1.6%) and VAD/CVAD (0%).

Table 36: HR and CrL for all treatments for OS (fixed effects model)

Comparison	Comparator	Median	95% CrI
PAD	vs.CTD/TD	0.87	0.63, 1.20
VD		0.87	0.56, 1.35
VTD		0.80	0.48, 1.34
PAD	vs. VAD/CVAD	0.80	0.62, 1.03
VD		0.80	0.54, 1.19
VTD		0.74	0.42, 1.28

Table 37: Probability of superiority with respect to OS for different treatment regimens

Intervention	Probability of being the most efficacious treatment for OS (%)	Probability of superiority of OS for different treatment regimens		
Comparators		**PAD (%)**	**VD (%)**	**VTD (%)**
CTD/TD	1.6	80.2	73.1	80.1
VAD/CVAD	0.0	96.1	86.7	86.2
VD	27.7	49.8	-	59.4
VTD	48.1	39.6	40.6	-
PAD	22.6	-	50.2	60.4

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

The FE model performed as the base case assumes no heterogeneity between the RCTs. This is consistent with the similarity between patient populations across the clinical trials as discussed in section 6.3.3 and 6.3.4.

A RE model for the MTC of TTP and OS was carried out as a sensitivity analysis to account for heterogeneity in the evidence base. It is important to note that a key assumption underlying RE models is that the effect sizes measurable in each pooled study are different, but exchangeable. As the number of studies within the MTC is small, the information required to estimate the between-study variability for the RE model may be insufficient.

A vague prior was assumed for the treatment effects (N(0,10000)) of the RE model and a weakly informative prior (uniform [0-2]) is used for the between study standard deviation within the RE model.

The prior distribution was somewhat dominating the posterior distribution, given the low number of trials in the analysis.

As with the FE model, the RE model was formed considering TTP and OS endpoints: results are presented in terms of a simultaneous assessment ranking of superiority, pairwise comparisons of superiority, and pairwise assessment of HRs.

Table 38 and Table 39 display these results with respect to the TTP outcome. The trend of probability of being the most efficacious treatment is similar to those results calculated using the FE model. As with the FE model, VTD in the RE model had the highest probability of being the most efficacious treatment. Bortezomib-based regimens, particularly VTD and PAD, had probabilities >50% of being superior to CTD.

Table 38: HR and CrL for all treatments for TTP (random effects model)

Comparison	Comparator	Median	95% CrI
PAD	vs.CTD/TD	0.84	0.06, 11.11
VD		0.87	0.06, 11.22
VTD		0.64	0.18, 2.32
PAD	vs. VAD/CVAD	0.79	0.13, 4.9
VD		0.82	0.13, 5.13
VTD		0.60	0.07, 5.58

Table 39: Probability of superiority with respect to TTP for different treatment regimens

Intervention	Probability of being the most efficacious treatment for TTP (%)	Probability of superiority of TTP for different treatment regimens		
Comparators		**PAD (%)**	**VD (%)**	**VTD (%)**
CTD/TD	3.4	66.6	62.4	87.0
VAD/CVAD	2.4	75.3	70.9	82.3
VD	18.2	53.9	-	71.3
VTD	56.2	30.1	28.7	-
PAD	19.8	-	46.1	69.9

Table 40 and Table 41 (RE pairwise HRs), present results with respect to the OS outcome. The three bortezomib-based regimens had similar probabilities of being the most efficacious treatment (25.5% to 33.7%). There was only a very low probability that VAD or CTD had the highest benefit in terms of survival (i.e. 4.6% and 9.8%, respectively).

Table 40: HR and CrL for all treatments for OS (random effects model)

Comparison	**Comparator**	**Median**	**95% CrI**
PAD	vs.CTD/TD	0.87	0.02, 30.23
VD		0.86	0.02, 30.97
VTD		0.80	0.06, 9.77
PAD	vs. VAD/CVAD	0.80	0.06, 10.09
VD		0.80	0.06, 9.64
VTD		0.74	0.02, 26.21

Table 41: Probability of superiority with respect to OS for different treatment regimens

Intervention	Probability of being the most efficacious treatment for OS (%)	Probability of superiority of OS for different treatment regimens		
Comparators		**PAD (%)**	**VD (%)**	**VTD (%)**
CTD/TD	9.8	56.5	56.5	61.8
VAD/CVAD	4.6	63.4	62.5	62.1
VD	26.5	49.8	-	52.7
VTD	33.7	46.9	47.3	-
PAD	25.5	-	50.2	53.1

6.7.8 **If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.**

All clinical trials included in the MTC analyses were considered relevant; therefore a sensitivity analysis excluding certain trials was not performed.

6.7.9 **Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.**

The direction and magnitude of pairwise comparisons are consistent across the MTC analyses that were performed.

As discussed in Section 6.7.3, an MTC is the only method which enables a comparison of bortezomib-based induction therapy to CTD. Therefore a comparison of direct and indirect evidence is not possible.

6.8 Non-RCT evidence

The systematic review (Section 6.1) retrieved five relevant RCTs which provided information relevant to the decision problem. No non-RCTs compared bortezomib with CTD in a head-to-head trial; therefore no non-RCTs are detailed in this submission (Section 6.2.7).

6.9 Adverse events

6.9.1 **If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care'** (www.york.ac.uk/inst/crd)**. Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.**

All five trials reported adverse events which will be described in Section 6.9.2.

6.9.2 **Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then**

present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

AEs that were reported in the post-transplant phase were not included as the drugs used as part of the procedure, and the process itself, which have associated side effects that are not relevant or related to the induction therapy under review. Similarly, AEs across the whole treatment protocol including a post-transplant maintenance period were not relevant to the decision problem or indication in question, and are therefore not reported in this submission.

Total AE rates

Across all trials a similar proportion of patients reported any AE, any grade 3/4 AE, and any serious AE in both the bortezomib and comparator treatment arms (Table 42). Relative risk (RR) ratios and 95% CI were calculated (183). There were statistically significant differences between bortezomib-based regimens and the VAD regimen with respect to: any reported AE (IFM), any grade 3/4 AEs (Hovon and Gimema), and any serious AEs (Hovon). However, the differences between these treatment groups were typically small (RR close to 1).

Treatment-related AE rates were similar in both treatment arms across trials. However, a significantly greater number of total treatment-related AEs were reported during induction in the VTD treatment arm compared to TD in the Pethema trial (RR=1.42; 95% CI: 1.17-1.73). The two most common treatment-related AEs in the Pethema trial (pneumonia and peripheral neuropathy) occurred more frequently in the VTD arm compared to the TD arm. No other bortezomib-relevant statistically significant differences in treatment-related AEs were reported during the induction phase.

Tolerability

Across all trials, a lower proportion of patients in the bortezomib arm withdrew from treatment than in the comparator arm; this was statistically significant for TD-treated patients compared to VTD-treated patients in the Pethema study (RR=0.51; Appendix 8). Across all trials, the main reason for withdrawal was due to adverse events. The total withdrawal rates, and reasons for withdrawal are tabulated in Appendix 8.

Table 42: Any reported adverse events across randomised groups for treatment arms across all trials (post-induction)

Induction regimen	Hovon			IFM			Pethema			Gimema			MRC MIX		
	PAD n (%)	**VAD n (%)**	**RR (95% CI)**	**VD n (%)**	**VAD n (%)**	**RR (95% CI)**	**VTD n (%)**	**TD n (%)**	**RR (95% CI)**	**VTD n (%)**	**TD n (%)**	**RR (95% CI)**	**CVAD n (%)**	**CTD n (%)**	**RR (95% CI)**
Safety population	410	411	-	239	239	-	130	126	-	236	238	-	556	555	-
Any AE	405 (98.78)	404 (98.3)	1 (0.99, 1.02)	231 (96.65)	221 (92.47)	**1.05 (1, 1.09)**	110 (84.62)	102 (80.95)	1.05 (0.93, 1.17)	-	-	-	-	-	-
Any grade 3/4 AE	323 (78.78)	294 (71.53)	**1.1 (1.02, 1.19)**	116 (48.54)	114 (47.7)	1.02 (0.84, 1.23)	52 (40)	47 (37.3)	1.07 (0.79, 1.46)	132 (55.93)	79 (33.19)	**1.69 (1.36, 2.08)**	-	-	-
Any serious AE	219 (53.41)	166 (40.39)	**1.32 (1.14, 1.53)**	68 (28.45)	82 (34.31)	0.83 (0.64, 1.08)	34 (26.15)	42 (33.33)	0.78 (0.54, 1.15)	31 (13.14)	30 (12.61)	1.04 (0.65, 1.66)	322 (57.91)	285 (51.35)	**1.13 (1.01, 1.26)**
Any treatment-related AE	394 (96.1)	394 (95.86)	1 (0.97, 1.03)	193 (80.75)	190 (79.5)	1.02 (0.93, 1.11)	97 (74.62)	66 (52.38)	**1.42 (1.17, 1.73)**	-	-	-	-	-	-

- data are not reported or non-calculable (zero events).

Bolded values are statistically significant

The AEs for the Hovon, IFM and Pethema trials are presented in Table 43, Table 44 and Table 45. The tables show the 10 most frequently occurring grade ≥3 AEs, as measured by total incidence. Where AEs had the same total incidence they were all included even though the number of AEs would be more than 10, AEs of special interest to bortezomib-based therapy i.e. herpes zoster and PN, and for thalidomide-based therapy i.e. deep-vein thrombosis were also included.

Table 43: Treatment emergent, drug-related grade ≥3 AEs reported during the Hovon trial, for induction and transplant phase: 10 most frequently occurring, plus AEs of special interest

Adverse event	Incidence		
	PAD (n=410)	VAD (n=411)	Total (n=821)
Leukopenia	61.0%	64.2%	62.6%
Thrombocytopenia	49.8%	39.7%	44.7%
Anaemia	15.1%	19.5%	17.3%
Pyrexia	15.4%	17.0%	16.2%
Nausea	16.8%	13.9%	15.3%
Mucosal inflammation	10.2%	10.2%	10.2%
Fatigue	8.5%	10.0%	9.3%
Hypocalcaemia	8.0%	9.5%	8.8%
Pneumonia	8.5%	9.0%	8.8%
Acute phase reaction	7.6%	9.2%	8.4%
Hepatic function abnormal	7.6%	9.2%	8.4%
Peripheral neuropathy - incl. motor, sensory and polyneuropathy	8.3%	1.7%	5.0%
Herpes Zoster	6.1%	1.7%	3.9%

Table 44: Treatment emergent, drug-related grade ≥3 AEs reported during the IFM trial, for induction and transplant phase: 10 most frequently occurring, plus AEs of special interest

Adverse event	Incidence		
	VD (n=239)	VAD (n=239)	Total (n=478)
Neutropenia	10.9%	15.5%	13.2%
Anaemia	9.6%	13.0%	11.3%
Leukopenia	9.2%	7.9%	8.6%
Thrombocytopenia	9.2%	6.3%	7.7%
Lymphopenia	10.0%	5.0%	7.5%
Nausea	6.3%	7.1%	6.7%
Back pain	5.9%	6.7%	6.3%
Pyrexia	3.3%	7.5%	5.4%
Mucosal inflammation	1.7%	6.7%	4.2%
Febrile neutropenia	4.6%	2.9%	3.8%
Vomiting	3.8%	3.8%	3.8%
Asthenia	4.6%	2.9%	3.8%
Pain	4.2%	3.3%	3.8%
Herpes Zoster	0.8%	0.4%	0.6%
Peripheral neuropathy incl. motor, sensory and polyneuropathy	6.3%	0.8%	3.6%

Table 45: Treatment emergent, drug-related grade ≥3 AEs reported during the Pethema trial, for induction and transplant phase: 10 most frequently occurring, plus AEs of special interest

Adverse event	Incidence		
	VTD (n=130)	TD (n=126)	Total (n=256)
Pneumonia	7.7%	4.0%	5.9%
Peripheral neuropathy - incl. motor, sensory and polyneuropathy	6.2%	0.0%	3.1%
Pyrexia	3.8%	1.6%	2.7%
Neutropenia	2.3%	3.2%	2.7%
Asthenia	3.8%	1.6%	2.7%
Respiratory tract infection	3.1%	2.4%	2.7%
Septic shock	2.3%	1.6%	2.0%
Anaemia	0.8%	2.4%	1.6%
Hypocalcaemia	0.8%	2.4%	1.6%
Renal failure	0.8%	2.4%	1.6%
Respiratory failure	2.3%	0.8%	1.6%
Arterial embolism	0.8%	2.4%	1.6%
Deep-vein thrombosis	0.8%	0.0%	0.4%
Herpes Zoster	0.0%	0.0%	0.0%

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The use of bortezomib in MM has a well established and recognised safety profile.

In these studies, bortezomib-based induction was generally well tolerated. VTD has a lower withdrawal rate from treatment compared to TD. Furthermore, there is no significant difference between VAD and bortezomib-based treatment with respect to treatment-related AE rates.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The primary clinical aims of bortezomib-based induction therapy in MM patients are to rapidly achieve a high response rate, whilst causing minimal toxicity, and to preserve haemopoietic stem cell function to ensure successful SCT. (Advisory Board Meeting minutes: Appendix 14). Hence, ORR, CR, PFS, and the proportion of patients who receive SCT, are clinically important endpoints in order to demonstrate the efficacy of induction therapy. The key findings from the clinical studies identified from the systematic review were as follows:

- There was a statistically significantly greater post-induction response rate following bortezomib-based treatment compared to comparators across trials. The response depth was increased following SCT, in all RCTs.

- There were significantly higher rates of Complete Response (CR) following bortezomib based treatment compared to the control arms. This is clinically relevant as post-induction CR correlates with improved overall survival in this patient population.

- Bortezomib-based treatment significantly improves PFS. PFS was maintained longer in patients treated with VTD versus TD (p=0.015 and p=0.0061 in the Pethema and Gimema trials, respectively). PFS was also higher in the bortezomib-based treatment arm compared to VAD in both the Hovon and IFM trials.

- The proportion of patients who underwent SCT was numerically higher in the bortezomib-based treatment groups compared to the non-bortezomib-based treatment groups across these trials. This difference was most pronounced in the Pethema trial, where 80.8% of patients underwent SCT in the VTD arm, compared to 61.4% in the TD arm.

An MTC was the only possible way to compare PFS and OS of bortezomib-based induction regimens with CTD. The MTC reported the probability of a treatment being the most efficacious in terms of PFS. The limitations and assumptions inherent in this approach have been fully described earlier in the submission.

- Pairwise comparisons of the HR for TTP showed that VTD induction therapy was superior to CTD (VTD 0.63 95% CrI 0.49-0.81). PAD and VD were also superior to CTD (0.84; 95% CrI: 0.66, 1.06) (0.87; 95% CrI: 0.65, 1.17), respectively. There was a 91.0% probability that VTD was the most efficacious induction regimen presented in this submission, whilst CTD/TD had a 0.0% probability of being the most efficacious.

- Pairwise comparisons of the HR with respect to OS showed that VTD induction therapy was superior to CTD, although the result was not statistically significant (0.80; 95% CrI: 0.48, 1.34). All bortezomib-based induction regimens have a higher probability than CTD of being the most efficacious treatment with respect to OS (VTD 48.1%; VD 27.7%; PAD 22.6%; CTD 1.6%)

AEs were experienced by over 80% of patients across all treatment arms; with similar proportions of patients reporting any AE, any grade 3/4 AE, and any serious AE in both the bortezomib and comparator treatment arms. Across all trials, a higher percentage of patients withdrew from treatment at induction in the comparator arm than in the bortezomib arm. The most commonly reported AEs following bortezomib-based treatment are in line with the established safety profile of bortezomib.

It is important to note that in the four bortezomib-based studies, bortezomib was given through the intravenous route. With the recently approved subcutaneous route of administration, the incidence of peripheral neuropathy is expected to decrease.

In summary, the clinical evidence presented in this submission demonstrates that bortezomib-based induction therapy improves patient outcomes, whilst maintaining a well-established safety and tolerability profile.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

A major strength of the clinical evidence base presented in this submission is that it is based upon five large, adequately-powered, independently conducted RCTs. Despite variations in their design, all trials consistently demonstrated that induction with a bortezomib-based regimen is more clinically effective than a range of standard comparator regimens. Furthermore, the quality of these RCTs is considered to be high (Section 6.4). The baseline characteristics of patients and the criteria for inclusion and exclusion are comparable between the four bortezomib RCTs and the MRC MIX RCT, allowing comparison between trial results and providing good external validity of the clinical outcomes.

The major limitations are as follows. Firstly, the studies use a mix of treatment combinations, trial designs and durations of treatment. This makes the selection of the most appropriate regimen challenging and adds complexity to the evidence base. The second limitation is that there are no available direct comparisons of bortezomib-based regimens to the main comparator of interest, CTD. This is due to the fact that the UK is the only country in which CTD is commonly used (section 2.6), thus the MRC MIX trial is the only RCT that includes CTD as a treatment arm. Consequently, an MTC was deemed to be the only means of comparing bortezomib based treatment to CTD. The evidence for the assumptions behind the MTC did not fully support the robustness of the MTC, as can be evidenced by the wide 95% CrLs associated with each of the comparisons. For TTP in the fixed effects model, the 95% CrIs were: 0.66-1.06 for PAD vs. CTD, 0.65-1.17 for VD vs. CTD and 0.49-0.81 for VTD vs. CTD. For OS the 95% CrLs were: 0.63-1.20 for PAD vs. CTD, 0.56-1.35 for VD vs. CTD and 0.48-1.34 for VTD vs. CTD.

The inclusion of consolidation and maintenance therapies in the key clinical trials are another limitation to the submission as they do not reflect UK clinical practice, and may hinder understanding and interpretation of the efficacy data. However, the fact that this submission focuses on response rate post-induction and post-transplant (i.e., before consolidation or maintenance) negates this issue. Whilst time to event data collection may have included patients who received maintenance or consolidation therapy, these data reflect the relative induction treatment effects as results were reported stratified by induction therapy randomisation. Hence, it is still possible to compare the relative effects of induction treatments.

6.10.3 Please 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.

The evidence base for addressing the decision problem (outlined in Section 5) is limited, as there are no RCTs that directly compare bortezomib-based induction to CTD induction therapies. The primary and secondary outcomes reported in the relevant RCTs are recognised by leading experts as being clinically important.

The lack of significant improvement observed in terms of OS in the MTC, following bortezomib-based induction therapy compared to CTD is not considered to be an indication of the efficacy of bortezomib-based induction therapy, since (1) the MTC results are uncertain and (2) OS rates are influenced heavily by the entire 1st line treatment package (and not only the induction therapies) as well as baseline patient profile. (Appendix 14) These trials all had quite different approaches to post SCT management, including maintenance treatment. A common facet however was that the original randomisation was invalidated by the way in which the studies were designed, making long term OS comparisons challenging. Furthermore, none of the four bortezomib RCTs was considered by clinical experts to be of sufficient duration to allow a difference in OS rates to be measured. (Appendix 14)

6.10.4 **Identify any factors that may influence the external validity 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 patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?**

The protocols for MM therapies used in the five RCTs are considered to be broadly representative of standard clinical practice by clinical experts (Appendix 14). The baseline characteristics of patients enrolled in these trials are considered representative of the UK MM patient population and the exclusion criteria for the RCTs prevented patients over 65 years, those with the most severe disease performance, and those diagnosed with non-secretory MM from being enrolled in the trials. These patients are uncommon amongst the general newly-diagnosed MM population.

The main differences in the study protocols compared to standard UK clinical practice were the use of consolidation, maintenance and intensification therapies following induction which is not routine practice. Similarly, the practice of receiving a double transplant as part of the first line treatment is not reflective of clinical practice in the UK. (Appendix 14)

Regardless of difference in study designs, the evidence presented in this submission demonstrates that bortezomib-based regimens have been demonstrated to be more effective induction treatments than alternative treatments including VAD and TD across a range of clinically relevant outcome measures. In that respect, results across these studies were consistent.

7 Cost effectiveness

Introduction to economic evaluation

Given the lack of head-to-head trials comparing bortezomib-based regimens with the most relevant comparator for the UK (CTD), the uncertainty surrounding the MTC, and the immaturity of the OS data in the trials presented in Section 6, the Sponsor has elected to use only three trials in the base case of the economic evaluation: the Pethema, Hovon and IFM trials. Response rate will be used as the main measure of efficacy in the modelled evaluation. This approach was chosen for the following reason:

- Median overall survival had not been reached in the majority of the trials presented in Section 6; this was not surprising, given the short duration of these trials compared to the relatively long survival in this patient population. Consequently, mature survival results of prospective studies in the first-line treatment of MM have only been published 9 to 13 years after study initiation(6). Moreover, it has been demonstrated that the survival curves of different regimens in this population only begin to diverge after several years post study initiation, given the relatively small number of patients enrolled in the pivotal studies in first-line treatment of MM(184). As a result, we have selected to model based upon the primary measure of efficacy in our trials (ie. response rate), as opposed to overall survival extracted directly from the currently immature trials. In our model, we have quantified the relationship between response rate and OS using long-term survival from the older RCTs in the same patient population, thereby incorporating a mature data set where median overall survival has been reached.

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 **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 as in section 9.10, appendix 10.**

A systematic search of the literature was conducted to identify studies of economic evaluations or burden of illness studies that evaluated the treatment of newly diagnosed MM. This review was designed to return both published cost-effectiveness evaluations described here, and also data to be used as cost and resource use inputs into the bortezomib economic model.

The following literature databases were searched to identify studies published between 1st January 2000 to November 2012; Cochrane (including Technology Assessments and Economic Evaluations databases) searched including records up to November 1st, MEDLINE (including MEDLINE In-Process, Other Non-Indexed

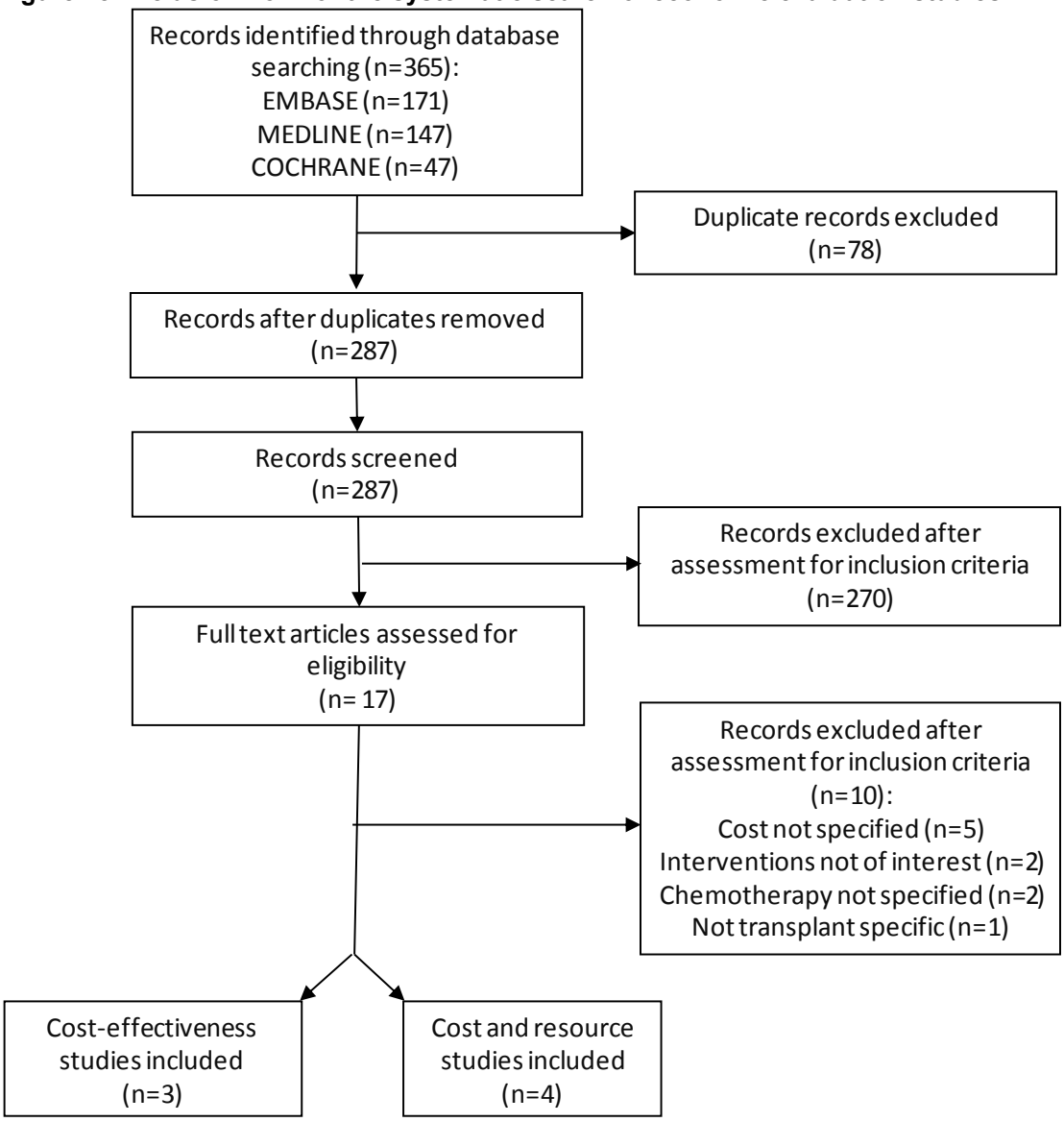
Citations) and Excerpta Medica Database (EMBASE) searched until November 13th. Clinical keywords and medical subject headings were included in the search strings, and these are fully detailed in Appendix 10. To be included in the review, studies had to meet pre-defined eligibility criteria. Only English language studies were included. Inclusion criteria for the review are detailed in Table 46. Studies were excluded if they reported data for a mixed patient population, but did not report results separately for MM or for adult patients.

Table 46: Inclusion criteria for economic evaluation systematic review

Inclusion criteria		Rationale
Study design	Budget impact analyses, Resource use studies, Cost/economic burden of illness studies, Cost analyses, Cost-minimisation analyses, Cost-effectiveness analyses, Cost-utility analyses, Cost-benefit analyses, Clinical trial-based analyses	These types of economic studies are potential sources of data to input into the economic model
Disease	MM	Relevant to the decision problem
Line of therapy	First line induction therapy prior to stem cell transplant	Relevant to the decision problem
Interventions	Bortezomib, Thalidomide, Vincristine, Cyclophosphamide, Lenalidomide,	All are relevant to the decision problem
Language	English language only	Models should be relevant to UK clinical practice
Publication date	2000 – November 2012	Stem cell transplant only became standard practice towards the end of the 1990s, so this date was chosen to ensure results reflected current clinical practice
Animal/in-vitro/human	Human only	Relevant to the decision problem
Children/Adult	Adults ≥18 years only	Relevant to the decision problem
Publication type	Only articles published in full	Abstracts and posters are unlikely to contain data to a sufficient level

Citations were first screened by a single reviewer based on the title and abstract supplied with each citation (Figure 18). In instances where it was not clear whether to include or exclude citations based on the abstract, the full-text copies were obtained. Those that did not match the eligibility criteria were excluded during this 'first pass'. A second reviewer checked the accuracy of the first reviewer's work and made changes if necessary. If uncertainty remained, a third reviewer was consulted. Following the title and abstract screen, full-text copies were obtained of all references that could potentially meet the eligibility criteria. The inclusion criteria (Table 46) were then applied to the remaining full-text citations.

Figure 18: Inclusion flow for the systematic search of economic evaluation studies



Description of identified studies

7.1.2 **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. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.**

The literature review identified three cost-effectiveness studies which met the inclusion criteria and were relevant to the decision problem within this submission; (185-187) (Table 47). Other cost-effectiveness studies identified during the literature search were excluded for the following reasons: the cost of treatment was not specified (n=5), the interventions were not relevant to this submission (n=2), the type or regimen of chemotherapy treatment was not specified (n=2), or the study was not specific to patients who received transplant (n=1; Figure 18).

Four cost and resource studies were also included within the review; these are discussed further in section 7.5

Table 47: Summary of relevant cost-effectiveness studies

Study	Country	Summary of the model	Patient population (median age in years)	Patient number (N)	QALYs (intervention, comparator)	Life Years (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Van Agthoven 2004(187)	Belgium and the Netherlands	Cost-utility based on published clinical trial data Perspective: Hospital, in addition to costs of (assessed) medication used at home Time horizon: 36 months Discounting: 4% for costs and for utility	Undiagnosed, untreated MM Intensive chemotherapy: -55 years (range 38–65) Myeloablative therapy: -56 years (range 32–65)	261	Intensive chemotherapy: 1.81 Myeloablative treatment: 1.57	Intensive chemotherapy 2.46 life years Myeloablative treatment: 2.32 life years	Euros Intensive chemotherapy €67,563 Myeloablative treatment €80,630	-€54,446 / QALY (Discounted) -€93,336 / LYG (Discounted)
Gulbrandsen 2001(188)	Norway	Cost-utility based on published clinical trial data Perspective: NR Time horizon: NR Discounting: 5% for costs	Newly diagnosed, symptomatic MM SCT group: 51 years MP group: 54 years	334	SCT versus MP Average QALY gain: 1.2	SCT: 5.2 life years MP: 3.7 life years	Norwegian Kroner (NOK)† (US Dollar) SCT: NOK 314,000 ($34,000) MP: NOK 87,900 ($9,500)	NOK 49,000/ QALY ($27,000/ QALY)
Kouroukis 2003(189)	Canada	Cost-utility based on published clinical trial data Perspective: Ontario Ministry of Health Time horizon: Life time Discounting: 3% for survival and 5% for costs	Untreated MM SCT group: -56.3 years (range 31.9–65.6) MP group: -56.5 years (range 45.6–64.1)	42	Not measured	SCT: 53.5 life years MP: 34.2 life years	Canadian dollar SCT: $32,320 MP: $1,803	$25,710 / LYG (Undiscounted)

†Average cost per patient (discounted) ($1 = NOK 9.25); ICER: Incremental cost-effectiveness ratio; LYG: Life Years Gained; MP: melphalan and prednisolone; NOK: Norwegian Kroner; QALY(s): Quality-adjusted life year(s)

7.1.3 **Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)2 or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.**

The three relevant cost-effectiveness studies identified were assessed for quality in accordance with criteria published by Drummond and Jefferson (1996) (190) (Table 97).

[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.
[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Table 48 Quality assessment of cost-effectiveness studies included

Study question	Grade (yes / no / not clear / N/A)		
	van Agthoven 2004	Gulbrandsen 2001	Kouroukis 2003
Study design			
1. Was the research question stated?	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	No	No
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes – stated No - justification	Yes – stated No - justification	Yes – stated No - justification
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Yes	Yes
5. Were the alternatives being compared clearly described?	Yes	Yes	Yes
6. Was the form of economic evaluation stated?	Yes	Yes	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Yes	Yes
Data collection			
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Yes	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	N/A	Yes
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Yes	N/A
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	Yes	Yes	Yes
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Yes	Yes
14. Were productivity changes (if included) reported separately?	N/A	No	N/A
15. Was the relevance of productivity changes to the study question discussed?	N/A	Yes	N/A
16. Were quantities of resources reported separately from their unit cost?	Yes	Yes	Not clear
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	No – inflation N/A - Currency conversion	No	No – inflation N/A - Currency conversion
20. Were details of any model used given?	N/A	N/A	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	N/A	Yes
Analysis and interpretation of results			
22. Was the time horizon of cost and benefits stated?	Yes	Yes	Yes
23. Was the discount rate stated?	Yes	Yes	Yes
24. Was the choice of rate justified?	No	No	No
25. Was an explanation given if cost or benefits were not discounted?	N/A	N/A	N/A
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes – details of statistical tests reported No –confidence intervals not reported	No	Yes – details of statistical tests reported No –confidence intervals not reported

27. Was the approach to sensitivity analysis described?	Yes	Yes	Yes
28. Was the choice of variables for sensitivity analysis justified?	Yes	No	Yes
29. Were the ranges over which the parameters were varied stated?	No	Yes	Not clear
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Yes	Yes
31. Was an incremental analysis reported?	Yes	Yes	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Yes	Yes
33. Was the answer to the study question given?	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	No	No	No
36. Were generalisability issues addressed?	No	No	No
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination			

7.2 De novo analysis

Patients

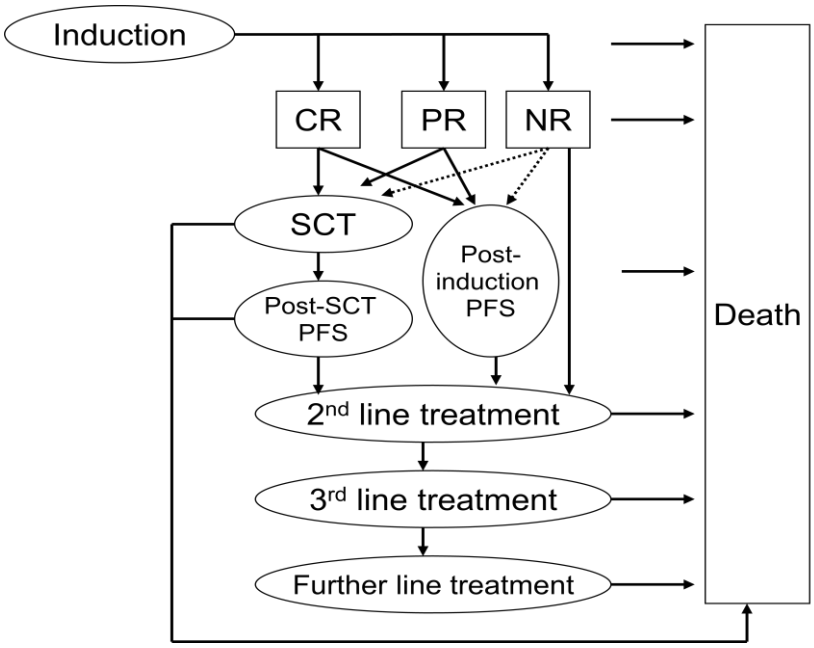
7.2.1 **What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.**

The patient group included in this economic evaluation are adult patients with previously untreated multiple myeloma, eligible for HDT-SCT in line with the scope of this appraisal and the expected therapeutic indication to be granted.

7.2.2 **Please provide a diagrammatical representation of the model you have chosen.**

The model structure reflects the clinical pathway of care for MM patients eligible to a stem cell transplant first line. A state transition model was developed to assess the cost-effectiveness of bortezomib-based versus thalidomide-based induction regimens, Figure 19.

Figure 19. Schematic of the state transition model



Note: Most patients in the NR health states would move directly to 2nd line treatment. However, a few patients moved to post-induction PFS or even to SCT health states, as reported in the Pethema trial.

Legend: CR: complete response; NR: non responders; PFS: progression free survival; PR: partial response; SCT: stem cell trasnplantation

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

A state transition model was developed to evaluate the cost-effectiveness of bortezomib-based regimens for induction of newly diagnosed myeloma compared to alternative induction regimens. This model structure was chosen for several reasons:

- This framework provides a structure which is representative of the clinical pathway of care for transplant-eligible MM patients, enabling consideration of the very distinct phases of treatment, from induction prior to SCT, SCT, and post-SCT.

- The key treatment goal in the induction setting is to achieve the maximum possible depth of response as this has been proven to give patients the highest chance of proceeding to SCT.(7) This modelling approach, which is designed to capture these effects, is based upon the post-induction response rate, thereby isolating the attributable effect of induction on OS.

- Median overall survival had not been reached in the pivotal trials due to the short duration of the trial compared to the relatively long survival in this patient population. Accordingly, mature survival results of prospective studies in the first-line treatment of MM have only been published 9 to 13 years after study initiation.(6) Moreover, it has been demonstrated that the survival curves of different regimens in this population only begin to diverge after several years post study initiation, (184). Given the trials were not powered to detect a statistically significant difference in OS, a much larger sample size would have been required to detect a clinically meaningful difference in OS. As a result, we have selected to model based upon response rate, as opposed to OS extracted directly from these currently immature trials. In our model, we have quantified the relationship between response rate and OS using long-term survival from the older RCTs in the same patient population, thereby incorporating a mature data set where median overall survival has been reached.

- Although response rates are clearly improved with novel agent combinations such as VTD, PAD and VD, the demonstration of a significant OS advantage will always be difficult given the long duration of follow-up required. Accordingly, clinical experts have recommended three-drug combination therapies such as VTD as induction therapy prior to HDT-SCT, based upon surrogate markers for outcome (i.e. response rates, depth of response, and PFS).(7;13)

In approaching the decision problem, a number of potential model structures were considered. However, it was felt that alternative approaches lacked both the face and structural validity of the final model that was selected

7.2.4 Please define what the health states in the model are meant to capture.

The state transition model (displayed in Figure 19 above), is described as follows:

In clinical practice, newly diagnosed MM patients eligible for HDT-SCT would receive induction therapy. A clinical decision would subsequently be taken to offer the patient (or not) the opportunity to receive a stem cell transplant, based on the post-induction

response and a patient's willingness and ability to receive HDT and deal with AEs associated with SCT(191).

In this context, patients enter the model at the start of the induction therapy (randomly assigned to either VTD or TD, PAD or VAD, and VD or VAD). Post-induction, patients enter one of three health states: complete response (CR), partial response (PR), or less than partial response (NR). Patients subsequently proceed to HDT-SCT (SCT group) or post-induction period (non-SCT group) depending upon their post-induction response rate. The post-induction response rate also defines the patient's overall survival.

Post-induction response is the most relevant outcome for an induction regimen as it directly influences the decision to proceed to SCT. Post-induction response is also a good surrogate of post-transplant response and 1st line progression free survival, which are two other key outcomes for MM patients who received a SCT.

Post-induction, several factors can influence the choice of treatment regimen and the probability that a patient proceeds to transplant. Influencing factors include co-morbidities, whether a patient can mobilise enough stem cells to harvest, and whether a patient progresses during the induction, harvest and HDT phases. As these influencing factors are mainly driven by the characteristics of the patient, rather than the induction treatment, the state transition model focuses on the post-induction response rate.

Post-induction, all patients are assumed to incur the same survival benefit which is dependent only upon the response rate they achieve following the induction phase and is independent of the actual induction regimen that they received. Given the data limitations associated with the available trials, we believe this is the optimal way to isolate the effect of VTD over TD, PAD over VAD, and VD over VAD.

Upon progression of disease, patients would then receive a second-line treatment, followed by a 3rd line treatment after progression on 2nd line therapies, and potentially some further lines of treatment after progression on 3rd line of therapies for the patients still alive.

Patients entering the model incur utilities, treatment and monitoring costs, and AE-associated disutility value and costs (during induction phase) relative to each health state.

Patients entering the 'absorbing' death health state incur an end of life cost.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model captures two key outcomes that are central to the clinical treatment pathway for MM patients eligible for a SCT: firstly the post-induction response rate which is the key treatment-related element that determines if a patient can receive a transplant: and secondly, OS which represents the outcome of primary importance from a therapy in MM. Broadly, the aim of treatment in MM is to control the disease in order to prolong survival and maximise patient's HRQoL.(7)

In the model, patients who achieve a post-induction response of at least a PR have a high probability of receiving (≥ 82%) a SCT and subsequently would enter a post-transplant progression free health state until disease progression and start of 2nd line treatment or death.

Patients who do not achieve a strong enough post-induction response have a lesser chance of receiving a SCT (≤ 25%) than those who achieve at least a PR. Those who do not receive a SCT will directly enter a post-induction progression free health state until disease progression and start of 2nd line treatment.

The ultimate outcome for treating MM patients is to prolong their survival.(7) The state transition model incorporates OS data post-induction in order to capture this final treatment outcome. In the base case, in order to model long-term survival based upon the post-induction response rates, 5-year OS data segmented by response rate were extracted from the MRC VII trial, described in section 7.3.1. below.(12)

Intermediate outcomes were also considered as part of the economic modelling to capture how progression of disease over time affects both patient's HRQoL and treatment and patient management related costs. In order to capture these additional treatment and monitoring costs as well as and change in HRQoL due to disease progression, post-induction / post-transplant time to progression (TTP) from the Pethema trial was used to determine the transition to start of 2nd line therapies.

Similarly, transitions from 2nd line treatment to 3rd line treatment and from 3rd line treatment to further lines of treatment have been taken into account in the state transition model. These transitions were estimated using the APEX trial data, which represents the main trial supportive of the use of bortezomib as second-line therapy in MM patients, which is considered as the standard of care in this line of therapy in the UK.(39) The APEX trial was a randomized clinical trial comparing bortezomib monotherapy (n=333) vs. high dose dexamethasone (n=336) in patients with relapsed MM who had received one to three previous therapies.(192)

Other key aspects captured in the model are grade 3 and above AEs (during the induction phase) and quality of life associated with each health state.

7.2.6 **Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.**

Table 49: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Life time	A life time horizon (30 years) was adopted to ensure that all relevant costs and effects were captured.	Guide to the methods of technology appraisal (2008)
Cycle length	Monthly	This reflects the length of a course of treatment with VTD (i.e. 28 days) and clinical outcomes are reported in months.	Appendix 1, draft SmPC
Half-cycle correction	None	The cycle length is fairly short (1 month), thus no half-cycle correction is required.	-
Were health effects measured in QALYs; if not, what was used?	Yes	Utilitv values as reported in the thesis by Segeren, publication by van Agthoven, an HTA report and puiblication on bendamustine for chronic lymphoid leukemia were used in the base-case analysis.	(187;193-195)
Discount of 3.5% for utilities and costs	Yes	The discount rate applied to both costs and outcomes in the reference case was 3.5% per year.	Guide to the methods of technology appraisal (2008)
Perspective (NHS/PSS)	NHS	The model takes the perspective of the NHS England and Wales.	Guide to the methods of technology appraisal (2008)
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life-years; SmPC: summary of product characteristics; VTD: Velcade® (bortezomib), thalidomide and dexamethasone			

Technology

7.2.7 **Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?**

Dosage and administration of the bortezomib-based interventions used in the model (ie VTD, PAD and VD) are included in the model according to the draft SmPC of bortezomib, as per the expected Marketing Authorisation.

Both of the comparative regimens (i.e. TD and VAD) are unlicensed regimens.

7.2.8 **Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.**

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

There is no treatment continuation rule specified in the draft SmPC for bortezomib (Appendix 1). In each of the RCTs, induction regimens were administered for a pre-determined number of cycles as per each relevant study protocol. Clinical experts have also stated that in UK clinical practice, all induction regimens would be administered for a set number of between 3 – 6 cycles, which is consistent with the draft SmPC, which recommends the use of 4-6 cycles, depending on regimen used. (Appendix 14)

7.3 *Clinical parameters and variables*

7.3.1 **Please demonstrate how the clinical data were implemented into the model**.

In this section, we are presenting the clinical data that has been used to populate the model and establish the transitions between the different health states.

From the Induction health state to post-induction response health states

Post-induction response rates (Table 24) obtained from the PETHEMA, Hovon and IFM trials were used as the main measure of efficacy in the models. An alternative source of data for post-induction response rate following administration of VTD and TD induction regimens was used in sensitivity analysis (the GIMEMA trial).

Table 50: Post-induction response rates(70-72)

	VTD N=130	**TD N=127**
CR (CR+nCR+VgPR)	64 (49.2%)	22 (17.3%)
PR	46 (35.4%)	56 (44.1%)
NR (MR+SD+PD)	20 (15.4%)	49 (38.6%)
	PAD N=417	**VAD N=416**
CR (CR+nCR+VgPR)	209 (50.1%)	81 (19.5%)
PR	142 (34.1%)	174 (41.8%)
NR (MR+SD+PD)	66 (15.8%)	161 (38.7%)
	VD without DCEP N=121	**VAD without DCEP N=121**
CR (CR+nCR+VgPR)	49 (40.8%)	19 (15.7%)
PR	44 (36.7%)	53 (43.8%)
NR (MR+SD+PD)	27 (22.5%)	49 (40.5%)

CR: complete response; NR: non responders; MR: minimal response; PD: progressed disease; PR: partial response; SD: stable disease; TD: thalidomide and dexamethasone; VgPR: very good PR; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD Velcade® (bortezomib), dexamethasone

The mortality rate during the induction phase was sourced using the Pethema, Hovon and IFM studies (Table 51).

Table 51: Mortality rate during the induction period(70-72)

	Mortality rate during induction (6 months)	**Monthly probability of death during induction**
VTD	3.8% (5/130)	0.7%
TD	4.8% (6/126)	0.8%
PAD	4.6% (19/410)	1.6%
VAD	5.6% (23/411)	1.9%
VD	0.7% (1/135)	0.2%
VAD	3.7% (5/136)	0.9%

SCT: stem cell transplant; TD: thalidomide and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD Velcade® (bortezomib), dexamethasone

For the induction period, the impact of AEs (grade 3 and above) on patient's HRQoL and disease management costs were incorporated into the model. The incidence of grade 3 and above AEs were obtained from the safety population datasets, including all subjects randomised who have received at least one dose of study induction drug. In addition to AEs of special interest for bortezomib and thalidomide, the ten most common treatment-related AEs (by total incidence) as reported in the CSR of the Pethema trial were incorporated into the economic model.

From SCT health state to 1st line progression-free health state

In the model, the SCT rates were determined using the proportion of patients who received a SCT, extracted from the three trials (Table 52).

Table 52: Total SCT rates (70-72)

	Total SCT
VTD (N=130)	105 (80.8%)
TD (N=127)	78 (61.4%)
PAD (N=417)	354 (84.9%)
VAD (N=416)	348 (83.7%)
VD (N=121)	100 (82.6%)
VAD (N=121)	106 (87.6%)

SCT: stem cell transplant; TD: thalidomide and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD Velcade® (bortezomib), dexamethasone

The mortality rate during the transplant phase was sourced using the three trials (**Table 58**).

Table 53: Mortality rate during the transplant period(70-72)

	Mortality rate during SCT (3 months)	Monthly probability of death during SCT
VTD	0.8% (1/130)	0.3%
TD	0.0% (0/126)	0.0%
PAD	1.2% (5/352)	0.5%
VAD	1.0% (4/347)	0.4%
VD	0.7% (1/106)	0.3%
VAD	0.7% (1/100)	0.3%

SCT: stem cell transplant; TD: thalidomide and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD Velcade® (bortezomib), dexamethasone

From post-induction to death

In order to model long-term survival based upon the post-induction response rates, OS data segmented by response rate was extracted from the MRC VII trial(12;194). The MRC VII trial was the second RCT to investigate whether HDT with transplant was more effective than conventional chemotherapy in the treatment of previously untreated MM patients. It confirmed the results of the landmark IFM90 study(196) that established HDT-SCT as the standard of care in this patient population, and further provided support for the notion that response is related to survival.

The MRC VII trial randomised a total of 407 previously untreated MM patients <65 years of age to conventional chemotherapy (n=200), or HDT followed by autologous SCT (n=201); 6 patients were excluded after randomisation. The objective of the trial was to compare the two treatment groups with respect to PFS and OS, thus the trial was powered to detect a statistically significant difference in OS. Response rates were also compared in the trial, as per the criteria in

Table 54 below.

Table 54: Response criteria in MRC VII trial (Child et al., 2003)

Response	Definition
Complete response (CR)	Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 6 weeks.
Partial response (PR)	>50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks.
Minimal response (MR)	25–49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 weeks.
Progressive disease (PD)	>25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/l and confirmed by at least one repeated investigation.

Note: This table is adapted from Blade et al (1998), which outlines the response criteria of the European Group for Blood and Marrow Transplantation-International Bone Marrow Transplant Registry (EBMT-IBMTR)

After five years of follow-up, patients in the HDT-SCT group were analysed to determine whether response was related to OS. The five-year survival was 88.6 months [95%CI: 61.4-upper CI not reported] amongst the patients who had a CR (defined as the 'CR' health state in the economic model), 39.8 months [95%CI: 33.8-61.4] amongst the patients who had PR (defined as the 'PR' health state in the economic model), and 25.6 months [95% CI: 7.0-31.3] amongst the patients who had MR (defined as the non-responders 'NR' health state in the economic model).

OS was used to transition patients from the post-induction assessment to death; the 5-year survival rates from MRC VII trial are presented in Table 55 below.

Table 55: Overall survival by category of post-induction response for scenario analysis from MRC VII(12)

	5 year survival rate			Monthly survival probability	Monthly probability of death
	Number of months	95%CI min	95% CI max		
CR	88.6	61.4	Not reported	99.2%	0.8%
PR	39.8	33.8	61.4	98.3%	1.7%
NR	25.6	7.0	31.3	97.3%	2.7%

CI: confidence interval; CR: complete response; NR: non responders; PR: partial response

Another source of long term survival data was used in the model in the scenario analyses: IFM90 trial.(196)

From 1st line progression-free health state to 2nd line treatment health state

Post-transplant time to progression (TTP) was used to determine the transition probabilities to the start of 2nd line therapies. These disease progression outcomes were derived from the pivotal trials. An exponential distribution was adopted for the post-transplant TTP data.

From 2nd to 3rd line of treatment and from 3rd line to further lines of treatment health states

As per the scope of this appraisal, the objective of the model is to demonstrate the cost-effectiveness of bortezomib-based induction regimen. In this context, constant transition probabilities were used for the 2nd and 3rd line health states between the two interventions.

The estimates for all treatments in 2nd and 3rd line were derived from the APEX trial from the subgroups of patients with one and two prior lines of treatment respectively. The APEX trial was chosen as the data source as there is no publication reporting the outcomes of interest by line of therapy for the 2nd and 3rd line treatments (i.e. bortezomib in combination with dexamethasone (Vel+HDD), cyclophosphamide, thalidomide, dexamethasone (CTD), lenalidomide, dexamethasone (RD)).

Since the monthly transition probabilities from 2nd line to 3rd line treatment health states and from 3rd line to further lines of treatment health state, using the APEX data are very high, the economic results are not very sensitive to the choice of any parametric distribution. An exponential distribution was, therefore, adopted for the 2nd and 3rd line TTP.

From further lines (4+) of treatment to death

It was assumed that all patients would transition to death from this further line of treatment health state, therefore, only long term survival data from the MRC VII trial was applied to this health state.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition probabilities from Induction to post-transplant progression free health state

Post-induction response rates observed during the three trials were used to determine the post-induction response categories and predict related post-transplant overall survival rates. Patients who received a transplant would then enter a post-transplant progression-free health state. Mortality rates during induction and transplant phases were derived directly from the three trials.

Transition probabilities from post-induction to death

During the period from post-induction onwards, transition to death was estimated using OS rates from the MRC VII trial.(12) An exponential distribution was fitted to the MRC VII data, and the parameters of the time to event curve are presented in Table 87.

Transition probabilities from post-transplant progression free health state to start of 2nd line treatment health state

Transition from the post-transplant progression-free health state to start of the 2nd line treatment health state was calculated using TTP from the three trials.

The transition probabilities from the post-transplant progression free health state were calculated using an exponential time to event curve fitted onto the trial TTP. The formulas used to fit the exponential distribution are presented below(197):

Hazard function: $h(t) = \lambda$ for $0 \leq t < \infty$ where λ is a positive constant and t is time.

Survivor function: $S(t) = \exp\left\{-\int_0^t \lambda du\right\} = e^{-\lambda t}$

Transition probabilities from the 2nd to 3rd line health state and from 3rd to further lines of treatment health state

Patients who began a 2nd line treatment subsequently remained on 2nd line treatment for a progression-free period, which was estimated using TTP from the APEX trial. Patients who progressed are moved to the 3rd line of treatment, and subsequently remained on 3rd line treatment for a progression-free period, which was estimated using TTP from the APEX trial.

An exponential distribution was applied to the TTP data from the APEX trial, as the shape parameter equals 1 (i.e. Weibull distribution equals an exponential distribution). In this context, the same transition probability formula was used to calculate the exponential transition probabilities in second and further lines. The parameters of the time to event curves using the APEX data are presented in Table 87.

Transition probabilities from the further line of treatment health state to death

The OS data from the MRC VII trial was used to determine the duration of time that patients remain in the further lines of treatment health state and when they will transition to death.(12) An exponential distribution was fitted to the MRC VII data, and the parameters of the time to event curve are presented in Table 87.

Summary of transition probabilities

A summary table of all shape and scale parameters for the different time to event curves is presented in Table 56 and Table 57.

Table 56: Parameters of all time to event curves used following 1st line treatment in the economic model (rounded to 4 decimals)

Description	**PETHEMA From post-transplant PFS to starting 2nd line**					
Distribution	**Exponential**					
	VTD			**TD**		
	CR	PR	NR	CR	PR	NR
TTP scale	0.0004	0.0005	0.0014	0.0002	0.0005	0.0032
TTP shape	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
OS scale	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
OS shape	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
	HOVON From post-transplant PFS to starting 2nd line					
Distribution	**Exponential**					

	PAD			VAD		
	CR	PR	NR	CR	PR	NR
TTP scale	0.0005	0.0006	0.0007	0.0006	0.0008	0.0008
TTP shape	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
OS scale	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
OS shape	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
	IFM From post-transplant PFS to starting 2nd line					
Distribution	**Exponential**					
	VD			**VAD**		
	CR	PR	NR	CR	PR	NR
TTP scale	0.0004	0.0005	0.0011	0.0006	0.0008	0.0008
TTP shape	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
OS scale	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
OS shape	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*

n/a := not applicable OS: overall survival; TD: thalidomide and dexamethasone; TTP: time to progression; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD Velcade® (bortezomib), dexamethasone

Table 57: Parameters of all time to event curves used in 2nd, 3rd and further lines of treatment in the economic model (rounded to 5 decimals)

Description	APEX From starting 2nd line to starting 3rd line	APEX From starting 3rd line to further line
Distribution	Exponential	Exponential
TTP scale	0.0035	0.0042
TTP shape	1.0000	1.0000
OS scale	*n/a*	*n/a*
OS shape	*n/a*	*n/a*

TTP: time to progression; OS: overall survival

The transition matrices by post-induction response category which is calculated within the state transition model is shown below.

Table 58: Transition matrices for by post-induction response category

VTD vs. TD					
CR after TD induction		**To**			
		2nd line	**3rd line**	**Further line**	**Death**
From	**Post-induction / SCT PFS**	0.7%			0.8%
	2nd line		10.2%		0.8%
	3rd line			12.0%	0.8%
	Further line				0.8%
PR after TD induction		**To**			
		2nd line	**3rd line**	**Further line**	**Death**
From	**Post-induction / SCT PFS**	1.4%			1.7%
	2nd line		10.2%		1.7%
	3rd line			12.0%	1.7%
	Further line				1.7%
NR after TD induction		**To**			
		2nd line	**3rd line**	**Further line**	**Death**
From	**Post-SCT PFS**	9.3%			2.7%
	2nd line		10.2%		2.7%

	3rd line			12.0%	2.7%
	Further line				2.7%
CR after VTD induction		**To**			
		2nd line	**3rd line**	**Further line**	**Death**
From	**Post-induction / SCT PFS**	1.1%			0.8%
	2nd line		10.2%		0.8%
	3rd line			12.0%	0.8%
	Further line				0.8%
PR after VTD induction		**To**			
		2nd line	**3rd line**	**Further line**	**Death**
From	**Post-induction / SCT PFS**	1.4%			1.7%
	2nd line		10.2%		1.7%
	3rd line			12.0%	1.7%
	Further line				1.7%
NR after VTD induction		**To**			
		2nd line	**3rd line**	**Further line**	**Death**
From	**Post-SCT PFS**	4.2%			2.7%
	2nd line		10.2%		2.7%
	3rd line			12.0%	2.7%
	Further line				2.7%
PAD vs. VAD					
CR after VAD induction			**To**		
		2nd line	**3rd line**	**Further line**	**Death**
From	Post-induction / SCT PFS	1.7%			0.8%
	2nd line		10.2%		0.8%
	3rd line			12.0%	0.8%
	Further line				0.8%
PR after VAD induction			**To**		
		2nd line	**3rd line**	**Further line**	**Death**
From	**Post-induction / SCT PFS**	2.3%			1.7%
	2nd line		10.2%		1.7%
	3rd line			12.0%	1.7%
	Further line				1.7%
NR after VAD induction			**To**		
		2nd line	**3rd line**	**Further line**	**Death**
From	**Post-SCT PFS**	2.5%			2.7%
	2nd line		10.2%		2.7%
	3rd line			12.0%	2.7%
	Further line				2.7%
CR after PAD induction			**To**		
		2nd line	**3rd line**	**Further line**	**Death**
From	**Post-induction / SCT PFS**	1.4%			0.8%
	2nd line		10.2%		0.8%
	3rd line			12.0%	0.8%
	Further line				0.8%
PR after PAD induction			**To**		

		2nd line	3rd line	Further line	Death
From	Post-induction / SCT PFS	1.8%			1.7%
	2nd line		10.2%		1.7%
	3rd line			12.0%	1.7%
	Further line				1.7%
NR after PAD induction			To		
		2nd line	3rd line	Further line	Death
From	Post-SCT PFS	2.0%			2.7%
	2nd line		10.2%		2.7%
	3rd line			12.0%	2.7%
	Further line				2.7%
VD vs. VAD					
CR after VAD induction			To		
		2nd line	3rd line	Further line	Death
From	Post-induction / SCT PFS	1.7%			0.8%
	2nd line		10.2%		0.8%
	3rd line			12.0%	0.8%
	Further line				0.8%
PR after VAD induction			To		
		2nd line	3rd line	Further line	Death
From	Post-induction / SCT PFS	2.4%			1.7%
	2nd line		10.2%		1.7%
	3rd line			12.0%	1.7%
	Further line				1.7%
NR after VAD induction			To		
		2nd line	3rd line	Further line	Death
From	Post-SCT PFS	2.5%			2.7%
	2nd line		10.2%		2.7%
	3rd line			12.0%	2.7%
	Further line				2.7%
CR after VD induction			To		
		2nd line	3rd line	Further line	Death
From	Post-induction / SCT PFS	1.1%			0.8%
	2nd line		10.2%		0.8%
	3rd line			12.0%	0.8%
	Further line				0.8%
PR after VD induction			To		
		2nd line	3rd line	Further line	Death
From	Post-induction / SCT PFS	1.5%			1.7%
	2nd line		10.2%		1.7%
	3rd line			12.0%	1.7%
	Further line				1.7%
NR after VD induction			To		
		2nd line	3rd line	Further line	Death
From	Post-SCT PFS	3.2%			2.7%
	2nd line		10.2%		2.7%
	3rd line			12.0%	2.7%
	Further line				2.7%

tp=transition probability, TTP=time to progression, RR: response rate; SCTR/ SCT rate; OS=overall survival; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: 131incristine, doxorubicin, dexamethasone; VD Velcade® (bortezomib), dexamethasone

7.3.3 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.

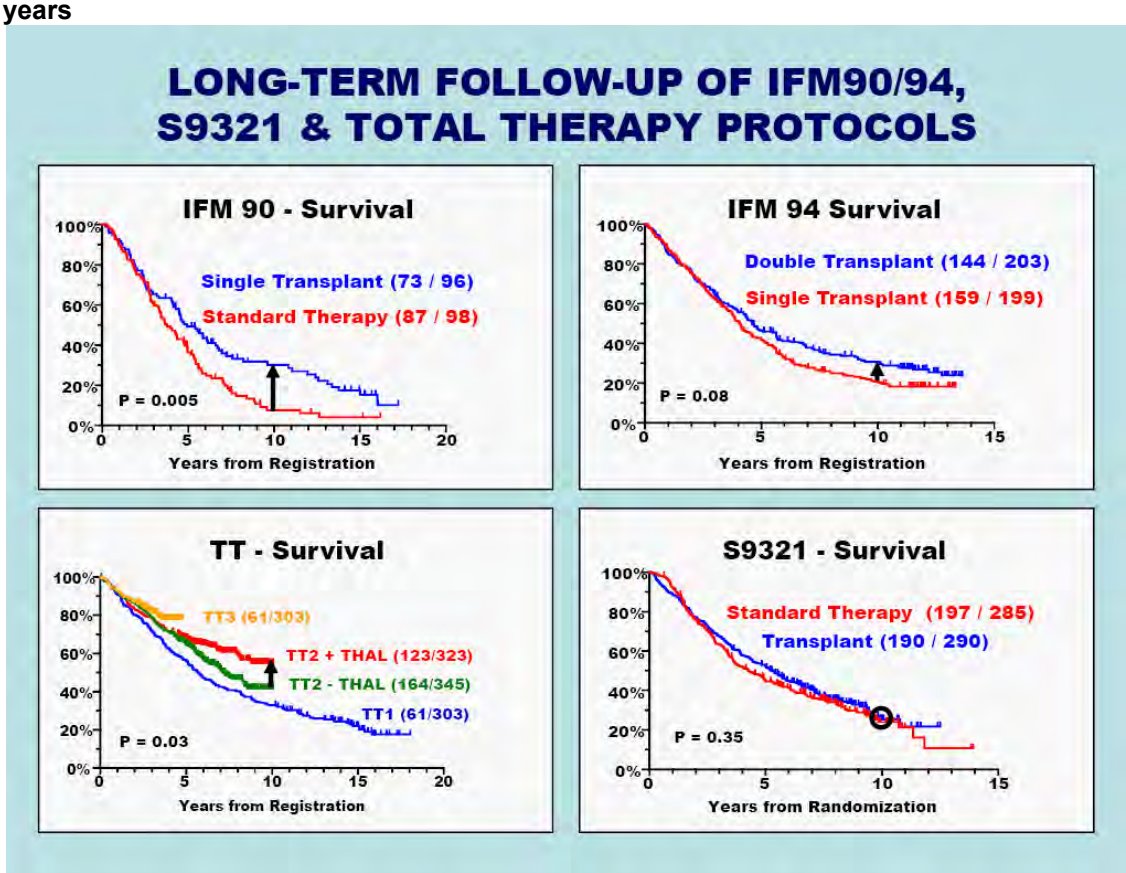
The extrapolated results generated using the state transition model in this submission calibrate extremely well with those long term results reported in the MRC VII and IFM90 trials. (see Table 86) These results demonstrating both internal as well as external validity were calculated under the assumption of constant mortality rates in second, third and further line therapies. Given the paucity of data for the later lines of therapy, the assumption of constant mortality rates was considered appropriate and not felt to impact negatively on the results of the analysis, particularly with the robust external validity demonstrated by the model.

The Apex trial results indicate the time-to-progression becomes shorter as disease progresses. Therefore, the transition probability used in the model is to the third line treatment is higher than that to the second line treatment.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Median overall survival had not been reached in the majority of the trials presented in section 6; this was not surprising, given the short duration of these trials compared to the relatively long survival in this patient population. Consequently, mature survival results of prospective studies in the first-line treatment of MM have only been published 9 to 13 years after study initiation(6). Moreover, Barlogie et al.(184) analysed the long-term follow-up of eight trials in the MM patient population eligible for transplant, conducted by the Intergroupe Francophone du Myelome (IFM; known as the IFM 90/94/99-02/99-04 trials), the Southwest Oncology Group (SWOG; known as the S9321 trial), and the University of Arkansas for Medical Sciences (Total Therapy [TT], known as the TT1/2/3 trials). He demonstrated that the survival curves of different regimens in this population only begin to clearly diverge after several years post study initiation, given the relatively small number of patients enrolled in these pivotal studies, coupled with the relatively long survival in this population (refer to the accompanying 2009 ASCO presentation to Barlogie's 2010 publication and Figure 20 below).

Figure 20: Long-term follow-up of IFM90, IFM94, TT and S9321 trials, overall survival at 10 years



As a result, we have selected to model based upon response rate, as opposed to overall survival extracted directly from these currently immature trials. In our model, we have **quantified the relationship between response rate and OS** using long-term survival from the historical, UK-based MRC VII trial(12), thereby incorporating a mature data set where median overall survival has been reached. The long-term OS from the IFM90 study (displayed in Figure 20 above) is used in the scenario analysis.

In order to further assess the association between maximal response and long-term outcomes, van de Velde et al (2007) performed a meta-analysis of 21 prospective and retrospective published studies that specifically reported on the response rate post-induction/pre-HDT/SCT, which is the comparison of interest to this submission. The association between post-induction, pre-HDT/SCT response and overall survival was highly statistically significant (p=0.0015; refer to Table 3, p1404 in the van de Velde paper), thus confirming the **strong relationship between depth of response from induction and overall survival.**

In summary, demonstrating an OS advantage during a clinical trial requires a large number of patients and a long duration of follow-up. It is therefore widely accepted that response rate, depth of response, and PFS are appropriate markers for final outcomes (such as OS) for therapies used in MM. Importantly, on the basis of these surrogate outcomes, three-drug induction regimens (such as VTD) are now the current standard of care prior to transplantation(13).

7.3.5 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:**

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

An advisory board was conducted on 26th October 2012 with four clinical experts, out of the 7 approached. The objectives were to seek input into the impact of intensive management of MM patients on the overall care pathway, review the relevant comparators and several clinical assumptions considered in the model.

Prior to the advisory board, clinicians completed a questionnaire on the management of MM patients eligible for a transplant. Responses were discussed during the advisory board to obtain a consensus. Clinical papers of the four bortezomib-based trials and the MRC MIX were also provided to the clinical experts. More details on the questionnaire and the participants are available in appendix 14.

Clinical experts estimated the range of cycles they would use for the induction therapies as well as the distribution of the 2nd and 3rd line treatments according to their clinical practice. (Section 7.4.10) These input data are reported in section 7.3.6. The minutes of the advisory board are provided in appendix 14.

Summary of selected values

7.3.6 **Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.**

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 59. Summary of variables applied in the economic models

Variable	Value	CI (distribution)	Reference to section in submission
MODEL SETTING			
Cycle length (months)	1	n/a	Section 7.2.6
Time horizon	Lifetime	n/a	Section 7.2.6
Discount rate for costs	3.5%	n/a	Section 7.2.6
Discount rate for health benefits	3.5%	n/a	Section 7.2.6
EFFECTIVENESS			
From start of treatment to post-induction			
VTD vs. TD			
Median number of induction cycle	VTD=6, TD=6		(71)
Induction period (months)	Equals the number of induction cycles (6 months)	n/a	(71), appendix 1
Response rate		95% CI Beta distribution	Section 6.5.3
	VTD	**Min** **Max**	Section 7.3.1.
	CR 49,2%	40,7% 57,8%	
	PR 35,4%	27,4% 43,8%	
	NR 15,4%	9,7% 22,0%	
	TD	**Min** **Max**	
	CR 17,3%	11,3% 24,3%	
	PR 44,1%	35,6% 52,8%	
	NR 38,6%	30,3% 47,2%	
Mortality rate during induction phase		95% CI Beta distribution	Section 7.3.1.
		Min **Max**	
	VTD 3.8%	1% 8%	
	TD 4.8%	2% 9%	
PAD vs. VAD			
Median number of induction cycle	PAD=3, VAD=3		(70)
Induction period (months)	Equals the number of induction cycles (3 months)	n/a	(70) appendix 1
Response rate		95% CI Beta distribution	Section 6.5.3
	PAD	**Min** **Max**	Section 7.3.1.
	CR 50.1%	45.3% 54.9%	
	PR 34.1%	29.6% 38.7%	
	NR 15.8%	12.5% 19.5%	
	VAD	**Min** **Max**	
	CR 19.5%	15.8% 23.4%	

Variable	Value		CI (distribution)		Reference to section in submission
	PR	41.8%	37.1%	46.6%	
	NR	38.7%	34.1%	43.4%	
Mortality rate during induction phase			95% CI Beta distribution		Section 7.3.1.
			Min	**Max**	
	PAD	4.6%	2.8%	6.9%	
	VAD	5.6%	3.6%	8.0%	
VD vs. VAD					
Median number of induction cycle	VD=4, VAD=4				Reference to be inserted
Induction period (months)	Equals the number of induction cycles (4 months)		n/a		, reference to be inserted, appendix 1
Response rate			95% CI Beta distribution		Section 6.5.3
	VD		**Min**	**Max**	
	CR	40.8%	32.2%	49.7%	Section 7.3.1.
	PR	36.7%	28.3%	45.4%	
	NR	22.5%	15.5%	30.4%	
	VAD		**Min**	**Max**	
	CR	15.7%	9.8%	22.7%	
	PR	43.8%	35.1%	52.7%	
	NR	40.5%	32.0%	49.3%	
Mortality rate during induction phase			95% CI Beta distribution		Section 7.3.1.
			Min	**Max**	
	VD	0.7%	0.0%	2.7%	
	VAD	3.7%	1%	7.4%	
From post-induction to SCT					
VTD vs. TD					
SCT rate			95% CI Beta distribution		Section 6.5.3
			Min	**Max**	Section 7.3.1.
	VTD	80.8%	73.6%	87.0%	
	TD	61.4%	52.8%	69.7%	
Mortality rate during SCT phase			95% CI Beta distribution		Section 7.3.1.
			Min	**Max**	
	VTD	0.8%	0.0%	3%	
	TD	0.0%	-	-	
PAD vs. VAD					
SCT rate			95% CI Beta distribution		Section 6.5.3
			Min	**Max**	Section 7.3.1.
	PAD	84.9%	80.0%	87.0%	
	VAD	83.7%	81.3%	88.2%	
Mortality rate during SCT phase			95% CI Beta distribution		Section 7.3.1.
			Min	**Max**	

Variable	Value	CI (distribution)	Reference to section in submission
	PAD 1.2% **VAD** 1.0%	0.4% 2.5% 0.3% 2.1%	
VD vs. VAD			
SCT rate	**VD** 87.6% **VAD** 82.6%	95% CI Beta distribution **Min** **Max** 81.2% 92.9% 75.4% 88.8%	Section 6.5.3 Section 7.3.1.
Mortality rate during SCT phase	**VD** 0.7% **VAD** 0.7%	95% CI Beta distribution **Min** **Max** 0.0% 2.7% 0.0% 2.7%	Section 7.3.1.
From post-induction to death			
OS from post-induction to further line of treatment	MRC VII data **survival** CR 0.8% PR 1.7% NR 2.7%	95% CI **Min** **Max** 0.6% 1.1% 1.1% 2.0% 2.2% 9.4%	Section 7.3.1.
From post-SCT to starting 2nd line			
TTP from post-SCT to start of 2nd line treatment	Exponential distribution From the pivotal trials, TTP post-transplant for patients who receive a SCT and TTP post-induction for patients who did not receive a SCT		Section 7.3.7
From 2nd line to starting 3rd line			
Distribution	**Vel+HDD** 80% **CTD** 15% **HDD** 5%	Dirichlet distribution **Min** **Max** 63% 98% 8.4% 23% 1.6% 10%	Appendix 14 (advisory board report)
Time to progression to 3rd line treatment	Exponential distribution From the APEX trial, patients at 2nd line therapy (i.e. 1 prior line therapy): TTP for HDD and Velcade monotherapy applied to Vel+HDD and CTD		Section 7.3.7
From 3rd line to starting further lines of treatment			
Distribution	**RD** 75%	Dirichlet distribution **Min** **Max** 59% 93%	Appendix 14 (advisory board report)

Variable	Value	CI (distribution)	Reference to section in submission
	CTD 20% **HDD** 5%	12% 30% 1.6% 10%	
Time to progression to further line treatment	Exponential distribution From the APEX trial, patients at 3rd line therapy (i.e. 2 prior lines therapy): TTP for HDD and Velcade monotherapy (applied to RD and CTD).		Section 7.3.7
UTILITIES		**Beta distribution* 95%CI**	
1st line treatment			
From start treatment until post-induction response	0.57	0.50-0.63	Section 7.4.9
From post-induction to post-SCT response	0.65	0.56-0.73	Section 7.4.9
SCT patients (by response)	CR=0.83 PR=0.76 NR=0.65	0.67-0.94 0.64-0.87 0.56-0.73	Section 7.4.9
Non-SCT patients	Up to 3mos=0.77 3-6mos=0.81 6-9mos=0.79 9-12mos=0.80 12-18mos=0.81 18+mos=0.77	0.64-0.88 0.66-0.92 0.65-0.90 0.66-0.91 0.66-0.92 0.64-0.88	Section 7.4.9
2nd and 3rd line treatments	0.69	0.59-0.78	Section 7.4.9
Further lines	0.64	0.56-0.72	Section 7.4.9
DISUTILITIES			
Induction period	VTD=0.0072 TD=0.0048	VTD: 0.00719 - 0.00721 TD: 0.004795 - 0.004805	0.02 decrement weighted the incidence of each AE
COSTS		**Gamma distribution* 95% CI**	
1st line treatment			
VTD vs. TD			
Drug + administration + prophylaxis + monitoring (tests and consultant visits)	**VTD** £27,889 **TD** £8,720	**Min** **Max** £22,591 £33,736 £7,064 £10,548	Section 7.5.5
HDT-SCT	£20,511	£16,615 - £24,811	Section 7.5.5
Ongoing treatment and monitoring costs during progression-	£83 for all induction therapies	£67-£100	Section 7.5.5

Variable	Value	CI (distribution)	Reference to section in submission
free period			
AE management costs during induction period	**VTD** £146 **TD** £145	**Min** **Max** £118 £176 £117 £175	Section 7.5.5
PAD vs. VAD			
Drug + administration + prophylaxis + monitoring (tests and consultant visits)	**PAD** £11,074 **VAD** £2,060	**Min** **Max** £8,970 £13,396 £1,668 £2,491	Section 7.5.5
HDT-SCT	£20,511	£16,615 - £24,811	Section 7.5.5
Ongoing treatment and monitoring costs during progression-free period	£83 for all induction therapies	£67-£100	Section 7.5.5
AE management costs during induction period	**PAD** £283 **VAD** £271	**Min** **Max** £229 £342 £220 £328	Section 7.5.5
VD vs. VAD			
Drug + administration + prophylaxis + monitoring (tests and consultant visits)	**VD** £14,104 **VAD** £2,732	**Min** **Max** £11,425 £17,061 £2,213 £3,305	Section 7.5.5
HDT-SCT	£20,511	£16,615 - £24,811	Section 7.5.5
Ongoing treatment and monitoring costs during progression-free period	£83 for all induction therapies	£67-£100	Section 7.5.5
AE management costs during induction period	**VD** £54 **VAD** £51	**Min** **Max** £44 £66 £42 £62	Section 7.5.5
2nd line treatment			
Drug + administration + prophylaxis + monitoring	**Vel+HDD** £28,044 **CTD** £12,911 **HDD** £1,373	I **Min** **Max** £22,716 £33,923 £10,459 £15,619 £1,112 £1,660	Section 7.5.5
Market share of 3rd line regimens	**Vel+HDD** 80% **CTD** 15% **HDD** 5%		Appendix 14

Variable	Value		CI (distribution)		Reference to section in submission
3rd line treatment					
Drug + administration + prophylaxis + monitoring			**Min**	**Max**	Section 7.5.5
	Vel+HDD	£42,693	£34,583	£51,645	
	CTD	£10,996	£8,907	£13,301	
	HDD	£1,033	£837	£1,250	
Market share of 3rd line regimens	**Vel+HDD**	75%			Appendix 14
	CTD	20%			
	HDD	5%			
Further lines treatment					
Patient monitoring cost	£83		£67-£100		Section 7.5.5.
Death					
All lines – end of life cost	£3,627		£2,938 - £4,388		(198)

* A 20% variation around the mean estimate of both costs and utility values was assumed.
Legend: CI=confidence interval; CR: complete response; CTD: thalidomide in combination with dexamethasone and cyclophosphamide; HDD: high dose dexamethasone; NR: non responders; OS: overall survival; PR: partial response; RD: lenalidomide and dexamethasone; SCT: stem cell transplant; TD: thalidomide and dexamethasone; TTP: time to progression; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: 139incristine, doxorubicin, dexamethasone; VD Velcade® (bortezomib), dexamethasone

7.3.7 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 intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Life years gained, QALYs and costs are extrapolated beyond the trial follow-up period. Induction treatment effects are assumed beyond the length of the trials until patients progress or die.

From the induction health state to post-induction response health states

The post-induction response rates are obtained from the PETHEMA, Hovon and IFM trial data.

From SCT health state to 1st line progression-free health state

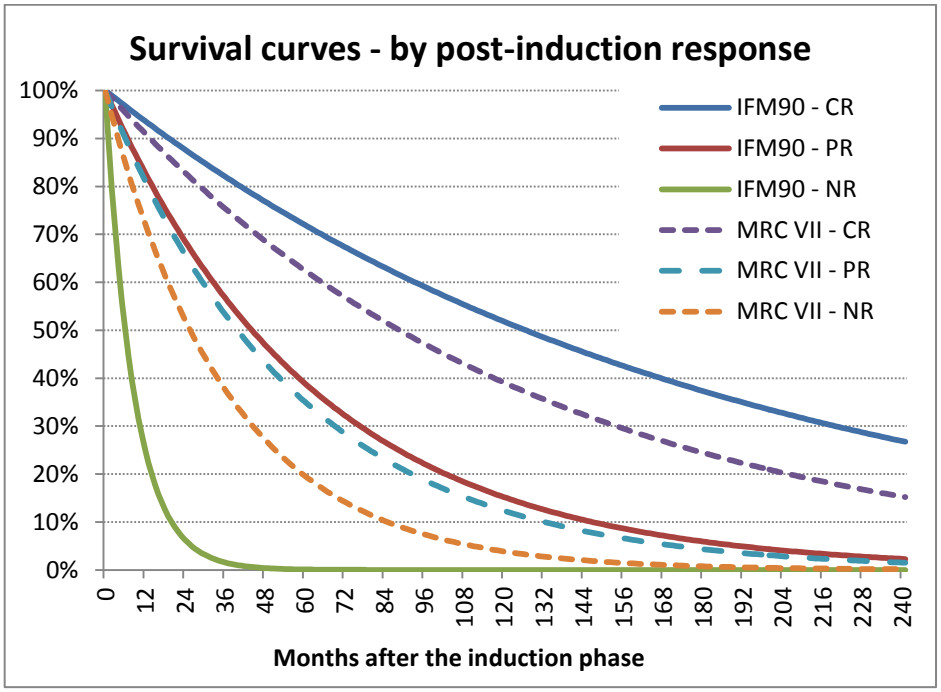
The SCT rates are obtained from the PETHEMA , Hovon and IFM trial data.

From post-induction to death

The rates of progression from post-induction to start of 2nd line treatment are obtained from the PETHEMA, Hovon and IFM trial data. The rate of death for the period when patients entering the post-induction health state onwards was extrapolated using the median OS data from the MRC VII trial.

Due to limited data availability, the only parametric distribution that could be fitted on the MRC VII data was an exponential distribution.

Figure 21: Survival curves using MRC VII data



From 1st line progression free health state to 2nd line treatment health state

The rate of progression from post-transplant to start of 2nd line treatment was derived from the survival curves fitted on the PETHEMA, Hovon and IFM trial data (Appendix 19 for curve fittings to Kaplan-Meier plots).

Exponential, Weibull and log-logistic distributions were fitted to the patient-level post-induction TTP data from the Pethema, Hovon and IFM studiesby the induction treatment option (TD and VTD) and by post-induction response (CR, PR and NR).

The log-logistic curves had better (lower) Akaike Information Criteria (AIC) than the other two options (AIC for Exponential, Weibull, Log-logistic, respectively: For CR: 132.9, 120.8, 118.1; For PR: 198.2, 193.9, 191.5; For NR: 222.1, 216.9, 201.0). However, the log-logistic curves lack face validity and clinical plausibility because the fitted survival curve for patients with CR after the VTD induction is below that for those with PR beyond approximately 5 years. This would imply that patients with complete post-induction response would progress to the second line treatment faster than those with only partial response.

If the Weibull is used, the fitted survival curve for patients with CR after the VTD induction regimen is below that for PR after 4 years, and even for NR after 7 years. Therefore, the Weibull curves also lack face validity and clinical plausibility.

In contrast, the fitted exponential curves do not suffer from similar face validity issues. Therefore, the exponential distribution was selected for the base-case for the 1st line TTP (post-transplant / post-induction).

From 1st line progression-free health state to 2nd line treatment, and from 2nd to 3rd line of treatment and from 3rd line to further lines of treatment health states

As described in section 7.3.1, when post-transplant patients progress they are assumed to move to second line of treatment in which all treatments have progression as observed in the APEX trial for patients who had received one prior treatment. When patients progress from 2nd line treatment, they move to 3rd line treatment, for whom progression data are obtained from patients of the APEX trial who have had two prior myeloma treatments.

The rate of progression and death associated with 2nd and 3rd line therapies are obtained from the survival curves fitted to the APEX trial data (Figure 22 and Figure 23) for curve fittings to Kaplan-Meier plots).

Figure 22. 2nd line – Time to progression – APEX

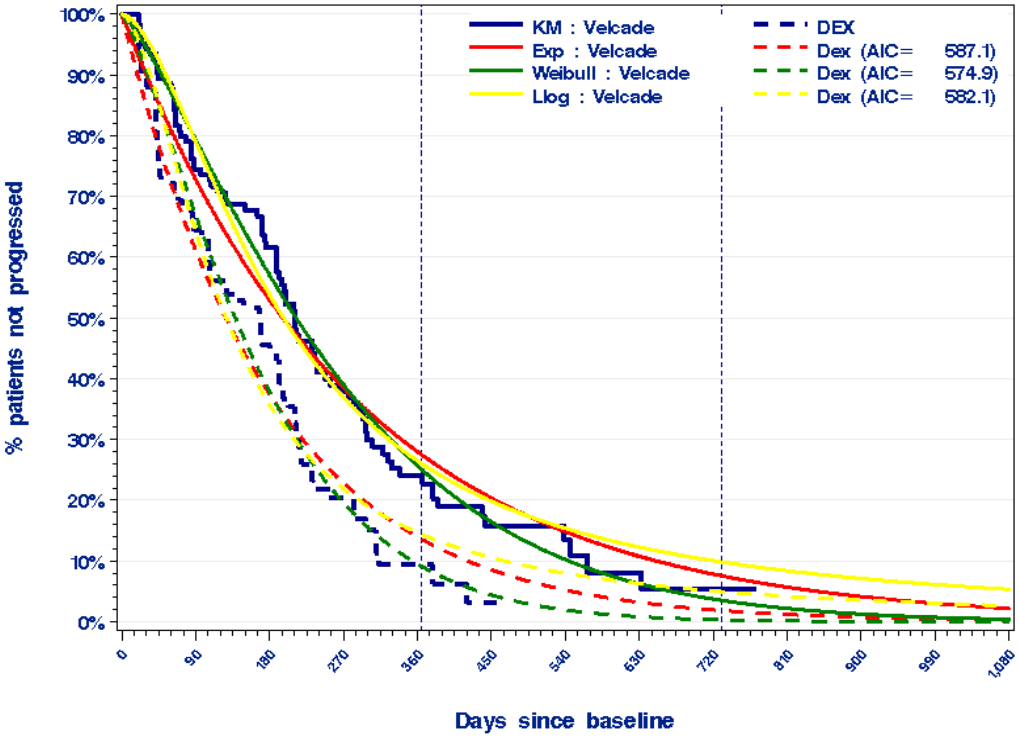
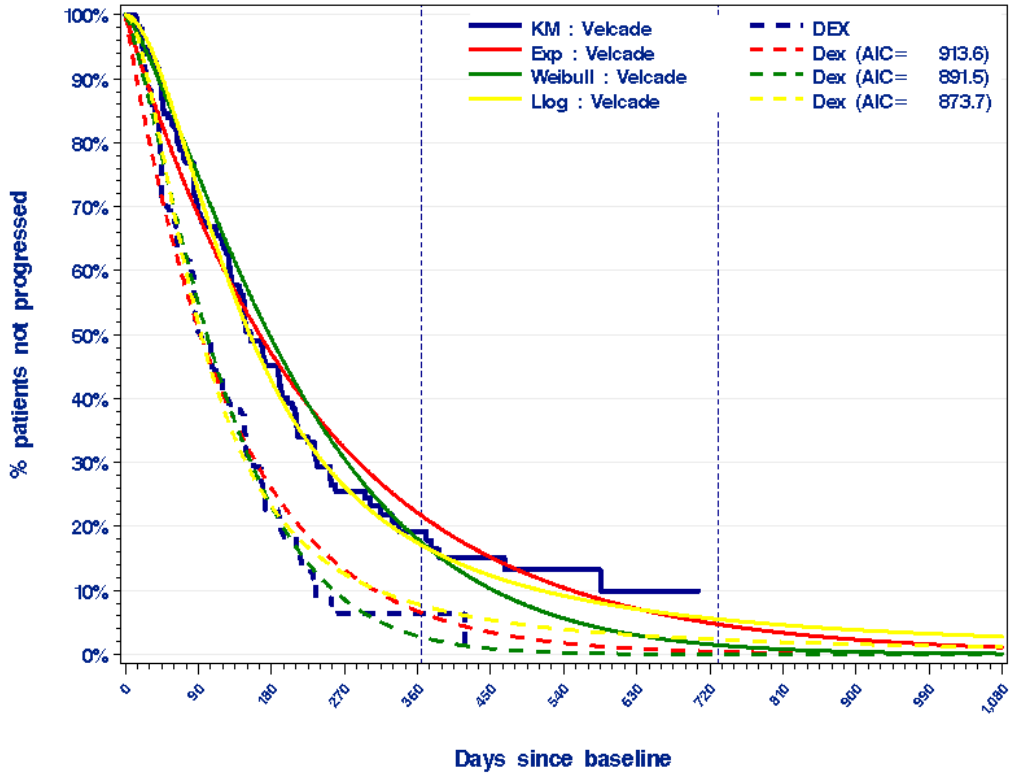


Figure 23. 3rd line – Time to progression – APEX



From further lines (4+) of treatment to death

Finally, when patients progress at 3rd line they move to the further lines of treatment health state in which they stay until they die, according to the death rates extrapolated from the MRC VII study.

All parametric survival analyses were performed using the proc lifereg procedure in SAS version 9.2, with the distribution specified as exponential, weibull and log-logistic.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumptions	Rationale
From post-induction to death	
MRC VII OS data by post-induction response categories were used to estimate post-induction survival	The MRC VII study is the only long term UK-based study which provides mortality probabilities based on post-induction response.
2nd line treatment	
TTP for Vel+HDD, CTD are assumed to be the same as for Bortezomib monotherapy	There are no published data reporting the TTP and OS censored for progression curves for Vel+HDD and CTD in myeloma patients with one prior therapy
Constant probabilities for the 2nd and 3rd line health states were assumed. Exponential distribution was fitted to the 2nd and 3rd line TTP.	Section 7.3.7
3rd line treatment	
TTP for RD and CTD are assumed to be the same as for bortezomib monotherapy	There are no published data reporting the TTP curves for CTD, RD in myeloma patients with two prior therapies.
Further lines	
All patients in the further lines of treatment health state (those who progressed and those who are progression free) will transition to the death health state.	

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Figure 1 in section 2.1 shows the natural course of MM, which encompasses an asymptomatic, symptomatic and an acute terminal phase. The clinical presentation of MM during the symptomatic phase includes bone disease, renal failure, anaemia, repeated infections, and hypercalcaemia. Bone disease, occurring in 80-90% of patients, can result in pain, lytic lesions, pathological fractures and spinal cord compression(7), whilst renal failure can result in up to 13% of patients requiring dialysis support (199). Anaemia can present as fatigue, poor exercise tolerance and breathlessness even after mild exertion and has been associated with a loss in HRQoL(200). Common infections early on in the disease involve the respiratory tract, frequently resulting in bronchitis and pneumona, whilst severe hypercalcaemia is associated with polydipsia, polyuria, dehydration, constipation and neurological manifestations(201;202). These clinical events contribute to the morbidity associated with MM and compromise mobility, day-to-day independence and emotional wellbeing, impacting patients' HRQoL.

The effect on HRQoL was confirmed in two large studies in over 800 newly diagnosed MM patients which showed that pain, fatigue, reduced physical and role function seem to have an especially distressing effect on patients' HRQoL (203;204) with symptoms such as nausea, vomiting, dyspnoea, constipation and diarrhoea being less important (203;204). Appetite loss and sleep disturbances, although not so important in the study by Wisloff et al., appeared as some of the more important symptoms in the study by Gulbrandsen et al. and Segeren(194), respectively.

The importance of clinical symptoms on HRQoL was also highlighted in a review of the issues which matter most to MM patients. It listed impact on independence/physical function, social/participatory function, libido/sexual function, role function/changes, leisure activities/fun and disease-related symptoms, amongst others, as important (205).

7.4.2 **Please describe how a patient's HRQL is likely to change over the course of the condition**.

As shown in section 2.1, MM is an incurable and progressive disease. Without treatment to prevent disease progression or provide symptomatic relief, patients will experience worsening of symptoms and an associated decline in HRQoL.

In newly diagnosed MM patients, HRQoL can be expected to improve during 1st line treatment as patients undergo chemotherapy induction (or longer cycles of chemotherapy if not undergoing a transplant) which decreases the tumour cell burden and improves disease symptoms. In patients intending to undergo a transplant, drug treatment to assist with the stem cell mobilisation, harvesting, ablation and transplant and the associated procedures may cause adverse events that temporarily decrease HRQoL over a few days or several months. Following successful treatment and recovery of the SCT procedure, patients typically experience a period of remission with no sign of active disease in the body, allowing them to experience prolonged time without chemotherapy and improved HRQoL as disease related symptoms are absent. Despite the expected change in HRQoL during the 1st line treatment, maximising patients' quality of life is not the goal of induction therapy, nor is HRQoL considered an important outcome with regards to the choice of induction therapy. As the disease progresses, supportive treatment such as bisphosphonates for bone disease and analgesics for pain relief will alleviate some of the symptoms associated with MM, but inevitably subsequent relapses and remissions will occur with worsening symptoms and HRQoL, until palliative care remains the only option. As remission typically becomes shorter, time in good HRQoL becomes less.

HRQL data derived from clinical trials

7.4.3 **If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.**

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.

- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

No quality of life data were collected in the RCTs, as maximising quality of life for patients newly diagnosed with multiple myeloma and eligible for HDT-SCT is not the primary goal of induction therapy. As discussed above, the primary goal of induction therapy is to increase the depth of response in order to allow patients to proceed to HDT-SCT.

Mapping

7.4.4 **If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.**

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Not applicable

HRQL studies

7.4.5 **Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.**

A systematic search of the literature was conducted to identify publications that identified HRQoL information of relevance to the decision problem.

Published literature databases were examined from 1st January 2000 (since SCT only became standard practice towards the end of 1990s) until 1st November (Cochrane®), and 13th November 2012 (Embase® and Medline®). The search strategies and interfaces of the electronic databases used are provided in appendix 12. The electronic literature databases included:

- Cochrane® (including CENTRAL, the HTA database, and NHS EED)
- Embase®
- MEDLINE® (including MEDLINE In-Process®)

To be included in the review, citations had to meet pre-defined eligibility criteria (Table 60). In summary, studies were excluded if they did not report results for first line induction therapy prior to SCT in adult patients (>18 years of age) with MM. Citations were also excluded if they reported data with respect to mixed patient populations but did not report separate subgroup data with respect to adults with MM.

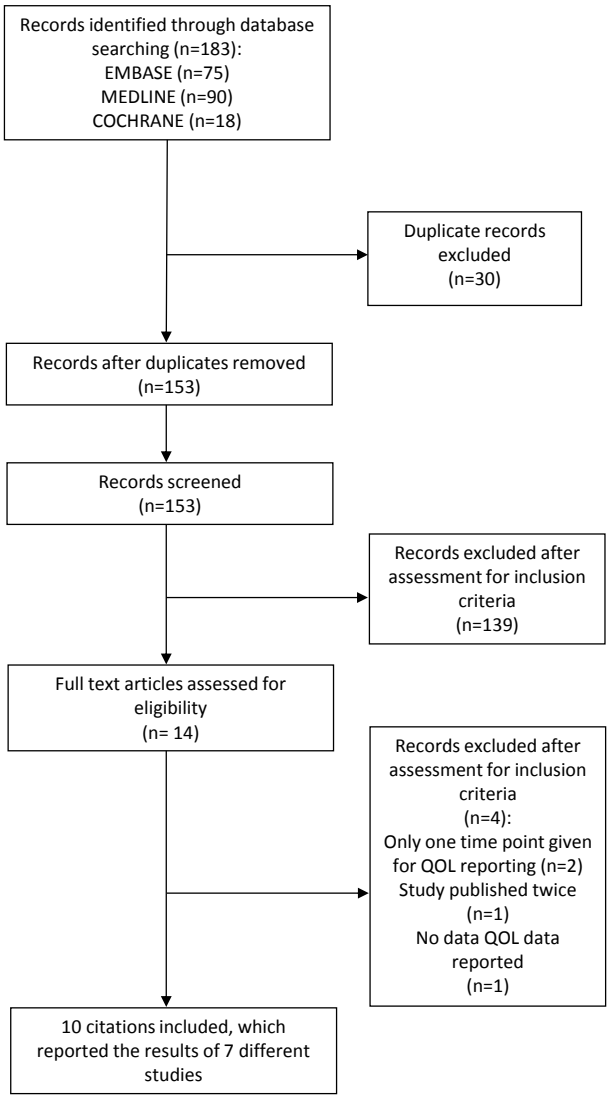
Table 60: Inclusion criteria for HRQoL literature review

Inclusion criteria		Rationale
Study design	Studies or articles reporting the utility or QoL of patients diagnosed with MM who underwent SCT as first line	Relevant to the decision problem
Disease	MM	Relevant to the decision problem
Line of therapy	First line induction therapy prior to SCT	Relevant to the decision problem
Interventions	Bortezomib, Thalidomide, Vincristine, Cyclophosphamide, Lenalidomide	All are relevant to the decision problem
Utility/ QoL instruments	EQ5D, SF-36, and EORTC-QLQ-C30	Required by HTA bodies: EORTC-QLQ-C30 may be mapped to EQ5D
Language	English language only	Model inputs should be relevant to UK clinical practice
Publication date	2000 – November 2012	Stem cell transplant only became standard practice towards the end of the 1990s, so this date was chosen to ensure results reflected current clinical practice
Animal/in-vitro/human	Human only	Relevant to the decision problem
Children/Adult	Adults ≥18 years only	Relevant to the decision problem
Publication type	Only articles published in full	Abstracts and posters are unlikely to contain a sufficient level of data

Citations were first screened by a single reviewer based on the title and abstract supplied with each citation (Figure 24). In instances when it was not possible to include or exclude citations based on the abstract, full-text copies were obtained. Those that did not match the eligibility criteria were excluded at this 'first pass'. A second reviewer checked the accuracy of the first reviewer's work and made changes if necessary. If uncertainty remained, a third reviewer was consulted. Following the title and abstract screen, full-text copies of all references that could potentially meet the eligibility criteria were obtained. The eligibility criteria were then applied to the full-text citations.

The search of literature databases identified 183 citations; following removal of duplicates (n=30), screening of these citations based on the prespecified inclusion and exclusion criteria excluded 139 citations. Full texts were then screened according to the inclusion criteria listed in Table 60. The literature review identified 10 citations that assessed HRQoL in a relevant patient population (186;187;204;206-212). Four publications reported data taken from a common patient group (186;204;206;212).

Figure 24: Inclusion flow for the systematic search of HRQoL studies



Of the citations identified, none compared HRQoL in patients who received induction therapy as described in the decision problem (i.e. bortezomib and thalidomide based regimens, section 5). Furthermore, the older studies incorporated treatment not considered as current clinical practice in the UK (e.g. the use of VAD as induction chemotherapy, tandem transplant and use of interferon as maintenance therapy).

Of the 10 citations returned by the review, 5 studies (1 as base case, 4 as sensitivity analyses) were chosen as appropriate to inform the economic model and were assessed using the following criteria:

- Utilities assessed using the preferred EQ-5D instrument
- Included induction therapies relevant to the decision problem i.e. bortezomib- and thalidomide-based regimens
- Reflective of clinical practice in the UK

- Reflective of the patient population in the UK who would undergo transplant
- Provided sufficient data to populate the economic model i.e. post-induction utility values, long term utility values (>12 months), utility values for progression (i.e. 2+ lines of treatment), monthly or similar regular measurements

The assessment process results are displayed in Table 61. The study published by Gulbrandsen and colleagues in 2004 was assessed separately to linked publications as it excluded results from patients who had been randomised to interferon maintenance therapy (unlike results from the linked publications) (188;204;206)

Table 61: Summary of utility study suitability for use in the economic model

Assessment item	Citation							
	Delea 2012	**Etto 2011**	**Frodin 2011**	**Iversen 2010**	**Uyl-de Groot 2005**	**van Agthoven 2004**	**Gulbrandsen 2004**	**Gulbrandsen 2001a, Gulbrandsen 2001b, Wisloff 2000**
EQ5D	✓	×	×	×	✓	✓	×	×
Bortezomib- and/ or thalidomide-based regimens	✓ thalidomide × bortezomib	? – insufficient information	? – insufficient information	×	×	×	×	×
Reflect current clinical practice in UK	× Maintenance therapy used	? – insufficient information	? – insufficient information	× Induction regimen not relevant to decision problem	× Induction regimen not relevant to decision problem × Type of transplant not used in UK	× Induction regimen not relevant to decision problem × Total body irradiation not used anymore × Maintenance therapy used	× Induction regimen not relevant to decision problem	× Induction regimen not relevant to decision problem × Maintenance therapy used
Reflects the UK patient population	✓ UK patient population ×Transplant specific information not presented in publication	× Socio-economic differences	? – insufficient information	? – insufficient information	× Inclusion criteria based on age	× Inclusion criteria based on age	× Inclusion criteria based on age	× Inclusion criteria based on age
Utility data allows population of the economic model	× Fits model structure × Long term values ✓ Excluded if progressed × Further lines not included	× Fits model structure × Long term values ? Excluded if progressed × Further lines not included	× Fits model structure partially, no post-induction values ✓ Long term values × Excluded if progressed × Further lines not included	× Fits model structure partially, no long term values × Long term values ? Excluded if progressed × Further lines not included	✓ Fits model structure ✓ Long term values × Excluded if progressed × Further lines not included	✓ Fits model structure ✓ Long term values ✓ Excluded if progressed × Further lines not included	✓ Fits model structure ✓ Long term × Excluded if progressed × Further lines not included	✓ Fits model structure ✓ Long term × Excluded if progressed × Further lines not included
Suitable for base case	×	×	×	×	×	✓	×	×
Suitable for sensitivity analyses	×	×	×	×	✓	×	✓	×

7.4.6 **Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.**

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

The study designs of the citations which inform utility values in the economic model are summarised in Table 62.

The studies did not reported adverse event frequency.

Table 62: Study design and population of the HRQoL studies identified as relevant

Study	Study type	Country	Population, mean age (SD)	Recruitment	Interventions	Sample size (N)	Elicitation	QoL instrument
van Agthoven 2004(187)	Cost-utility based on an RCT	Belgium and Netherlands	Undiagnosed, untreated MM Age: 54	NR	VAD followed by 2x melphalan 70mg/m^2 with SCT Comparator: VAD without SCT (both groups received interferon maintenance)	261	NR	EQ-5D
Gulbrandsen 2004(204)	Two prospective studies: comparison to reference population through regression	Denmark, Norway and Sweden	Newly diagnosed MM Age: (mean NR) HDM <60 MP >60	Patients in over 100 hospitals	3 cycles of VAD followed by cyclophosphamide (4 g/m^2) followed by G-CSF 5 mg/kg followed by high-dose melphalan (200 mg/m^2) then SCT Control: intermittent courses of MP	424 (221 HDC, 203 MP treatment) 3000 from general population	Patient self-reporting via questionnaires	EORTC QLQ-C30
Uyl-de-Groot 2005(207)	Prospective, longitudinal cohort study	Netherlands	Newly diagnosed MM; untreated or undergoing first-line treatment Age: 53 (7.2)	All patients scheduled for intensive therapy at VU University, Amsterdam, and patients who had started treatment, but had not passed the last two QoL measurement points	2 cycles of VAD or Comparator: 2 cycles VAMP Both treatments followed by HDC (melphalan 140mg/m^2) and then double SCT	51	Patient self-reporting via questionnaires	EQ-5D, EORTC QLQ-C30

As part of a cost-utility analysis, van Agthoven and colleagues compared chemotherapy (n=129) versus intensive chemotherapy followed by myeloablative chemotherapy with SCT (n=132) and total body irradiation treatment regimens in patients in the Netherlands and Belgium under the age of 65 years with newly diagnosed and untreated MM(187). Patients received 3-4 cycles of VAD and two cycles of intermediate dose melphalan (IDM), whereafter they were randomised to either receive SCT and interferon maintenance, or interferon maintenance only. Utility values were derived during this study, but reported in full separately in a thesis by the co-author Segeren for nine time points - from baseline to 24 months post-randomisation(194). Utility values reported in the van Agthoven and colleagues publication were based on the EQ5D and ranged from 0.81 (six months post-randomisation) to 0.77 (24 months post-randomisation) in the intensive chemotherapy only arm and 0.75 (24 months post-randomisation) to 0.62 (12 months post-randomisation). The thesis by Segeren reported utility values at baseline (0.4), post-VAD (0.57) and post-IDM (0.65). The authors state that patients in an undefined state following intentionally curative primary therapy would have HRQoL 19.5% lower than those in the general population, i.e. 0.644. These utility values are displayed in Table 63.

The selection of the van Agthoven study as the base case source of utility values was based on several factors, but primarily that the utility values were obtained using the EQ5D, thus eliminating uncertainties around mapped utility results. Using the van Agthoven publication, the HRQoL values obtained were the most extensive in terms of the frequency of measurement (pre-induction, post-induction and regularly post-SCT/no SCT), with only the study by Frödin and the NMSG (Gulbrandsen and colleagues) studies offering longer duration (24 months vs. 36 months, respectively). Use of these data allow a more accurate estimation of the evolution of HRQoL of MM patients who undergo SCT compared to the use of studies of shorter duration or fewer measurements, and fits in with the structure of the Markov model which has monthly cycles, thus providing more confidence in the QALY results.

Of the studies chosen to inform utility values in the economic model sensitivity analyses, two derived utility values using the EQ-5D (187;194;207) (Table 63). The study reported by Uyl-de-Groot and colleagues also assessed HRQoL using the EORTC QLQ C-30. The study reported by Gulbransen and colleagues assessed HRQoL using the EORTC QLQ C-30 only (this study did not use EQ-5D).

It was attempted to map the EORTC QLQ C-30 data to EQ5D for use as part of the sensitivity analyses. A series of different mapping algorithms were considered(213-215) .
Use of algorithms were to be determined according to:

- The availability of sufficient EORTC QLQ C-30 data points required for each mapping algorithm

- The accuracy of the mapping algorithms was assessed by comparing the results from the EQ5D studies with results from the study where mapping was applied

Unfortunately Gulbransen and colleagues only reported 6 out of 15 items on the EORTC QLQ-C30 which was insufficient data points for the mapping algorithms identified. Therefore no mapping was possible and this paper was not used in the sensitivity analysis.

Table 63: Utility values reported across different HRQoL studies which assessed utility using the EQ-5D questionnaire

Study author	Health states reported	Utility points reported (at time points)	Study arm	---------- Time from baseline mean (SD) ---------->								
				Baseline	3 months				6 months	12 months	18 months	24 months
Segeren 2002(194) Van Agthoven 2004 (187)	HRQoL of patients newly diagnosed and untreated with MM	EQ-5D – baseline to post-VAD, post-IDM, 3, 6, 12, 18, and 24 months post-randomisation to interferon maintenance	SCT	0.57*	0.65*		0.59*		0.65**	0.62**	0.69**	0.75**
			No SCT	0.57*	0.65*		0.77*		0.81**	0.80**	0.81**	0.77**
Uyl de Groot 2005(207)	HRQoL of patients with MM that was newly diagnosed and untreated or were undergoing first-line treatment for MM	EQ-5D – for patients who completed the questionnaire both at baseline [2 weeks after completion of VAD/VAMP] and at 12 months (n=12)		0.60 (0.33)						0.77 (0.13)		
		EQ-5D change from baseline (2 weeks after completion of VAD/VAMP);T2=Day of hospital discharge after HDM, T3=1 month after hospital discharge after HDM T4=Day of hospital admission for SCT, Time points after hospital discharge following SCT: T5=Day of discharge, T6=6 months after, T7=12 months after		0.52 (0.33)	T2: 0.03†	T3: 0.14†	T4: 0.14†	T5: -0.14†	T6: 0.12†	T7: 0.17†		

Note: Time scales vary between trials (i.e. baseline definition differs)

*Segeren
** van Agthoven
† Data is mean change from baseline

7.4.7 **Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.**

The utility data derived from the literature search represent the only utility data available; neither HRQoL nor utility were assessed during the clinical trials described in section 6.

Adverse events

7.4.8 **Please describe how adverse events have an impact on HRQL.**

None of the studies identified in the HRQoL systematic literature review specifically evaluated the effect of adverse events with induction therapy on HRQoL, which is the therapy of interest in this submission.

Two studies which evaluated HRQoL in the transplant setting and measured HRQoL post-induction therapy have shown an increase in QoL from diagnosis to post-induction therapy and post-HDT using the EQ5D(194;207;216), or an increase in all functional scales on the EORTC QLQ-C30 from diagnosis to post-treatment/pre-SCT(194;216). Adverse events experienced with induction therapies may have been included indirectly through its negative effects on HRQoL, however, as this was not measured and HRQoL increased during this period, the effect of adverse events on HRQoL cannot be ascertained.

It should be noted that induction therapy forms only the first step of the MM treatment pathway and that adverse events associated with induction therapy at this stage have little impact on the overall HRQoL that a patient experiences during the course of their disease. Additionally, the negative effects of adverse events with induction therapy on HRQoL may be considered acceptable as they are only experienced in the short term. Moreover, induction therapy enables patients to proceed to SCT, which extends the number of treatment options and thus the number of progression-free intervals a patient may experience.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 **Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.**

The systematic literature search, presented in section 7.4.5, did not return any utility values for multiple myeloma patients achieving different level of response to their induction treatment. Consequently, an additional literature search was conducted in haematological cancers (i.e. multiple myeloma, lymphomas and leukaemia) and in the stem cell transplant setting to identify utility values for different level of response to induction therapies. The search was conducted in the HTAInsite database.

Four separate searches were conducted in the HTAinsite database for both the NICE and SMC submissions using the following terms for each search: 1) multiple myeloma, 2) leukaemia, 3) lymphoma and 4) stem cell transplant. The documents retrieved included the NICE and SMC guidance documents, the assessment reports and manufacturers submissions. The documents were screened to identify utility values used and where relevant, cited papers were retrieved.

Only one HTA report included utility values for each category of response (complete responders, partial responders and non responders) (Table 64).(193) The utilities included in this HTA report were based upon two sources: the baseline utility value in the trial assessing bendamustine for the 1st line treatment of chronic lymphocytic leukaemia in patients for whom fludarabine combination chemotherapy is not appropriate, and the publication by Beusterien et al(195).

In their study, Beusterien et al measured preferences for health states associated with chronic lymphocytic leukaemia in 89 members of the general population in England and Scotland. Utilities were obtained using a vignette approach and elicited using the standard gamble method.

In our economic model, these utilities were therefore applied to the non-stem cell transplant (SCT) patients only as patients in the bendamustine trial did not receive a SCT (Table 64). It is important to segment utility values by response category for patients that do not receive a SCT only, as response rate will have a large impact on patient QoL if they do not undergo transplant. Conversly, for patients undergoing SCT, the transplant itself has such a pronounced impact on quality of life that segmenting by response level is not necessary. The impact of level of response, in this instance, is outweighed by the impact of the SCT procedure.

Table 64. Published utility values by category of response rate and utility values used in the economic model

Published utilities (HTA report Bendamustine in CLL). (*Adapted from Hoyle et al. Table 12 page 65*)		**Utility values used in the economic model**	
Health state	**Mean utility***	**Health state**	**Mean utility**
First line (Bendamustine / chlorambucil)		First line, post-induction phase for patients without stem cell transplant (non-SCT patients)	
CR (complete response)	0.83	CR (complete response)	0.83
PR (partial response)	0.76	PR (partial response)	0.76
SD (stable disease)	0.70	NR (minimal response, stable disease and progressive disease)	0.65 (the mid-point between 0.60 and 0.70 was used)
PD (progressive disease)	0.60		

*Example of calculation for the complete response health state: utility of 0.70 (baseline utility from the bendamustine RCT) + 0.91 (CR from Beusterien et al) – 0.78 (SD from Beusterien et al) =0.83

A full summary of the utility values used in the base case model is presented in the Table 65 below.

Table 65: Summary of utility values for cost-effectiveness analysis

UTILITIES	Utility value	Confidence interval	Reference in submission (Section 7.4.6)	Justification
1st line treatment				
From start treatment until post-induction response	0.57	0.34-0.78	Segeren thesis: value after VAD administered.	van Agthoven et al. does not report the utilities during induction therapy
From post-induction to post-SCT response	0.65	0.38-0.88	Segeren thesis: value after 2nd intermediate dose melphalan (IDM) administered.	van Agthoven et al. does not report the utilities during induction therapy. Assumption that this would be reasonable for the whole period as no other value (e.g. immediate post SCT) is available
SCT patients	Up to 3mos=0.59	0.35-0.81	Segeren. Thesis. Value is for reported value at 3 months post-randomisation	van Agthoven et al. does not report values at 3 months.
	3-6mos=0.65	0.38-0.88	Van Agthoven et al.	Van Agthoven et al. used as it's in a published article.
	6-9mos=0.68	0.39-0.91	Segeren thesis	van Agthoven et al. does not report values up to 9 months
	9-12mos=0.62	0.37-0.84	Van Agthoven et al.	Segeren does not report values post 12 months.
	12-18mos=0.69	0.39-0.92		
	18+mos=0.75	0.41-0.97		
Non-SCT patients	Complete response (CR)=0.83	0.67-0.94	Beusterien et al.	Segeren does not report values by level of response, which is an important factor in the quality of life of patients that do not undergo transplant.
	Partial response (PR)=0.76	0.64-0.87		
	Non-response (NR)=0.65	0.56-0.73		
2nd and 3rd line treatments	0.69	0.39-0.92	Van Agthoven et al.	Average are for the time points from baseline (0.4) to post treatment to 18 month
Further lines	0.644	0.38-0.87		As calculated in van Agthoven et al. publication.

A disutility of 0.02 was applied to each patient experiencing an adverse event with an induction therapy. (section 6.9) A weighted average was then calculated to derive a disutility for the induction health state. (Table 66)

Table 66: Summary of disutility values associated with adverse events for cost-effectiveness

DISUTILITIES	Disutility value	Confidence interval	Reference in submission	Justification
1st line treatment	0.02	0.013-0.029	ScHARR HTA report. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. Aug 2012.(217)	This disutility value reported in a previous HTA submission was used, given the lack of alternative suitable disutility values in the literature

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Not applicable

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQoL fluctuations can be expected during 1st line treatment, as patients undergo chemotherapy induction, stem cell mobilisation, harvesting, ablation with HDM and the stem cell transplant. Typically, patients will experience an increase in HRQoL during and after induction chemotherapy as the cancerous cells are destroyed and symptoms improve. Following transplant, patients experience a period of low HRQoL due to the intensive nature of the procedure, followed by a gradual improvement in HRQoL until a plateau is reached. The utility estimates for 1st line treatment in the economic model incorporate (where possible due to the model structure), the average HRQoL for patients in this health state.

When patients progress their HRQoL may decrease as the tumour burden increases and the disease symptoms present. On receiving further treatment to decrease the tumour burden, an improvement in HRQoL can be expected as the patient goes into remission and the disease symptoms improve. When the myeloma enters a stable phase and there are no signs of progression, HRQoL may remain stable. In the acute terminal phase HRQoL would continue to decline as the patient becomes terminally ill, until the patient dies.

These variances are not accounted for in the HRQoL for 2nd, 3rd and further lines treatment. Instead, a constant HRQoL value is used throughout each line of treatment. For 2nd and 3rd line the HRQOL is lower than 1st line to reflect the progressive nature of the disease. Similarly, for further lines it is lower than 2nd and 3rd line to reflect the progressive nature of the disease for which there are fewer treatment options available than for 1st, 2nd or 3rd line treatment, and increased age of the patient (nearly 40% of patients survive for five years and 15-19% survive to 10 years post diagnosis(3)).

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No studies were identified that captured utility values for the interventions relevant to the decision problem, so although not explicitly excluded, any effects they may have had were not included. Instead, the effect of another induction therapy (VAD) was reflected in the utilities used for 1st line therapy as this was the only data available.

The baseline utility value i.e. prior to the start of induction therapy, was not included as the model starts from commencement of induction therapy. No other utility values for the base case were excluded.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

As described in section 7.4.11, HRQoL changes over time according to the course of the disease and lines of therapy available. HRQoL is assumed to be constant over time as long as a patient remains within the same health state.

7.4.15 **Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.**

Not applicable

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 **Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.**

For all lines of therapy the tariffs relevant to the clinical management of MM patients are the 2012-13 Chemotherapy Regimens List(65), the 2011-12 National Schedule Reference Cost(66) and the British National Formulary(BNF), November 2012 edition (218).

Specifically, the cost of chemotherapy and prophylactic medication were collected from the BNF whilst administration of chemotherapy drugs was based on the delivery HRG corresponding to the regimen name in the Chemotherapy Regimens List i.e. for regimens containing only oral drugs the HRG was *SB11Z - Deliver exclusively Oral Chemotherapy (outpatient)* and for regimens containing parenteral chemotherapy the codes were *SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case)* and *SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case).*

The costs relating to stem cell mobilisation, harvest and transplant was determined similarly e.g. *SA34Z - Peripheral Blood Stem Cell Harvest* and *SA26A – PBSCT –Autologous 19 years and over.*

Outpatient visits and tests as part of disease and treatment monitoring were based upon the corresponding HRG, Outpatient Attendance (OPATT) and Other Currencies description in the National Schedule of Reference Cost e.g. for follow up attendance with a consultant the OPATT code was *Service code 303 – Clinical Haematology, Consultant Led: Follow up Attendance Non-Admitted Face to Face* and a biochemistry test was the currency code *DAP841 – Biochemistry.*

The costs associated with treating adverse events were based upon inpatient, outpatient or day case visit codes in the National Schedule of Reference Cost. See section 7.5.7 for the justification for codes.

7.5.2 **Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.**

As described in 7.5.1, the NHS references cost, PBR tariffs and BNF are appropriate for costing the interventions in this submission.

Resource identification, measurement and valuation studies

7.5.3 **Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:**

The search and inclusion screening process performed to identify cost and resource inputs to the economic model was the same as the search used to identify published economic evaluations relevant to the decision model (section 7.1.1). The flow diagram for the review is displayed in Figure 18.

Four trials were identified to provide cost and resource inputs to the economic model (219-222).

Of the four cost and resource studies returned by the review (Table 67), none were used to provide costs inputs for the economic analysis; the results of these studies were not applicable to the UK (219-222). Two studies were completed in the USA (221;222). Both used US-specific cost sources (such as average wholesale prices), and were carried out in a private healthcare setting. Therefore, the results are not applicable from a UK-NHS perspective. Results for the remaining two studies, which were carried out in Norway, were presented in US dollars and included indirect costs. Therefore these costs were not applicable to UK practice (219;220).

Table 67: Health costs valuated and the total mean cost per patient

Study	Healthcare costs evaluated	Total mean cost per patient
Hosing 2011 (222)	Chemotherapy for remobilisation Prophylactic drug use during remobilisation Laboratory tests during remobilisation phase Blood products used during remobilisation Preapheresis Apheresis Postapheresis/cryopreservation Hospital readmission Procedure costs	$24,968 for remobilisation $20,740 for apheresis procedures $13,041 for hospital readmission
Porter 2007 (221)	Drug administration Drugs Hospitalisation for adverse events Tests Transfusions Concomitant medication	$35,846 for pegylated VAD $34,442 for low dose VAD
Mishra 2005 (191)	Direct and indirect cost of mobilisation Harvesting and cryopreservation HDT with infusion of stem cells Hospitilisation Supportive care following SCT	Mean cost per patient ranged across four different hospitals: $19,092, $27,052, $31,944, and $50,550
Mishra 2003 (219)	Disease status Mobilisation and collection of stem cells HDT with transfusion of stem cells Hospitalisation after transfusion for stem cells Pharmacy and blood products Indirect cost for clinical and nonclinical services	$14,656 for evaluation/mobilisation $23,530 for HDT and SCT

Legend: HDT: high dose therapy; SCT: stem cell transplantation; VAD: vincristine, adriamycin, dexamethasone

7.5.4 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:**

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Details on the advisory board and method to collect clinicians' opinion were presented in section 7.3.5 and appendix 14.

At an advisory board held on the 26th October 2012, clinicians provided input on the drugs to be used for stem cell mobilization (i.e. cyclophosphomide 1.5g/m^2, lenograstim as G-CSF) and ablation (melphalan 200mg/m^2 for 75% of patients and melphalan 140 mg/m^2 for 25% of patients). Clinical input into the drugs used as prophylaxis for all of the induction regimens was also provided and the information is presented in Appendix 14.

7.5.5 **Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

The cost associated with the induction regimens VTD (bortezomib, thalidomide, doxorubicin) vs. TD (thalidomide, dexamethasone) in the Pethema trial and PAD (bortezomib, doxorubicin, dexamethasone) vs. VAD (vincristine, doxorubicin, dexamethasone) in the Hovon trial and VD (bortezomib, dexamethasone) vs. VAD (vincristine, doxorubicin, dexamethasone) in the IFM trial, are presented below. VD vs. VAD had been performed using the clinical data of the arms VD without DCEP and VAD without DCEP.

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 68: Unit costs associated with the 1st line induction therapies: drugs, prophylaxis, administration and monitoring

	VTD	TD
Median N cycles	6	6
Average cost of a course of treatment (section 1.10)	£24,840	£8,720
Prophylaxis (drug, dose and cost)		
DVT*	£192.24	£192.24
Herpes Zoster	£54.57	NA
Tumor lysis syndrome	£7.32	£7.32
Anti-infective	£89.69	£89.69
Gastroprotection	£9.72	£9.72
Administration		
Code	SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case) SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case)	SB11Z - Deliver exclusively Oral Chemotherapy (outpatient)
cost	£1,645.00	£828.00
Monitoring cost (laboratory tests and consultant visit) – section 2.9	£1,050.00	£1,050.00
TOTAL	**£28,034**	**£8,865**
	PAD	**VAD**
Dosage	28 day cycles bortezomib 1.3 mg/m2, days, 1, 4, 8, 11, doxorubicin 9 mg/m2, days 1-4, dexamethasone 40mg, days 1-4, 9-12, 17-20	28 day cycles of: Vincristine 0.4 mg days 1-4, doxorubicin 9mg/m2 days 1-4, dexamethasone 40 mg days 1-4, 9-12, and 17-20
Median N cycles	3	3
Average cost of a course of treatment (section 1.10)	£9,692.09	£705.17
Prophylaxis (drug, dose and cost)		
DVT*	NA	NA
Herpes Zoster**	£27.28	NA
Tumor lysis syndrome	£3.66	£3.66
Anti-infective	£44.85	£44.85
Gastroprotection	£4.86	£4.86
Total prophylaxis	£80.65	£53.37
Administration		
Code	SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case) SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case)	SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case) SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case)
Cost	£781.00	£781.00
Monitoring cost (laboratory tests and consultant visit)	£520.06	£520.06
TOTAL	**£11,073.80**	**£2,059.60**

	VD	VAD
Dosage	3-week cycles of bortezomib 1.3 mg/m2 intravenously days 1, 4, 8, and 11 Dexamethasone 40 mg days 1 to 4 (all cycles) and days 9 to 12 (cycles 1 and 2).	28 day cycles of: Vincristine 0.4 mg/day on days 1-4, doxorubicin 9mg/m2 days 1-4, dexamethasone 40 mg days 1-4 (all cycles), 9-12, and 17-20 (cycles 1 and 2)
Median N cycles	4	4
Average cost of a course of treatment (section 1.10)	£12,260.91	£898.34
Prophylaxis		
DVT*	NA	NA
Herpes Zoster - acyclovir	£27.28	NA
Tumor lysis syndrome - allopurinol	£3.66	£4.88
Anti-infective: co-trimoxazole	£44.85	£59.79
Gastroprotection: omeprazole	£4.86	£6.48
Total prophylaxis	£80.65	£71.15
Administration		
Code	SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case) SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case)	SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case) SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case)
Cost	£1,069.00	£1,069.00
Monitoring cost (laboratory tests and consultant visit)	£693.42	£693.42
TOTAL	**£14,103.98**	**£2,731.91**

*For DVT prophylaxis assumed 60% aspirin and 40% low molecular weight heparin (see appendix 14)
Legend: DVT: Deep vein thrombosis; TD: thalidomide and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

Table 69: Unit costs associated with the stem cell transplant in 1st line

	Drugs / intervention	Costs	Administra-tion costs	Total costs	Reference	Assumption
Mobilisation	Cyclophosphamide 1.5 g/m^2 body surface	£31.98	£203.00	£234.98	National Schedule of Reference Costs 2011-12 for NHS trusts and NHS foundation trusts. Code: SB12Z – Deliver simple parenteral chemotherapy at first attendance. (66;219) Advisory board – Appendix 14	1.85m^2, 2.78g per person i.e 3x1g vials
	G-CSF: Lenograstim 19.2 MU/m^2 daily	£312.70	£0.00	£312.70	Advisory board – Appendix 14- lenograstim, duration ranged from 5 days to until neutrophil count stable. PETHEMA(71)	1.85m^2 body surface. Assume G-CSF given with cyclophosphomi de, so no additional administration cost
	Harvest		£823.00	£823.00	National Schedule of Reference Costs 2011-12 for NHS trusts and NHS foundation trusts. Code: SA34Z - Peripheral Blood Stem Cell Harvest(66)	Day case
Ablation	High Dose Chemotherapy costs: High dose melphalan (200 mg/m^2) or Immediate dose melphalan (140 mg/m^2)	£248.48	£203.00	£451.5	National Schedule of Reference Costs 2011-12 for NHS trusts and NHS foundation trusts. Code: SB12Z – Deliver simple parenteral chemotherapy at first attendance(66) BNF. November 2012.(218) Advisory board – Appendix 14: 75% used 200mg/m2 dose, remainder use 140mg/m2 dose	Assume 1.85m^2, 370mg per person
Transplant	ASCT		£17,813	£17,813	National Schedule of Reference Costs 2011-12 for NHS trusts and NHS foundation trusts. Code: SA26A – PBSCT – Autologous 19 years and over(66)	
Post transplant	G-CSF: Lenograstim 19.2 MU/m^2 daily	£875.56		£875.56		Assume 14 days of lenograstim use. This is the upper end of engraftment period. Advisory board. Appendix 14
Total cost				**£20,510.72**		

Table 70: Unit costs associated with the 2nd line treatments: drugs, prophylaxis, administration and monitoring

2nd line costs (£)	Vel+HDD	CTD	HDD
Dosage	Up to 8 cycles, one cycle is 21 days 1.5mg/m^2 bortezomib on days 1, 4, 8, and 11 oral dexamethasone 20mg on the day of and the day after each dose of bortezomib, for a total dose of 160 mg every 21 days (corresponding to 5.60 months of treatment)	Cyclophosphamide 250 mg/ m^2 / week Thalidomide 150 mg/day Oral dexamethasone 20 mg/day for 4 days every 28 days (corresponding to 12.00 months of treatment)	Dexamethasone 40 mg on days 1-4, 9-12 and 17-20 of cycles 1-4 (35-day cycles) and on days 1-4 of cycles 5-9 (28-day cycles) Maximum treatment period of 280 days (corresponding to 9.33 months of treatment)
Average cost of a course of treatment	£24,479.94*	£11,624.11	£178.02
Prophylaxis (drug, dose and cost)			
DVT: Dalteparin	NA	£423.00	0
Herpes Zoster	£54.57	NA	0
Administration			
Code	SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case) SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case)	SB11Z - Deliver exclusively Oral Chemotherapy (outpatient)	370 - Medical oncology outpatient attendance – 1st visit
Cost	£2,191.00	£1,656.00	£168.00
Cost (drug + prophylaxis + admin)			
For the whole treatment phase (all cycles completed)	£26,725.50	£13,703.11	£346.02
Per month			
Drug costs	£4,772.41	£1,141.93	£37.07
Monitoring cost (during treatment)	£173.35	£175.00	£173.33
Monitoring costs (after treatment)	£82.61	£82.61	£82.61
Based on mean duration of 2nd line treatment			
Mean duration of 2nd line (months)	9.80	9.80	6.52
TOTAL****	**£28,043.61**	**£12,911.50**	**£1,372.62**

Legend: CTD: thalidomide in combination with dexamethasone and cyclophosphamide;; HDD: high dose dexamethasone; Vel+HDD: Velcade® (bortezomib) and dexamethasone

*The Velcade Response Scheme was not modeled. No rebate was assumed.

** Only the costs associated with the transplant (drugs + administration) was considered.

*** If the 2nd line health state (mean duration of 2nd line) is shorter than the whole treatment phase recommended, there is no monitoring cost associated with the progression free phase.

****Calculated by the sum of the costs incurred during the treatment phase (drug + prophylaxis + administration and monitoring costs) and the costs incurred during the progression free phase (monitoring costs) of the 2nd line health state.

Table 71: Unit costs associated with the 3rd line treatments: drugs, prophylaxis, administration and monitoring

3rd line costs (£)	RD	CTD	HDD
Dosage	Lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. 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 Treatment continues until disease progression (calculation for a one-year period)	Cyclophosphamide 250 mg/ m2 / week Thalidomide 150 mg/day Oral dexamethasone 20 mg/day for 4 days every 28 days (corresponding to 12.00 months of treatment)	Dexamethasone 40 mg on days 1-4, 9-12 and 17-20 of cycles 1-4 (35-day cycles) and on days 1-4 of cycles 5-9 (28-day cycles) Maximum treatment period of 280 days (corresponding to 9.33 months of treatment)
Average cost of a course of treatment	£57,160.29	£11,600.55	£178.02
Prophylaxis (drug, dose and cost)			
DVT: Dalteparin	£1,029.30	£423.00	n/a*
Administration			
Code	SB11Z - Deliver exclusively Oral Chemotherapy (outpatient)	SB11Z - Deliver exclusively Oral Chemotherapy (outpatient)	370 - Medical oncology outpatient attendance – 1st visit
Cost	£1,798.93	£1,656.00	£168.00
Cost (Treatment + Prophylaxis + Admin)			
For the whole treatment phase (all cycles completed)	£59,988.51	£13,679.55	£346.02
Per month			
Drug costs	£4,930.56	£1,139.96	£37.07
Monitoring cost (during treatment)	£175.00	£175.00	£173.33
Monitoring costs (after treatment)	£82.61	£82.61	£82.61
Based on mean duration of 3rd line treatment			
Mean duration of 3rd line (months)	8.36	8.36	4.91
TOTAL****	**£42,693.48**	**£10,995.92**	**£1,032.93**

CTD: thalidomide in combination with dexamethasone and cyclophosphamide; HDD: high dose dexamethasone; n/a: not applicable; RD: lenalidomide and dexamethasone

* The HDD regimen is not associated with DVT, therefore no cost of DVT prophylaxis is incurred with this regimen.

*** If the 2nd line health state (mean duration of 2nd line) is shorter than the whole treatment phase recommended, there is no monitoring cost associated with the progression free phase.

****Calculated by the sum of the costs incurred during the treatment phase (drug + prophylaxis + administration and monitoring costs) and the costs incurred during the progression free phase (monitoring costs) of the 2nd line health state.

Table 72: Unit cost of prophylaxis drugs (based on BNF, November 2012)

	Prophylaxis drug	Cost per dose
DVT: Dalteparin by SC, 5000 units / 24 hours Aspirin: 75mg / day	Dalteparin 5000 units	£2.82
	Aspirin 75mg (dispersible)	£0.03
Tumor lysis syndrome. Allopurinol 100mg daily	Allopurinol 100mg	£0.04
Herpes. Zoster: Acyclovir 200–400 mg 4 times daily	Acyclovir 200mg	£0.08
Anti-infective: Co-trimoxazole 960mg	Co-trimoxazole 480mg	£0.62
Gastroprotection: Omeprazole 20mg daily	Omeprazole 20mg	£0.06

Health-state costs

7.5.6 **Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.**

The costs in each health state are presented in sections 7.3.6 and 7.5.5. The individual components of the monitoring costs are presented in section 2.9.

Adverse-event costs

7.5.7 **Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

Costs of treating grade 3 and above adverse events were estimated for all lines of therapy assuming treatment in the secondary care setting. The UK National Schedule of Reference Costs, Year 2011-2012(66) was used. (Section 7.5.1)

Table 73: List of adverse events (induction phase) and summary of costs included in the economic model

Adverse events	Treatments	Item – Setting	Value	Reference
Acute Phase reaction	PAD, VAD	Outpatient	£175	National Schedule of Reference Costs 2011-12. OPATT. Service Code 314 - Clinical Immunology & Allergy. Total Unit cost
Anaemia	VTD, VD , PAD, TD, VAD	Day case	£306	National Schedule of Reference Costs 2011-12. HRG. Currency Code: SA08F - Other Haematological or Splenic Disorders w/o cc. Unit day case cost
Arterial embolism	VTD, TD	Outpatient	£160	National Schedule of Reference Costs 2011-12. OPATT. Service code 303 - Clinical Haematology. Total Unit Cost
Asthenia	VTD, VD, TD, VAD	Outpatient	£150	National Schedule of Reference Costs 2011-12. OPATT. Service Code 300 - General Medicine. Total Unit cost
Back pain	VD, VAD	Outpatient	£125	National Schedule of Reference Costs 2011-12. OPATT. Service Code 191 - Pain Management. Total Unit cost
Deep-vein thrombosis	VTD, TD	Outpatient	£160	National Schedule of Reference Costs 2011-12. OPATT. Service code 303 - Clinical Haematology. Total Unit Cost
Fatigue	PAD, VAD	Outpatient	£150	National Schedule of Reference Costs 2011-12. OPATT. Service Code 300 - General Medicine. Total Unit cost
Febrile neutropenia	VD, VAD	Day case	£306	National Schedule of Reference Costs 2011-12. HRG. Currency Code: SA08F - Other Haematological or Splenic Disorders w/o cc. Unit day case cost
Hepatic function abnormal	PAD, VAD	Outpatient	£196	National Schedule of Reference Costs 2011-12. OPATT. Service Code 309 - Hepatology. Total Unit cost
Herpes Zoster	VTD, VD, PAD, TD, VAD	Outpatient	£150	National Schedule of Reference Costs 2011-12. OPATT. Service Code 300 - General Medicine. Total Unit cost
Hypocalcaemia	VTD, PAD, TD, VAD	Non-elective inpatient	£372	National Schedule of Reference Costs 2011-12. HRG. Currency Code: KC05F. Fluid and Electrolyte Disorders 69 years and under without CC. Nonelective inpatient (short stay) cost
Leukopenia	VD, PAD, VAD	Day case	£306	National Schedule of Reference Costs 2011-12. HRG. Currency Code: SA08F - Other Haematological or Splenic Disorders w/o cc. Unit day case cost
Lymphopenia	VD, VAD	Day case	£306	National Schedule of Reference Costs 2011-12. HRG. Currency Code: SA08F - Other Haematological or Splenic Disorders w/o cc. Unit day case cost
Mucosal inflammation	VD, PAD, VAD	Outpatient	£150	National Schedule of Reference Costs 2011-12. OPATT. Service Code 300 - General Medicine. Total Unit cost
Nausea	VD, PAD, VAD	Outpatient	£150	National Schedule of Reference Costs 2011-12. OPATT. Service Code 300 - General Medicine. Total Unit cost

Neutropenia	VTD, VD, TD, VAD,	Day case	£306	National Schedule of Reference Costs 2011-12. HRG. Currency Code: SA08F - Other Haematological or Splenic Disorders w/o cc. Unit day case cost
Pain	VD, VAD	Outpatient	£125	National Schedule of Reference Costs 2011-12. OPATT. Service Code 191 - Pain Management. Total Unit cost
Peripheral neuropathy incl. motor, sensory and polyneuropathy	VTD, VD, PAD, TD, VAD	Outpatient	£169	National Schedule of Reference Costs 2011-12. OPATT. Service Code 400 - Neurology. Total Unit Cost
Pneumonia	VTD, PAD, TD, VAD	Non-elective inpatient	£536	National Schedule of Reference Costs 2011-12. HRG. Currency Code: PA16B – Major infections without cc. Inpatient Non-elective (short stay) cost
Pyrexia	VTD, VD , PAD, TD, VAD, HDD	Day case	£386	National Schedule of Reference Costs 2011-12. HRG. Currency Code: PA20B – Fever unspecified without CC. Unit day case cost
Renal failure	VTD, TD	Non-elective inpatient	£3,543	National Schedule of Reference Costs 2011-12. HRG. Currency Code: PA38D – Renal Disease with Renal Failure, with length of stay 1 day or more. Inpatient Non-elective (short stay) cost
Respiratory failure	VTD, TD	Non-elective inpatient	£249	National Schedule of Reference Costs 2011-11. OPATT. Code: DZ27C –Respiratory Failure with Intubation, without CC. Inpatient Non-elective (short stay)
Respiratory tract infection	VTD, TD	Outpatient	£143	National Schedule of Reference Costs 2011-12. OPATT. Service code 340 - Respiratory medicine. Total Unit Cost
Septic shock	VTD, TD	Non-elective inpatient	£527	National Schedule of Reference Costs 2011-12. HRG. Currency Code: WA03V – Septicaemia with Major CC. Inpatient Non-elective (short stay) cost
Thrombocytopenia	VD, PAD, VAD	Day case	£441	National Schedule of Reference Costs 2011-12. HRG. Currency Code: SA12F – Thrombocytopenia. Unit day case cost
Vomiting	VD, VAD	Outpatient	£128	National Schedule of Reference Costs 2011-12. OPATT. Service Code 301 - Gastroenterology. Total Unit cost
VTD: bortezomib, thalidomide, dexamethasone, PAD: bortezomib, doxorubicin, dexamethasone, VD: bortezomib, dexamethasone, TD: Thalidomide, dexamethasone, VAD: Vincristine, doxorubicin, dexamethasone				

Miscellaneous costs

7.5.8 **Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.**

Not applicable

7.6 Sensitivity analysis

7.6.1 **Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis**.

Several analyses have been conducted to explore the sensitivity of the economic results to key assumptions.

Post-induction response rates

The post-induction response rates used in the base case model were obtained from the PETHEMA, IFM and Hovon studies and have been tested as part of the probabilistic sensitivity analysis (PSA).

A scenario analysis was also conducted using the only other study available (GIMEMA) investigating the use of VTD vs TD in MM patients eligible for a SCT.(8) The response rates used in this scenario analysis are presented in Table 74.

All other assumptions used in the model remained unchanged, as it is not possible to determine the proportion of patients who had undergone a SCT for each of the post-induction response categories using the GIMEMA data.(8)

Table 74: Post induction response rate(8)

	VTD N=236	TD N=238
CR (CR+nCR+VgPR)	146 (62%)	66 (28%)
PR	74 (31%)	121 (51%)
NR (MR+SD+PD)	16 (7%)	51 (21%)

CI: confidence interval; CR: complete response; NR: non responders; MR: minimal response; PD: progressed disease; PR: partial response; SD: stable disease; TD: thalidomide and dexamethasone; ; VgPR: very good PR; VTD: Velcade® (bortezomib), thalidomide and dexamethasone;

Sensitivity analyses have been conducted to test several extreme scenarios using upper or lower 95% confidence interval limit for each of the post-induction response rate categories.

Table 75: Scenario analyses around post-induction response rate

Parameter	Base case value	Alternate value	Rationale
Post-induction response rates – VTD	CR = 49.2% PR = 35.4% NR = 12.8%	57.0% 43.0% 0.0%	95% CI max 95% CI max Adjusted for total of 100%*
	CR = 49.2% PR = 35.4% NR = 12.8%	34.2% 43.8% 22.0%	Adjusted for total of 100%* 95% CI max 95% CI max
	CR = 49.2% PR = 35.4% NR = 12.8%	40.7% 27.4% 31.9%	95% CI min 95% CI min Adjusted for total of 100%*
	CR = 49.2% PR = 35.4% NR = 12.8%	62.9% 27.4% 9.7%	Adjusted for total of 100%* 95% CI min 95% CI min
Post-induction response rates – TD	CR = 17.3% PR = 44.1% NR = 38.6%	24.3% 52.8% 22.9%	95% CI max 95% CI max Adjusted for total of 100%*
	CR = 17.3% PR = 44.1% NR = 38.6%	0% 52.8% 47.2%	Adjusted for total of 100%* 95% CI max 95% CI max
	CR = 17.3% PR = 44.1% NR = 38.6%	11.3% 35.6% 53.1%	95% CI min 95% CI min Adjusted for total of 100%*
	CR = 17.3% PR = 44.1% NR = 38.6%	34.1% 35.6% 30.3%	Adjusted for total of 100%* 95% CI min 95% CI min
Post-induction response rates – PAD	CR = 50.1% PR = 34.1% NR =	54.9% 38.7% 6.4%	95% CI max 95% CI max Adjusted for total of 100%*
	CR = 50.1% PR = 34.1% NR =	57.0% 43.0% 0.0%	Adjusted for total of 100%* 95% CI max 95% CI max
	CR = 50.1% PR = 34.1% NR =	40.7% 27.4% 31.9%	95% CI min 95% CI min Adjusted for total of 100%*
	CR = 50.1% PR = 34.1% NR =	62.9% 27.4% 9.7%	Adjusted for total of 100%* 95% CI min 95% CI min
Post-induction response rates – VAD	CR = PR = NR =	23.4% 46.6% 30.0%	95% CI max 95% CI max Adjusted for total of 100%*
	CR = PR = NR =	10.0% 46.6% 43.4%	Adjusted for total of 100%* 95% CI max 95% CI max
	CR = PR = NR =	15.8% 37.1% 47.1%	95% CI min 95% CI min Adjusted for total of 100%*
	CR = PR = NR =	28.8% 37.1% 34.1%	Adjusted for total of 100%* 95% CI min 95% CI min
Post-induction response rates – VD	CR = PR = NR =	49.7% 45.4% 4.8%	95% CI max 95% CI max Adjusted for total of 100%*
	CR = PR = NR =	24.2% 45.4% 30.4%	Adjusted for total of 100%* 95% CI max 95% CI max

Parameter	Base case value	Alternate value	Rationale
	CR = PR = NR =	32.2% 28.3% 39.5%	95% CI min 95% CI min Adjusted for total of 100%*
	CR = PR = NR =	56.2% 28.3% 15.5%	Adjusted for total of 100%* 95% CI min 95% CI min
Post-induction response rates – VAD	CR = PR = NR =	22.7% 52.7% 24.6%	95% CI max 95% CI max Adjusted for total of 100%*
	CR = PR = NR =	0.0% 51.6% 48.4%	Adjusted for total of 100%* 95% CI max 95% CI max
	CR = PR = NR =	9.8% 35.1% 55.1%	95% CI min 95% CI min Adjusted for total of 100%*
	CR = PR = NR =	32.9% 35.1% 32.0%	Adjusted for total of 100%* 95% CI min 95% CI min

* Note: The addition of CR, PR and NR rates should always equal to 100%. In the following scenarios, one of the these post-induction response category was adjusted to control for 100%

Overall survival

The base case model assumes an exponential distribution of OS by post-induction response category , using the data from a long term follow-up clinical trial (MRC VII). However, the published OS data from MRC VII did not provide enough information to allow testing of different distributions of OS.(12) Therefore, sensitivity around OS data could only be tested by using an alternative source of data, namely the IFM90 study.

In the scenario analysis, 5-year OS data segmented by post-induction response rate were extracted from the IFM90 trial(196). The IFM90 trial was the first RCT to investigate whether HDT with transplant was more effective than conventional chemotherapy in the treatment of previously untreated MM patients. It was the landmark study that established HDT-SCT as the standard of care in this patient population, and was also the first study to demonstrate that a **complete response is the most important prognostic factor for survival**. Other studies that followed confirmed this finding.(12;43)

The IFM90 trial enrolled a total of 200 previously untreated MM patients, and randomised them to conventional chemotherapy (n=100), or HDT followed by transplant (n=100). The objective of the trial was to compare the two treatment groups with respect to OS five years after diagnosis. Response rates were also compared in the trial, as per the criteria in Table 76 below:

Table 76: Response criteria in IFM90 trial(196)

Response	Definition
Complete remission/complete response (CR)	Absence of paraprotein on electrophoresis of serum and urine, ≤5% plasma cells with normal morphologic features in a bone marrow aspirate
Very good partial response (VgPR)	Decrease of 90% in serum paraprotein level
Partial response (PR)	Decrease of 50% in serum paraprotein level (in patients who had Bence Jones protein) and a decrease of 90% in Bence Jones protein
Minimal response (MR)	Decrease of 25% in serum paraprotein level

Stable disease (SD)	No change in paraprotein level
Progressive disease (PD)	Increase of 25% in serum paraprotein level after two cycles of initial chemotherapy

Abbreviations: CR=complete response; MR=minimal/minor response; PD= progressive disease; PR=partial response; SD=stable disease; VgPR=very good partial response

After five years of follow-up, 178 patients who had survived >1 year after diagnosis were analysed to determine whether response to treatment was related to survival. The five-year probability of survival was 72% [95%CI: 42-91%] amongst the 51 patients who had CR/VgPR (defined as the 'CR' health state in the economic model), 39% [95%CI: 23-58%] amongst the 81 patients who had PR (defined as the 'PR' health state in the economic model), and 0% amongst the 46 patients who had less than a PR, ie those with MR, SD, or PD as per Table 76 above (defined as the non-responders 'NR' health state in the economic model).

OS was used to transition patients from the post-induction assessment to death; the 5-year survival rates from IFM90 trial are presented in Table 77 below.

Table 77: 5-year survival rates for a scenario analysis (196)

	5 year survival rate			Monthly probability of death
	%	95%CI min	95% CI max	
CR	72,0%	42,0%	91,0%	0,5%
PR	39,0%	23,0%	58,0%	1,6%
NR	0,1%	0,1%	1,0%	10,9%

CI: confidence interval; CR: complete response; NR: non responders; PR: partial response. Note: Attal et al. 1996, reported 5-year survival of 0%for those with less than PR. However, for survival analysis purposes, 0.1% is used in the economic model to enable the probability calculation.

TTP distribution

The sensitivity of the survival distribution for the 1st line TTP (post-transplant/post-induction) has been investigated in scenario analyses using the log-logistic and Weibull parametric curve.

Table 78: Parameters of the Log-logistic and Weibull distributions for the 1st line TTP

	Weibull			Log-logistic		
	CR	PR	NR	CR	PR	NR
TD						
scale (λ)	0.0000	0.0000	0.0131	-18.5020	-12.4622	-6.3281
shape (γ)	2.0661	1.4539	0.7672	2.4716	1.7319	1.2870
VAD (from Hovon)						
scale (λ)	0.0001	0.0000	0.0001	-11.0414	-14.2847	-11.6016
shape (γ)	1.2905	1.6287	1.3721	1.5635	2.1155	1.7286
VAD (from IFM)						
scale (λ)	0.0000	0.0000	0.0044	-20.7946	-17.9167	-6.1853
shape (γ)	2.7278	2.1730	0.7483	3.0340	2.6617	0.9193

Table 79: Parameters of the Log-logistic and Weibull distributions for the 1st line TTP

	Weibull			Log-logistic		
	CR	PR	NR	CR	PR	NR
VTD						
scale (λ)	0.0000	0.0000	0.0066	-17.7610	-12.3083	-7.3556
shape (γ)	2.0661	1.4539	0.7672	2.4716	1.7319	1.2870
PAD						
scale (λ)	0.0001	0.0000	0.0001	-11.2694	-14.8451	-11.9673
shape (γ)	1.2905	1.6287	1.3721	1.5635	2.1155	1.7286
VD						
scale (λ)	0.0000	0.0000	0.0057	-21.7970	-18.5787	-5.7154
shape (γ)	2.7278	2.1730	0.7483	3.0340	2.6617	0.9193

Number of induction regimen cycles with VTD and TD

The number of induction regimen cycles considered in the base case model was the median number of cycles reported in the PETHEMA study for both treatment arms.(71)

Based upon clinical expert opinion, the number of induction regimen cycles used in clinical practice will vary from one patient to another (between 4 and 6 cycles) and patients are likely to be assessed after 3 to 4 cycles to determine if more cycles of therapy is needed. It is estimated that on average, patients receive around 4 cycles.

Scenario analyses were conducted using 4, 5 and 6 cycles of induction therapies. All other assumptions in the model remained unchanged.

Health-state utility values

HRQoL data from a longitudinal study were incorporated into the model assumptions including start of induction therapy and post treatment utility scores.(187;194) As previously reported in section 7.4.6, alternative utility estimates are available from another longitudinal and prospective study, using the EQ-5D patient reported outcome measure, and are presented in section 7.4.9.(207) All other assumptions in the model remained unchanged.

Table 80: Health-state utility values derived from Uyl-de-Groot et al.(207)

UTILITIES	Utility value
1st line treatment	
From start treatment until post-induction response	0.52
From post-induction to post-SCT response	0.66
SCT patients	Up to 3mos=0.38
	3-6mos=0.64
	6-9mos=0.64
	9-12mos=0.64
	12-18mos=0.69
	18+mos=0.69
Non-SCT patients	Up to 3mos=0.69
	3-6mos=0.69
	6-9mos=0.69
	9-12mos=0.69
	12-18mos=0.69
	18+mos=0.69
2nd and 3rd line treatments	0.59
Further lines	0.52

SCT: stem cell transplantation

During an advisory board, clinical experts indicated that based on their clinical practice, they would expect MM patients who had undergone a SCT to recover and experience the same level of HRQoL than patients who did not receive a SCT at 6 months following the end of their therapy. A scenario analysis using amended utility values from the base case, and allowing the same level of HRQoL at 6 months after the end of their therapy for both patients groups was conducted. The utility values used in this scenario analysis are presented in Table 81.

Table 81: Health-state utility values based on expert opinion for use in scenario analysis

UTILITIES	Utility value
1st line treatment	
From start treatment until post-induction response	0.57
From post-induction to post-SCT response	0.65
SCT patients	Up to 3mos=0.59
	3-6mos=0.65
	6-9mos=0.79
	9-12mos=0.80
	12-18mos=0.81
	18+mos=0.77
Non-SCT patients	Up to 3mos=0.77
	3-6mos=0.81
	6-9mos=0.79
	9-12mos=0.80
	12-18mos=0.81
	18+mos=0.77
2nd and 3rd line treatments	0.69
Further lines	0.644

SCT: stem cell transplantation

AE-related disutility values

The base case model incorporates a utility decrement of 0.02 associated with AEs experienced during three health states/ from start of treatment until post-induction response assessment. Due to the lack of HRQoL data available to determine the precise impact of AEs in MM patients, a scenario analysis was conducted to explore the impact of a higher utility decrement associated with AEs on the economic results. A utility decrement of 0.05 was applied to each patient experiencing an adverse event with an induction therapy (see Table 82). A weighted average for each induction was then calculated to derive a disutility for each health state.

Table 82: Summary of disutility values based on a 0.05 decrement per adverse event

	Disutility values
From start treatment until post-induction response	VTD – 0.018 TD – 0.012 PAD – 0.045 VAD (Hovon) – 0.043 VD – 0.010 VAD (IFM) – 0.010

TD: thalidomide and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

Discount rates

Following the NICE method guide, outcomes and costs are to be discounted at 0% and 6% alternatively and simultaneously as part of scenario analyses.

Time horizon

The lifetime horizon of the model was reduced to 10 and 15 years.

Summary of scenario analyses

The scenario analyses are summarised in the table below.

Table 83: Summary of scenario analyses

<table>
<tr><th>Parameters</th><th>Base-case</th><th>Scenario analyses</th></tr>
<tr><td>Post-induction response rates</td><td>Pethema (section 7.3.1)</td><td>Cavo et al (2010) – GIMEMA study
<table>
<tr><th></th><th>VTD</th><th>TD</th></tr>
<tr><td>CR</td><td>62%</td><td>28%</td></tr>
<tr><td>PR</td><td>31%</td><td>51%</td></tr>
<tr><td>NR</td><td>7%</td><td>21%</td></tr>
</table></td></tr>
<tr><td>Post induction response rate</td><td>Pethema, Hovon, IFM</td><td>Use of 95% CI to test the impact of each post-induction response category.</td></tr>
<tr><td>OS by post-induction response category up to death” health-state</td><td>MRC VII (section 7.3.1)</td><td>IFM90 trial
<table>
<tr><th></th><th>Monthly probability of death</th></tr>
<tr><td>CR</td><td>0.5%</td></tr>
<tr><td>PR</td><td>1.6%</td></tr>
<tr><td>NR</td><td>10.9%</td></tr>
</table></td></tr>
<tr><td>TTP for 1st line (post-transplant / post-induction)</td><td>Pethema, Hovon, IFM (section 7.3.1)</td><td>A log-logistic distribution of TTP data will be tested.</td></tr>
</table>

Parameters	Base-case	Scenario analyses
Number of cycles with VTD and TD	Section 7.3.6	4 cycles for all inductions therapies 5 cycles for all induction therapies 6 cycles for all induction therapies
Number of cycles with PAD and VAD	Section 7.3.6	1 cycles for all patients on induction therapy 2 cycles for all patients on induction therapy 3 cycles for all patients on induction therapy
Number of cycles with VD and VAD	Section 7.3.6	2 cycles for all patients on induction therapy 3 cycles for all patients on induction therapy 4 cycles for all patients on induction therapy
Health state utility values	Van Agthoven et al.; Beusterien et al.	• Uyl-de-Groot et al.

UTILITIES	Utility value
1st line treatment	
From start treatment until post-induction response	0.52
From post-induction to post-SCT response	0.66
SCT patients	Up to 3mos=0.38
	3-6mos=0.64
	6-9mos=0.64
	9-12mos=0.64
	12-18mos=0.69
	18+mos=0.69
Non-SCT patients	Up to 3mos=0.69
	3-6mos=0.69
	6-9mos=0.69
	9-12mos=0.69
	12-18mos=0.69
	18+mos=0.69
2nd and 3rd line treatments	0.59
Further lines	0.52

- Decline in HRQoL following SCT only lasts approximately 6 months

At the advisory board, clinical experts indicated that they would expect that 'the decline in HRQoL following transplant would only last around 6 months, compared to the 24 months experienced in the Sergeren study'. Hence, the clinicians would expect that at 6-12 months, the HRQoL values in the SCT group would have improved to the same level as those who did not receive a SCT. The values for the non-SCT patients from 6 months onwards have therefore been allocated to SCT patients from 6 months onward.

UTILITIES	Utility value
1st line treatment	
From start treatment until post-induction response	0.57
From post-induction to post-SCT response	0.65
SCT patients	Up to 3mos=0.59
	3-6mos=0.65
	6-9mos=0.79
	9-12mos=0.80
	12-18mos=0.81

Parameters	Base-case	Scenario analyses		
				18+mos=0.77
			Non-SCT patients	Up to 3mos=0.77
				3-6mos=0.81
				6-9mos=0.79
				9-12mos=0.80
				12-18mos=0.81
				18+mos=0.77
			2nd and 3rd line treatments	0.69
			Further lines	0.644
AE-related disutility values	0.02 decrement (section 7.4.9.)	• 0.05 utility decrements		
Time horizon	Life time	10 years, 15 years		
Discount rate	3.5% for costs and outcomes	3.5% costs and 0% outcomes 3.5% costs and 6% outcomes 0% costs and 3.5% outcomes 6% costs and 3.5% outcomes		

AE: adverse event; CR: complete response; mos: months; NR: non responders; PR: partial response; SCT: stem cell transplantation; TD: thalidomide and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The model explores both structural and parameter uncertainty in both one-way and probabilistic sensitivity analyses. Key model drivers are tested through one-way sensitivity analyses (Table 84).

Table 84: One-way sensitivity analyses explored in the model

Parameter	Base case value	Alternate value	Rationale
Health-state costs			
Induction costs – VTD	£28,034		+/- 20%
Induction costs – TD	£8,865		+/- 20%
Induction costs – PAD	£11,356		+/- 20%
Induction costs – VAD (Hovon)	£2,331		+/- 20%
Induction costs –VD	£14,158		+/- 20%
Induction costs – VAD (IFM)	£2,783		+/- 20%
Transplant costs (all lines of therapy)	£20,511		+/- 20%
2nd line costs (all lines of therapy)	£24,440		+/- 20%
3rd line costs (all lines of therapy)	£34,271		+/- 20%
Further line costs (all lines of therapy)	£83		+/- 20%
End of life costs (all lines of therapy)	£3,627		+/- 20%
AE-related costs during induction therapy			

Parameter	Base case value	Alternate value	Rationale
- VTD	£146		+/- 20%
- TD	£145		+/- 20%
- PAD	£283		+/- 20%
- VAD (Hovon)	£271		+/- 20%
- VD	£54		+/- 20%
- VAD (IFM)	£51		+/- 20%
Utility values			
- from start of treatment to post-induction assessment	0.57	0.50-0.63	95% CI
- from post-induction assessment to post-SCT response	0.65	0.56-0.73	95% CI
SCT patients			
- up to 3 months	0.59	0.52-0.66	95% CI
- 3-6 months post SCT	0.65	0.56-0.73	95% CI
- 6-9 months post SCT	0.68	0.58-0.77	95% CI
- 9-12 months post SCT	0.62	0.54-0.70	95% CI
- 12-18 months post SCT	0.69	0.59-0.78	95% CI
- 18+ months post SCT	0.75	0.63-0.85	95% CI
Non-SCT patients			
- up to 3 months	0.77	0.64-0.88	95% CI
- 3-6 months	0.81	0.66-0.92	95% CI
- 6-9 months	0.79	0.65-0.90	95% CI
- 9-12 months	0.80	0.66-0.91	95% CI
- 12-18 months	0.81	0.66-0.92	95% CI
- 18+ months	0.77	0.64-0.88	95% CI
- 2nd and 3rd line treatments	0.69	0.59-0.78	95% CI
- Further lines treatment	0.65	0.56-0.73	95% CI
AE-related dis-utilities during induction therapy			
- VTD	0.007		95% CI
- TD	0.005		95% CI
- PAD	0.018		95% CI
- VAD (Hovon)	0.017		95% CI
- VD	0.004		95% CI
- VAD (IFM)	0.004		95% CI

AE: adverse event; CR: complete response; NR: non responders; PR: partial response; SCT: stem cell transplantation; TD: thalidomide and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A probabilistic sensitivity analysis (PSA) has been undertaken to account for multivariate and stochastic uncertainty in the model. The uncertainty in the individual parameters was characterised using probabilistic distributions and analysed using Monte Carlo simulation (10,000 iterations) in which the parameters are all varied

simultaneously. The parameters varied and the probability distributions used are presented in section 7.3.6.

Table 85: Probabilistic sensitivity analysis parameters and distributions

Parameter	Distribution
TRANSITION PROBABILITIES	
Clinical Data	
Post-induction response rate by induction treatment group TD (PETHEMA), VAD (Hovon and IFM)	Beta
Post-induction response rate by induction treatment group VTD PAD, VD	Beta
Post-induction response rate by induction treatment group TD: GIMEMA Study	Beta
Post-induction response rate by induction treatment group VTD: GIMEMA Study	Beta
Patients who receive stem cell transplant	Beta
Mortality Data	
Induction phase -	Beta
Transplant -	Beta
Post-induction phase (by post-induction response)	Beta
Transition Probabilities calculations – 2nd line	
TTP during post-induction period - CR	Lognormal
TTP during post-induction period - PR	Lognormal
TTP during post-induction period - NR	Lognormal
Transition probabilities to 3rd & further line treatments	
TP to 3rd line treatments - APEX study	Lognormal
TP to further line treatments - APEX study	Lognormal
POST-INDUCTION RESPONSE RATES	
- VTD, PAD, VD	
CR	Beta
PR	Beta
NR	Beta
- TD, VAD (Hovon, IFM)	
CR	Beta
PR	Beta
NR	Beta
SCT RATES	
- VTD, PAD, VD	
CR	Beta
PR	Beta
NR	Beta
- TD, VAD (Hovon, IFM)	
CR	Beta
PR	Beta
NR	Beta
UTILITIES	
- from start of treatment to post-induction assessment	Beta
- From post-induction assessment to post-SCT response	Beta
- up to 3 months post SCT	Beta
SCT patients	Beta
- 3-6 months post SCT	Beta
- 6-9 months post SCT	Beta
- 9-12 months post SCT	Beta

- 12-18 months post SCT	Beta
- 18+ months post SCT **Non-SCT patients** - 3-6 months - 6-9 months - 9-12 months - 12-18 months	Beta Beta Beta Beta Beta
- 18+ months - 2nd and 3rd line treatments	Beta Beta
- Further lines treatment ***AE-RELATED DISUTILITIES during induction*** - VTD, PAD, VD	Beta Beta
- TD, VAD (Hovon, IFM) *AE-RELATED COSTS during induction* - VTD, PAD, VD	Beta Gamma
- TD, VAD (Hovon, IFM) ***HEALTH STATE COSTS*** Induction costs – VTD, PAD, VD Induction costs – TD, VD (Hovon, IFM) Transplant costs 2nd line costs 3rd line costs Further line costs	Gamma Gamma Gamma Gamma Gamma Gamma Gamma

Legend: AE: adverse event; CR: complete response; NR: non responders; PR: partial response; SCT: stem cell transplantation; TD: thalidomide and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

7.7 Results

Clinical outcomes from the model

7.7.1 **For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

Clinical plausibility/external validity of our results

In order to explore the clinical plausibility of the extrapolated portions of the model, we searched the literature to obtain 1) any clinical trial data in a similar patient group with longer follow-up; and 2) long-term registry data for MM patients. Only data involving patients eligible to receive a single transplant, as per the scope of this submission, were included. The following results were obtained, displayed in Table 86 below.

Table 86: Long-term survival data in multiple myeloma undergoing single transplantation

Source of evidence	Description of evidence	Long-term OS (by response category if available)	Comparison to model results
Follow-up of IFM90 trial (Barlogie et al., 2010)	10-year follow-up OS data was reported for the landmark IFM90 trial	At 10 years of follow-up, 160/194 (82%) of all patients (both the transplant and conventional chemotherapy arms) had died.	At year 10, 75% and 85% of patients in VTD and TD arm, respectively, are predicted to have died.
Follow-up of MRC VII trial (Child et al., 2003)	5-year follow-up OS data by response status was reported for the UK-based MRC VII trial	At 5 years of follow-up, median OS was reported by response as follows: CR: 88.6 months PR: 39.8 months MR: 25.6 months	Median post-induction OS by response is predicted to be as follows: CR: 88.1 months PR: 40.1 months NR: 26.0 months
British Society of Blood and Marrow Transplantation (BSBMT) registry (Cook et al., 2011)	Analysis of UK transplantation registry data; patients with MM who underwent a single autologous SCT; 9-year OS data by response status at SCT was reported	At 9 years of follow-up, OS was reported by response as follows: CR: 35% [95% CI: 21-50%] PR: 35% [95% CI: 26-44%] MR/SD/PD: 23% [95% CI: 10-39%]	At year 9, post-induction OS is predicted to be as follows: CR: 43% PR: 15% NR: 5%

BSBMT=British Society of Blood and Marrow Transplantation; CR=complete response; MR=minimal/minor response; MRC=Medical Research Council; OS=overall survival; PD= progressive disease; PR=partial response; SCT=stem cell transplantation; SD=stable disease

As demonstrated in Table 86 above, the OS estimates calculated by our model appear to be consistent with the long-term OS data from the prospective clinical trials, such as the MRC VII and the IFM90 studies.

As discussed in Section 7.6.1, the 5-year OS data from the IFM90 study (196) were included as a scenario analysis to investigate the impact of long-term OS on the ICER. Note that we could not use the 10-yr OS data from this trial (reported in Barlogie et al., 2010, as per Table 17 above), as it was not reported by response category. However, our model predicts that between 75% and 85% of patients have died by year 10 when using the 5-year OS data from the Attal et al (1996) paper in the scenario analysis. This is consistent with the 82% of patients that we know have died by year 10. This provides our model with external validity.

Cook et al (2011) reported the long-term OS rates of patients undergoing autologous SCT in the UK, which reported OS at 9 years post-transplant. As these results were derived from a retrospective transplant registry, and only included patients that actually received a transplant (thereby overestimating the survival of those patients that were eligible but never received a transplant), we chose not to use these data in our modeled evaluation.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The full Markov traces for all treatments (denoted with ○) in the following comparisons (denoted with ●) are presented in separate spreadsheets within the economic model. Table 87 and Table 88 below provide the first 20 rows of the Markov trace for VTD and TD, PAD and VAD, and VD and VAD.

- VTD vs. TD
  - VTD (PETHEMA)
  - TD (PETHEMA)

Table 87: 20 first rows of the Markov trace

VTD											
Month	Induction period	With SCT					Without SCT				Death
		SCT period	PFS post-SCT	2nd line	3rd line	Further line	PFS post-induction	2nd line	3rd line	Further line	
1	1.00										0.00
2	0.99										0.01
3	0.99										0.01
4	0.98										0.02
5	0.97										0.03
6	0.97										0.03
7	0.00	0.78					0.16	0.03			0.04
8	0.00	0.77					0.15	0.03			0.04
9	0.00	0.77					0.15	0.03	0.00		0.05
10	0.00	0.00	0.77				0.15	0.03	0.01		0.05

11	0.00	0.00	0.75	0.01			0.14	0.03	0.01	0.00	0.07
12	0.00	0.00	0.72	0.03			0.14	0.02	0.01	0.00	0.08
13	0.00	0.00	0.70	0.04	0.00		0.14	0.02	0.01	0.00	0.09
14	0.00	0.00	0.68	0.04	0.00		0.13	0.02	0.01	0.00	0.10
15	0.00	0.00	0.66	0.05	0.01	0.00	0.13	0.02	0.01	0.00	0.12
16	0.00	0.00	0.64	0.06	0.01	0.00	0.13	0.02	0.01	0.00	0.13
17	0.00	0.00	0.62	0.06	0.01	0.00	0.12	0.02	0.01	0.01	0.14
18	0.00	0.00	0.60	0.06	0.02	0.00	0.12	0.02	0.01	0.01	0.15
19	0.00	0.00	0.59	0.07	0.02	0.00	0.12	0.02	0.01	0.01	0.16
20	0.00	0.00	0.57	0.07	0.02	0.01	0.11	0.02	0.01	0.01	0.18

PAD

Month	Induction period	With SCT					Without SCT				Death
		SCT period	PFS post-SCT	2nd line	3rd line	Further line	PFS post-induction	2nd line	3rd line	Further line	
1	1.00										0.00
2	0.98										0.02
3	0.97										0.03
4	0.00	0.81					0.12	0.02			0.05
5	0.00	0.81					0.12	0.02			0.05
6	0.00	0.80					0.11	0.02	0.00		0.06
7	0.00	0.00	0.80				0.11	0.02	0.00		0.06
8	0.00	0.00	0.78	0.01			0.11	0.02	0.01	0.00	0.08
9	0.00	0.00	0.75	0.03			0.11	0.02	0.01	0.00	0.09
10	0.00	0.00	0.73	0.04	0.00		0.10	0.02	0.01	0.00	0.10
11	0.00	0.00	0.71	0.04	0.00		0.10	0.02	0.01	0.00	0.11
12	0.00	0.00	0.69	0.05	0.01	0.00	0.10	0.02	0.01	0.00	0.13
13	0.00	0.00	0.67	0.06	0.01	0.00	0.09	0.02	0.01	0.00	0.14
14	0.00	0.00	0.65	0.06	0.01	0.00	0.09	0.02	0.01	0.00	0.15
15	0.00	0.00	0.63	0.07	0.02	0.00	0.09	0.02	0.01	0.01	0.16
16	0.00	0.00	0.61	0.07	0.02	0.00	0.09	0.02	0.01	0.01	0.17
17	0.00	0.00	0.59	0.07	0.03	0.01	0.09	0.02	0.01	0.01	0.18
18	0.00	0.00	0.57	0.07	0.03	0.01	0.08	0.02	0.01	0.01	0.19
19	0.00	0.00	0.56	0.08	0.03	0.01	0.08	0.02	0.01	0.01	0.21
20	0.00	0.00	0.54	0.08	0.04	0.01	0.08	0.01	0.01	0.01	0.22

VD

Month	Induction period	With SCT				Without SCT					Death
		SCT period	PFS post-SCT	2nd line	3rd line	Further line	PFS post-induction	2nd line	3rd line	Further line	
1	1.00										0.00
2	1.00										0.00

3	1.00										0.00
4	0.99										0.01
5	0.00	0.87					0.10	0.03			0.01
6	0.00	0.87					0.09	0.03			0.01
7	0.00	0.87					0.09	0.03	0.00		0.02
8	0.00	0.00	0.86				0.09	0.02	0.01		0.02
9	0.00	0.00	0.84	0.01			0.09	0.02	0.01	0.00	0.03
10	0.00	0.00	0.81	0.03			0.08	0.02	0.01	0.00	0.05
11	0.00	0.00	0.78	0.04	0.00		0.08	0.02	0.01	0.00	0.06
12	0.00	0.00	0.76	0.05	0.00		0.08	0.02	0.01	0.00	0.08
13	0.00	0.00	0.73	0.06	0.01	0.00	0.08	0.02	0.01	0.00	0.09
14	0.00	0.00	0.71	0.06	0.01	0.00	0.08	0.02	0.01	0.00	0.11
15	0.00	0.00	0.69	0.07	0.02	0.00	0.07	0.02	0.01	0.01	0.12
16	0.00	0.00	0.67	0.07	0.02	0.00	0.07	0.01	0.01	0.01	0.13
17	0.00	0.00	0.65	0.08	0.02	0.00	0.07	0.01	0.01	0.01	0.15
18	0.00	0.00	0.63	0.08	0.03	0.01	0.07	0.01	0.01	0.01	0.16
19	0.00	0.00	0.61	0.08	0.03	0.01	0.07	0.01	0.01	0.01	0.17
20	0.00	0.00	0.59	0.08	0.04	0.01	0.07	0.01	0.01	0.01	0.18

Table 88: 20 first rows of the Markov trace

TD											
Month	Induction period	With SCT					Without SCT				Death
		SCT period	PFS post-SCT	2nd line	3rd line	Further line	PFS post-induction	2nd line	3rd line	Further line	
1	1.00										0.00
2	0.99										0.01
3	0.98										0.02
4	0.98										0.02
5	0.97										0.03
6	0.96										0.04
7	0.00	0.58					0.23	0.14			0.05
8	0.00	0.58					0.22	0.14			0.05
9	0.00	0.58					0.21	0.13	0.01		0.06
10	0.00	0.00	0.58				0.21	0.11	0.03		0.07
11	0.00	0.00	0.55	0.02			0.20	0.10	0.03	0.00	0.09
12	0.00	0.00	0.52	0.05			0.20	0.09	0.04	0.00	0.10
13	0.00	0.00	0.49	0.06	0.00		0.19	0.08	0.04	0.01	0.12
14	0.00	0.00	0.46	0.08	0.01		0.19	0.07	0.05	0.01	0.14
15	0.00	0.00	0.44	0.08	0.01	0.00	0.18	0.07	0.05	0.02	0.15
16	0.00	0.00	0.41	0.09	0.02	0.00	0.18	0.06	0.05	0.02	0.17
17	0.00	0.00	0.39	0.09	0.02	0.00	0.17	0.06	0.05	0.02	0.19

18	0.00	0.00	0.37	0.10	0.03	0.00	0.17	0.05	0.05	0.03	0.20
19	0.00	0.00	0.36	0.10	0.03	0.01	0.16	0.05	0.05	0.03	0.22
20	0.00	0.00	0.34	0.09	0.04	0.01	0.16	0.04	0.05	0.04	0.23
VAD (Hovon)											
Month	**Induction period**	**With SCT**					**Without SCT**				
		SCT period	**PFS post-SCT**	**2nd line**	**3rd line**	**Further line**	**PFS post-induction**	**2nd line**	**3rd line**	**Further line**	**Death**
1	1.00										0.00
2	0.98										0.02
3	0.96										0.04
4	0.00	0.79					0.09	0.06			0.06
5	0.00	0.79					0.09	0.06			0.06
6	0.00	0.78					0.09	0.05	0.01		0.07
7	0.00	0.00	0.78				0.08	0.05	0.01		0.07
8	0.00	0.00	0.75	0.02			0.08	0.05	0.01	0.00	0.09
9	0.00	0.00	0.72	0.03			0.08	0.04	0.02	0.00	0.11
10	0.00	0.00	0.69	0.05	0.00		0.08	0.04	0.02	0.00	0.12
11	0.00	0.00	0.66	0.06	0.00		0.07	0.04	0.02	0.00	0.14
12	0.00	0.00	0.63	0.07	0.01	0.00	0.07	0.03	0.02	0.01	0.16
13	0.00	0.00	0.61	0.07	0.01	0.00	0.07	0.03	0.02	0.01	0.17
14	0.00	0.00	0.58	0.08	0.02	0.00	0.07	0.03	0.02	0.01	0.19
15	0.00	0.00	0.56	0.09	0.02	0.00	0.06	0.03	0.02	0.01	0.20
16	0.00	0.00	0.54	0.09	0.03	0.00	0.06	0.02	0.02	0.01	0.22
17	0.00	0.00	0.52	0.09	0.03	0.01	0.06	0.02	0.02	0.02	0.23
18	0.00	0.00	0.49	0.09	0.04	0.01	0.06	0.02	0.02	0.02	0.25
19	0.00	0.00	0.48	0.09	0.04	0.01	0.06	0.02	0.02	0.02	0.26
20	0.00	0.00	0.46	0.09	0.04	0.02	0.05	0.02	0.02	0.02	0.27
VAD (IFM)											
Month	**Induction period**	**With SCT**					**Without SCT**				**Death**
		SCT period	**PFS post-SCT**	**2nd line**	**3rd line**	**Further line**	**PFS post-induction**	**2nd line**	**3rd line**	**Further line**	
1	1.00										0.00
2	0.99										0.01
3	0.98										0.02
4	0.97										0.03
5	0.00	0.80					0.10	0.07			0.04
6	0.00	0.79					0.10	0.07			0.04
7	0.00	0.79					0.09	0.06	0.01		0.05
8	0.00	0.00	0.79				0.09	0.06	0.01		0.05
9	0.00	0.00	0.76	0.02			0.09	0.05	0.02	0.00	0.07

10	0.00	0.00	0.72	0.03			0.08	0.05	0.02	0.00	0.09
11	0.00	0.00	0.69	0.05	0.00		0.08	0.04	0.02	0.00	0.11
12	0.00	0.00	0.66	0.06	0.00		0.08	0.04	0.02	0.01	0.12
13	0.00	0.00	0.64	0.07	0.01	0.00	0.07	0.04	0.02	0.01	0.14
14	0.00	0.00	0.61	0.08	0.01	0.00	0.07	0.03	0.02	0.01	0.16
15	0.00	0.00	0.58	0.08	0.02	0.00	0.07	0.03	0.03	0.01	0.17
16	0.00	0.00	0.56	0.09	0.02	0.00	0.07	0.03	0.02	0.01	0.19
17	0.00	0.00	0.54	0.09	0.03	0.01	0.06	0.03	0.02	0.02	0.21
18	0.00	0.00	0.51	0.09	0.03	0.01	0.06	0.03	0.02	0.02	0.22
19	0.00	0.00	0.49	0.10	0.04	0.01	0.06	0.02	0.02	0.02	0.24
20	0.00	0.00	0.47	0.10	0.04	0.01	0.06	0.02	0.02	0.02	0.25

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

In the state transition model, the QALYs are calculated as the number of patients in each health state at the end of each cycle multiplied by the utility value associated with the respective health state. The model also considered adverse events, the incidence of which was obtained from the patient level data of the clinical trials. The average disutility value was calculated by taking the sum product of the incidences and the corresponding disutility value for each AE. This value was then multiplied by the number of patients that enter that health state in that cycle to obtain the disutility associated with the AEs in each health state. This disutility was then substracted from the QALYs in that cycle.

Cumulative QALYs are accrued through each subsequent cycle and health state of the model for each intervention.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 89: Model outputs by clinical outcomes (discounted)

	LY	QALY	Cost (£)	LY	QALY	Cost (£)
Outcome	**VTD**			**TD**		
Induction treatment	0.49	0.28	£25,784	0.49	0.28	£7,320
Stem cell transplant	0.19	0.12	£15,528	0.14	0.09	£11,725
Post-induction PPT	2.69	1.96	£2,668	1.92	1.41	£1,902
Post-progression survival	2.58	1.65	£28,835	2.02	1.28	£28,467
Overall survival	5.95	4.00	£72,815	4.57	3.06	£49,414
Outcome	**PAD**			**VAD**		
Induction treatment	0.24	0.14	£10,669	0.24	0.14	£2,190
Stem cell transplant	0.20	0.13	£16,302	0.19	0.13	£15,916
Post-induction PPT	2.49	1.80	£2,473	1.75	1.24	£1,737
Post-progression survival	2.78	1.78	£30,187	2.22	1.41	£29,515

	LY	QALY	Cost (£)	LY	QALY	Cost (£)
Overall survival	5.72	3.84	£59,632	4.41	2.91	£49,359
Outcome	**VD**			**VAD**		
Induction treatment	0.33	0.19	£13,669	0.33	0.19	£2,536
Stem cell transplant	0.21	0.14	£17,488	0.20	0.13	£16,010
Post-induction PPT	2.64	1.90	£2,616	1.71	1.21	£1,700
Post-progression survival	2.46	1.57	£29,101	2.19	1.39	£29,918
Overall survival	5.64	3.79	£62,874	4.42	2.91	£50,163

LY, life years; QALY, quality-adjusted life year; TD: thalidomide and dexamethasone; TTP: time to progression; VTD: Velcade® (bortezomib), thalidomide and dexamethasone, PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 90: Summary of QALY gain by health state

Heath state	QALY VTD	QALY TD	Increment	Absolute increment	% absolute increment
Induction period	0.27	0.27	-0.00	0.00	0.0%
SCT period	0.12	0.09	+0.03	0.03	3.1%
Post-induction PFS	1.96	1.41	+0.55	0.55	55.8%
2nd line	0.22	0.24	-0.01	0.01	1.5%
3rd line	0.17	0.17	-0.00	0.00	0.5%
Further line	1.25	0.87	+0.39	0.39	39.2%
Total	4.00	3.06	+0.95	0.99	100.0%
Heath state	**QALY PAD**	**QALY VAD**	**Increment**	**Absolute increment**	**% absolute increment**
Induction period	0.14	0.13	+0.00	0.00	0.0%
SCT period	0.13	0.13	+0.00	0.00	0.3%
Post-induction PFS	1.80	1.24	+0.56	0.56	60.2%
2nd line	0.23	0.23	-0.00	0.00	0.0%
3rd line	0.18	0.17	+0.01	0.01	0.6%
Further line	1.36	1.00	+0.36	0.36	38.7%
Total	3.84	2.91	+0.93	0.93	100.0%
Heath state	**QALY VD**	**QALY VAD**	**Increment**	**Absolute increment**	**% absolute increment**
Induction period	0.19	0.18	+0.00	0.00	0.2%
SCT period	0.14	0.13	+0.01	0.01	1.3%
Post-induction PFS	1.90	1.21	+0.69	0.69	75.0%
2nd line	0.23	0.24	-0.01	0.01	1.4%
3rd line	0.17	0.17	-0.01	0.01	0.6%
Further line	1.17	0.98	+0.20	0.20	21.5%
Total	3.79	2.91	+0.88	0.92	100.0%

PFS, progression free survival; QALY, quality-adjusted life year; SCT, stem cell transplant ; TD, thalidomide and dexamethasone; VTD, Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin,

dexamethasone; VD: Velcade® (bortezomib), dexamethasone

Table 91: Summary of costs by health state

Heath state	Cost VTD	Cost TD	Increment	Absolute increment	% absolute increment
Induction period	£25,784	£7,320	+£18,464	£18,464	71.5%
SCT period	£15,528	£11,725	+£3,803	£3,803	14.7%
Post-induction PFS	£2,668	£1,902	+£765	£765	3.0%
2nd line	£10,669	£9,679	+£990	£990	3.8%
3rd line	£13,400	£14,419	-£1,020	£1,020	3.9%
Further line	£1,931	£1,335	+£596	£596	2.3%
End of life	£2,836	£3,033	-£197	£197	0.8%
Total	£72,815	£49,414	+£23,401	£25,835	100.0%
Heath state	**Cost PAD**	**Cost VAD**	**Increment**	**Absolute increment**	**% absolute increment**
Induction period	£10,669	£2,190	+£8,479	£8,479	79.6%
SCT period	£16,302	£15,916	+£387	£387	3.6%
Post-induction PFS	£2,473	£1,737	+£736	£736	6.9%
2nd line	£11,218	£10,922	+£296	£296	2.8%
3rd line	£14,004	£13,996	+£8	£8	0.1%
Further line	£2,100	£1,545	+£555	£555	5.2%
End of life	£2,865	£3,052	-£187	£187	1.8%
Total	£59,632	£49,359	+£10,274	£10,648	100.0%
Heath state	**Cost VD**	**Cost VAD**	**Increment**	**Absolute increment**	**% absolute increment**
Induction period	£13,669	£2,536	+£11,134	£11,134	74.5%
SCT period	£17,488	£16,010	+£1,478	£1,478	9.9%
Post-induction PFS	£2,616	£1,700	+£916	£916	6.1%
2nd line	£10,919	£11,072	-£153	£153	1.0%
3rd line	£13,497	£14,292	-£795	£795	5.3%
Further line	£1,804	£1,501	+£303	£303	2.0%
End of life	£2,880	£3,052	-£172	£172	1.2%
Total	£62,874	£50,163	+£12,710	£14,950	100.0%

PFS, progression free survival; QALY, quality-adjusted life year; SCT, stem cell transplant ; TD, thalidomide and dexamethasone; VTD, Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

Table 92: Summary of predicted resource use by category of cost

Heath state	Cost VTD	Cost TD	Increment	Absolute increment	% absolute increment
Induction - chemo drug	£22,966	£5,493	+£17,473	£17,473	67.6%
Induction - prophylaxis	£327	£251	+£76	£76	0.3%
Induction -	£2,492	£1,576	+£915	£915	3.5%

monitoring					
SCT - mobilisation	£1,038	£784	+£254	£254	1.0%
SCT - ablation	£342	£258	+£84	£84	0.3%
SCT - transplant	£13,486	£10,183	+£3,303	£3,303	12.8%
SCT - post-transplant	£663	£501	+£162	£162	0.6%
Post-induction PFS	£2,668	£1,902	+£765	£765	3.0%
2nd line - VD	£8,535	£7,743	+£792	£792	3.1%
2nd line - CTDa	£1,600	£1,452	+£148	£148	0.6%
2nd line - HDD	£533	£484	+£49	£49	0.2%
3rd line - RD	£10,050	£10,815	-£765	£765	3.0%
3rd line - CTD	£2,680	£2,884	-£204	£204	0.8%
3rd line - HDD	£670	£721	-£51	£51	0.2%
Further line	£1,931	£1,335	+£596	£596	2.3%
End of life	£2,836	£3,033	-£197	£197	0.8%
Total	£72,815	£49,414	+£23,401	£25,835	100.0%
Heath state	**Cost PAD**	**Cost VAD**	**Increment**	**Absolute increment**	**% absolute increment**
Induction - chemo drug	£9,338	£750	+£8,588	£8,588	78.7%
Induction - prophylaxis	£78	£57	+£21	£21	0.2%
Induction - monitoring	£1,254	£1,384	-£130	£130	1.2%
SCT - mobilisation	£1,089	£1,064	+£26	£26	0.2%
SCT - ablation	£359	£350	+£9	£9	0.1%
SCT - transplant	£14,158	£13,822	+£336	£336	3.1%
SCT - post-transplant	£696	£679	+£17	£17	0.2%
Post-induction PFS	£2,473	£1,737	+£736	£736	6.7%
2nd line - VD	£8,974	£8,738	+£237	£237	2.2%
2nd line - CTDa	£1,683	£1,638	+£44	£44	0.4%
2nd line - HDD	£561	£546	+£15	£15	0.1%
3rd line - RD	£10,503	£10,497	+£6	£6	0.1%
3rd line - CTD	£2,801	£2,799	+£2	£2	0.0%
3rd line - HDD	£700	£700	+£0	£0	0.0%
Further line	£2,100	£1,545	+£555	£555	5.1%
End of life	£2,865	£3,052	-£187	£187	1.7%
Total	£59,632	£49,359	+£10,274	£10,908	100.0%
Heath state	**Cost VD**	**Cost VAD**	**Increment**	**Absolute increment**	**% absolute increment**
Induction - chemo drug	£11,883	£834	+£11,049	£11,049	73.9%
Induction - prophylaxis	£78	£66	+£12	£12	0.1%
Induction - monitoring	£1,708	£1,636	+£72	£72	0.5%
SCT - mobilisation	£1,169	£1,070	+£99	£99	0.7%
SCT - ablation	£385	£352	+£33	£33	0.2%
SCT - transplant	£15,187	£13,904	+£1,283	£1,283	8.6%
SCT - post-transplant	£747	£683	+£63	£63	0.4%
Post-induction PFS	£2,616	£1,700	+£916	£916	6.1%
2nd line - VD	£8,735	£8,857	-£122	£122	0.8%
2nd line - CTDa	£1,638	£1,661	-£23	£23	0.2%

2nd line - HDD	£546	£554	-£8	£8	0.1%
3rd line - RD	£10,123	£10,719	-£596	£596	4.0%
3rd line - CTD	£2,699	£2,858	-£159	£159	1.1%
3rd line - HDD	£675	£715	-£40	£40	0.3%
Further line	£1,804	£1,501	+£303	£303	2.0%
End of life	£2,880	£3,052	-£172	£172	1.2%
Total	£62,874	£50,163	+£12,710	£14,950	100.0%

PFS, progression free survival; QALY, quality-adjusted life year; SCT, stem cell transplant ; TD, thalidomide and dexamethasone; VTD, Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

Base-case analysis

7.7.6 **Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.**

Base case results from the modelled evaluation are presented in Table 93 below.

Table 93: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) incre-mental (QALYs)
VTD	£72,815	5.95	4.00	+£23,401	+1.38	+0.95	£24,683
TD	£49,414	4.57	3.06				
VAD (Hovon)	£49,359	4.41	2.91	+£10,274	1.31	0.93	£11,041
PAD	£59,632	5.72	3.84				
VAD (IFM	£50,163	4.42	2.91	+£12,710	1.22	0.88	£14,446
VD	£62,874	5.64	3.79				

Sensitivity analyses

7.7.7 **Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.**

The results of the deterministic sensitivity analysis detail the influence of the parameters across their ranges on the incremental cost-effectiveness ratio. In all instances the ICER remains below approximately £36,000/QALY. Figure 25 plots all the deterministic sensitivity analysis results, with the most sensitive parameters reported in

VD vs. VAD

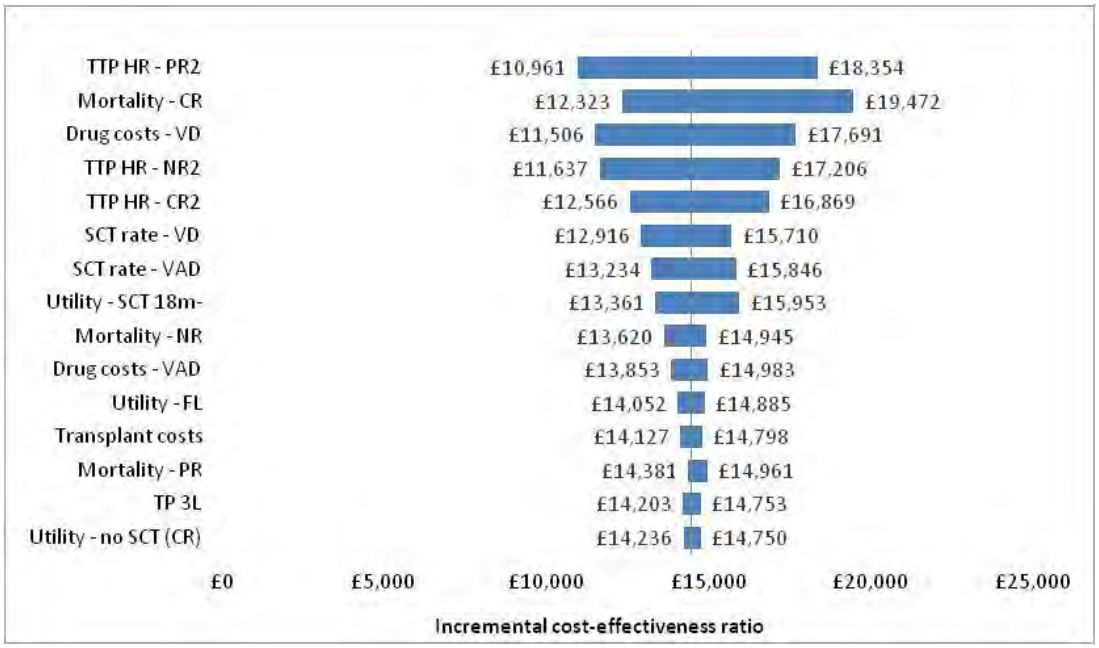
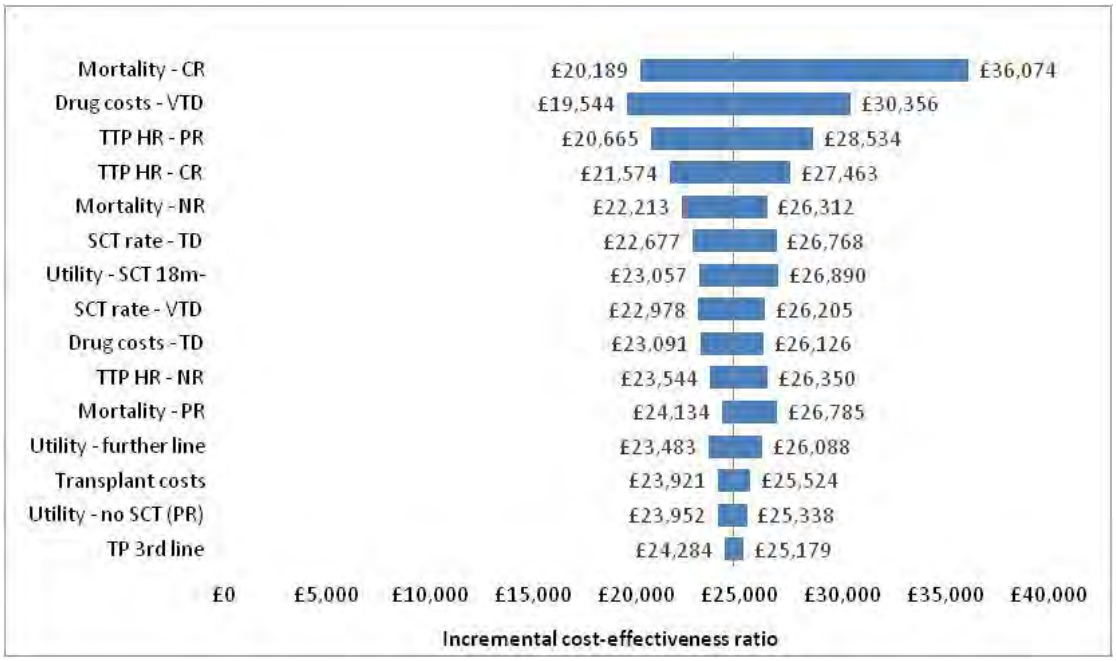


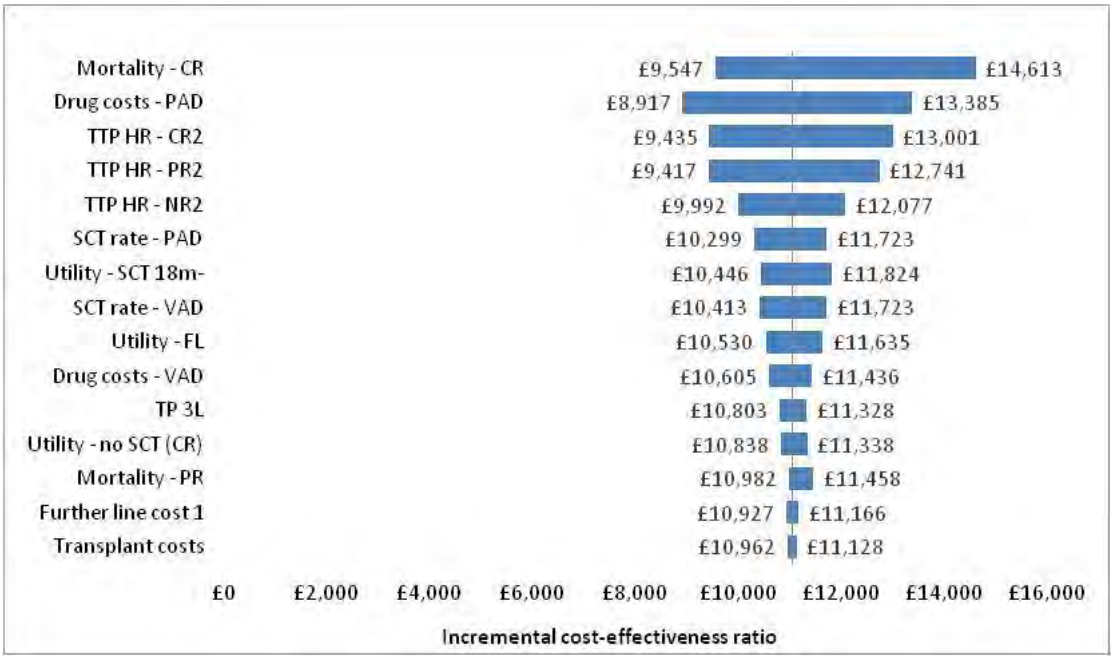
Table 94.

Figure 25: Tornado diagrams

VTD vs. TD



PAD vs. VAD



VD vs. VAD

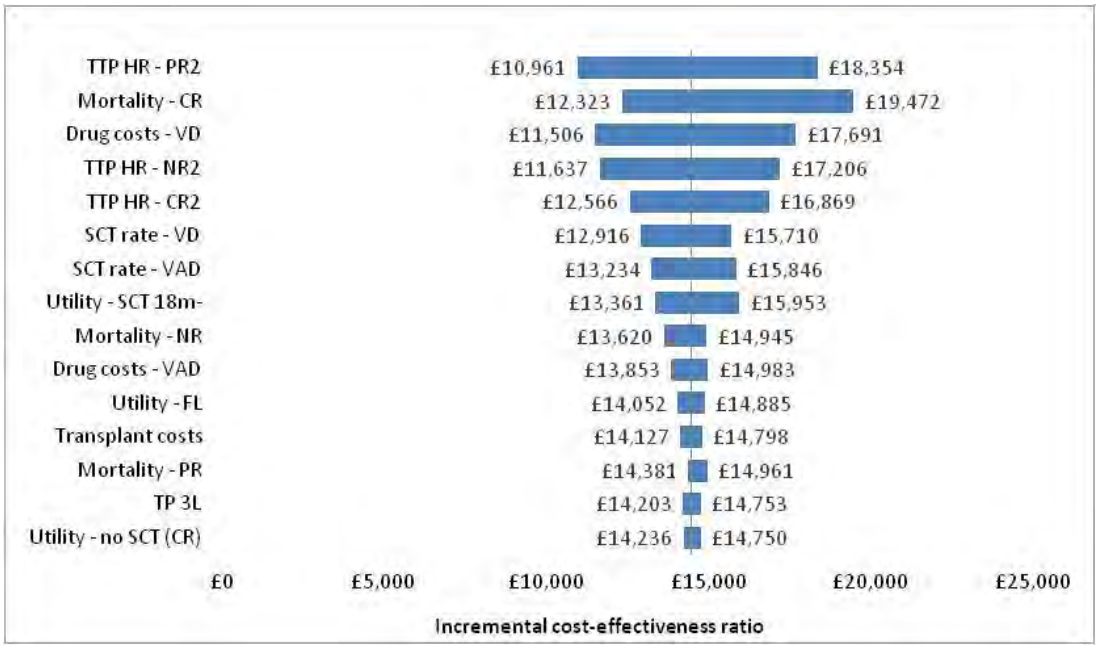


Table 94: Deterministic sensitivity analysis results for most sensitive parameters

Parameter	Lower input	Base case	Higher input	Lower input ICER	Higher input ICER	Difference
VTD vs. TD						
Mortality - CR	0.6%	0.8%	1.1%	£20,189	£36,074	£15,885
Drug costs - VTD	£22,591	£27,889	£33,736	£19,544	£30,356	£10,812
TTP HR - PR	0.538	1.007	1.886	£20,665	£28,534	£7,869
TTP HR - CR	0.609	1.615	4.282	£21,574	£27,463	£5,889
Mortality - NR	2.2%	2.7%	9.4%	£26,312	£22,213	£4,099
SCT rate - TD	52.8%	61.4%	69.7%	£26,768	£22,677	£4,091
Utility - SCT 18m-	0.630	0.750	0.853	£26,890	£23,057	£3,833
SCT rate - VTD	73.6%	80.8%	87.0%	£22,978	£26,205	£3,228
Mortality - CR	0.6%	0.8%	1.1%	£26,126	£23,091	£3,035
Drug costs - TD	£7,064	£8,720	£10,548	£26,126	£23,091	£3,035
TTP HR - NR	0.230	0.441	0.845	£23,544	£26,350	£2,806
Mortality - PR	1.1%	1.7%	2.0%	£26,785	£24,134	£2,652
Utility - further line	0.559	0.644	0.725	£26,088	£23,483	£2,605
Transplant costs	£16,615	£20,511	£24,811	£23,921	£25,524	£1,603
Utility - no SCT (PR)	0.636	0.760	0.865	£23,952	£25,338	£1,386
TP 3rd line	6.2%	10.2%	16.5%	£25,179	£24,284	£895
PAD vs. VAD						
Mortality - CR	0.6%	0.8%	1.1%	£9,547	£14,613	£5,065
Drug costs - PAD	£8,970	£11,074	£13,396	£8,917	£13,385	£4,468
TTP HR - PR	0.576	0.774	1.039	£9,435	£13,001	£3,566
TTP HR - CR	0.431	0.811	1.524	£9,417	£12,741	£3,325
Mortality - NR	2.2%	2.7%	9.4%	£9,992	£12,077	£2,085
SCT rate - VAD	80.0%	83.7%	87.0%	£10,299	£11,723	£1,424
Utility - SCT 18m-	0.630	0.750	0.853	£11,824	£10,446	£1,378

SCT rate - PAD	81.3%	84.9%	88.2%	£11,723	£10,413	£1,311
Drug costs - VAD	£1,668	£2,060	£2,491	£11,635	£10,530	£1,106
TTP HR - NR	0.640	0.830	1.076	£11,436	£10,605	£831
Mortality - PR	1.1%	1.7%	2.0%	£11,328	£10,803	£525
Utility - further line	0.559	0.644	0.725	£11,338	£10,838	£500
Transplant costs	£16,615	£20,511	£24,811	£11,458	£10,982	£477
Utility - no SCT (PR)	0.636	0.760	0.865	£10,927	£11,166	£238
TP 3rd line	6.2%	10.2%	16.5%	£10,962	£11,128	£166
VD vs. VAD						
Mortality - CR	0.6%	0.8%	1.1%	£10,961	£18,354	£7,394
Drug costs - VD	£11,425	£14,104	£17,061	£12,323	£19,472	£7,149
TTP HR - PR	0.354	0.631	1.125	£11,506	£17,691	£6,185
TTP HR - CR	0.272	0.636	1.486	£11,637	£17,206	£5,569
Mortality - NR	2.2%	2.7%	9.4%	£12,566	£16,869	£4,303
SCT rate - VAD	75.4%	82.6%	88.8%	£12,916	£15,710	£2,794
Utility - SCT 18m-	0.630	0.750	0.853	£15,846	£13,234	£2,612
SCT rate - VD	81.2%	87.6%	92.9%	£15,953	£13,361	£2,591
Drug costs - VAD	£2,213	£2,732	£3,305	£14,945	£13,620	£1,324
TTP HR - NR	0.699	1.309	2.451	£14,983	£13,853	£1,130
Mortality - PR	1.1%	1.7%	2.0%	£14,885	£14,052	£834
Utility - further line	0.559	0.644	0.725	£14,127	£14,798	£671
Transplant costs	£16,615	£20,511	£24,811	£14,961	£14,381	£580
Utility - no SCT (PR)	0.636	0.760	0.865	£14,753	£14,203	£551
TP 3rd line	6.2%	10.2%	16.5%	£14,750	£14,236	£514

CR, complete remission; HR, hazard ratio; NR, no response (less than PR); PR, partial response; SCT, stem cell transplant; TD, thalidomide and dexamethasone; TP, transition probabilities; VTD, Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

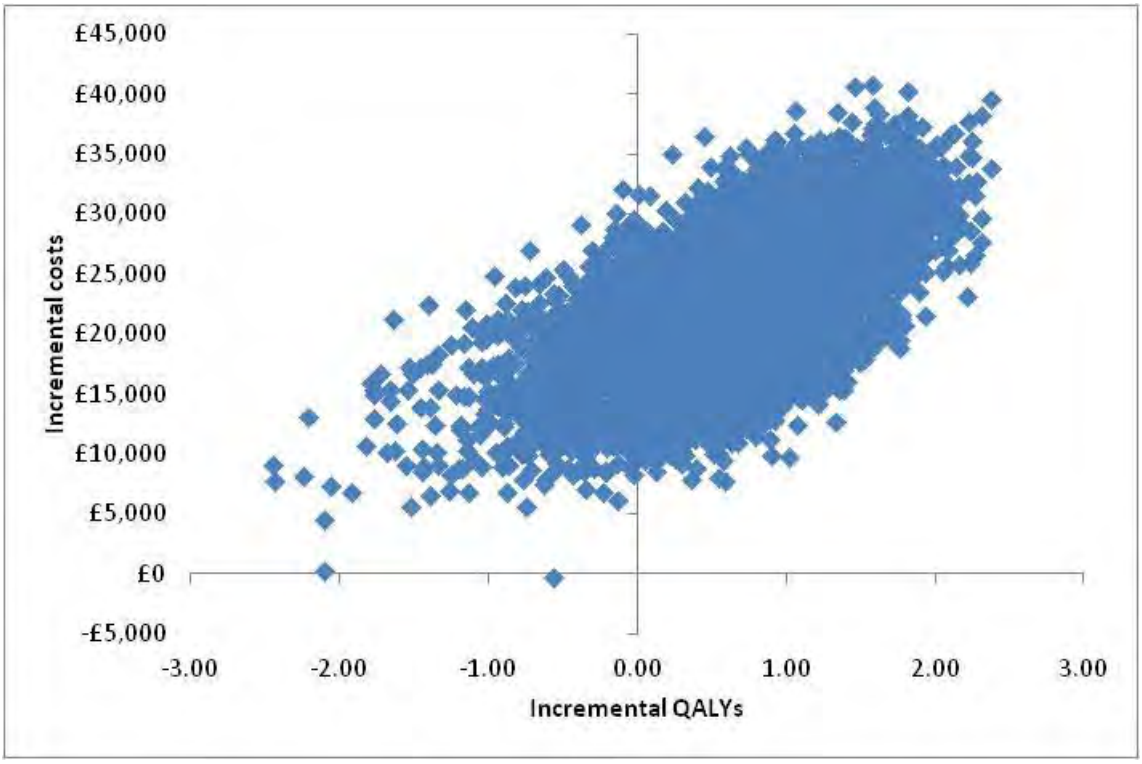
7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The probabilistic analysis performed on the base case included 10, 000 simulations and is presented in the following cost-effectiveness plane (Figure 26).

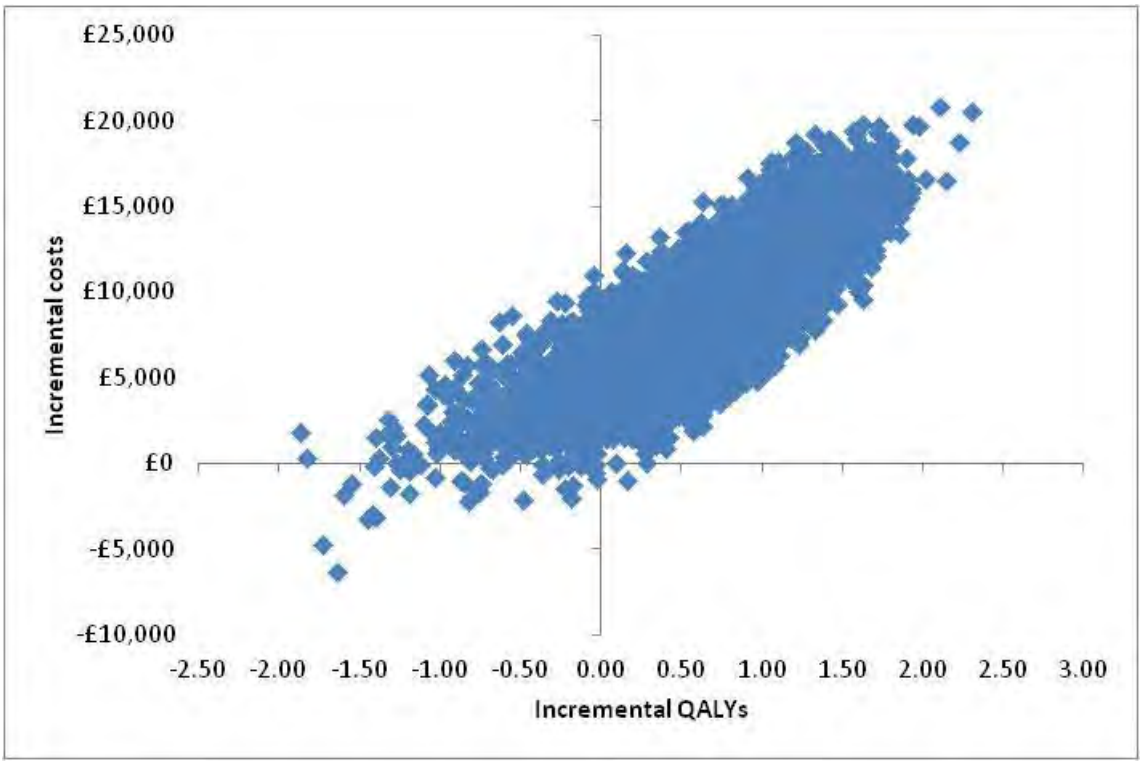
The cost-effectiveness acceptability curves are presented in Figure 27. The probability that the bortezomib-based induction regimen VTD is a cost effective option over the thalidomide-based induction regimen TD at £20,000 and £30,000 thresholds is estimated to be 18.58% and 54.83%, respectively. The probability that PAD is a cost effective option over VAD induction regimen at £20,000 and £30,000 thresholds is estimated to be 84.25% and 88.73%, respectively. Similarly, the probability that VD is a cost effective option over VAD at £20,000 and £30,000 thresholds is estimated to be 68.92% and 83.17%, respectively.

Figure 26: Cost effectiveness planes

VTD vs. TD



PAD vs. VAD



VD vs. VAD

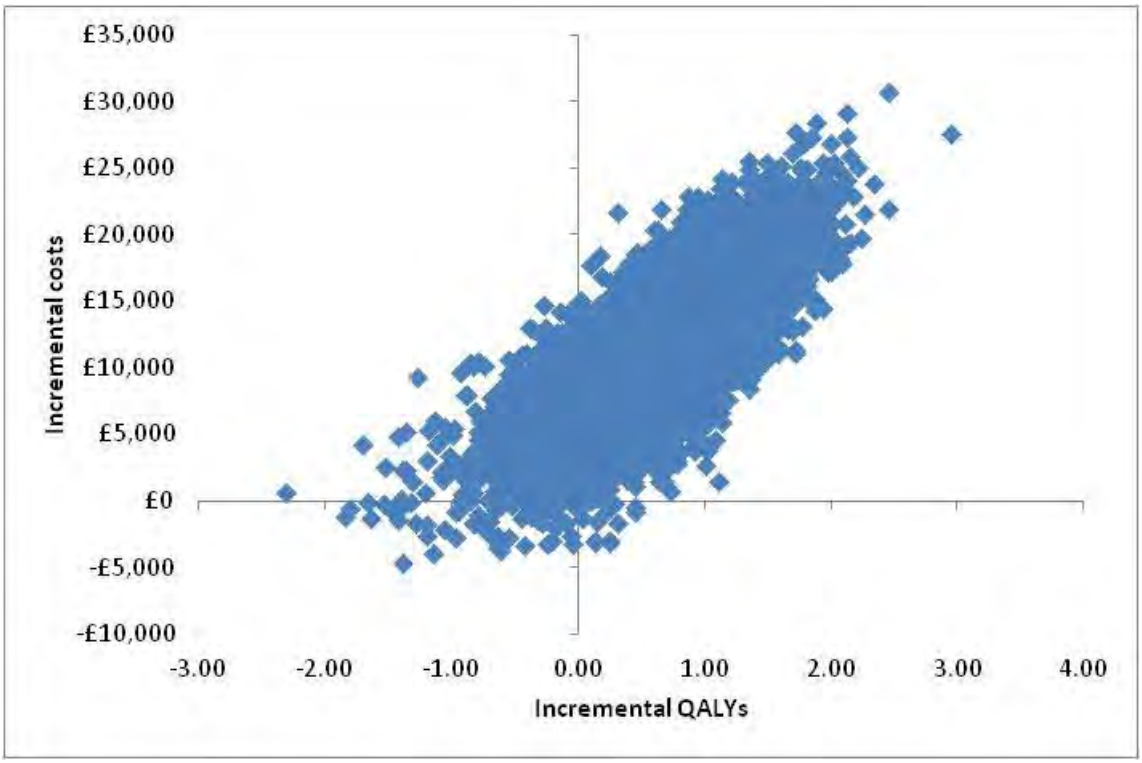
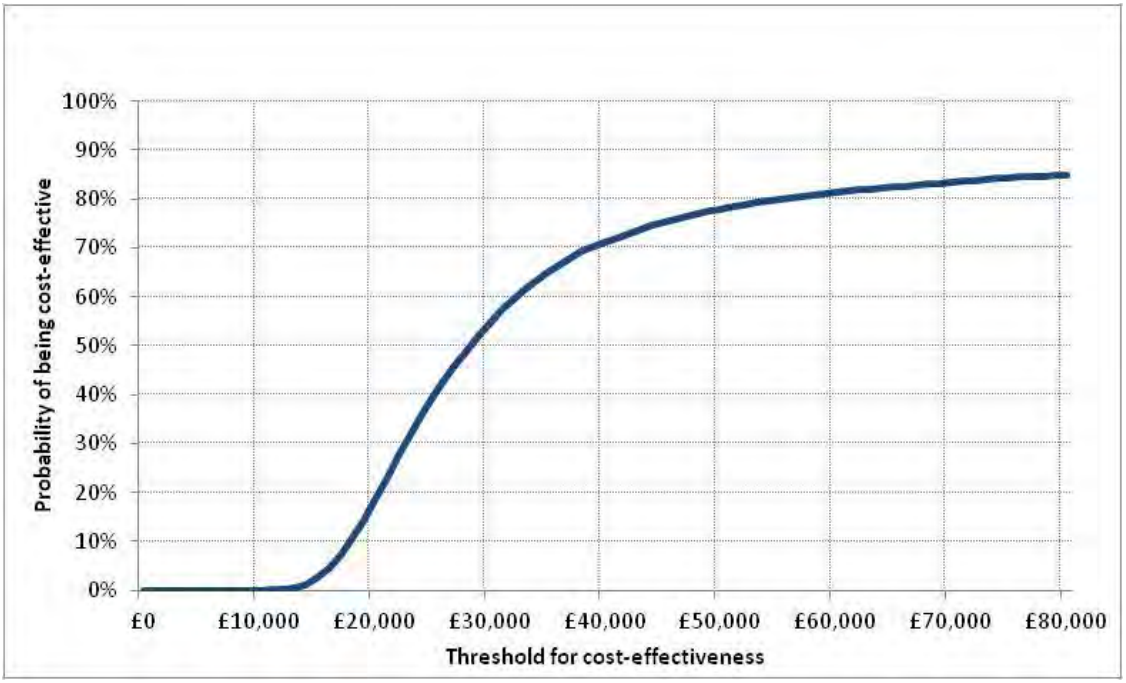
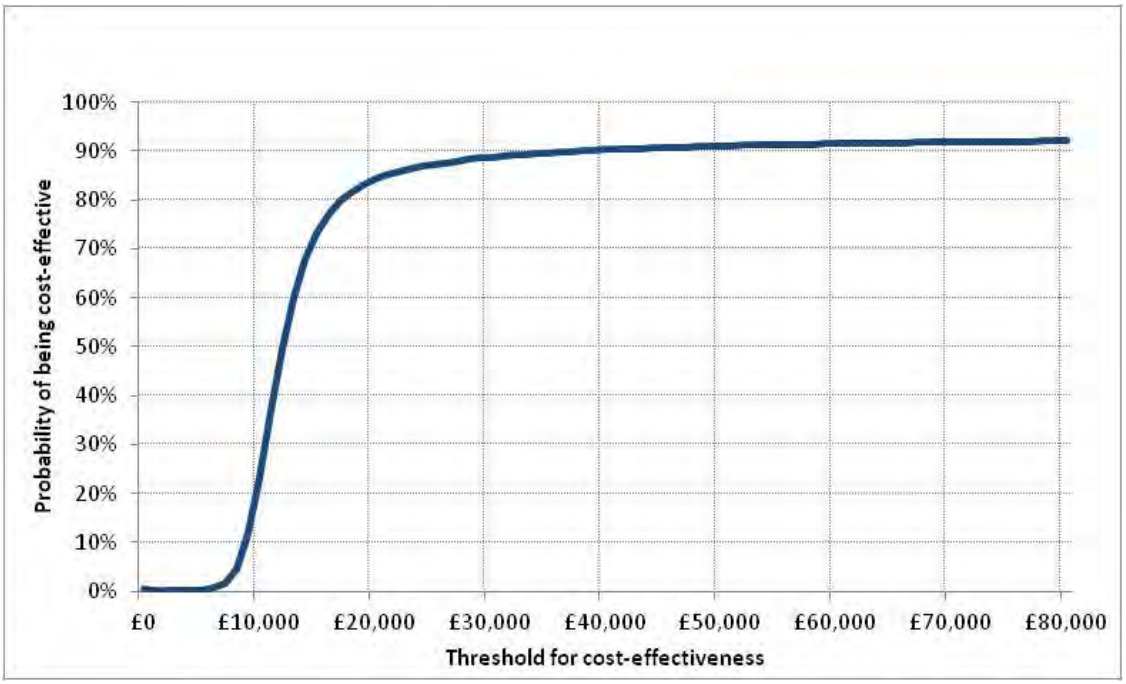


Figure 27: Cost effectiveness acceptability curves

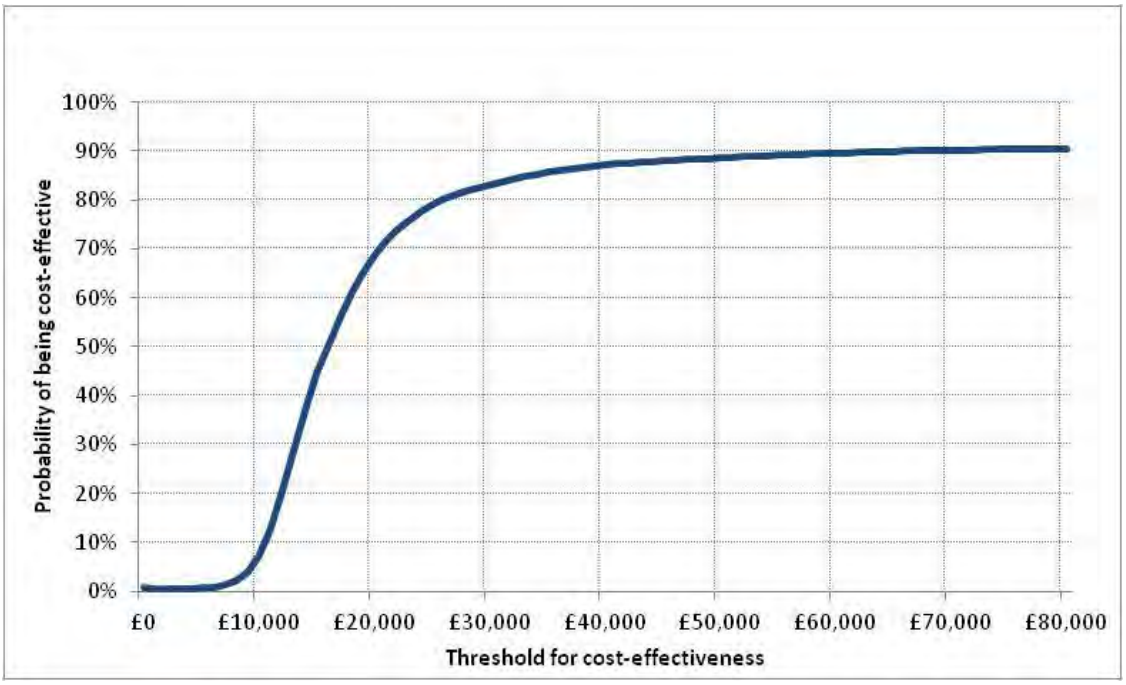
VTD versus TD



PAD vs. VAD



VD vs. VAD



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 95 shows the results of the scenario analyses.

Table 95: Results of scenario tested in the variability analyses

Scenario	Incremental costs	Incremental QALYs	ICER
VTD vs. TD			
Base case	£23,401	0.95	£24,683
Post-induction response rates			
GIMEMA study	£25,357	0.89	£28,482
VTD: CR=57.0%, PR=43.0%, NR=0.0%	£23,292	1.27	£18,344
VTD: CR=34.2%, PR=43.8%, NR=22.0%	£22,418	0.54	£41,226
VTD: CR=40.7%, PR=27.4%, NR=31.9%	£23,502	0.60	£39,272
VTD: CR=62.9%, PR=27.4%, NR=9.7%	£24,312	1.31	£18,522
TD: CR=24.3%, PR=52.8%, NR=22.9%	£24,653	0.62	£39,742
TD: CR=0.0%, PR=52.8%, NR=47.2%	£23,116	1.46	£15,860
TD: CR=11.3%, PR=35.6%, NR=53.1%	£22,229	1.24	£17,915
TD: CR=34.1%, PR=35.6%, NR=30.3%	£23,672	0.46	£51,990
OS by post-induction response			
IFM90 study	£28,881	1.57	£18,395
TTP for 2nd line (post-transplant / post-induction)			
Weibull distribution	£24,769	0.92	£26,831
Log-logistic distribution	£24,883	0.92	£26,926

Scenario	Incremental costs	Incremental QALYs	ICER
Number of cycles with VTD and TD			
4 cycles for all patients on induction therapy	£17,381	0.95	£18,333
5 cycles for all patients on induction therapy	£20,513	0.95	£21,636
6 cycles for all patients on induction therapy	£23,644	0.95	£24,939
Health state utility values			
Uyl-de-Grrot et al.	£23,401	0.83	£28,048
Decline in HRQoL following SCT only lasts 6 months	£23,401	0.98	£23,829
AE-related disutility value			
0.05 utility decrements	£23,401	0.94	£24,916
Time horizon			
10 years	£21,939	0.56	£39,304
15 years	£22,852	0.75	£30,415
Discount rates			
3.5% costs and 0% outcomes	£23,401	1.37	£17,040
3.5% costs and 6% outcomes	£23,401	0.76	£30,980
0% costs and 3.5% outcomes	£25,538	0.95	£26,936
6% costs and 3.5% outcomes	£22,314	0.95	£23,536
PAD vs. VAD			
Base case	£10,274	0.93	£11,041
Post-induction response rates			
PAD: CR=54.9%, PR=38.7%, NR=6.4%	£11,089	1.12	£9,906
PAD: CR=41.9%, PR=38.7%, NR=19.5%	£9,409	0.71	£13,179
PAD: CR=45.3%, PR=29.6%, NR=25.1%	£9,464	0.74	£12,741
PAD: CR=57.9%, PR=29.6%, NR=12.5%	£11,086	1.13	£9,774
VAD: CR=23.4%, PR=46.6%, NR=30.0%	£9,479	0.77	£12,314
VAD: CR=10.0%, PR=46.6%, NR=43.4%	£11,294	1.18	£9,571
VAD: CR=15.8%, PR=37.1%, NR=47.1%	£11,027	1.08	£10,189
VAD: CR=28.8%, PR=37.1%, NR=34.1%	£9,273	0.69	£13,521
OS by post-induction response			
IFM90 study	£15,304	1.55	£9,853
TTP for 2nd line (post-transplant / post-induction)			
Weibull distribution	£11,163	0.92	£12,155
Log-logistic distribution	£10,413	0.93	£11,222
Number of cycles with VTD and TD			
1 cycles for all patients on induction therapy	£4,798	0.93	£5,157
2 cycles for all patients on induction therapy	£7,743	0.93	£8,322
3 cycles for all patients on induction therapy	£10,635	0.93	£11,429
Health state utility values			
Uyl-de-Grrot et al.	£10,274	0.83	£12,411
Decline in HRQoL following SCT only lasts 6 months	£10,274	0.95	£10,806
AE-related disutility value			
0.05 utility decrements	£10,274	0.93	£11,044
Time horizon			
10 years	£8,836	0.56	£15,741
15 years	£9,725	0.75	£13,049
Discount rates			

Scenario	Incremental costs	Incremental QALYs	ICER
3.5% costs and 0% outcomes	£10,274	1.34	£7,690
3.5% costs and 6% outcomes	£10,274	0.75	£13,770
0% costs and 3.5% outcomes	£11,933	0.93	£12,824
6% costs and 3.5% outcomes	£9,482	0.93	£10,190
VD vs. VAD			
Base case	£12,710	0.88	£14,446
Post-induction response rates			
VD: CR=49.7%, PR=45.4%, NR=4.8%	£13,031	1.26	£10,377
VD: CR=24.2%, PR=45.4%, NR=30.4%	£11,593	0.41	£28,034
VD: CR=32.2%, PR=28.3%, NR=39.5%	£12,398	0.52	£23,954
VD: CR=56.2%, PR=28.3%, NR=15.5%	£13,746	1.31	£10,512
VAD: CR=22.7%, PR=52.7%, NR=24.6%	£11,235	0.59	£19,184
VAD: CR=0.0%, PR=51.6%, NR=48.4%	£14,374	1.30	£11,039
VAD: CR=9.8%, PR=35.1%, NR=55.1%	£14,029	1.14	£12,317
VAD: CR=32.9%, PR=35.1%, NR=32.0%	£10,890	0.42	£26,105
OS by post-induction response			
IFM90 study	£16,251	1.40	£11,587
TTP for 2nd line (post-transplant / post-induction)			
Weibull distribution	£15,834	0.83	£19,025
Log-logistic distribution	£15,324	0.84	£18,157
Number of cycles with VTD and TD			
1 cycles for all patients on induction therapy	£7,243	0.88	£8,234
2 cycles for all patients on induction therapy	£10,062	0.88	£11,437
3 cycles for all patients on induction therapy	£12,872	0.88	£14,630
Health state utility values			
Uyl-de-Grrot et al.	£12,710	0.80	£15,912
Decline in HRQoL following SCT only lasts 6 months	£12,710	0.91	£13,997
AE-related disutility value			
0.05 utility decrements	£12,710	0.88	£14,447
Time horizon			
10 years	£11,199	0.55	£20,420
15 years	£12,128	0.72	£16,957
Discount rates			
3.5% costs and 0% outcomes	£12,710	1.25	£10,179
3.5% costs and 6% outcomes	£12,710	0.71	£17,877
0% costs and 3.5% outcomes	£14,282	0.88	£16,232
6% costs and 3.5% outcomes	£11,977	0.88	£13,613

AE, adverse event; CR, complete remission; HRQoL, health-related quality of life; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NR, no response (less than PR); OS, overall survival; PR, partial response; QALY, quality-adjusted life year; SCT, stem cell transplant; TD, thalidomide and dexamethasone; TTP, time to progression; VTD, Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone

7.7.10 What were the main findings of each of the sensitivity analyses?

The deterministic sensitivity analyses highlighted that the results are most sensitive to the mortality rate for patients with CR after the induction therapy, and the VTD drug costs. If the CR mortality rate is varied within its 95% confidence interval, other things being equal, the ICER ranges from £20,189/QALY to £36,074/QALY. For the VTD drug costs, the ICER range is £19,544/QALY to £30,356/QALY. For all other parameters, the ICER remains within the £20,000/QALY-£29,000/QALY range. (

VD vs. VAD

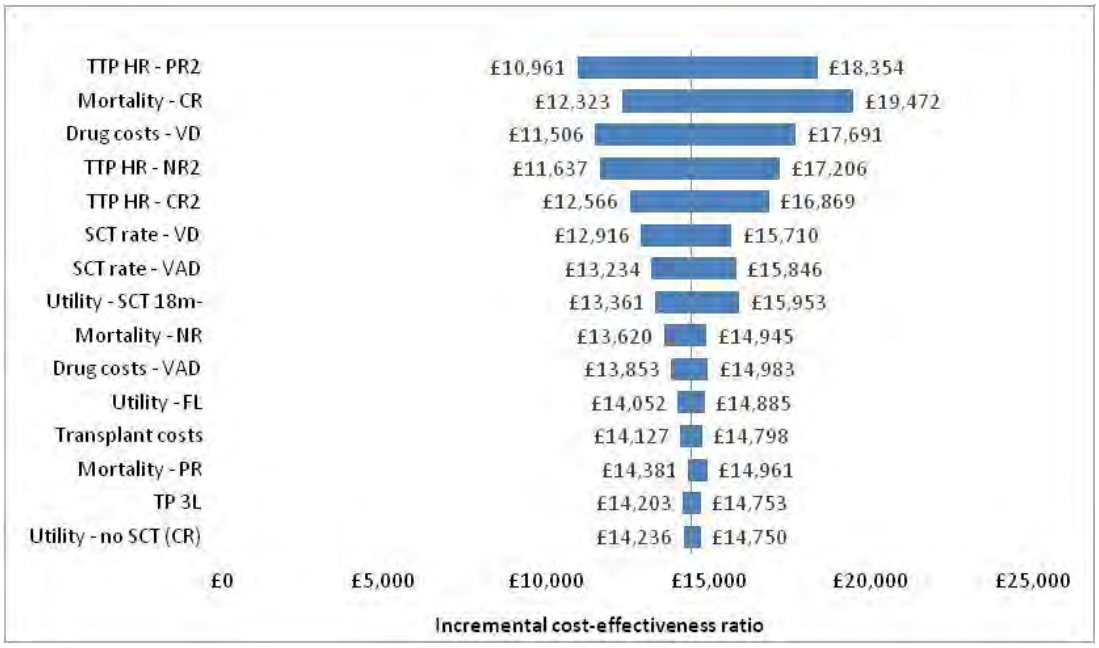


Table 94).

The scenarios analyses further supported the cost-effectiveness of bortezomib-based induction regimen (VTD) with ICERs generally remaining below £30,000/QALY, with the exception of scenarios where low CR rates for VTD, or a time horizon of 10 years is applied (see Table 95). The CR rates used in the scenario analyses were at the extreme end of 95% confidence interval. Also, given that around 20% of MM patients may be alive 10 years after the induction therapy, the 10-year time horizon for the economic modelling appears too short.

At the £20,000 and £30,000 willingness to pay thresholds, the probability for VTD to be cost-effective vs. TD is 18.6% and 54.8%, respectively. The probability that PAD is a cost effective option over VAD induction regimen at £20,000 and £30,000 thresholds is estimated to be 84.25% and 88.73%, respectively. Similarly, the probability that VD is a cost effective option over VAD at £20,000 and £30,000 thresholds is estimated to be 68.92% and 83.17%, respectively. (Table 96).

Therefore, the range of sensitivity analyses has demonstrated that VTD is likely to be a cost-effective treatment option for the relevant patient population compared to TD. Similarly, PAD is likely to be a cost-effective treatment option for the relevant patient population compared to VAD, as is VD compared to VAD.

Table 96: Cost-effectiveness of bortezomib based regimens vs. relevant comparators at the £20,000 and £30,000 willingness to pay thresholds

Willingness-to-pay threshold	Probability that VTD is cost-effective against TD
£20,000	18.6%
£30,000	54.8%
Willingness-to-pay threshold	**Probability that PAD is cost-effective against VAD**
£20,000	84.25%
£30,000	88.73%
Willingness-to-pay threshold	**Probability that VD is cost-effective against VAD**
£20,000	68.92%
£30,000	83.17%
TD, thalidomide and dexamethasone; VTD, Velcade® (bortezomib), thalidomide and dexamethasone; PAD: Velcade® (bortezomib), doxorubicin, dexamethasone; VAD: vincristine, doxorubicin, dexamethasone; VD: Velcade® (bortezomib), dexamethasone	

7.7.11 What are the key drivers of the cost-effectiveness results?

As discussed above, the main drivers of the cost-effectiveness results include mortality rates (particularly for patients with post-induction CR), the induction drug costs, and the hazard ratios for time-to-progression to the second line treatment.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The previous economic model for this submission had a number of major flaws, which were discovered shortly before the submission deadline. Therefore, the new model had to be constructed within one week. The external validation of the model will be completed in the coming weeks.

7.9 Subgroup analysis

7.9.1 **Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.**

An economic evaluation based upon subgroups was not undertaken.

7.9.2 **Please clearly define the characteristics of patients in the subgroup.**

Not applicable

7.9.3 **Please describe how the statistical analysis was undertaken.**

Not applicable

7.9.4 **What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).**

Not applicable

7.9.5 **Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.**

Not applicable

7.10 Interpretation of economic evidence

7.10.1 **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?**

There is no published economic model exploring the cost-effectiveness of bortezomib-based induction regimens vs. relevant comparators in the population of interest.

7.10.2 **Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?**

The results presented in the base case are reflective of the potential outcomes expected in the UK patient population.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths of the evaluation

The model is populated with clinical data from three methodologically robust pivotal trials providing a comparison between VTD and TD, PAD and VAD, and VD and VAD.

The chosen structure of the economic model follows the clinical pathway for the patient population relevant to the decision problem. Also, the modelling approach is based on post-induction response rate, which is strongly correlated with OS, the most patient-relevant outcome.

Extensive deterministic and probabilistic sensitivity analyses were performed, and the ICER appears robust to the sensitivity analyses.

Limitations of the evaluation

The OS data from the Pethema, Hovon and IFM trials are too immature to be incorporated into the economic model, thus we had to rely on long-term OS data from published literature in order to derive a cost per QALY estimate over a lifetime horizon. Also, utility values used in the model have been derived from the published literature due to the lack of quality of life data measured directly in the three trials. However, we have conducted extensive sensitivity analyses, which demonstrated the robustness of the ICER estimate to changes in OS and utility values.

Due to the lack of head-to-head evidence of bortezomib-based regimens vs. CTD, i.e. the current standard of care in the UK, we had to assume clinical equivalence of CTD and TD. Without this assumption, we would not have been able to use the pivotal trial data for this economic evaluation.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

In the future, once the Pethema, Hovon and IFM trial data become mature, the economic evaluation could be repeated using OS derived directly from the trial.

Table 97: Quality assessment of cost-effectiveness studies included

Study question	Grade (yes / no / not clear / N/A)		
	van Agthoven 2004	Gulbrandsen 2001b	Kouroukis 2003
Study design			
1. Was the research question stated?	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	No	No
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes – stated No - justification	Yes – stated No - justification	Yes – stated No - justification
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Yes	Yes
5. Were the alternatives being compared clearly described?	Yes	Yes	Yes
6. Was the form of economic evaluation stated?	Yes	Yes	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Yes	Yes
Data collection			
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Yes	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	N/A	Yes
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Yes	N/A
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	Yes	Yes	Yes
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Yes	Yes
14. Were productivity changes (if included) reported separately?	N/A	No	N/A
15. Was the relevance of productivity changes to the study question discussed?	N/A	Yes	N/A
16. Were quantities of resources reported separately from their unit cost?	Yes	Yes	Not clear
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	No – inflation N/A - Currency conversion	No	No – inflation N/A - Currency conversion
20. Were details of any model used given?	N/A	N/A	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	N/A	Yes
Analysis and interpretation of results			
22. Was the time horizon of cost and benefits stated?	Yes	Yes	Yes
23. Was the discount rate stated?	Yes	Yes	Yes
24. Was the choice of rate justified?	No	No	No
25. Was an explanation given if cost or benefits were not discounted?	N/A	N/A	N/A
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes – details of statistical tests reported No –confidence intervals not reported	No	Yes – details of statistical tests reported No –confidence intervals not reported

27. Was the approach to sensitivity analysis described?	Yes	Yes	Yes
28. Was the choice of variables for sensitivity analysis justified?	Yes	No	Yes
29. Were the ranges over which the parameters were varied stated?	No	Yes	Not clear
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Yes	Yes
31. Was an incremental analysis reported?	Yes	Yes	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Yes	Yes
33. Was the answer to the study question given?	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	No	No	No
36. Were generalisability issues addressed?	No	No	No
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination			

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

It is estimated that 661 newly diagnosed MM patients will be eligible for HDT-SCT in England and Wales in 2013. This estimation is based on:

- the projected population over 20 years old in England and Wales.(3;23;24)
- the age standardized incidence rate for men and women in 2010 (8.5 per 100,000 and 6.6 per 100,000 in England; 9 per 100,000 and 8.6 per 100,000 in Wales).(25;26)
- A proportion of 20% of newly diagnosed myeloma patients eligible for HDT-SCT was estimated.(27)

No subgroup was considered.

The estimated number of patients that would be eligible for HDT-SCT in England and Wales for 2013 and the subsequent four years is shown in Table 98 and Table 99.

Table 98: Estimated Myeloma patient population eligible for HDC and STC (from 2013 to 2015)

	2013			2014			2015		
	England	**Wales**	**Total**	**England**	**Wales**	**Total**	**England**	**Wales**	**Total**
Total Population (projected)	54,068,352	3,048,120	57,116,472	54,548,568	3,065,689	57,614,257	55,022,729	3,083,294	58,106,023
Men ≥20 years (projected)	20,066,833	1,134,083	21,200,916	20,281,655	1,143,432	21,425,087	20,483,341	1,152,000	21,635,341
MM incidence in men (8.5 per 100,000 in England; 9 per 100,000 in Wales)	1,706	102	1,808	1,724	103	1,827	1,741	104	1,845
Women ≥20 years (projected)	21,141 357	1,210,296	22,351,653	21,319,599	1,217,412	22,537,011	21,488,484	1,224,000	22,712,484
MM incidence in women (6.6 per 100,000 in England; 8.6 per 100,000 in Wales)	1,395	104	1,499	1,407	105	1,512	1,418	105	1,523
Total number of new MM cases (men and women)	3,101	206	3,307	3,131	208	3,339	3,159	209	3,368
MM cases for which HDC and STC may be considered appropriate (estimated at 20%)	620	41	**661**	626	42	**668**	632	42	**674**

Table 99: Estimated Myeloma patient population eligible for HDC and STC (from 2016 to 2018)

	2016			2017			2018		
	England	**Wales**	**Total**	**England**	**Wales**	**Total**	**England**	**Wales**	**Total**
Total Population (projected)	55,486,580	3,100,952	58,587,532	55,938,178	3,118,460	59,056,638	56,383,132	3,135,921	59,519,053
Men ≥20 years (projected)	20,683,226	1,160,000	21,843,226	20,876,388	1,169,000	22,045,388	21,059,255	1,177,000	22,236,255
MM incidence in men (8.5 per 100,000 in England; 9 per 100,000 in Wales)	1,758	104	1,862	1,774	105	1,879	1,790	106	1,896
Women ≥20 years (projected)	21,655,211	1,231,000	22,886,211	21,821,710	1,237,000	23,058,710	21,979,961	1,243,000	23,222,961
MM incidence in women (6.6 per 100,000 in England; 8.6 per 100,000 in Wales)	1,429	106	1,535	1,440	106	1,546	1,451	107	1,558
Total number of new MM cases (men and women)	3,187	210	3,397	3,214	211	3,425	3,241	213	3,454
MM cases for which HDC and STC may be considered appropriate (estimated at 20%)	637	42	**679**	643	42	**685**	648	43	**691**

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

CTD is the most commonly used induction regimen in UK clinical practice.(7) (Appendix 14) In addition, there is some usage of bortezomib based regimens and more particularly of bortezomib in combination with dexamethasone (VD).

It is expected that the use of bortezomib-based regimens, and more particularly VTD, will increase over the next few years while the use of CTD is expected to decrease slightly over the next five years.

8.3 What assumption(s) were made about market share (when relevant)?

The estimated market shares presented in Table 100 are based on the assumption that bortezomib-based regimen receive positive NICE guidance in Q1 2014.

Table 100: Estimated market shares for bortezomib-based regimens

	2013	2014	2015	2016	2017	2018
VTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All bortezomib-based regimens	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

In addition to the technology costs, only the administration cost was taken into account in the budget impact analysis.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit drug costs for the induction regimens are presented in section 1.10.

For each induction regimen, the average cost of a course of treatment and the cost of administration based on the mean number of cycles received is sum in Table 101.

Table 101: Costs associated with VTD, PAD, VD and CTD

	VTD	PAD	VD	CTD
Median number of cycle	6 (71)	3(70)	4 (72)	5(58)
Average cost of a course of treatment	£24,840.10	£9,692.09	£12,260.91	£4,164.50
Administration				
Code	SB12Z - Deliver	SB12Z - Deliver	SB12Z - Deliver	SB11Z - Deliver

	VTD	PAD	VD	CTD
	simple Parenteral Chemotherapy at first attendance (Day case) SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case)	simple Parenteral Chemotherapy at first attendance (Day case) SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case)	simple Parenteral Chemotherapy at first attendance (Day case) SB15Z - Deliver subsequent elements of a Chemotherapy cycle (day case)	exclusively Oral Chemotherapy (outpatient)
Cost	£1,645.00	£771.00	£1,055.00	£690.00
Total cost	**£26,485.10**	**£10,463.09**	**£13,315.91**	**£4,854.50**

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8.6 Were there any estimates of resource savings? If so, what were they?

It was assumed that the introduction of bortezomib-based induction regimens would not be associated with any resource savings.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS is presented in Table 102, Table 103 and Table 104.

Table 102: Estimated budget impact associated with the future use of bortezomib-based induction regimens

	2013	2014	2015	2016	2017	2018
Eligible population for HDC and STC	661	668	674	679	685	691
FUTURE TREATMENT OPTIONS						
Thalidomide-based regimens						
CTD*						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	357	327	310	292	281	269
CTD treatment cost (5 cycles at £4,164.50)	£ 1,486,727	£ 1,361,792	£ 1,290,995	£ 1,216,034	£ 1,170,225	£ 1,120,251
CTD administration cost (5 cycles at £690.00)	£ 246,330	£ 225,630	£ 213,900	£ 201,480	£ 193,890	£ 185,610
Total CTD cost	£ 1,733,057	£ 1,587,422	£ 1,504,895	£ 1,417,514	£ 1,364,115	£ 1,305,861
Bortezomib-based regimens						
VTD						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	33	67	121	163	185	200
VTD treatment cost (6 cycles at £24,840.10)	£ 819,723	£ 1,664,287	£ 3,005,652	£ 4,048,936	£ 4,595,419	£ 4,968,020
VTD administration cost (6 cycles at £1,645.00)	£ 54,285	£ 110,215	£ 199,045	£ 268,135	£ 304,325	£ 329,000
Total VTD cost	£ 874,008	£ 1,774,502	£ 3,204,697	£ 4,317,071	£ 4,899,744	£ 5,297,020
VD						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	152	147	115	88	69	55
VD treatment cost (4 cycles at £12,260.91)	£ 1,863,658	£ 1,802,354	£ 1,410,005	£ 1,078,960	£ 846,003	£ 674,350
VD administration cost (4 cycles at £1,055.00)	£ 160,360	£ 155,085	£ 121,325	£ 92,840	£ 72,795	£ 58,025
Total VD cost	£ 2,024,018	£ 1,957,439	£ 1,531,330	£ 1,171,800	£ 918,798	£ 732,375
PAD						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	33	33	34	34	34	35
PAD treatment costs (3 cycles at £9,692.09)	£ 319,839	£ 319,839	£ 329,531	£ 329,531	£ 329,531	£ 339,223
PAD administration cost (3 cycles at £771.00)	£ 25,443	£ 25,443	£ 26,214	£ 26,214	£ 26,214	£ 26,985
Total PAD cost	£ 345,282	£ 345,282	£ 355,745	£ 355,745	£ 355,745	£ 366,208
Budget impact (future regimens)	**£ 4,976,365**	**£ 5,664,644**	**£ 6,596,667**	**£ 7,262,130**	**£ 7,538,401**	**£ 7,701,464**
Other treatment options (lenalidomide-based regimens and others)**						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	86	94	94	102	116	131

* CTD is the most commonly used thalidomide-based induction regimen ** The market shares of the other treatment options are presented so that the total market shares each year equal 100%

Table 103: Estimated budget impact associated with the use of current regimens in clinical practise

	2013	2014	2015	2016	2017	2018
Eligible population for HDC and STC	661	668	674	679	685	691
CURRENT TREATMENT OPTIONS						
Thalidomide-based regimens						
CTD*						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	357	361	364	367	363	359
CTD treatment cost (5 cycles at £4,164.50)	£ 1,486,727	£ 1,503,385	£ 1,515,878	£ 1,528,372	£ 1,511,714	£ 1,495,056
CTD administration cost (5 cycles at £690.00)	£ 246,330	£ 249,090	£ 251,160	£ 253,230	£ 250,470	£ 247,710
Total CTD cost	£ 1,733,057	£ 1,752,475	£ 1,767,038	£ 1,781,602	£ 1,762,184	£ 1,742,766
Bortezomib-based regimens						
VTD						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	33	33	34	34	27	28
VTD treatment cost (6 cycles at £24,840.10)	£ 819,723	£ 819,723	£ 844,563	£ 844,563	£ 670,683	£ 695,523
VTD administration cost (6 cycles at £1,645.00)	£ 54,285	£ 54,285	£ 55,930	£ 55,930	£ 44,415	£ 46,060
Total VTD cost	£ 874,008	£ 874,008	£ 900,493	£ 900,493	£ 715,098	£ 741,583
VD						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	152	147	148	149	151	145
VD treatment cost (4 cycles at £12,260.91)	£ 1,863,658	£ 1,802,354	£ 1,814,615	£ 1,826,876	£ 1,851,397	£ 1,777,832
VD administration cost (4 cycles at £1,055.00)	£ 160,360	£ 155,085	£ 156 ,40	£ 157,195	£ 159,305	£ 152,975
Total VD cost	£ 2,024,018	£ 1,957,439	£ 1,970,755	£ 1,984,071	£ 2,010,702	£ 1,930,807
PAD						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	33	33	34	27	27	28
PAD treatment costs (3 cycles at £9,692.09)	£ 319,839	£ 319,839	£ 329,531	£ 261,686	£ 261,686	£ 271,379
PAD administration cost (3 cycles at £771.00)	£ 25,443	£ 25,443	£ 26,214	£ 20,817	£ 20,817	£ 21,588
Total PAD cost	£ 345,282	£ 345,282	£ 355,745	£ 282,503	£ 282,503	£ 292,967
Budget impact (current regimens)	**£ 4 976 365,09**	**£ 4 929 203,54**	**£ 4 994 031,14**	**£ 4 948 668,92**	**£ 4 770 487,04**	**£ 4 708 121,77**
Other treatment options (lenalidomide-based regimens and others)**						
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	86	94	94	102	116	131

* CTD is the most commonly used thalidomide-based induction regimen ** The market shares of the other treatment options are presented so that the total market shares each year equal 100%

Table 104: Overall budget impact of bortezomib-based regimens uptake upon CTD

	2013	2014	2015	2016	2017	2018
OVERALL BUDGET IMPACT (budget impact with future regimens minus budget impact with current regimens)	-	£ 735,440	£ 1,602,636	£ 2,313,462	£ 2,767,914	£ 2,993,342
Incremental cost versus previous year	-	£ 735,440	£ 867,195	£ 710,826	£ 454,452	£ 225,428

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not applicable

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10 Appendices

The appendices are provided under a separate file.

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

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

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

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises 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 FAD or ACD to consultees and commentators, all the evidence seen by the Committee should 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'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When 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 checklist of confidential information should be completed: if it is not provided, NICE 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 must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential 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 which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE'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. NICE 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 NICE 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 ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE 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 NICE 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 NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.