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

Addendum to the original submission made in February 2013

Janssen

July 2013

Contents

CONTENTS 2
LIST OF TABLES 3
BACKGROUND TO THIS ADDENDUM 4
SECTION A – DECISION PROBLEM 5
1 DESCRIPTION OF TECHNOLOGY UNDER ASSESSMENT 5
2 CONTEXT 8
3 EQUALITY 8
4 INNOVATION 8
5 STATEMENT OF THE DECISION PROBLEM 8
SECTION B – CLINICAL AND COST EFFECTIVENESS 11
6 CLINICAL EVIDENCE 11
7 COST EFFECTIVENESS 19
SECTION C – IMPLEMENTATION 37
8 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES 37
9 REFERENCES 38
10 APPENDICES 38

List of tables

Table 1: Comparison of draft and final SmPC 4
Table 2: Unit costs of technology being appraised 6
Table 3: Abbreviations of treatment regimens for the relevant RCTs reported 11
Table 4: Post-induction response rates (2;6) 14
Table 5: Post-induction response and a number of VTD cycles in the Pethema trial 15
Table 6: Post-induction response and a number of TD cycles in the Pethema trial 15
Table 7: Summary of trials identified for the attempted MTC 17
Table 8: Impact of the discontinuation rule on treatment duration (Pethema trial) 20
Table 9: Summary of scenario analyses 24
Table 10: First 20 rows of the Markov trace for VTD 27
Table 11: First 20 rows of the Markov trace for TD 28
Table 12: Model outputs by clinical outcomes (discounted) 28
Table 13: Summary of QALY gain by health state 29
Table 14: Summary of costs by health state 29
Table 15: Summary of predicted resource use by category of cost 29
Table 16: Base-case results 30
Table 17: Deterministic sensitivity analysis results for most sensitive parameters 31
Table 18: Results of the same sensitivity analyses as in the original submission performed on the new base case 33
Table 19: Threshold analysis for post-induction response rates from TD 34
Table 20: Threshold analysis for overall survival 34
Table 21: Assumption related to the patient level data analysis 34
Table 22: Median observed survival for multiple myeloma patients by period of diagnosis (8) 35
Table 23: Cost-effectiveness of VTD vs. relevant comparators at the £20,000 and £30,000 willingness to pay thresholds 36

List of figures

Figure 1: Overall response rate and complete response from the Pethema trial (6) 13
Figure 2: Proportion of patients who underwent SCT in the Pethema trial (6) 16
Figure 3: OS Kaplan-Meier curves from the Pethema trial (6) 16
Figure 4: Network diagram for the five trials 17
Figure 5: Proportion of patients who would have received 1-6 cycles of VTD in the Pethema trial with or without the discontinuation rule 21
Figure 6: Post-induction response rates from the Pethema trial (6) 22
Figure 7: Tornado diagram 30
Figure 8: Cost effectiveness plane for VTD versus TD 32
Figure 9: cost effectiveness acceptability curve for VTD versus TD 32

Background to this addendum

The manufacturer's submission by Janssen for bortezomib for induction therapy in multiple myeloma prior to high dose chemotherapy and autologous stem cell transplantation was originally made in February 2013. A positive opinion was received from the Committee for Medicinal Products for Human Use (CHMP) on 27 June 2013. The final licence from the EMA differs materially from that which was submitted for regulatory approval by the company, and which formed the basis of the original scope and the manufacturer's NICE submission.

The key changes from the original licence application (and NICE submission) are as follows.

- **A discontinuation rule now applies to use of the VTD** (bortezomib, thalidomide and dexamethasone) regimen stating that "Four VELCADE treatment cycles are administered. It is recommended that patients with at least partial response receive 2 additional cycles" (1). As a result, some patients will receive only 4 cycles of VTD before stopping, rather than continuing for 6 cycles. This impacts both the incremental cost and incremental effectiveness of VTD compared to TD (Table 1). Therefore, **the results of the economic evaluation for VTD in the manufacturer's original submission (both the base case and sensitivity analyses) are no longer valid and must be disregarded**.

- The **PAD regimen** (bortezomib, adriamycin, dexamethasone) was part of the regulatory package to the EMA, but through the review process it **was deemed to be not approvable by CHMP** (Table 1). Therefore, the sections of the manufacturer's original submission related to use of the PAD regimen are now redundant.

Table 1: Comparison of draft and final SmPC

	Draft (correct at the time of the NICE submission in Feb 2013)	**Final license as per the SmPC** (1)
Posology for VTD	The recommended VELCADE dose is 1.3 mg/m^2 administered twice weekly on days 1, 4, 8 and 11 in a 28 day treatment cycle. Six cycles are administered.	Four VELCADE treatment cycles are administered. It is recommended that patients with at least partial response receive 2 additional cycles
Regimens	VTD, VD, PAD	VTD, VD

PAD: Velcade® (bortezomib), Adriamycin® (doxorubicin), and dexamethasone; VD: Velcade® (bortezomib) and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone

Given this background, Janssen was invited by NICE to submit an addendum in order to explain the implications of the licensed regimens and posology to the new, revised base case.

For ease of cross-referencing, this addendum has a similar structure to the STA submission template and highlights the major differences from the original submission.

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?**

Please refer to the original submission.

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).**

A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was issued on 27 June 2013. The marketing authorisation is expected to be granted in September 2013.

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 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 on-going 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 is currently approved in Canada.

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 Q3 2013 with a decision expected in Q4 2013/Q1 2014.

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 2: 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) - Thalidomide 50mg: £10.66 (price for 28 capsules=£298.48)
Method of administration	Subcutaneous bortezomib in combination with: - Oral dexamethasone (VD) or - Oral thalidomide and oral dexamethasone (VTD)
Doses of	The recommended dose of bortezomib is 1.3 mg/m^2, in combination with: - Dexamethasone 40mg (VD) or - Thalidomide: 50mg (up to 200mg) and dexamethasone 40mg (VTD)
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). *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 (VD):* 4 cycles of 21 days *In combination with dexamethasone and thalidomide (VTD):* 4 cycles of 28 days. 2 additional cycles of 28 days for patients with at least partial response after the 4th cycle

Average cost of a course of treatment	*Combination therapy with dexamethasone (VD):* the median number of cycles observed in the trial is 4, resulting in a median treatment cost of £12,260.91 *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 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

Please refer to the original submission.

3 Equality

Please refer to the original submission.

4 Innovation

Please refer to the original submission.

5 Statement of the decision problem

	Final scope issued by NICE	**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 thalidomide and dexamethasone (VTD) for4- 6 cycles of 28 days each (4 cycles are administered. Patients with at least partial response receive 2 additional cycles.)	N/A

Comparator	Chemotherapy regimens containing thalidomide	- The cost-effectiveness of VTD will be assessed vs. TD as per the Pethema trial in the base-case analysis	Section 2.6 - CTD was the main comparator in the decision scope given its widespread experience in UK clinical practice - 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), CTD was assumed to have similar clinical efficacy to TD by UK clinicians (appendix 14 of the original submission). Consequently, 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 (2;3) although this regimen is not as commonly used in UK clinical practice as CTD. (4) (Appendices 14)
Outcomes	- Response rate - Proportion of people undergoing high dose chemotherapy and autologous stem cell transplantation - Progression-free survival - Overall survival - Adverse effects of treatment - Health-related quality of life	In this submission, the following outcome 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	The response rate post-induction is used as the primary measure of efficacy in the economic model.

		published literature is used in the economic model	
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 Markov model that compares the bortezomib-based regimen VTD to TD based upon the RCT Pethema. 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.	N/A
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 regimen 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

Please refer to the original submission.

6.2 Study selection

Table 14 from the original submission is reproduced below.

Table 3: 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

Please refer to the original submission for further information.

6.3 Summary of methodology of relevant RCTs

RCT study designs

<u>Pethema (3)</u>

The Pethema trial was a randomised, open-label study to compare the efficacy and safety of three induction regimens including VTD and TD. Patients received up to 6 cycles of VTD or TD.

While the Pethema trial did not incorporate the discontinuation rule as per the SmPC, compared to the Gimema trial where subjects received only 3 cycles, its study design better reflects how the VTD regimen is expected to be used in the UK.

For this addendum, patient-level data analyses have been performed in order to assess the impact of the discontinuation rule on clinical- and cost-effectiveness of the bortezomib-based regimen. The results are discussed in Sections 6.5 and 7.3.

Please refer to the original submission for further information about the Pethema trial.

Gimema (2)

The Gimema trial was a randomised, open-label, Phase III study designed to compare the efficacy and safety of 3 cycles of VTD versus 3 cycles of TD as induction treatment prior to SCT and to evaluate consolidation thereafter.

In contrast to the recommended posology as per the SmPC, subjects randomised to the VTD induction group received only 3 cycles of bortezomib-based treatment.

Please refer to the original submission for further information about the Gimema trial.

Outcomes

As discussed in the original submission (Section 2.5), the clinical aims of induction therapy are to achieve a high response rate rapidly with minimal toxicity, to preserve haemopoietic stem cell function to ensure successful mobilisation of peripheral blood stem cells, and to bring patients to transplant (4). Maximising post-induction response rate is important as meta-analyses have shown a clear correlation between the maximal response achieved and overall survival (5). Therefore, the results presented in the original submission and this addendum focus on **post-induction response rates** in order to assess the effectiveness of induction therapy. Post-induction response rates allow a non-confounded assessment of disease response following induction treatment. Subsequent assessments, such as post-transplant response rate, are potentially confounded by study design features that were introduced to ensure treatment success, to accommodate local practice, or to investigate other aspects of the overall treatment scheme.

In the Pethema trial, although uniform procedures for stem cell collection, conditioning with melphalan and SCT were provided in the protocol, unlike the induction phase, these procedures could be replaced by institutional preferences, if required. Only general criteria were specified for advancement to stem cell collection or HDT/SCT. The protocol required a single course of HDT/SCT, and the minimum number of CD34+ cells to be collected was left to the discretion of each centre, as were other procedures related to stem cell cryopreservation, storage, thawing, and infusion. In the event of mobilisation failure with G-CSF, use of a second mobilisation scheme including use of high doses of cyclophosphamide followed by normal or pegylated G-CSF or any other scheme used as part of the centre's standard clinical practice could be used.

It is not known how these practices in Spain would differ from UK clinical practice or how they differed between the investigator hospitals and regions. Therefore, using the post-SCT response rates introduces an element of uncertainty in the model which can be negated by the use of post-induction response rates.

6.4 Critical appraisal of relevant RCTs

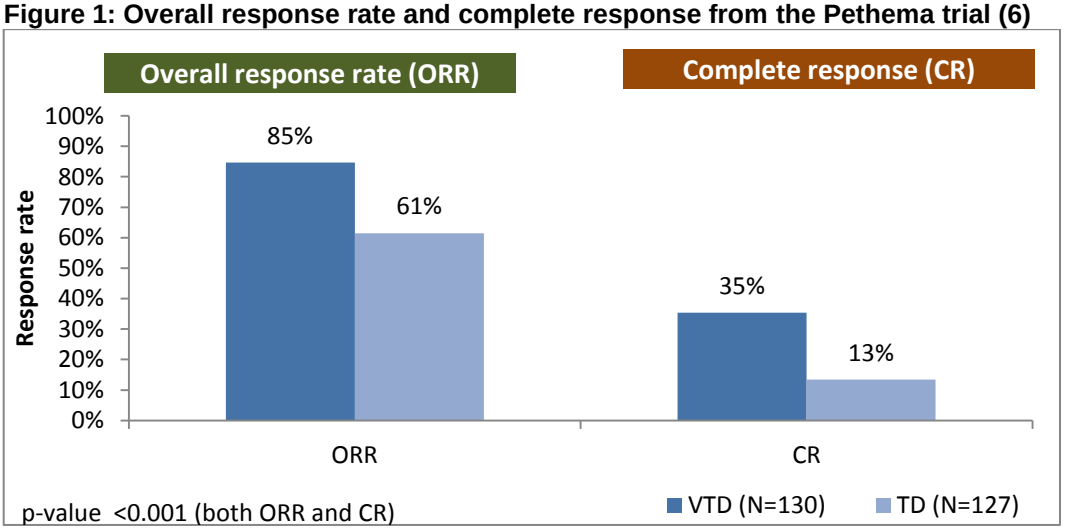
Please refer to the original submission.

6.5 Results of the relevant RCTs

Response rates

In the Pethema trial, post-induction overall response rates (ORR) and complete response rates (CR) were statistically significantly higher in the VTD group compared to the TD group (Figure 1, Table 4) (6). Similar results were demonstrated in the Gimema trial (Table 4).

Figure 1: Overall response rate and complete response from the Pethema trial (6)



Also, the Pethema trial 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) (6).

Table 4: Post-induction response rates (2;6)

Study name	Induction regimen	% (n/N)	P value	Ref.
		Post-induction		
Overall response rate (ORR)				
Pethema	VTD	84.6 (110/130)	<0.001	(6)
	TD	61.4 (78/127)		
Gimema	VTD	93.2 (220/236)	<0.0001	(2)
	TD	78.6 (187/238)		
Complete response (CR)				
Pethema	VTD	35.4 (46/130)	<0.001	(6)
	TD	13.4 (17/127)		
Gimema	VTD	18.6 (44/236)	<0.0001	(2)
	TD	4.6 (11/238)		
Near complete response (nCR)				
Pethema	VTD	13.8 (18/130)	-	(6)
	TD	3.9 (5/127)		
Gimema	VTD	-	-	
	TD	-		
Very good partial response (VGPR)				
Pethema	VTD	25 (33/130)	-	(3)
	TD	15 (19/127)		
Gimema	VTD	-	-	
	TD	-		
Partial response (PR)				
Pethema	VTD	35.4 (46/130)	-	(6)
	TD	44.1 (56/127)		
Gimema	VTD	-	-	
	TD	-		
Progressive disease				
Pethema	VTD	6.2 (8/130)	0.0004	(6)
	TD	23.6 (30/127)		
Gimema	VTD	0.0 (0/236)	0.0005	(2)
	TD	5.0 (12/238)		

'-' indicates that the information was not reported

Treatment duration

As discussed earlier, the approved posology now incorporates a discontinuation rule whereby patients who do not achieve at least PR after the 4th cycle of VTD discontinue treatment. In order to evaluate the impact of the discontinuation rule on treatment duration, effectiveness and cost, additional patient-level analyses of the Pethema trial have been conducted for this addendum to the NICE submission.

Originally, we sought to obtain the details of each patient's clinical response after each cycle of VTD, i.e. trajectory of response for each patient throughout the induction period. However, this type of data was not available to Janssen as investigators were not required to routinely monitor patients' responses after each cycle in the Pethema study.

Nevertheless, we were able to retrieve a data set with the number of patients by final post-induction response, and by the total number of cycles they received (Table 5). For example, of the 18 patients who achieved nCR, [redacted] received 5 cycles and [redacted] received 6 cycles. Also, of the 130 patients who were randomised to the VTD arm, [redacted] received full 6 cycles, and [redacted] received fewer than 6 cycles.

Table 5: Post-induction response and a number of VTD cycles in the Pethema trial

Final response during trial	Number of cycles received						
	1	2	3	4	5	6	TOTAL
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46
nCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46
MR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2
NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	130

Please refer to Section 7.3 below for how these analysis results and the discontinuation rule was incorporated into the economic evaluation.

For completeness, Table 6 displays a similar set of data for the TD regimen. Fewer subjects received the full 6 cycles of induction therapy in the TD arm than in the VTD arm ([redacted] vs. [redacted]) mainly because discontinuation due to disease progression occurred more frequently in the TD arm than in the VTD arm ([redacted] vs. [redacted]) (6). Whilst TD is not currently licensed for use in the UK for the indication relevant to the decision problem, we have assumed that it is not subject to the same discontinuation rule as for VTD.

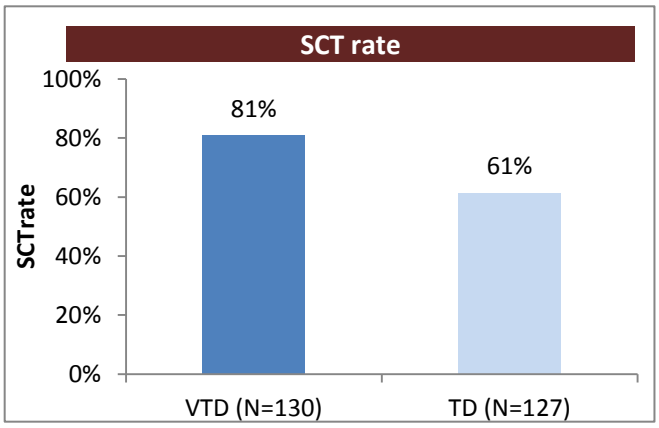
Table 6: Post-induction response and a number of TD cycles in the Pethema trial

Final response during trial	Number of cycles received						
	1	2	3	4	5	6	TOTAL
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17
nCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56
MR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9
NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	126

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. In the Pethema trial, a higher percentage of patients underwent SCT following induction therapy with bortezomib, compared to TD (Figure 2) (6). Please refer to the original submission for further details.

Figure 2: Proportion of patients who underwent SCT in the Pethema trial (6)

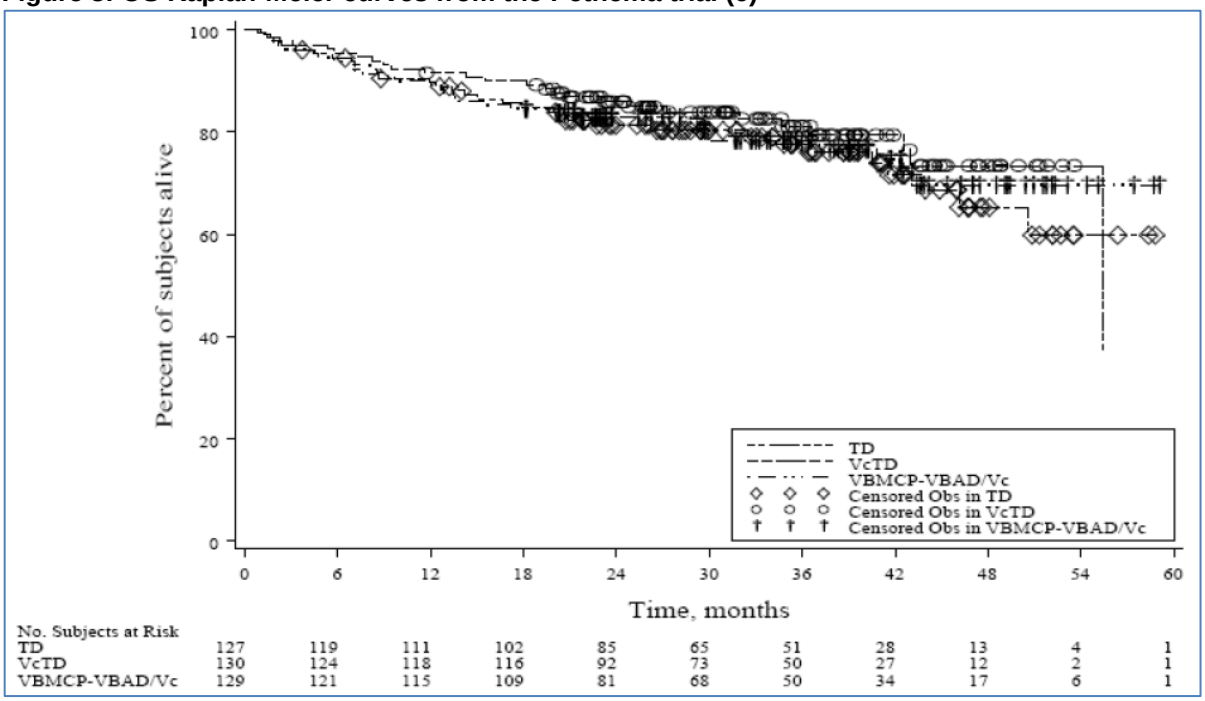


Overall Survival

As discussed in the original submission, median OS had not been reached across the majority of trials and treatment groups.

Furthermore, for the Pethema trial, OS data are heavily censored after approximately 20 months, thus the numbers of subjects at risk decline to less than half of the initial values by 30-36 months, and then to single digits by 54 months (Figure 3) (6).

Figure 3: OS Kaplan-Meier curves from the Pethema trial (6)



6.6 Meta-analysis

Please refer to the original submission.

6.7 Indirect and mixed treatment comparisons

The PAD regimen was included in the regulatory filing to the EMA, and was therefore incorporated into the MTC that was included in the original submission. The inclusion of the PAD regimen in the MTC is now inappropriate in light of the CHMP decision.

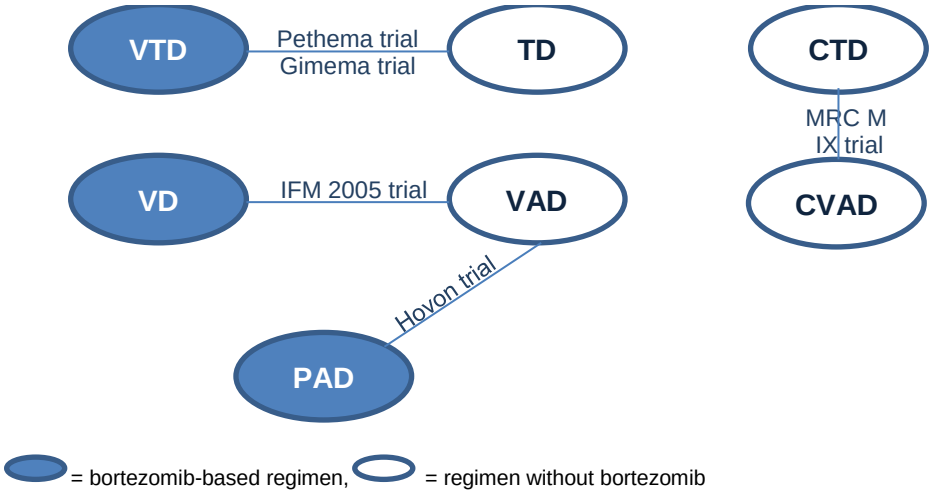
Trials identified for the attempted MTC and regimens compared in each trial are presented in Table 7. (See Sections 6.1-2 of the original submission for identification and selection of studies.)

Table 7: Summary of trials identified for the attempted MTC

RCT name	Intervention	Comparator
IFM 2005	VD	VAD
HOVON	PAD	VAD
MRC Myeloma IX	CTD	CVAD
GIMEMA & PETHEMA	VTD	TD

The network diagram for the evidence structure comprising the four bortezomib trials and the MRC M IX trial is presented in Figure 4.

Figure 4: Network diagram for the five trials



This diagram clearly illustrates 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 current standard of care in the UK. Moreover, VD cannot be linked to any thalidomide-based regimen, a comparator specified in the final scope for this STA. It also means an incremental economic analysis comparing VTD and VD, two approved regimens in this setting, cannot be performed reliably.

We considered the plausibility of using a set of assumptions (see Section 6.7.3 of the original submission) to overcome these network limitations. However, we concluded

that the considerable uncertainties generated by use of these assumptions means that the results were unreliable. Therefore, the economic evaluation of the bortezomib-based regimen focuses only on the comparison of VTD vs. TD using the Pethema trial results in the base case.

Please refer to the original submission for further information.

6.8 Non-RCT evidence

Please refer to the original submission.

6.9 Adverse events

The adverse event analyses presented in the original submission did not take into account the discontinuation rule for the VTD regimen. It may marginally alter the frequency and severity of AEs due to a small proportion of patients who do not achieve at least a PR after the 4th cycle receiving up to 2 fewer cycles of VTD, but the impact of this will be negligible. The patient-level data necessary to analyse the impact of the discontinuation rule on AEs were not available. Therefore, the economic evaluation presented in Section 7 utilises the same AE assumptions as in the original submission.

6.10 Interpretation of clinical evidence

Please refer to the original submission.

7 Cost effectiveness

As the cost-effectiveness analysis discussed in the original submission did not incorporate the discontinuation rule for the VTD regimen, **all of the results presented in Section 7.7 of the original submission are no longer valid**.

Also, since the PAD regimen was deemed to be not approvable by CHMP, the economic evaluation presented in the earlier addendum (submitted in February 2013) is no longer relevant to the decision problem and thus must be disregarded.

Please see below for the revised base case and sensitivity analyses.

7.1 Published cost-effectiveness evaluations

Please refer to the original submission.

7.2 De novo analysis

Clinical continuation rule

The SmPC specifies a clinical discontinuation rule for the VTD regimen as follows; "Four VELCADE treatment cycles are administered. It is recommended that patients with at least partial response receive 2 additional cycles" (1). This was introduced after the original submission was made in February 2013.

There is no similar discontinuation rule for the VD regimen. Also, the discontinuation rule is not specific to any patient subgroup.

The discontinuation rule is based upon the measure of response routinely used in clinical practice and clinical trials (see Section 2.1 of the original submission). The European Group of Blood and Bone Marrow Transplant (EBMT) criteria and the International Myeloma Working Group (IMWG) criteria are commonly used to measure response.

Therefore, the use of a discontinuation rule that relies on routine myeloma assessments is unlikely to result in additional costs.

7.3 *Clinical parameters and variables*

Since the discontinuation rule has implications for both the incremental costs and incremental benefits of VTD compared to TD, the results of the economic evaluation presented in the original submission are no longer relevant to the decision problem.

In this section, we discuss how the key clinical data, particularly the results of the patient level data analyses, are used in the economic model for the revised cost-effectiveness analysis.

Numbers of treatment cycles

The economic model requires numbers of patients who received at least 1, 2, 3, 4, 5 cycles or full 6 cycles of VTD so that the costs associated with the VTD regimen can be correctly estimated for each monthly Markov cycle.

As discussed in Section 6.5 above, patient level data analyses revealed a proportion of patients who received 5 or 6 cycles of VTD but who would have stopped at the 4th cycle if the discontinuation rule had had been in place (Table 5).

It was not possible to obtain data which would allow us to track each patient's response throughout the induction period. Therefore, certain assumptions must be made so that the data in Table 5 can be utilised for the economic evaluation.

Table 8: Impact of the discontinuation rule on treatment duration (Pethema trial)

Final response during trial	Number of cycles received						
	1	2	3	4	5	6	TOTAL
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46
nCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46
MR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2
NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	130

	At least 1 cycle	At least 2 cycles	At least 3 cycles	At least 4 cycles	At least 5 cycles	All 6 cycles	
No discont'n rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
With discont'n rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

First, patients in the Pethema trial who achieved less than PR and received 5 or 6 cycles of VTD (i.e. [redacted] patients in the blue rectangular area in Table 8) are assumed to have achieved less than PR after the 4th cycle, and therefore, with the discontinuation rule, would not have received the 5th and 6th cycles of VTD. This assumption allows us to exclude [redacted] and [redacted] patients from the number of patients who received at least 5 cycles and all 6 cycles, respectively.

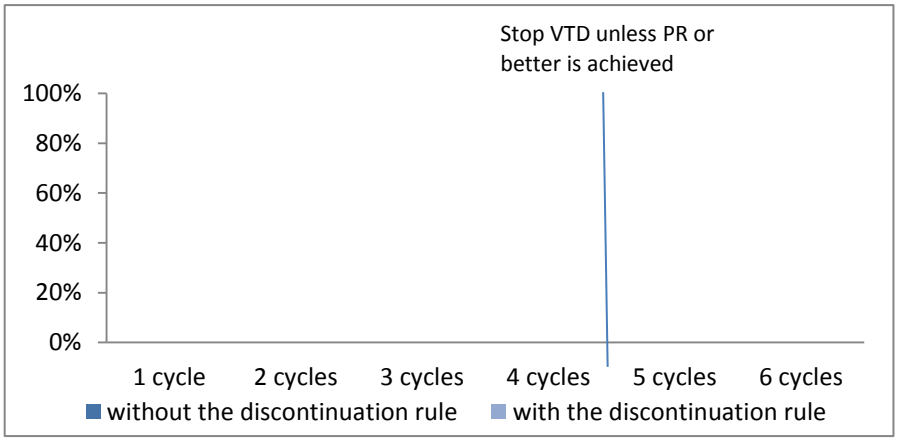
Second, patients in the Pethema trial who achieved at least PR and received 5 or 6 cycles of VTD ([redacted] patients in the red dotted rectangle in Table 8) are assumed to have achieved at least PR after the 4th cycle already, and thus, even with the discontinuation rule, would have continued treatment with VTD beyond the 4th cycle. This assumption allows us to include these [redacted] and [redacted] patients to the number of patients who received at least 5 cycles and all 6 cycles, respectively.

The first assumption appears plausible unless patients who achieve PR or better after the 4th cycle are likely to deteriorate to below PR during the 5th and 6th cycle. The second assumption although plausible, requires further testing through sensitivity analysis as it is possible that some of patients who achieved PR or better after receiving 6 cycles may not have achieved PR or better after the 4th cycle, and thus would have discontinued treatment under the discontinuation rule (see Section 7.6-7).

Under these assumptions, with the discontinuation rule, the number of patients who would have been eligible to receive all 6 cycles of VTD is [redacted], rather than [redacted] as actually observed in the Pethema trial. Therefore, the discontinuation rule would reduce the costs associated with VTD regimen during the induction phase.

Figure 5 displays the proportion of patients who actually received 1 to 6 cycles of VTD in the Pethema trial, and that of those who would have received 1 to 6 cycles of VTD with the discontinuation rule. The latter proportions were used in the economic model for the new base case.

Figure 5: Proportion of patients who would have received 1-6 cycles of VTD in the Pethema trial with or without the discontinuation rule

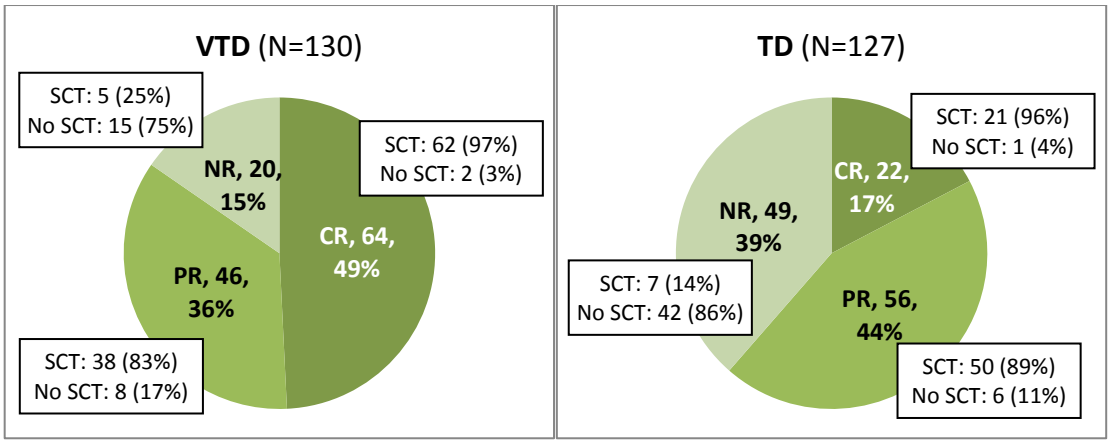


Post-induction response rates and SCT rates

In the Pethema trial, a significantly higher proportion of patients in the VTD arm achieved CR post-induction compared to the TD arm (Table 4, Figure 6). Also, a higher proportion of patients received a SCT in the VTD arm than in the TD arm (Figure 2). Additionally, the Pethema study showed that the likelihood of a patient receiving SCT is positively associated with the depth of response to the induction therapy (Figure 6). (6)

Post-induction response rates from the Pethema trial were used as the main measure of efficacy in the economic model. Also, SCT rates for each response category in each treatment arm from the Pethema trial (Figure 6) were used in the economic model.

Figure 6: Post-induction response rates from the Pethema trial (6)



CR = CR+nCR+VgPR; NR = MR+SD+PD
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

Given the two assumptions discussed above, the discontinuation rule would not alter VTD's post-induction response rates as input parameters for the economic model. This is firstly because the discontinuation rule would not change the final post-induction responses for those who received 4 or fewer cycles of VTD. Also, the second assumption implies all of the 46 CR patients would have received full 6 cycles with or without the discontinuation rule. The same logic applies to the 18 nCR patients, and the 43 PR patients who received full 6 cycles. Finally, [redacted] patients who would have discontinued VTD treatment after the 4th cycle would be in the 'NR' category (MR or below) for modelling purposes.

7.4 Measurement and valuation of health effects

Please refer to the original submission.

7.5 Resource identification, measurement and valuation

Please refer to the original submission.

7.6 Sensitivity analysis

In order to fully test the robustness of the revised base case result, a set of comprehensive sensitivity analyses have been undertaken. All of the sensitivity analyses described in the original submission have been performed again. In addition, a number of other sensitivity analyses were also performed (see below). Please refer to the original submission for more details.

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**.

Sensitivity analyses performed in the original submission

We repeated the same sensitivity analyses as in the original submission on the new base case. Please refer to the original submission for further details.

Additional sensitivity analyses performed in this addendum

1. Threshold analysis for post-induction response rates

Whilst CTD is the combination for which there is the most clinical experience in the UK for induction prior to SCT, a lack of clinical evidence comparing VTD to CTD makes it impossible to conduct a robust economic analysis for this pair of regimens. Therefore, the economic evaluation comparing VTD against TD is presented in the original submission as well as in this addendum. As clinical experts suggested that the TD and CTD would have similar clinical effectiveness (Appendix 14 to the original submission), the economic evaluation comparing VTD and TD is of relevance to the UK clinical practice.

However, given the uncertainty of the relative effectiveness of TD compared to CTD, a sensitivity analysis was undertaken in the form of a threshold analysis whereby post-induction response rates for TD were increased until the ICER reached £30,000 per QALY gained.

2. Threshold analysis for overall survival

Due to the immaturity of OS data from the Pethema trial, historical data from the MRC VII trial were used in the base case analysis. However, treatment of multiple myeloma has advanced since the MRC VII trial results were published in 2003 (7), possibly narrowing the gap in OS between those who have achieved CR and those who have not. If this were the case, the incremental benefit of VTD over TD would be smaller than in the base case since the difference in OS across induction response categories is one of the drivers of the incremental benefit. In order to assess the robustness of the base case results, threshold analyses were conducted whereby median survival for PR and 'NR' (MR and below) were increased by the same number of months until the ICER reached £30,000 per QALY gained.

3. Assumption related to the patient level data analysis

A number of assumptions must be made in order to adapt the patient level data analysis results from Pethema in the economic evaluation incorporating the discontinuation rule (Section 6.5 above). In particular, it is assumed that those patients who achieve at least a PR after the 6th cycle will have achieved that level of response after the 4th cycle.

In a sensitivity analysis, a proportion of patients who achieved PR as the final post-induction response were assumed not to have achieved PR after the 4th cycle (thus would have discontinued the VTD regimen without receiving the 5th and 6th cycles), and this proportion was varied to assess its impact on the ICER,

Summary of scenario analyses

The scenario analyses are summarised in the table below. Analyses that are new in this addendum are shown in the **blue bold font**.

Table 9: Summary of scenario analyses

<table>
<tr><th>Parameters</th><th>Base-case</th><th>Scenario analyses</th></tr>
<tr><td rowspan="3">Post-induction response rates</td><td rowspan="3">Pethema (section 7.3.1 of the original submission)</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>Use of 95% CI to test the impact of each post-induction response category</td></tr>
<tr><td>Threshold analysis whereby response rates for TD are improved until the ICER reached £30,000 per QALY gained</td></tr>
<tr><td rowspan="2">OS by post-induction response category up to death” health-state</td><td rowspan="2">MRC VII (section 7.3.1 of the original submission)</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>Threshold analysis whereby median survival for PR and NR are increased by the same number of months until the ICER reached £30,000 per QALY gained</td></tr>
<tr><td>TTP for 1st line (post-transplant / post-induction)</td><td>Pethema (section 7.3.1 of the original submission)</td><td>A log-logistic distribution of TTP data from Pethema will be tested.</td></tr>
<tr><td rowspan="2">Number of cycles with VTD and TD</td><td rowspan="2">VTD: Section 7.3 above
TD: Section 7.3.6 of the original submission</td><td>4 cycles for all induction therapies
5 cycles for all induction therapies
6 cycles for all induction therapies</td></tr>
<tr><td>In the VTD arm, out of those who achieved PR;
• 5% achieved less than PR after cycle 4
• 10% achieved less than PR after cycle 4
• 25% achieved less than PR after cycle 4
thus discontinued VTD after cycle 4</td></tr>
</table>

Health state utility values	Van Agthoven 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
	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

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**.

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).**

Please refer to the original submission.

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.**

Please refer to the original submission.

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 are presented in separate spreadsheets within the economic model. Table 10 and Table 11 below provide the first 20 rows of the Markov trace for VTD and TD.

Table 10: First 20 rows of the Markov trace for 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	1.00										0.00
3	0.99										0.01
4	0.99										0.01
5	0.98										0.02
6	0.98										0.02
7	0.00	0.79					0.08	0.11			0.02
8	0.00	0.79					0.07	0.11			0.03
9	0.00	0.79					0.07	0.10	0.01		0.04
10	0.00	0.00	0.78				0.07	0.09	0.02		0.04
11	0.00	0.00	0.76	0.01			0.07	0.08	0.03	0.00	0.05
12	0.00	0.00	0.74	0.02			0.06	0.07	0.03	0.00	0.07
13	0.00	0.00	0.72	0.03	0.00		0.06	0.06	0.03	0.01	0.08
14	0.00	0.00	0.71	0.04	0.00		0.06	0.05	0.04	0.01	0.09
15	0.00	0.00	0.69	0.04	0.01	0.00	0.06	0.05	0.04	0.01	0.11
16	0.00	0.00	0.67	0.05	0.01	0.00	0.06	0.04	0.04	0.02	0.12
17	0.00	0.00	0.65	0.05	0.01	0.00	0.06	0.04	0.04	0.02	0.13
18	0.00	0.00	0.64	0.06	0.02	0.00	0.05	0.03	0.04	0.02	0.14
19	0.00	0.00	0.62	0.06	0.02	0.00	0.05	0.03	0.03	0.03	0.15
20	0.00	0.00	0.61	0.06	0.02	0.00	0.05	0.03	0.03	0.03	0.17

Table 11: First 20 rows of the Markov trace for 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					0.05	0.31			0.05
8	0.00	0.58					0.05	0.31			0.06
9	0.00	0.58					0.05	0.27	0.03		0.07
10	0.00	0.00	0.58				0.05	0.24	0.06		0.07
11	0.00	0.00	0.56	0.01			0.05	0.21	0.07	0.00	0.09
12	0.00	0.00	0.55	0.02			0.05	0.18	0.09	0.01	0.11
13	0.00	0.00	0.53	0.03	0.00		0.04	0.16	0.10	0.02	0.13
14	0.00	0.00	0.51	0.04	0.00		0.04	0.14	0.10	0.03	0.14
15	0.00	0.00	0.49	0.04	0.01	0.00	0.04	0.12	0.10	0.03	0.16
16	0.00	0.00	0.48	0.04	0.01	0.00	0.04	0.11	0.10	0.04	0.18
17	0.00	0.00	0.46	0.05	0.01	0.00	0.04	0.10	0.10	0.05	0.19
18	0.00	0.00	0.45	0.05	0.01	0.00	0.04	0.08	0.09	0.06	0.21
19	0.00	0.00	0.44	0.05	0.02	0.00	0.04	0.07	0.09	0.07	0.22
20	0.00	0.00	0.42	0.05	0.02	0.00	0.04	0.06	0.09	0.08	0.24

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.**

Please refer to the original submission.

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 12: Model outputs by clinical outcomes (discounted)

	LY	QALY	Cost (£)	LY	QALY	Cost (£)
Outcome	**VTD**			**TD**		
Induction treatment	0.49	0.28	£25,167	0.49	0.27	£7,265
Stem cell transplant	0.19	0.12	£16,691	0.14	0.09	£12,405
Post-induction PFS	2.63	1.89	£2,611	1.80	1.29	£1,782
Post-progression survival	2.72	1.73	£31,706	2.14	1.36	£34,042
Overall survival	6.03	4.02	£76,174	4.57	3.01	£55,493

LY, life years; QALY, quality-adjusted life year; TD: thalidomide and dexamethasone; TTP: time to progression; VTD: Velcade® (bortezomib), thalidomide and 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 13: Summary of QALY gain by health state

Heath state	QALY VTD	QALY TD	Increment	Absolute increment	% absolute increment
Induction period	0.28	0.27	+0.00	0.00	0.2%
SCT period	0.12	0.09	+0.03	0.03	3.0%
Post-induction PFS	1.89	1.29	+0.60	0.60	56.9%
2nd line	0.24	0.26	-0.02	0.02	1.9%
3rd line	0.18	0.19	-0.00	0.00	0.4%
Further line	1.31	0.91	+0.40	0.40	37.6%
Total	4.02	3.01	+1.01	1.06	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

Table 14: Summary of costs by health state

Heath state	Cost VTD	Cost TD	Increment	Absolute increment	% absolute increment
Induction period	£25,167	£7,265	+£17,903	£17,903	67.4%
SCT period	£16,691	£12,405	+£4,286	£4,286	16.1%
Post-induction PFS	£2,611	£1,782	+£829	£829	3.1%
2nd line	£12,391	£14,127	-£1,735	£1,735	6.5%
3rd line	£14,476	£15,480	-£1,004	£1,004	3.8%
Further line	£2,014	£1,402	+£612	£612	2.3%
End of life	£2,824	£3,033	-£209	£209	0.8%
Total	£76,174	£55,493	+£20,682	£26,578	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

Table 15: Summary of predicted resource use by category of cost

Heath state	Cost VTD	Cost TD	Increment	Absolute increment	% absolute increment
Induction - chemo drug	£22,493	£5,493	+£17,000	£17,000	64.0%
Induction - prophylaxis	£253	£194	+£59	£59	0.2%
Induction - monitoring	£2,421	£1,577	+£844	£844	3.2%
SCT - mobilisation	£1,295	£962	+£333	£333	1.3%
SCT - ablation	£347	£258	+£89	£89	0.3%
SCT - transplant	£13,702	£10,183	+£3,518	£3,518	13.2%
SCT - post-transplant	£1,347	£1,001	+£346	£346	1.3%
Post-induction PFS	£2,611	£1,782	+£829	£829	3.1%
2nd line - VD	£9,913	£11,301	-£1,388	£1,388	5.2%
2nd line - CTDa	£1,859	£2,119	-£260	£260	1.0%
2nd line - HDD	£620	£706	-£87	£87	0.3%
3rd line - RD	£10,857	£11,610	-£753	£753	2.8%
3rd line - CTD	£2,895	£3,096	-£201	£201	0.8%
3rd line - HDD	£724	£774	-£50	£50	0.2%
Further line	£2,014	£1,402	+£612	£612	2.3%
End of life	£2,824	£3,033	-£209	£209	0.8%
Total	£76,174	£55,493	+£20,682	£26,578	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

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 16 below.

Table 16: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) incre-mental (QALYs)
VTD	£55,493	4.57	3.01	+£20,682	+1.47	+1.01	**£20,468**
TD	£76,174	6.03	4.02				

Sensitivity analyses

7.7.7 **Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.**

The deterministic sensitivity analysis illustrates the influence of the parameters across their ranges on the incremental cost-effectiveness ratio. In all cases, the ICER remains below £30,000/QALY (Figure 7, Table 17).

Figure 7: Tornado diagram

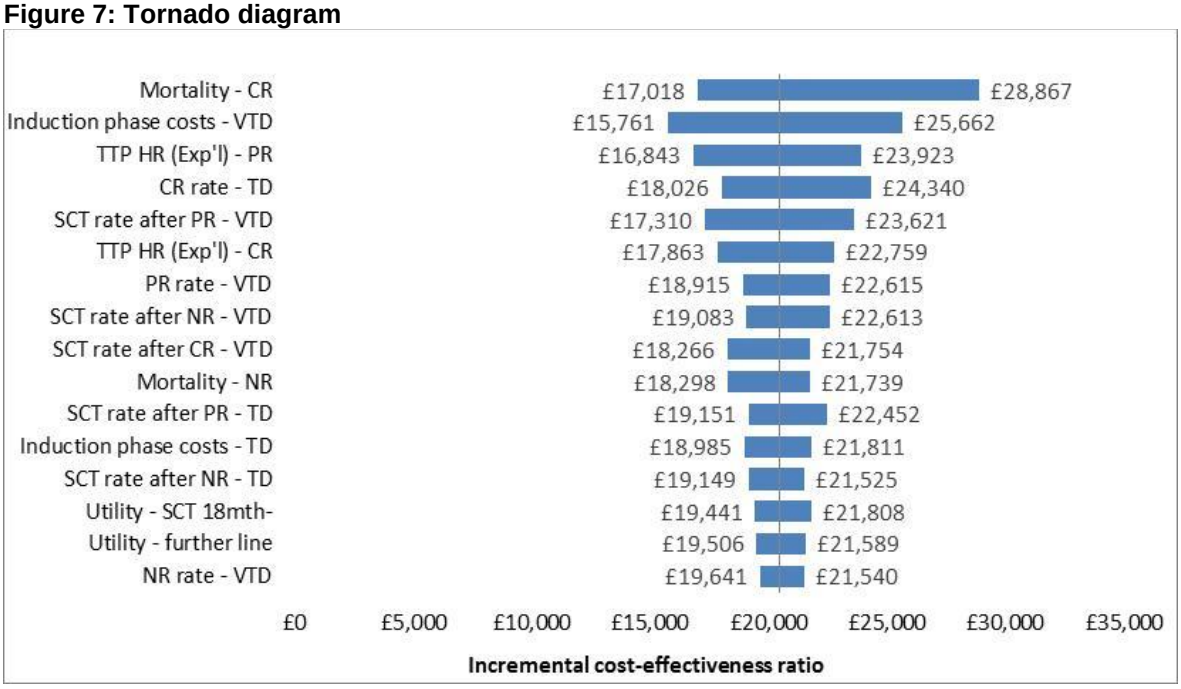


Table 17: Deterministic sensitivity analysis results for most sensitive parameters

Parameter	Lower input	Base case	Higher input	Lower input ICER	Higher input ICER	Difference
Mortality - CR	0.6%	0.8%	1.1%	£17,018	£28,867	£11,848
Induction phase costs - VTD	£22,513	£27,793	£33,620	£15,761	£25,662	£9,901
TTP HR (Exp'l) - PR	0.538	1.007	1.886	£16,843	£23,923	£7,080
CR rate - TD	11.3%	17.3%	24.3%	£18,026	£24,340	£6,315
SCT rate after PR - VTD	70.5%	82.6%	92.0%	£17,310	£23,621	£6,311
TTP HR (Exp'l) - CR	0.609	1.615	4.282	£17,863	£22,759	£4,896
PR rate - VTD	27.4%	35.4%	43.8%	£18,915	£22,615	£3,700
SCT rate after NR - VTD	9.1%	25.0%	45.6%	£19,083	£22,613	£3,530
SCT rate after CR - VTD	91.5%	96.9%	99.6%	£18,266	£21,754	£3,488
Mortality - NR	2.2%	2.7%	9.4%	£18,298	£21,739	£3,441
SCT rate after PR - TD	80.0%	89.3%	95.9%	£19,151	£22,452	£3,301
Induction phase costs - TD	£7,009	£8,653	£10,467	£18,985	£21,811	£2,826
SCT rate after NR - TD	6.1%	14.3%	25.2%	£19,149	£21,525	£2,377
Utility - SCT 18mth-	0.630	0.750	0.853	£19,441	£21,808	£2,368
Utility - further line	0.559	0.644	0.725	£19,641	£21,540	£1,899

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

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 cost-effectiveness plane in Figure 8. The cost-effectiveness acceptability curve is presented in Figure 9. The probability that bortezomib-based induction regimen (VTD) is a cost effective option over thalidomide-based induction regimen (TD) at £20,000 and £30,000 thresholds is estimated to be 35.4% and 71.3%, respectively.

Figure 8: Cost effectiveness plane for VTD versus TD

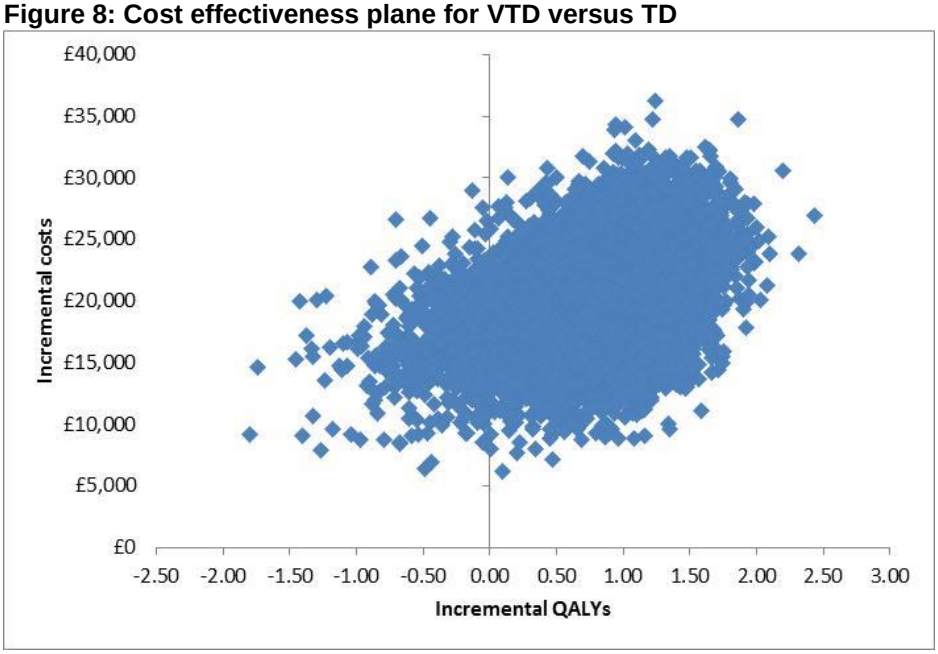
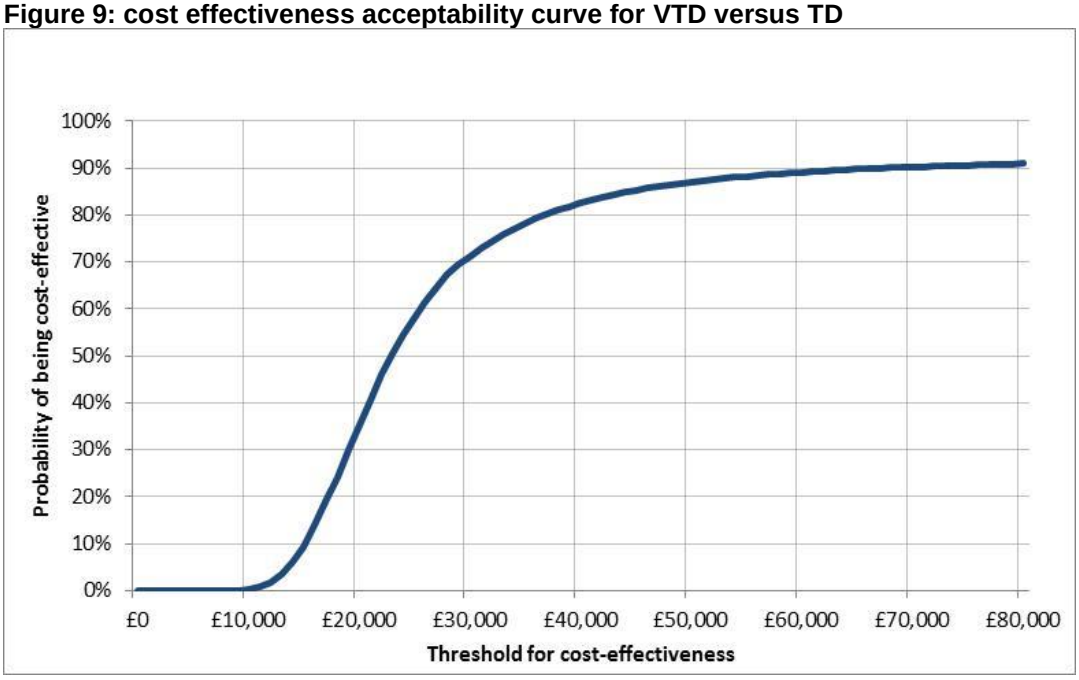


Figure 9: cost effectiveness acceptability curve for VTD versus TD



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 18 shows the results of the same sensitivity analyses as in the original submission performed on the new base case.

Table 18: Results of the same sensitivity analyses as in the original submission performed on the new base case

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	+£20,682	+1.01	**£20,468**
Post-induction response rates			
GIMEMA study	+£21,484	+0.88	**£24,321**
VTD: CR=57.0%, PR=43.0%, NR=0.0%	+£19,855	+1.01	**£19,581**
VTD: CR=34.2%, PR=43.8%, NR=22.0%	+£19,715	+0.80	**£24,624**
VTD: CR=40.7%, PR=27.4%, NR=31.9%	+£21,548	+1.00	**£21,477**
VTD: CR=62.9%, PR=27.4%, NR=9.7%	+£21,598	+1.20	**£17,935**
TD: CR=24.3%, PR=52.8%, NR=22.9%	+£21,096	+0.81	**£25,898**
TD: CR=0.0%, PR=52.8%, NR=47.2%	+£21,064	+1.42	**£14,816**
TD: CR=11.3%, PR=35.6%, NR=53.1%	+£20,279	+1.18	**£17,157**
TD: CR=34.1%, PR=35.6%, NR=30.3%	+£20,309	+0.61	**£33,166**
OS by post-induction response			
IFM90 study	+£25,177	+1.64	**£15,339**
TTP for 2nd line (post-transplant / post-induction)			
Weibull distribution	+£22,111	+0.99	**£22,444**
Log-logistic distribution	+£22,163	+0.99	**£22,449**
Number of cycles with VTD and TD			
4 cycles for all patients on induction therapy	+£15,412	+1.01	**£15,252**
5 cycles for all patients on induction therapy	+£18,532	+1.01	**£18,340**
6 cycles for all patients on induction therapy	+£21,637	+1.01	**£21,413**
Health state utility values			
Uyl-de-Grrot et al.	+£20,682	+0.90	**£23,099**
Decline in HRQoL following SCT only lasts 6 months	+£20,682	+1.04	**£19,829**
AE-related disutility value			
0.05 utility decrements	+£20,682	+1.01	**£20,504**
Time horizon			
10 years	+£19,179	+0.61	**£31,507**
15 years	+£20,117	+0.81	**£24,891**
Discount rates			
3.5% costs and 0% outcomes	+£20,682	+1.45	**£14,248**
3.5% costs and 6% outcomes	+£20,682	+0.81	**£25,532**
0% costs and 3.5% outcomes	+£22,922	+1.01	**£22,685**
6% costs and 3.5% outcomes	+£19,537	+1.01	**£19,335**

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

Tables below (Table 19, Table 20, Table 21) show the results of the additional sensitivity analyses performed in this addendum.

Table 19: Threshold analysis for post-induction response rates from TD

	Post-induction response to TD			Incremental costs	Incremental QALYs	ICER
	CR	PR	NR			
Base case: *Pethema trial*						
	17.3%	44.1%	38.6%	+£20,682	+1.01	**£20,468**
Scenario 1: *Higher CR, lower PR, same NR rates vs. base case*						
	32.6%	28.8%	38.6%	+£19,991	+0.67	**£30,000**
Scenario 2: *Same NR rate as VTD in Pethema. Higher CR, lower PR rates vs. base case*						
	28.2%	56.4%	15.4%	+£21,270	+0.71	**£30,000**

Table 20: Threshold analysis for overall survival

	Median survival (months)			Incremental costs	Incremental QALYs	ICER
	CR	PR	NR			
Base case: *MRC VII*						
	88.6	39.8	25.6	+£20,682	+1.01	**£20,468**
Scenario: *Median survival same for CR, but higher for PR and NR by the same number of months vs. base case*						
	88.6	62.7	48.5	+£19,128	+0.64	**£30,000**
Difference vs. base case						
months	±0	+22.9	+22.9			
percentage	±0%	+58%	+89%			

Table 21: Assumption related to the patient level data analysis

% of PR patients in VTD arm of Pethema who have achieved less than PR after cycle 4	Incremental costs	Incremental QALYs	ICER
Base case: *0% (All PR patients in VTD arm will have achieved PR after cycle 4 already)*			
	+£20,682	+1.01	**£20,468**
Scenario 1: *5% of PR patients in VTD arm will have achieved less than PR after cycle 4*			
	+£20,533	+1.01	**£20,320**
Scenario 2: *10% of PR patients in VTD arm will have achieved less than PR after cycle 4*			
	+£20,384	+1.01	**£20,173**
Scenario 3: *25% of PR patients in VTD arm will have achieved less than PR after cycle 4*			
	+£19,937	+1.01	**£19,730**

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 £17,018/QALY to £28,867/QALY. For the VTD drug costs, the ICER range is £15,761/QALY to £25,662/QALY. For all other parameters, the ICER remains within the £16,000/QALY-£25,000/QALY range.

The scenarios analyses further supported the cost-effectiveness of VTD with ICERs remaining below £30,000/QALY for most of scenarios, except where CR rates for TD

are nearly double compared to the actual result from Pethema, or a time horizon of 10 years is applied (see Table 18). Given that approximately 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.

The threshold analysis for TD's post-induction response rates (Table 19) examines how much clinical benefit cyclophosphamide would have to provide when added to TD alone in order for the ICER to reach the £30,000/QALY-mark. The analysis results indicate that additional benefit from cyclophosphamide would have to be substantial for this to be the case. For example, in scenario 1, the CR rate would have to be nearly double that observed in the Pethema result with TD (32.6% vs. 17.3%) for the ICER for VTD to increase to above £30,000/QALY. This threshold analysis indicates that the base case result is not particularly sensitive to the addition of cyclophosphamide to the TD regimen. As stated in our original submission, clinical experts suggested that TD and CTD regimens would be expected to have similar effectiveness.

In another threshold analysis, we investigated how high median survival for patients with post-induction response of PR and NR would have to rise before the ICER reached £30,000/QALY. The results in Table 20 indicate that the gap in median OS between CR- and PR-/NR-patients would have to narrow by nearly 2 years (22.9 months) and median OS would have to rise by 58% and 98% for PR- and NR-patients, respectively, in order for the ICER to reach £30,000/QALY. It may not be realistic for the OS for PR- and NR-patients to have improved by this magnitude, while, at the same time, OS for CR-patients has remained at the same level since the MRC VII was published in 2003 (7). According to the Scottish Cancer Registry, an improvement in OS of a similar magnitude can only be observed when the median survival of the MM patients who were diagnosed in 2003-2007 is compared against that of those who were diagnosed in 1980's (Table 22) (8).

Table 22: Median observed survival for multiple myeloma patients by period of diagnosis (8)

	Period of diagnosis				
	1983-1987	1988-1992	1993-1997	1998-2002	2003-2007
Median observed survival (years)	1.5	2.0	2.3	2.8	3.6

The analysis in Table 21 demonstrates that it is conservative to assume that those patients who achieve PR or better after the 5th or 6th cycle will have achieved this response after the 4th cycle already. If some of PR patients were to achieve less than PR after the 4th cycle, the ICER would decrease, making VTD more cost-effective against TD than in the base case, because incremental costs would decline while incremental QALYs would remain the same.

At the £20,000 and £30,000 willingness to pay thresholds, the probability for VTD to be cost-effective vs. TD is 35.4% and 71.3%, respectively (Table 23).

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.

Table 23: Cost-effectiveness of VTD 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	35.4%
£30,000	71.3%
TD, thalidomide and dexamethasone; VTD, Velcade® (bortezomib), thalidomide and 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), and the induction drug costs.

7.8 Validation

7.9 Subgroup analysis

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 VTD vs. TD 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 the independently conducted, methodologically robust Pethema trial providing a comparison between VTD and a thalidomide-based induction regimen (TD). Also, a comprehensive systematic literature search was conducted to identify data relevant to the model.

The chosen structure of the economic model follows the clinical pathway for the patient population relevant to the decision problem. Moreover, the modelling approach is based upon the primary end-point of the Pethema trial (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 trial 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 Pethema trial. 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 VTD vs. CTD, i.e. the current standard of care in the UK, we had to assume similar clinical effectiveness between CTD and TD. Without this assumption, we would not have been able to use the Pethema trial data for this economic evaluation. Nevertheless, the threshold analysis demonstrated that the ICER is not sensitive to this assumption.

7.10.4	**What further analyses could be undertaken to enhance the robustness/completeness of the results?**

In the future, once the Pethema trial data become mature, the economic evaluation could be repeated using OS derived directly from the trial.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

Please refer to the original submission, but ignore the market share and budget impact related to the PAD regimen.

9 References

Reference List

(1) Janssen-Cilag Ltd. Bortezomib Summary of Product Characteristics (Draft). 2013 Jul 19.

(2) Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomised phase 3 study. Lancet 2010;376(9758):2075-85.

(3) Rosinol L, Oriol A, Teruel A.I. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood 2012;120(8):1589-96.

(4) Bird JM, Owen RG, D'Sa S, Snowden JA, Pratt G, Ashcroft J, et al. Guidelines for the diagnosis and management of multiple myeloma 2011. Br J Haematol 2011 Jul;154(1):32-75.

(5) van de Velde HJ, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Haematologica 2007 Oct;92(10):1399-406.

(6) Janssen-Cilag Ltd. CSR Protocol 26866138-MMY-3010 (GEM05MENOS65): A phase III national, open label, multicenter, randomized, comparative study of VBMCP-VBAD/Velcade versus thalidomide/dexamethasone versus Velcade/thalidomide/dexamethasone as induction therapy, followed by high-dose chemotherapy with autologous hematopoietic transplantation and subsequent maintenance treatment with interferon alpha-2b versus thalidomide versus thalidomide/Velcade in patients with multiple myeloma. 2012.

(7) Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003 May 8;348(19):1875-83.

(8) ISD Scotland. Trends in cancer survival in Scotland, 1983-2007. ISD Scotland . 2013.
Ref Type: Online Source

10 Appendices

Appendix 1 Draft SmPC for Velcade