[redacted] – Appraisals
Centre for Health Technology Evaluation

12th April 2013

Dear [redacted],

Re: Single Technology Appraisal – Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT)

Thank you for providing Janssen with an opportunity to respond to the issues that were raised by the Evidence Review Group (Southampton Health Technology Assessment Centre) and the technical team at NICE. The clarification questions provided were helpful in laying out those areas of our submission that required further clarification. We have addressed each of these comments in turn in this letter.

Please do not hesitate to contact me should you require further information.

Yours sincerely,

[redacted]

Section A: Clarification on effectiveness data

General

A1. The references supplied separately from the submission (on compact disc) contained 215 of 220 references – references 37, 85, 126, 163 & 216 were not included. Please could you supply these?

The 5 references have been sent to NICE on a CD on Friday 5th April 2013.

Literature searching

A2. Were any searches for ongoing trials carried out? If so, please supply details of what sources were searched, dates and studies identified.

A search for ongoing trials was carried out in clinicaltrials.gov on 18 September 2012. A total of eight relevant ongoing trials were identified (Table 1). None of these reported study results. The search strategy is presented in Appendix 1.

Table 1. Ongoing trials identified

Title	URL
Study to Compare VMP With HDM Followed by VRD Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma	http://ClinicalTrials.gov/show/NCT01208766
Randomized Study of Velcade-based Regimen With Autologous Stem Cell Transplantation in Newly-diagnosed Myeloma Patients	http://ClinicalTrials.gov/show/NCT00984828
Combination Chemotherapy With or Without Thalidomide in Treating Patients With Multiple Myeloma	http://ClinicalTrials.gov/show/NCT00028886
High-Dose Chemotherapy and Stem Cell Transplant in Treating Patients With Newly Diagnosed Stage I, Stage II, or Stage III Multiple Myeloma	http://ClinicalTrials.gov/show/NCT00526734
Study of Combination Thalidomide Plus Glucocorticoid Therapy Versus Glucocorticoid Therapy Alone as Induction Therapy for Previously Untreated Subjects With Multiple Myeloma	http://ClinicalTrials.gov/show/NCT00057564
Velcade (Bortezomib) Consolidation After Transplant	http://ClinicalTrials.gov/show/NCT01539083
SWOG-9321 Melphalan, TBI, and Transplant vs Combo Chemo in Untreated Myeloma	http://ClinicalTrials.gov/show/NCT00002548
Study in Myeloma Patients Newly Diagnosed Treated as an Induction With Velcade-Dex or Velcade (Bortezomib) Thalidomide Dexamethasone (VTD)	http://ClinicalTrials.gov/show/NCT00910897

Clinical effectiveness

A3. The last box in the flow diagram in figure 3, page 45, reports 53 studies, including 15 RCTs – please clarify whether the remaining 38 studies were non-RCTs.

The remaining 38 studies were non-RCTs.

A4. Table 16, page 51-52: the submission reports safety as an 'other endpoint' for the PETHEMA trial whilst the journal publication reports it as a secondary outcome; also, the submission reports a median duration of follow-up of 35.9 months whilst the publication reports 35.2 months. Please clarify these discrepancies.

We are aware of a number of discrepancies between the clinical study report (CSR) and the publication of the Pethema, Hovon and IFM trials and this issue was communicated to NICE during the decision problem teleconference in December

2012. These numerous discrepancies could not be clarified because these trials were all independently conducted and not sponsored by Johnson & Johnson.

When discrepancies were identified Janssen presented the data from the CSR.

In the CSR of the Pethema trial, safety is not listed as a secondary endpoint (page 38) and the median duration of follow-up is 35.9 months (page 75).

A5. **Priority question.** We note that the submission identifies the two primary outcomes in the PETHEMA trial as complete response, near complete response and partial response (CR+nCR+PR) and CR/nCR. However, these appear have been reported as complete response in the corresponding journal publication for the PETHEMA trial. Please could you clarify this?

As stated in our response to question A4, there are discrepancies between the data reported in the CSR and the publication of the trials. As mentioned, the studies were conducted independently by the investigators; therefore Janssen cannot explain why the investigators have chosen to report the endpoints differently.

The two primary efficacy endpoints reported in our submission are described in the CSR of the Pethema trial on pages 37 and 38.

A6. **Priority question.** With regard to the IFM trial, it is stated on page 54 (section 6.3.2.2) that '*.... the results of the VD and VAD arms with DCEP are not reported*'. On page 82 it is stated that '*stratified results based upon patient receipt of DCEP are not reported.*' However, results from the IFM trial (reported in relevant tables 24 – 53) have different n values (VAD n=121 or 242; VD n=121 or 240). Please clarify and submit the correct data.

The statement on page 54 is incorrect. The statement on page 82 is correct. The results of the VD and VAD arms in the IFM trial presented in tables 24 to 45 include all patients in the VD (n=240) and VAD (n=242) arms (with and without DCEP). All results presented in section 7 on cost-effectiveness (tables 46 to 53) are those of the VD without DCEP (n=120) and VAD without DCEP (n=121) arms. They are based upon a re-analysis of patient level data of the IFM trial as these were not reported in the publication or the CSR of the trial.

In order to align the clinical section with the economic section, we present the following results of the VD (n=120) and VAD (n=121) arms without DCEP in the IFM trial:

- Efficacy endpoints:
    - Response rates
    - Progression free survival
    - Time to progression
    - Overall survival
    - Proportion of patients receiving a stem cell transplant.

- Updated mixed treatment comparison, based on the inclusion of the VD and VAD arms without DCEP in the IFM trial.

- Adverse events

Table 2. Response rates post-induction and post-transplant for the VD and VAD arms without DCEP

Study name	Induction regimen	% (n/N)	Odds ratio (95% CI), p value	% (n/N)	Odds ratio (95% CI), p value	Reference
		ORR post-induction*		**ORR post-transplant***		Re-analysis of patient level data
IFM	VD	77.5 (93/120)	2.34 (1.34-4.11), p=0.0029	93.4 (99/106)	1.75 (0.65-4.70), p=0.2689	
	VAD	59.5 (72/121)		89.0 (89/100)		
		CR post-induction		**CR post-transplant**		
IFM	VD	6.7 (8/120)	4.25 (1.04-28.56), p=0.071	18.9 (20/106)	1.32 (0.64-2.78), p=0.4609	
	VAD	1.7 (2/121)		15.0 (15/100)		
		Near CR post-induction		**Near CR post-transplant**		
IFM	VD	12.5 (15/120)	2.95 (1.34-7.01), p=0.0095	21.7 (23/106)	1.52 (0.86-2.71), p=0.1536	
	VAD	5.8 (7/121)		16.0 (16/100)		
		VGPR post-induction		**VGPR post-transplant**		
IFM	VD	21.7 (26/120)	3.70 (2.04-6.95), p<0.0001	33.0 (35/106)	2.57 (1.44-4.65), p=0.0015	
	VAD	8.3 (10/121)		21.0 (21/100)		
		Partial response post-induction		**Partial response post-transplant**		
IFM	VD	36.7 (44/120)	-2.34 (1.35-4.15), p=0.0029	19.8 (21/106)	1.75 (0.66-4.93), p=0.2689	
	VAD	43.8 (53/121)		37.0 (37/100)		
		Progressive disease post-induction		**Progressive disease post-transplant**		
IFM	VD	6.7 (8/120)	1.16 (0.40-3.42), p=0.7772	0.9 (1/106)	0.94 (0.11-7.97), p=0.9531	
	VAD	5.8 (7/121)		0 (0/100)		

* In the IFM trial ORR is defined as the sum of CR, near CR, VGPR and PR

Table 3. Median PFS (months), and HR of PFS for the VD and VAD arms without DCEP

Study name	Induction regimen	ITT N	Median (95% CI)	Setting adjustment	HR (95% CI) p value	Reference
IFM	VD	120	36.0 (32.4, --)	Unadjusted Read from survival curve	HR = 0.657 (0.457-0.943), p=0.0228	Re-analysis of patient level data
	VAD	121	26.6 (23.4-37.1)			

Figure 1. PFS Kaplan-Meier curves reported in the IFM trial (VD and VAD arms without DCEP)

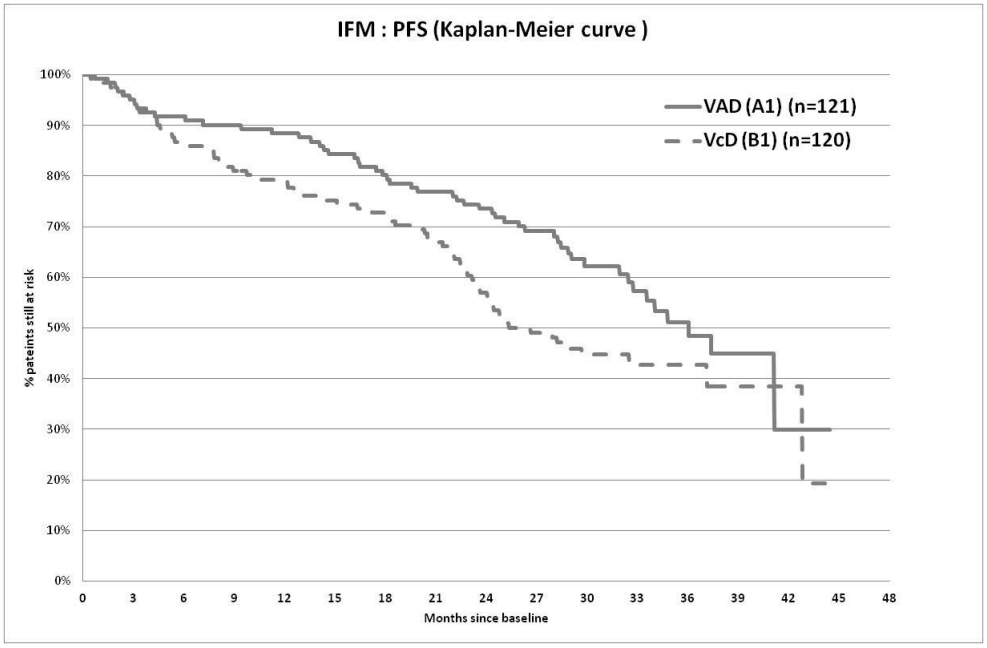

Table 4. Median TTP (months), and HR (hazard of progression) for TTP comparing VD and VAD arms without DCEP

Study name	Induction regimen	ITT N	Median (95% CI)	Setting adjustment	HR (95% CI); p value	Reference
IFM	VD	120	36.0 (32.7, --)	Unadjusted Read from survival curve	HR = 0.658 (0.455-0.953), p=0.0266	Re-analysis of patient level data
	VAD	121	27.9 (23.4, --)			

Figure 2. TTP Kaplan-Meier curves reported in the IFM trial (VD and VAD arms without DCEP)

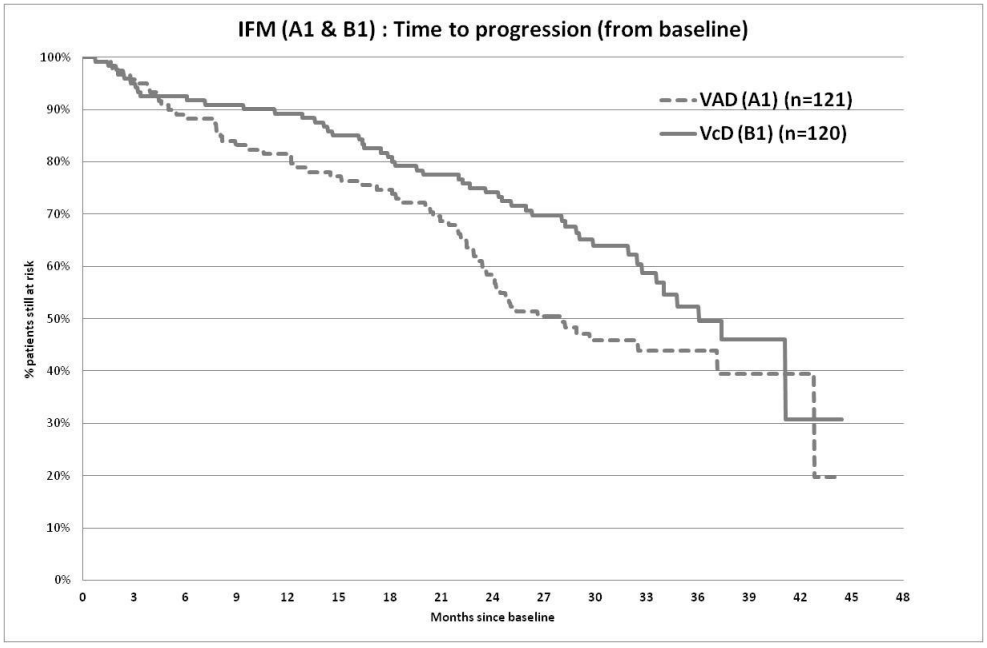

Table 5. Median OS (months) and HR of death comparing VD and VAD arms without DCEP

Study name	Induction regimen	ITT N	Median (95% CI)	Setting	HR (95% CI), p value	Reference
IFM	VD	120	Not reached	Unadjusted Read from survival curve	HR = 0.755 (0.414-1.379), p=0.3612	Re-analysis of patient level data
	VAD	121	Not reached			

Table 6. Proportion of randomised patients who underwent SCT following induction regimens

Study name	Induction regimen	% patients (n/N) *	Reference
IFM	VD	88.3% (100/121)	Re-analysis of patient level data
	VAD	82.6% (106/120)	

Mixed treatment comparison (MTC)

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. The FE model had the lowest DIC (best fit) for the TTP endpoint and was therefore selected for reporting results (Table 7, Table 8, Table 9) The RE (vague) model had the lowest DIC for the OS endpoint (Table 7); however the 95% CrI are wide and not clinically plausible. Therefore a fixed effect model was chosen for the OS endpoint in the base-case analysis of the MTC (Table 10, Table 11) and the results using a random effect model are presented in a sensitivity analysis (Table 12, Table 13).

Table 7. Comparison of DIC from fixed effect and random effect models

Response	Fixed effects	Random effects (flat)	Random effects (vague)	Random effects (weakly inf.)
OS	1.663	1.658	1.657	1.660
TTP	-2.902	-1.165	-1.392	-1.519

- **TTP endpoint**

Table 8: 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		0.70	0.47-1.04
VTD		0.63	0.49-0.81
PAD	vs. VAD/CVAD	0.79	0.66-0.95
VD		0.66	0.46-0.95
VTD		0.60	0.45-0.80

Table 9: Probability of superiority with respect to TTP for different treatment regimens (fixed effect model)

Intervention	Probability of superiority of TTP for different treatment regimens		
Comparators	**PAD (%)**	**VD (%)**	**VTD (%)**
CTD/TD	92.6	96.1	100.0
VAD/CVAD	99.4	98.7	100.0

- **OS endpoint – base case analysis: fixed effect model**

Table 10: 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		0.82	0.44-1.55
VTD		0.80	0.48-1.34
PAD	vs. VAD/CVAD	0.80	0.62-1.03
VD		0.75	0.42-1.38
VTD		0.74	0.42, 1.28

Table 11: Probability of superiority with respect to OS for different treatment regimens (fixed effects model)

Intervention	Probability of superiority of OS for different treatment regimens		
Comparators	**PAD (%)**	**VD (%)**	**VTD (%)**
CTD/TD	80.2	73.1	80.1
VAD/CVAD	96.1	82.2	86.2

- **OS endpoint – sensitivity analysis: random effect model (vague)**

Table 12: HR and CrL for all treatments for OS (random effects - vague)

Comparison	Comparator	Median	95% CrI
PAD	vs.CTD/TD	0.86	0.00-6,222.95
VD		0.82	0.00-6,348.67
VTD		0.79	0.00-478.19
PAD	vs. VAD/CVAD	0.80	0.00-423.27
VD		0.76	0.00-442.31
VTD		0.74	0.00-5,535.85

Table 13: Probability of superiority with respect to OS for different treatment regimens (random effects - vague)

Intervention	Probability of superiority of OS for different treatment regimens		
Comparators	**PAD (%)**	**VD (%)**	**VTD (%)**
CTD/TD	53.8	54.3	56.4
VAD/CVAD	57.1	57.5	56.2

Adverse events results

Table 14. Any reported adverse events for VD and VAD arms without DCEP (post-induction)

Induction regimen	IFM		
	VD n (%)	**VAD n (%)**	**RR (95% CI)**
Safety population	120	121	1
Any AE	120	121	1
Any grade 3/4 AE	88	94	0.94 [0.82-1.09]
Any serious AE	51	60	0.86 [0.65-1.13]
Any treatment-related AE	108	112	0.97 [0.90-1.05]

Table 15. 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	VD (n=121)	VAD (n=120)
Neutropenia	8%	10%
Anaemia	3%	5%
Leukopenia	8%	6%
Thrombocytopenia	12%	9%
Lymphopenia	9%	2%
Nausea	3%	4%
Back pain	0%	1%
Pyrexia	2%	4%
Mucosal inflammation	11%	18%
Febrile neutropenia	7%	6%
Vomiting	3%	1%
Asthenia	0%	3%
Pain	1%	0%
Herpes Zoster	0.8%	0.4%
Peripheral neuropathy incl. motor, sensory and polyneuropathy	6.3%	0.8%

A7. In Section 6.3.4 and table 18 (page 63-64), baseline characteristics were reported to be 'well balanced between treatment groups'. Please confirm if any statistical tests performed to support this? If so, please provide the results, for example the p-values, to support this.

No statistical test was performed.

A8. In section 6.3.6, page 68, the 'safety analysis set' is defined but no definition for the ITT population has been provided – please define.

The ITT population was defined as all patients randomised into each of the study arms, regardless of whether or not they actually received the study drug.

A9. In figure 11, page 76, the PETHEMA flow diagram reports 386 patients as randomised whilst the journal publication reports 390 patients were randomised but 4 were ineligible. Please explain the discrepancy in terms of the ITT population.

As stated in our response to question A4, there are discrepancies between the data reported in the CSR and the publication of the trials.

The CSR states that approximately 390 patients with a newly diagnosed, untreated, symptomatic multiple myeloma were planned to be enrolled in the study.

Figure 11 on page 76 of the submission is based upon figure 2 of the CSR of the Pethema trial (page 45), which shows that 386 patients are randomised into one of the three induction regimens:

- TD (thalidomide dexamethasone), N=127 patients
- VTD (bortezomib thalidomide dexamethasone), N=130

- VBMCP-VBAD/Vc (vincrystine/ bis-chloronitrosourea/ melphalan/ cyclophosphamide/prednisone, vincristine/ bis-chloronitrosourea/ Adriamycin/ dexamethasone, bortezomib), N=129

The number of patients randomised into each induction regimen group is the number of patients used for the ITT analysis.

A10. **Priority question.** Overall response rate (ORR) is defined as CR+nCR+VGPR+PR (page 67). However, in table 24 (page 83), for the PETHEMA and GIMEMA trials particularly, the data presented for ORR does not correspond to the sum of the data for the response rates individually. Please explain.

ORR is generally defined as CR+nCR+VGPR+PR, provided that all these response categories are reported and that patients only belong to one of them.

Pethema trial:

In the Pethema trial, response was assessed according to the criteria of the European Group for Blood and Bone Marrow Transplantation (EBMT, Table 5 of the submission). The publication states that the VGPR category was assessed in a post-hoc analysis. This explains why the VGPR category is not reported in the CSR.

In Table 24 of the submission, the CR and nCR are from the CSR and the VGPR is from the publication, as indicated by the references. The ORR reported in Table 24 is based on the CR, nCR and PR reported in the CSR.

Gimema trial:

In the Gimema trial, response was reported according to the criteria of the EBMT (Table 5 of the submission) with the addition of categories for nCR and VGPR.

ORR was defined as CR+nNR+VGPR+PR. The values for nCR, VGPR and PR are reported in Table 16 below in response to the question A11.

A11. **Priority question.** The GIMEMA trial publication reports 'VGPR *or better'* and 'PR *or better'* – how do these differ from VGPR and PR (values feeding into the ORR) reported in table 24 on page 83?

In the Gimema trial, 'VGPR or better' can be defined as the sum of VGPR, nCR and CR. 'PR or better', also known as ORR, can be defined as the sum of PR, VGPR, nCR and CR.

nCR, VGPR and PR from the Gimema trial have been omitted from Table 24. They can be calculated based upon the definition of 'VGPR or better' and 'PR or better' provided above. (Table 16)

Table 16. Post-induction and post-transplant response rates in the Gimema trial

Study name	Induction regimen	% (n/N)	P value	% (n/N)	P value	Reference
		ORR post-induction		**ORR post-1st transplant**		
Gimema	VTD	93 (220/236)	<0.0001	93 (220/236)	**0.0025**	(8)
	TD	79 (187/238)		84 (201/238)		
		CR post-induction		**CR post-1st transplant**		
Gimema	VTD	19 (44/236)	<0.0001	38 (89/236)	**0.0004**	
	TD	5 (11/238)		23 (54/238)		
		Near CR post-induction		**Near CR post-1st transplant**		
Gimema	VTD	12 (29/236)	-	14 (34/236)	-	
	TD	6 (16/238)		8 (20/1238)		
		VGPR post-induction		**VGPR post-1st transplant**		
Gimema	VTD	31 (73/236)	-	27 (63/236)	-	
	TD	17 (39/238)		27 (63/238)		
		Partial response post-induction		**Partial response post-1st transplant**		
Gimema	VTD	31 (74/236)	-	14 (34/236)	-	
	TD	51 (121/238)		26 (64/238)		
		Progressive disease post-induction		**Progressive disease post-1st transplant**		
Gimema	VTD	0.0 (0/236)	0.0005	<1 (1/236)	-	
	TD	5.0 (12/238)		7 (17/238)		

'-' indicates that the information was not reported

A12. **Priority question.** Please clarify how the response rates in table 24 (page 83) of the submission correspond with the response rates in the PETHEMA trial publication. For example, table 24 of the submission gives a percentage achieving PR of 35.4% on VTD, which compares with a figure of 25% for PR on VTD given in table 2 of the journal publication.

There are discrepancies in the response rate categories and percentage reported in the CSR and the publication of the Pethema trial. For example, nCR is reported in the CSR but not in the publication and VGPR is reported in the publication and not in the CSR because the VGPR category was assessed in a post-hoc analysis. The response rate of all patients is reported in the CSR (i.e. the sum of the patients in each category equals the total number of patients in the ITT analysis) while the response rate of some patients is missing in the publication (i.e. the sum of the patients for which a response rate is reported equals 108 in the VTD group while 130 patients were randomised to VTD and included in the ITT analysis). The differences between the response categories, % and number of responders in the CSR and the publication are presented in Table 17 below in blue font.

Table 17. Response rate post-induction in the Pethema trial

CSR % (n/N)			**Publication (Reference 9)** % (n*/N)		
Category of response	TD (n=127)	VTD (n=130)	Category of response	TD (n=127)	VTD (n=130)
CR	13.4 (17/127)	35.4 (46/130)	CR	14 (18/127)	35 (46/130)
nCR	3.9 (5/127)	13.8 (18/130)	VGPR	15 (19/127)	25 (33/130)
PR	44.1 (56/127)	35.4 (46/130)	PR	33 (42/127)	25 (33/130)
ORR (CR+nCR+PR)	61.4 (78/127)	84.6 (110/130)	ORR (CR+VGPR+PR)	62 (79/127)	75 (98/130)
PD	23.6 (30/127)	6.2 (8/130)	PD	23 (29/127)	7 (9/130)

*Only the % are reported in the publication. Therefore the 'n' have been calculated.

A13. Please clarify why some data points relating to progression-free survival are reported as "not reached" in table 25 on page 85 of the submission.

Not reached' was specified when the data was not available because the duration of follow-up was not long enough to provide the information. This is the case for the upper bound of the 95% CI for the median PFS in the Pethema trial.

The median PFS and 95% CI for the VTD and TD arms in the Gimema trial were not reported in the publication.

Table 18: 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)	Setting adjustment	HR (95% CI; p value)	Reference
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 reported	Unadjusted	0.63 (0.45, 0.88; p=0.0061)	(8)
	TD	238	Not reported			

Section B: Clarification on cost-effectiveness data

B1. **Priority question.** Please explain the approach and rationale taken in the economic model with respect to maintenance therapy during the post stem cell transplant (STC) period.

Maintenance therapy was administered post stem cell transplant in the Pethema, IFM and Hovon trials. This may confound the long-term outcomes in the trials such as overall survival, time to progression and progression free survival.

In the economic model, the only efficacy parameters driving the model are the post induction response rates (which is pre stem cell transplant) and overall survival. While the post-induction response rates are sourced from the Pethema, IFM and Hovon trials, overall survival is sourced from the MRC VII trial by Child et al. (reference 12 in the submission) Therefore, the efficacy in the model, as measured by overall survival and post-induction response rate, is not affected by the maintenance therapy post stem cell transplant.

Maintenance could affect the total costs in the model, however, as the transition probabilities from 1st line to 2nd line are based on the time to progression from the trials. It could be assumed that maintenance therapy would improve the time to progression; therefore adjusting for maintenance may shorten the time to progression. However, the trial data do not allow disentangling the induction treatment effect from the maintenance effect. In the Pethema trial, patients re-randomised to maintenance are mostly those achieving at least a partial response post-induction. In the IFM trial, patients with CR or VGPR after SCT were recruited to a follow on trial (IFM 2005-02) to evaluate maintenance treatment. In the Hovon trial, patients receiving the bortezomib-based induction regimen also received maintenance therapy with bortezomib. Therefore, no adjustment for maintenance was taken into account.

B2. **Priority question.** Please clarify if the figures in table 50 on page 123 of the submission relate to the PETHEMA or GIMEMA trial.

The figures for the VTD and TD arms in table 50 relate to the Pethema trial.

B3. **Priority question.** The caption for table 52 in the submission is 'Total SCT rates' but it has been noted that this was amended from 'SCT rates by post-induction response category' in an earlier version of the submission. If this data (i.e. breakdown by response category) is available please consider submitting it.

The SCT rates by post-induction response category are presented in Table 19, Table 20 and Table 21. Patients in the 'CR' category have a higher SCT rate than those in the PR or 'NR (non-responders)' category.

Table 19. SCT rate by post-induction response category in the Pethema trial

Post-induction response categories	Pethema	
	VTD % (n/N)	TD % (n/N)
CR category (CR+nCR)	**96.9 (62/64)**	**95.5 (21/22)**
CR	100% (46/46)	94.1 (16/17)
nCR	88.9 (16/18)	100 (5/5)
PR category	**82.6 (38/46)**	**89.3 (50/56)**
NR category (MR+No change+PD+Death+not evaluable)	**25.0 (5/20)**	**14.3 (7/49)**
MR	100 (2/2)	55.6 (5/9)
No change	42.9 (3/7)	14.3 (1/7)
PD	0 (0/8)	3.3 (1/30)
Death	0 (0/2)	0 (0/1)
Not evaluable / unknown	0 (0/1)	0 (0/1)
Total	**80.8 (105/130)**	**61.4 (78/127)**

Table 20. SCT rate by post-induction response category in the Hovon trial

Post-induction response categories	Hovon	
	PAD % (n/N)	VAD % (n/N)
CR category	**91.4 (191/209)**	**98.8 (80/81)**
CR	89.1 (41/46)	100.0 (12/12)
nCR	96.7 (29/30)	100.0 (14/14)
VGPR	91.0 (121/133)	98.2 (54/55)
PR category	**90.8 (129/142)**	**93.1 (162/174)**
NR category	**51.5 (34/66)**	**65.8 (106/161)**
MR	80.0 (12/15)	86.2 (56/65)
No change	83.3 (10/12)	69.0 (29/42)
PD	25.0 (1/4)	26.7 (4/15)
Not evaluable / unknown	31.4 (11/35)	43.6 (17/39)
Total	**84.9 (354/417)**	**83.7 (348/416)**

Table 21. SCT rate by post-induction response category in the IFM trial

Post-induction response categories	IFM	
	VD % (n/N)	VAD % (n/N)
CR category	**98.0 (48/49)**	**94.7 (18/19)**
CR	100.0 (8/8)	100.0 (2/2)
nCR	93.3 (14/15)	100.0 (7/7)
VGPR	100.0 (26/26)	90.0 (9/10)
PR category	**97.7 (43/44)**	**94.3 (50/53)**
NR category	**55.6 (15/27)**	**65.3 (32/49)**
MR	77.8 (7/9)	92.9 (13/14)
No change	66.7 (4/6)	82.4 (14/17)
PD	25.0 (2/8)	28.6 (2/7)
Not evaluable / unknown	50.0 (2/4)	27.3 (3/11)
Total	**88.3 (106/120)**	**82.6 (100/121)**

B4. In figure 14, page 85, please confirm that the graph marked (A) corresponds to the Hovon trial; that marked (B) corresponds to the IFM trial; that marked (C) corresponds to the PETHEMA trial and that marked (D) corresponds to the GIMEMA trial.

We confirm that the graph marked (A) corresponds to the Hovon trial; that marked (B) corresponds to the IFM trial; that marked (C) corresponds to the PETHEMA trial and that marked (D) corresponds to the GIMEMA trial.

Appendix 1. Search strategy for the ongoing studies

Source	Search strategy	Search result
Clinicaltrial.gov	**Search by Topic: Condition - Multiple myeloma; Study type - Interventional studies; Search term - Random**	336
Exclusions		
Study Phase	Phase I of the study	18
Intervention	Biological, Non-pharmacological, Behavioural	0
Patient Population	Children only	2
Trial Status	Suspended/Terminated/Withdrawn/completed	149
Disease		0
Objective		0
Total Exclusions		**169**
To be screened		167
Exclusions		
Study Phase	Phase I of the study	0
Intervention	Biological, Non-pharmacological, Behavioural	94
Patient Population	Children only	0
Trial Status	Suspended/Terminated/Withdrawn/completed	0
Disease	Other than MM	6
Objective	Preparative regimen/conditioning regimen/mobilisation phase	6
Chemotherapy vs. transplant		4
Transplant setting	Second-line or later/mixed line with no SGA	3
FL-CT	First line-chemotherapy setting	16
RRMM	Further line-chemotherapy setting	15
Maintenance transplant	Maintenance/consolidation regimen-First line transplant setting	6
Study Design	Single arm or non-comparator or Non-randomized	0
Tandem Transplantation		9
Total Exclusions		**159**
Included & extracted		
IR-FLT	Induction regimen-First line transplant setting	8