Section A: Literature searching

A1. There are no search methods or strategies reported in Section 4.12: Adverse Events. **Priority request:** Please clarify whether searches were conducted to identify adverse events data for the intervention and comparator treatments (Section 4.12: Adverse events). If searches were conducted, please provide full search strategies, as well as details of the databases and date searched. If separate adverse events searches were not conducted, please explain why this work was not carried out.

Independent literature searches were not performed for adverse events data as searches conducted to identify clinical effectiveness data were broad enough to have captured studies of any design and adverse event data was a specified outcome of interest within the methods of the clinical effectiveness systematic review.

A2. Please confirm whether the clinical effectiveness strategies presented in Appendix 3 (pages 57-65) are the same as those referred to in Appendix 15, Step 1 (page 207-208, 211).

Yes, the same searches were used for the systematic literature review presented in Appendix 3 as for the one presented in Appendix 15.

A3. Search dates are reported as 1.7.14 on page 210 and 217 for the Step 1 searches (Appendix 15), however different dates in July 2014 are reported in Appendix 3 (page 57). The ERG have assumed the later dates in Appendix 3 are correct, please could you confirm this?

Yes, the same searches were used for the systematic literature review presented in Appendix 3 as for the one presented in Appendix 15.

A4. The search methods in Appendix 14 (page 201) reported that additional terms for non-Hodgkin lymphoma (NHL) would be included in the searches, as it was expected there would be too few studies for mantle cell lymphoma (MCL) alone. However, the reported strategies did not include NHL terms. Please clarify this statement and, if available, provide correct strategies.

This statement is included in Appendix 14 (Cost and healthcare resource identification, measurement and valuation) in error, as it refers to the identification of utility values. For the identification of cost, resource use and cost-effectiveness studies searches were performed for MCL alone. Only for the literature review for quality of life were searches performed for a wider population including all patients with NHL (as reported in Appendix 13).

Section B: Clarification on effectiveness data

B1. According to section 4.7 of the company's submission[1], "the clinical cut-off date for the primary analysis presented in this submission was 2 December 2013" and "the final analysis is expected in 2017".
Priority request: Are there any additional interim results available? If so, please provide these for all outcomes of interest, especially overall survival (OS).

There are no additional interim analyses available between that provided in the submission (Dec 2013 cut-off) and the final analysis planned in 2017. There were 3 interim analysis conducted prior to the primary analysis (Dec 2013 cut-off) in 2009, 2010 and 2011; these do not provide additional clinical data (see section 3.11.4 of the CSR).

B2. According to table 9 of the company submission[1], no study centres in the UK were involved in LYM-3002. Figure 8 (page 62) provides further details on the regions

where participants were recruited for the trial: 73/243 in the VR-CAP arm and 77/244 in R-CHOP arm were from the European Union or North America, respectively.

Priority requests:

a. Can you confirm that no UK patients were included?
b. Please provide a list of participants by country.
c. Please provide the baseline characteristics for included participants by country and/or region.
d. Please provide subgroup-analyses for all outcomes (as specified in the final scope) for European or European/ North American participants.

a. We can confirm that no UK patients were included (see Table 8 of the LYM-3002 Clinical Study Report (CSR), reproduced below)

b. Please find this information reproduced below (from Table 8 of the CSR)

Table 8: Subject Enrollment by Region and Country; Intent-to-treat Analysis Set (Study 26866138-LYM-3002)

	R-CHOP	VcR-CAP	Total
Analysis set: intent-to-treat subjects	244	243	487
Region/country			
European Union	69 (28.3%)	67 (27.6%)	136 (27.9%)
Belgium	10 (4.1%)	16 (6.6%)	26 (5.3%)
Poland	9 (3.7%)	10 (4.1%)	19 (3.9%)
Czech Republic	5 (2.0%)	9 (3.7%)	14 (2.9%)
Spain	8 (3.3%)	6 (2.5%)	14 (2.9%)
Hungary	5 (2.0%)	8 (3.3%)	13 (2.7%)
Romania	9 (3.7%)	4 (1.6%)	13 (2.7%)
Austria	6 (2.5%)	4 (1.6%)	10 (2.1%)
Italy	6 (2.5%)	3 (1.2%)	9 (1.8%)
Germany	7 (2.9%)	1 (0.4%)	8 (1.6%)
Portugal	3 (1.2%)	4 (1.6%)	7 (1.4%)
France	1 (0.4%)	2 (0.8%)	3 (0.6%)
North America Region	8 (3.3%)	6 (2.5%)	14 (2.9%)
Canada	6 (2.5%)	1 (0.4%)	7 (1.4%)
United States of America	2 (0.8%)	5 (2.1%)	7 (1.4%)
Rest of World	167 (68.4%)	170 (70.0%)	337 (69.2%)
Russia	57 (23.4%)	42 (17.3%)	99 (20.3%)
People's Republic of China	34 (13.9%)	61 (25.1%)	95 (19.5%)
Ukraine	18 (7.4%)	16 (6.6%)	34 (7.0%)
Brazil	9 (3.7%)	13 (5.3%)	22 (4.5%)
Thailand	9 (3.7%)	10 (4.1%)	19 (3.9%)
Japan	11 (4.5%)	7 (2.9%)	18 (3.7%)
India	9 (3.7%)	3 (1.2%)	12 (2.5%)
Israel	5 (2.0%)	2 (0.8%)	7 (1.4%)
Tunisia	3 (1.2%)	3 (1.2%)	6 (1.2%)
Turkey	5 (2.0%)	1 (0.4%)	6 (1.2%)
Colombia	2 (0.8%)	3 (1.2%)	5 (1.0%)
Republic of Korea	2 (0.8%)	3 (1.2%)	5 (1.0%)
Chile	1 (0.4%)	2 (0.8%)	3 (0.6%)
Singapore	1 (0.4%)	2 (0.8%)	3 (0.6%)
Taiwan	1 (0.4%)	2 (0.8%)	3 (0.6%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.
Note: Percentages calculated with the number of subjects in each group as denominator.

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c. It may be helpful to clarify the nature of the regional subgroups available for the LYM3002 population:

- Analysis of Progression Free Survival (PFS) by three regional subgroups was pre-specified (European Union, North America Region and Rest of World (ROW))
    - The North America subgroup had very few subjects, most of whom had a PFS event (5 subjects with a PFS event out of 8 enrolled into the R-

CHOP group and 4 subjects out of 6 enrolled into the VR-CAP group) that resulted in a very large confidence interval (0.44, 41.96) for the HR, which is >1.0. This is likely a chance finding.

- Consequently, the EU and North America were combined post-hoc, as noted and presented in Figure 8 of the submission.
- In response to questions by the European Medicines Agency (EMA), further analysis of the EU subgroup was provided. These data are reproduced below in response to this clarification question.
- Preplanned analysis of some of the outcomes listed in the NICE scope (PFS, time to progression (TTP), overall response rate (ORR), complete response (CR), and overall survival (OS)) was also conducted for the Western European/North American subgroup. Baseline age and body surface area (BSA) of these patients are used to parameterise the cost effectiveness model, as described in the original submission at section 5.2. Baseline characteristics of this subgroup are presented in table 31 of the original submission, with confirmation that the outcomes for this subgroup are consistent with the ITT population presented in section 4.8 and Appendix 8. A full description of the outcomes for this subgroup is available in the CSR at section 5.6.1.4.
- Adverse event incidence was summarised by the three regions: EU, North American and ROW.

The baseline characteristics of the EU region subgroup are presented in Table 1. Whilst demographic characteristics were generally well balanced between treatment arms, stratification factors were not and some baseline disease characteristics were markedly imbalanced at baseline, favouring the R-CHOP treated group:

- The proportion of patients with ECOG performance status of 2 was higher in the VR-CAP group (13.4%) than the R-CHOP group (5.8%)
- The proportion of patients with IPI risk 4-5 was substantially greater in the VR-CAP group (31.3%) than in the R-CHOP group (15.9%)
- The proportion of patients with elevated LDH was 47.8% in the VR-CAP group and 31.9% in the R-CHOP group suggesting greater extent of disease for patients treated with VR-CAP.

Table 1: EU subgroup baseline characteristics

	VR-CAP (n=67)	R-CHOP (n=69)	Total (n=136)
Age: Median years (range) **Mean years (SD)**	69 (38; 82) 68.1 (6.83)	71 (43;80) 68.7 (7.53)	69.5 (38;82) 68.4 (7.17)
Male, n (%)	50 (72.5%)	47 (70.1%)	97 (71.3%)
White, n (%)	68 (98.6%)	67 (100%)	135 (99.3%)
BSA, mean m^2 (SD)[a]	1.85 (0.186)	1.90 (0.192)	1.88 (0.190)
ECOG PS, n (%)[a]	0: 31 (44.9%) 1: 34 (49.3%) 2: 4 (5.8%)	0: 34 (50.7%) 1: 24 (35.8%) 2: 9 (13.4%)	0: 65 (47.8%) 1: 58 (42.6%) 2: 13 (9.6%)
Disease stage, n (%)[b]	Stage II: 4 (5.8%) Stage III: 13 (18.8%) Stage IV: 52 (75.4%)	Stage II: 2 (3.0%) Stage III: 13 (19.4%) Stage IV: 52 (77.6%)	Stage II: 6 (4.4%) Stage III: 26 (19.1%) Stage IV: 104 (75.6%)
IPI risk, n (%)[b]	Low: 7 (10.1%) Low-int: 22 (31.9%) High-int: 29 (42.0%) High: 11 (15.9%)	Low: 6 (9.0%) Low-int: 16 (23.9%) High-int: 24 (35.8%) High: 21 (31.3%)	Low: 13 (9.6% Low-int: 38 (27.9%) High-int: 53 (39.0%) High: 32 (23.5%)
Histology, n (%)[c]	Diffuse: 25 (36.2%) Nodular: 8 (11.6%) Mantle zone: 33 (47.8%) Other 3 (4.3%)	Diffuse: 17 (26.2%) Nodular: 25 (38.5%) Mantle zone: 17 (26.2%) Other 6 (9.2%)	Diffuse: 42 (31.3%) Nodular: 33 (24.6%) Mantle zone: 33 (24.6%) Other 9 (6.7%)
Cellularity, n (%)[d]	Blastoid: 8 (11.8%) Nodular: 37 (54.4%) Other: 23 (33.8%)	Blastoid: 8 (12.3%) Nodular: 38 (58.5%) Other: 19 (29.2%)	Blastoid: 16 (12.0%) Nodular: 75 (56.4%) Other: 42 (31.6%)
Baseline LDH elevated, n (%)	22 (31.9%)	32 (47.8%)	54 (39.7%)
Bone marrow involved, n (%)	56 (81.2%)	54 (80.6%)	110 (80.9%)

Key: BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; IPI, International Prognostic Index; HSCT, haematopoietic stem cell transplantation; LDH, lactate dehydrogenase; PS, performance status; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; SD, standard deviation; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Source: Response to the Committee for Medicinal Products for Human Use Request for Supplementary Information (EMA/CHMP/564418/2014) Dated 25 September 2014[2]

d. Subgroup analyses are provided for OS, PFS, TTP, ORR and CR for the Western European/US/Canada subgroup in section 5.6.1.4 of the CSR. The hazard ratio for PFS was

0.77 (95% CI 0.43-1.38, p= 0.380), with results appearing to be influenced by the small subgroup of patients from North America. For the subgroup of subjects from Western Europe alone, the HR was 0.49 (95% CI 0.25-0.95, p=0.031).

The EU subpopulation includes patients enrolled in Austria, Belgium Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Romania and Spain. Subgroup analyses for all efficacy outcomes included in the scope are available for this subpopulation and are presented below, alongside the results in the overall population for ease of interpretation. Health related quality of life outcomes (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-C30) were included in LYM-3002 as exploratory outcomes and as such, subgroup analysis is not conducted. Table 3 presents the safety data for the EU subgroup.

The clinical benefits of VR-CAP noted for the overall population are also evidenced in the EU subgroup, as shown by all outcomes with the exception of OS. Whilst the full population showed a clear trend in OS favouring VR-CAP, analysis of OS was not consistent with the full population; notwithstanding that the median had not been reached in either treatment arm. This is explained by:

- An imbalance in the patient characteristics favouring the R-CHOP treatment group as described above.
- Greater imbalance in utilisation of subsequent therapies, with higher proportion of R-CHOP patients receiving temsirolimus (20% vs 12%), and bortezomib (18% vs 0%, R-CHOP vs VR-CAP, respectively).
- Three subjects included in the EU subpopulation received no treatment (2 early deaths prior to treatment in the VR-CAP arm and 1 non-treated subgroup in the R-CHOP arm).

Table 2: Summary of Efficacy Results for EU sub population and for Overall Study Population (study 26866138-LYM-3002)

	EU Subpopulation			**LYM-3002 study population**		
	R-CHOP	**VR-CAP**	**HR/OR (p-value)**	**R-CHOP**	**VR-CAP**	**HR/OR (p-value)**
	N=69	N=67		N=244	N=243	
Median PFS (IRC) (months)	13.9	22.4	0.68 (0.091)	14.4	24.7	0.63 (<0.001)
Median PFS (INV) (months)	17.4	30.7	0.58 (0.020)	16.1	30.7	0.51 (<0.001)
Median PFS (IRC alternative assessments of transient fluid collection)(months)	14.4	24.0	0.58 (0.019)	14.8	28.5	0.56 (<0.001)
Median TTP (IRC) (months)	14.4	24.7	0.58 (0.020)	16.1	30.5	(<0.0001)
Median TTP (INV) (months)	17.6	35.4	0.45 (0.001)	16.8	35.0	0.47 (<0.001)
Median TTNT (months)	26.3	38.1	0.59 (0.039)	24.8	44.5	0.50 (<0.001)
Median OS (months)	NE	NE	1.33 (0.406)	56.3	NE	0.80 (0.173)
4-year survival rate (%)	75.4	69.5		53.9	64.4	
	N=68	N=65		N=242	N=240	
Median TFI (months)	22.5	33.3	0.55 (0.020)	20.5	40.6	0.50 (<0.001)

	EU Subpopulation			LYM-3002 study population		
	R-CHOP	**VR-CAP**	**HR/OR (p-value)**	**R-CHOP**	**VR-CAP**	**HR/OR (p-value)**
	N=65	N=62		N=228	N=229	
Overall complete response (CR+Cru) (IRC) (%)	40.0	51.6	1.689 (0.156)	41.7	53.3	1.688 (0.007)
Overall radiological complete response (CR+Cru) (IRC) (%)	72.3	80.6	1.715 (0.218)	71.1	83.0	2.037 (0.002)
Overall response (CR+Cru+PR) (IRC) (%)	89.2	88.7	1.020(0.972)	89.5	92.1	1.428 (0.275)
Overall complete response (CR+Cru) (INV) (%)	23.1	41.9	2.716 (0.013)	27.6	41.5	1.884 (0.002)
Overall response (CR+Cru+PR) (INV) (%)	89.2	95.2	2.400 (0.195)	91.7	95.6	2.022 (0.073)
Time to response (IRC) (days)	64.0	42.0	2.33 (<0.001)	50.0	42.0	1.54
Time to response (INV) (days)	78.0	42.0	1.89 (0.002)	48.0	43.0	1.44 (<0.001)
Durable complete response (IRC) (%)	35.4	50.0	1.935 (0.077)	36.0	48.9	1.799 (0.003)
Durable response (IRC) (%)	66.2	72.6	1.520 (0.302)	66.2	75.1	
Durable complete response (INV) (%)	23.1	40.3	2.503 (0.023)	25.0	39.3	1.960 (0.001)
Durable response (INV) (%)	73.8	83.9	1.767 (0.192)	71.9	81.7	1.693 (0.018)
	N=26	N=32		N=95	N=122	
Median DoCR (CR+Cru) (IRC) (months)	17.8	34.9		18.0		
	N=15	N=26		N=63	N=95	
Median DoCR (CR+Cru) (INV) (months)	18.0	37.8		18.7	49.8	
	N=58	N=55		N=204	N=211	
Median DoR (CR+CRu+PR) (IRC) (months)	12.7	27.1		15.1	36.5	
	N=58	N=59		N=209	N=219	
Median DoR (CR+Cru+PR) (INV) (months)	16.1	34.0		16.1	34.8	

Table 3: Summary of Safety Results for EU sub population and for Overall Study Population (study 26866138-LYM-3002)

Table 83: Overview of Treatment-emergent Adverse Events by Region; Safety Analysis Set (Study 26866138-LYM-3002)

	R-CHOP				VcR-CAP			
		Region				Region		
	Total	EU	USA/CAN	ROW	Total	EU	USA/CAN	ROW
Analysis set: safety subjects	242	68	8	166	240	65	6	169
Any treatment-emergent adverse event	238 (98.3%)	66 (97.1%)	8 (100.0%)	164 (98.8%)	238 (99.2%)	64 (98.5%)	6 (100.0%)	168 (99.4%)
At least one related [a]	226 (93.4%)	66 (97.1%)	8 (100.0%)	152 (91.6%)	231 (96.3%)	62 (95.4%)	6 (100.0%)	163 (96.4%)
None related	12 (5.0%)	0	0	12 (7.2%)	7 (2.9%)	2 (3.1%)	0	5 (3.0%)
Any serious adverse event	72 (29.8%)	17 (25.0%)	0	55 (33.1%)	90 (37.5%)	33 (50.8%)	2 (33.3%)	55 (32.5%)
At least one related [a]	50 (20.7%)	11 (16.2%)	0	39 (23.5%)	78 (32.5%)	29 (44.6%)	1 (16.7%)	48 (28.4%)
None related	22 (9.1%)	6 (8.8%)	0	16 (9.6%)	12 (5.0%)	4 (6.2%)	1 (16.7%)	7 (4.1%)
Maximum severity of any AE	238 (98.3%)	66 (97.1%)	8 (100.0%)	164 (98.8%)	238 (99.2%)	64 (98.5%)	6 (100.0%)	168 (99.4%)
Grade 1	6 (2.5%)	0	1 (12.5%)	5 (3.0%)	2 (0.8%)	0	0	2 (1.2%)
Grade 2	26 (10.7%)	10 (14.7%)	1 (12.5%)	15 (9.0%)	13 (5.4%)	4 (6.2%)	0	9 (5.3%)
Grade 3	53 (21.9%)	16 (23.5%)	3 (37.5%)	34 (20.5%)	31 (12.9%)	5 (7.7%)	2 (33.3%)	24 (14.2%)
Grade 4	136 (56.2%)	38 (55.9%)	3 (37.5%)	95 (57.2%)	176 (73.3%)	49 (75.4%)	4 (66.7%)	123 (72.8%)
Grade 5	17 (7.0%)	2 (2.9%)	0	15 (9.0%)	16 (6.7%)	6 (9.2%)	0	10 (5.9%)
Treatment discontinuation due to AEs	17 (7.0%)	4 (5.9%)	0	13 (7.8%)	21 (8.8%)	7 (10.8%)	1 (16.7%)	13 (7.7%)
At least one related [a]	14 (5.8%)	4 (5.9%)	0	10 (6.0%)	19 (7.9%)	6 (9.2%)	1 (16.7%)	12 (7.1%)
None related	3 (1.2%)	0	0	3 (1.8%)	2 (0.8%)	1 (1.5%)	0	1 (0.6%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; AE=adverse event; EU=European Union;
USA/CAN=United States/Canada; ROW=Rest of World.
[a] Related to any study drug.
Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator. Percentages of region sub-groups calculated with number of subjects per sub-group as denominator.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Adverse events with missing toxicity grade are not included in the table.

B3. According to the final scope[3], "the most widely used regimens [for people with newly diagnosed mantle cell lymphoma] are rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), rituximab, fludarabine and cyclophosphamide (R-FC) and rituximab and bendamustine". This is in line with guidelines for the investigation and management of mantle cell lymphoma, cited in the company submission (reference 7)[4]: (a) Addition of rituximab to combination chemotherapy regimens improves outcomes. Rituximab should therefore be included in the first line chemotherapy regime in the treatment of MCL. (Strong, Moderate); (b) Older, less fit patients should receive R-chemo e.g. R-FC, R-CVP, R-CHOP, Rbendamustine, R-chlorambucil. (Strong, Moderate). However, the Advisory Board Summary Report (reference 6 of the company submission) mentions two additional treatments, i.e. R-CVP and R-chlorambucil.[5]

Priority requests:

a. Please confirm if any studies comparing R-CVP or R-chlorambucil to any other treatment have been excluded? If so, please provide a rationale.
b. In the Advisory Board Summary Report[5], it is stated that "R-CVP is the most commonly used alternative". If feasible, please provide details and results for any possible comparisons of R-CVP (R-chlorambucil) vs. VR-CAP.
c. Can you confirm that no network meta-analyses (NMA) were possible? If NMA were possible, please provide details.
d. Please provide subgroup-analyses for indirect comparisons (as detailed in B2, c.)

a. R-CVP and R-chlorambucil are outside of the scope of this submission. As noted within the NICE scoping process and the advisory board summary report provided, these two treatments are used to treat frailer patients who would not be eligible for VR-CAP:

"R-CVP … and R-chlorambucil are only used first-line in patients who are not considered fit enough to receive R-CHOP as they are associated with lower toxicity". As stated in the

advisory board meeting minutes, R-CVP is the most commonly used treatment for these frailer patients, who would not be able to receive VR-CAP.

As these are not relevant comparators, as determined by NICE in the final scope, studies including these two treatments are not presented within the submission.

b to d. As stated above, it is not relevant to make comparisons between R-CVP and R-chlorambucil and VR-CAP. Additionally, no RCTs were identified where either R-CVP or R-chlorambucil were given as a randomised treatment arm within the trial.

No NMA was carried out for the 2 comparisons possible (R-bendamustine vs VR-CAP and R-FC vs VR-CAP) as only 1 trial was available for each comparison. Use of more sophisticated statistical methods, for example, network meta-analysis, in this context was therefore not deemed appropriate since the nature of confounding within the available evidence base cannot be quantified using these methods. Using purer statistical methods and presenting the surrounding uncertainty might lead to an underestimation of the level of uncertainty associated with indirect comparison estimates based on the available evidence.

B4. Section 4.10 of the company submission presents results of indirect analyses of progression-free survival and overall survival.[1]

a. There are other efficacy outcomes that were analysed by the three main trials, i.e. overall response rate and complete response (remission rate). Please provide indirect analyses for these outcomes.
b. Indirect analysis was not used for safety-related outcomes. There do not appear to be any potential outcomes for the StiL NHL1 trial, but for the European MCL Elderly trial (induction phase R-FC vs VE-CAP) the following outcomes are comparable to the LYM 3002: Anaemia, neutropenia, lymphocytopenia, thrombocytopenia, nausea constipation, fatigue, infection, febrile neutropenia (table 2 in Kluin-Nelemans 2012 (reference 41 in the company submission) and company submission table 28).[1, 6] Please provide indirect analyses for these outcomes.

a. Indirect treatment comparisons for ORR and CR are presented in Table 4. Janssen reiterates the limitations of indirect comparison including these studies described in the company submission, given the between-study heterogeneity and, with respect to R-bendamustine, the small size and lack of detail on patient characteristics for the subgroup of MCL patients within the StiL NHL1 trial.

Table 4: Bucher indirect comparison analyses of ORR and CR

	OR	Lower 95% CI	Upper 95% CI
Overall response rate			
VR-CAP vs R-FC	2.42	1.09	5.39
VR-CAP vs R-bendamustine	3.54	0.61	20.69
Complete response			
VR-CAP vs R-FC	1.22	0.73	2.05
VR-CAP vs R-bendamustine	1.69	0.67	4.28

Key: CI, confidence interval; CR, complete response; OR, odds ratio; ORR, overall response rate; R-bendamustine, rituximab with bendamustine; R-FC, rituximab with fludarabine and cyclophosphamide; StiL, Study Group of indolent Lymphomas; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Notes: Investigator assessments for R-FC and R-bendamustine vs Independent Review Committee for VR-CAP

b. Indirect treatment comparisons for adverse events for which at least one event was reported in either the LYM-3002 trial or European MCL Elderly trial are presented in Table 5.[6]

Indirect comparison could not be conducted for the Rummel et al (2013) trial for R-bendamustine as adverse event data was not available for the subgroup of MCL patients.[7]

Table 5: Bucher indirect comparison analyses of adverse events

	OR	Lower 95% CI	Upper 95% CI
Anaemia			
VR-CAP vs R-FC	0.77	0.33	1.77
Leukopenia			
VR-CAP vs R-FC	1.55	0.90	2.69
Lymphopenia			
VR-CAP vs R-FC	3.81	1.98	7.31
Neutropenia			
VR-CAP vs R-FC	2.48	1.37	4.50
Thrombocytopenia			
VR-CAP vs R-FC	9.19	3.99	21.17
Febrile neutropenia			
VR-CAP vs R-FC	1.91	0.75	4.86

Key: CI, confidence interval; CR, complete response; OR, odds ratio; ORR, overall response rate; R-bendamustine, rituximab with bendamustine; R-FC, rituximab with fludarabine and cyclophosphamide; StiL, Study Group of indolent Lymphomas; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

B5. According to table 21 of the company submission, LYM-3002 included 80 patients (38/243 in VR-CAP arm, 42/244 in R-CHOP arm) that were "medically eligible for HSCT". The final scope[3] describes bortezomib as "indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation" which is line with the summary of product characteristics (table 2 of the company submission[1]) which describes the indication of bortezomib as “for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT”. Please explain how these patients were taken into account given they are outside of MA?

A small proportion of patients enrolled in the LYM-3002 trial (80/487, 16.4%) were not unsuitable for HSCT due to medical reasoning, ie. they were suitable for HSCT from a medical perspective but availability and/or socio-economic reasons prevented access. However, this population was balanced across the two treatment groups and post hoc analysis of survival outcomes demonstrated a consistent treatment effect regardless of medical (in)eligibility for HSCT, favouring VR-CAP (Table 21 of company submission). Furthermore, formal comparative assessment demonstrated no significant difference in survival outcomes for patients medically ineligible for HSCT versus patients medically eligible (Table 22 of company submission).

UK clinical experts agreed there was no clinical rationale not to use total population (ITT) analyses of the LYM-3002 trial to represent patients who are unsuitable for HSCT in UK clinical practice upon consultation.[5] Moreover, the CHMP felt these analyses (ITT population) supported an indication expansion for bortezomib to the treatment of adult

patients with previously untreated MCL who are unsuitable for HSCT, where they consider the availability of new medicinal products of greatest clinical value.[8]

Therefore, these patients were not formally taken into account in clinical effectiveness data analyses (outside of subgroup analyses previously discussed). In order to assess the degree of bias on cost-effectiveness results, a scenario analysis was conducted using data from the population considered medically ineligible for HSCT only (Table 72 of company submission; ICER of £20,489 vs £20,362 in the base case). Full trial outcomes for the population considered medically eligible for HSCT were provided in Appendix 16 of the company submission.

B6. According to table 2 of the company submission (page 15), participants received four doses of bortezomib during a 21 day treatment cycle.[1] Given that up to six cycles are given ("for patients with a response first documented at cycle 6, two additional cycles may be given"), it would be expected that participants might receive 24 or even more doses. However, according to table 5 (page 21), a median of 21 doses was assumed. Please clarify this assumption and provide further details for dosage (mean, median, range etc.).

The mean and median number of doses of bortezomib received can be found in Table 23 of the CSR. The mean number of doses was 19.9 and the median was 21 (range 2, 32). Not all patients received the full 6 cycles of bortezomib within the trial primarily due to adverse events (see Table 24 in the CSR).

B7. LYM-3002 was powered for the primary endpoint 'progression-free survival'. Please confirm whether power calculations were done for any of the other endpoints, e.g. overall survival. If so, please provide details.

No power calculations were made for any of the other endpoints.

Section C: Clarification on cost-effectiveness data

General

C1. **Priority request:** Please provide the results of an updated economic analysis using the data presented in response to clarification questions B1 and B2, if applicable (including all comparators, also the 'exploratory comparators', described in the scope using the hazard ratios obtained from the indirect treatment comparison).

No additional interim results are available. Including the results of the EU subpopulation in the economic model has not been undertaken as these results are not considered sufficiently robust. As noted earlier, there are marked imbalances between the treatment arms in important prognostic factors. Furthermore, the small size of the subpopulation would introduce unnecessary uncertainty; noting that the LYM-3002 study was not powered for subgroup analysis. As noted in our original submission, conducting indirect comparison using incomplete data from the European MCL Elderly study and the MCL subgroup of StiL NHL1 is also not considered robust. Introducing further uncertainty by including the LYM-3002 EU subpopulation would further invalidate this approach.

C2. The half-cycle correction was not applied.
   a. Please clarify and justify why the half-cycle correction was not applied.
   b. Please provide an additional analysis which includes the half-cycle correction to either the Company base case or to the updated economic analyses if applicable.

a.

No half-cycle correction has been applied as a cycle length of only one week was used. With this very short cycle length, the absence of a correction is expected to result in only a very minor estimation bias.[9] Therefore using half-cycle correction was not deemed necessary in this analysis.

b.

Model outcomes with application of half-cycle correction are presented in Table 6. As expected there is only a small increase in the ICER compared to the base case ICER of £20,362 originally presented in the company submission.

Table 6: Results of VR-CAP versus R-CHOP with the application of half-cycle correction

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
VR-CAP	£47,175	6.45	4.15				
R-CHOP	£30,246	5.70	3.36	£16,929	0.75	0.80	£21,293

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Overall survival, progression free survival and treatment-free interval

C3. **Priority request:** The choice for modelling survival separately for patients with and without progression has major implications for the incremental cost-effectiveness ratio. More information and justification is needed to assess whether the most appropriate methodology has been applied.

a. Please provide a justification for the statement in the company submission (page 102) that many of the survival curves fitted directly to OS were not plausible.[1] These extrapolated survival curves should preferably be compared with long-term survival data in patients with MCL.
b. It is stated that because of the immaturity of the data, progression is used as a surrogate for survival. Subsequently, survival is separately estimated for patients with and without progression. Please explain why these survival estimates are considered reliable while the overall survival is not.
c. Please explain why PPS is measured from start of the trial, while it is only applicable for patients with progression. Please confirm whether it should be measured from time of progression?
d. On page 104 of the company submission, it is stated that proportional hazards (PH) were assumed because of limited availability of data for PrePS to fit individual models.[1] Please provide details and justification of the PH assumption.
e. PPS is assumed to be similar for R-CHOP and VR-CAP, while it has been shown that type of second-line treatment differs after these treatments. Furthermore, some of these second-line treatment significantly impact PPS. Please provide an additional analysis in which PPS is corrected for differences in second-line treatment and the corresponding treatment effects.

a.

Few sources of long-term survival data for patients with MCL are available. OS of R-CHOP-treated patients in the LYM-3002 trial can be compared to two main sources; the

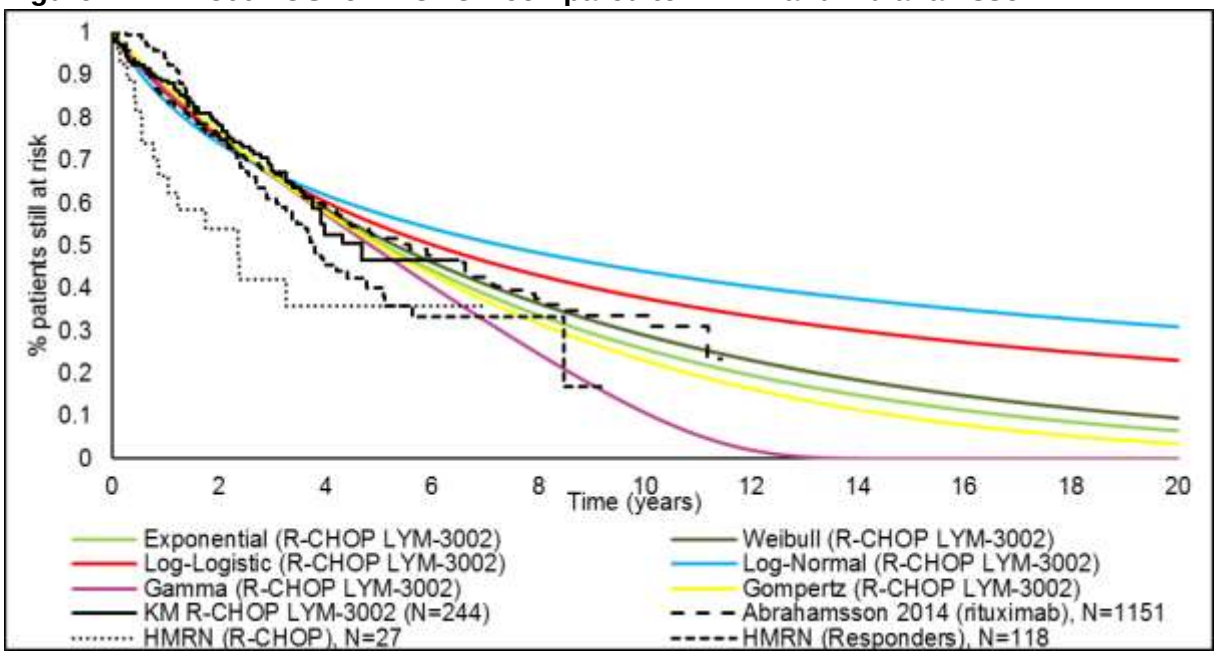
Haematological Malignancy Research Network (HMRN) analysis [10] and Abrahamsson 2014[11] (Figure 1).

OS data from HMRN are available for approximately the same duration as LYM-3002 trial data. Therefore comparison with these data is not very useful in making an assessment about extrapolation of OS data. Median OS of patients treated with R-CHOP first-line in the HMRN database is shorter than in the LYM-3002 trial (2.5 vs 4.7 years). Data from HMRN were from patients diagnosed between 2004 and 2012 and thus include older as well as more recent data. Furthermore, 46.8% of patients in this dataset were treated first-line with either FC or R-FC, indicating that this dataset does not fully reflect current UK practice. 16% of patients were treated with R-CHOP. OS for responders (to any therapy) is closer to the LYM-3002 R-CHOP OS suggesting that the OS for all patients in the HMRN database may be influenced by a low response to first-line therapy (58% response rate to first-line therapy in the HMRN database versus 89.5% overall response rate to R-CHOP in the LYM-3002 trial).[10]

Abrahamsson was a recent publication (2014) that included the OS of 1151 Swedish and Danish patients who had been treated with rituximab based chemotherapy. OS of patients treated with R-CHOP in the LYM-3002 trial closely followed that seen by Abrahamsson, but some of the fitted curves greatly underestimate or overestimate OS, when compared to the Abrahamsson data, and when considering clinically plausible outcomes for patients with MCL. It is also noted that the Abrahamsson OS estimate includes patients treated with a variety of rituximab based chemotherapies, that is, regimens with potentially better or worse efficacy that R-CHOP. Thus, selecting a curve directly fitted to the LYM-3002 OS data is problematic even when comparing with the available long-term survival data in patients with MCL.

Given the data for such analysis are few and the impact of an inappropriate selection was potentially high, it was considered more robust to estimate OS based upon progression.

Figure 1: LYM-3002 OS for R-CHOP compared to HMRN and Abrahamsson



Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Regardless of the above concerns, it can be assumed that the long-term survival for MCL patients is reasonably well reflected by the rituximab-treated patients in Abrahamsson analysis. Figure 1 suggests that the Weibull curve is the best fit and Table 7 shows that this curve is also among the best curve fits to the LYM-3002 trial data; assuming the Weibull for both R-CHOP and VR-CAP arms generates an ICER of £22,052 vs £20,421 in the base case (Table 8). The results in terms of life years projected are very similar to those in the base case (Table 9) which validates the approach taken. As there is no clinical evidence that there are differences between VR-CAP and R-CHOP in post-progression survival, the approach taken in the base case where post-progression survival is assumed equal across both arms, is likely the most appropriate approach.

Table 7: Goodness of fit of OS fitted to trial arms

Parametric curve	AIC	BIC
Exponential	966.67	975.05
Weibull	967.38	979.94
Log-logistic	972.91	985.47
Log-normal	987.46	1000.02
Gamma	965.33	982.08
Gompertz	1768.62	1781.18
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion		

Table 8: Results of VR-CAP versus R-CHOP using OS by arm, Weibull curve

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
VR-CAP	£43,219	6.42	4.07				
R-CHOP	£27,441	5.81	3.36	£15,777	0.60	0.72	£22,052
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.							

Table 9: Base case results, VR-CAP versus R-CHOP

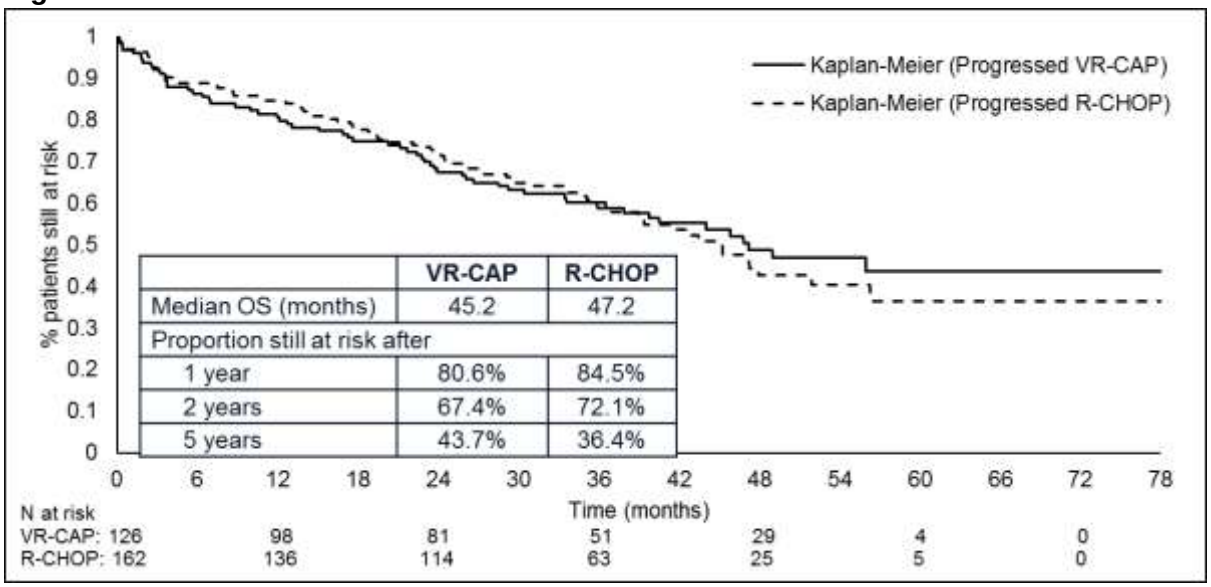
	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
VR-CAP	£45,838	6.44	4.15				
R-CHOP	£29,625	5.69	3.35	£16,213	0.75	0.80	£20,362
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.							

b.

Post-progression survival (PPS) was more complete than overall survival. At the clinical cut-off date, 64% of R-CHOP patients and 71% of VR-CAP patients were alive, whilst looking only at those who had progressed, 40% of patients were alive. Also, PPS is similar for the two treatments (Figure 2), and therefore PPS curves for both treatments can be pooled. The

fact that PPS is more complete and more patients can be included in the analysis due to pooling of the arms reduces fit uncertainty and therefore progression was used as a surrogate for survival. The use of PFS as a surrogate for OS is supported be available literature within both MCL (see Appendix 16 of the company submission) and NHL (Lee et al demonstrate that improvements in 3-year EFS/PFS are highly correlated with improvements in 5-year OS in aggressive NHL).[12] This is a conservative approach as a trend of better survival with VR-CAP is seen.

Figure 2: PPS in the LYM-3002 trial



	VR-CAP	R-CHOP
Median OS (months)	45.2	47.2
Proportion still at risk after		
1 year	80.6%	84.5%
2 years	67.4%	72.1%
5 years	43.7%	36.4%

Key: N, number; PPS, post-progression survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

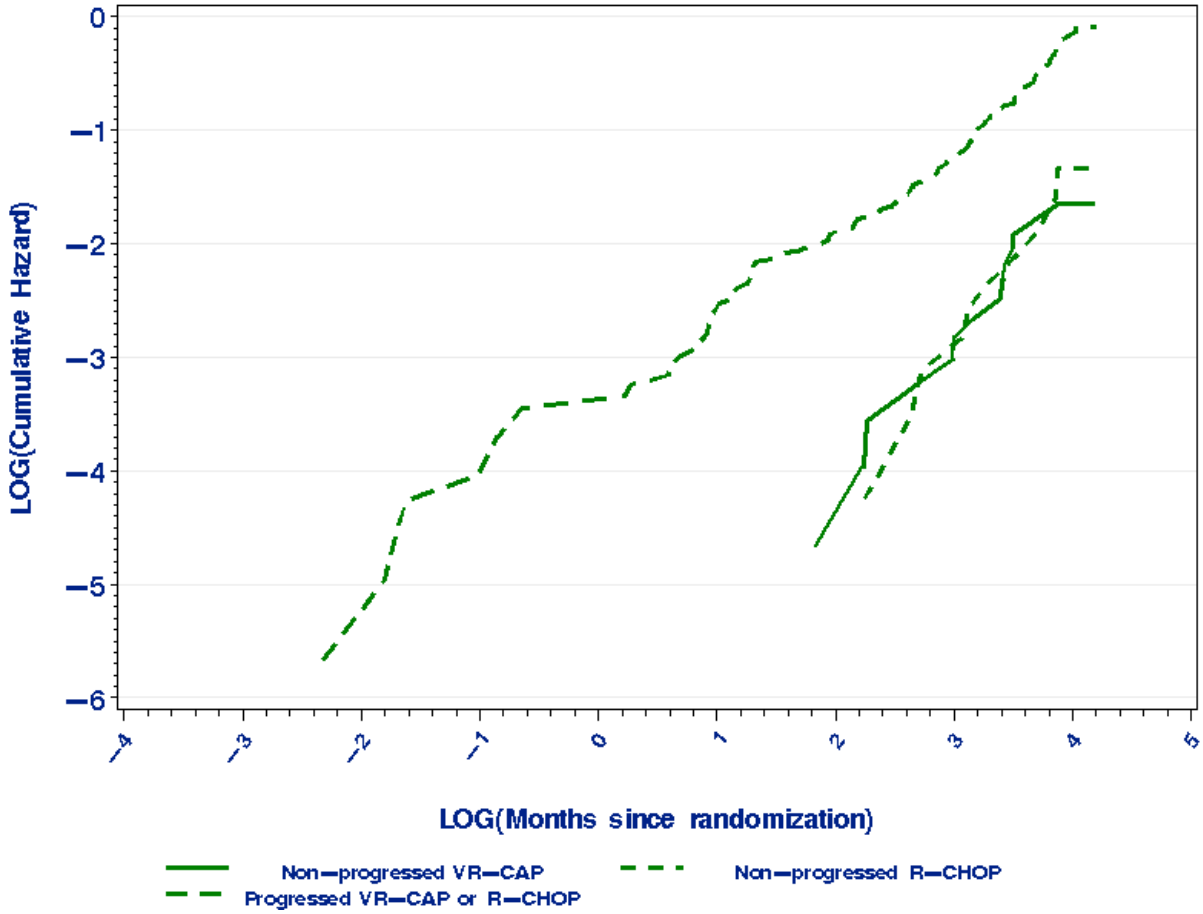
c.

PPS is measured in the trial as the overall survival of patients that have progressed in the trial. Therefore it is measured from the start of the trial and should also be applied from the start of the model. Patients in the model that have not progressed follow the PrePS curves. Once they have progressed, they follow the shape of the PPS curve.

d.

Too few events were observed within the LYM-3002 for PrePS, to justify fitting individual models to the Kaplan–Meier data as this would introduce significant uncertainty. Log cumulative hazard plots for non-progressed patients (PrePS) treated with VR-CAP or R-CHOP are reasonably parallel to each other (Figure 3) indicating that a proportional hazards assumption may be justifiable. It should be noted that PrePS accounts for only a small number of expected deaths within the model (14%), with the vast majority of deaths attributable either to progression (63%) or adverse events (22%), therefore the impact of assumptions surrounding PrePS is relatively limited.

Figure 3: Log cumulative hazard plots overall survival



Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

e.

Whilst type of second-line treatment differs after VR-CAP compared to R-CHOP, it was also shown that only rituximab + chemotherapy agents based treatments (category 2) have a significant impact on OS from the start of second-line treatment (Table 38 and Figure 24 of the company submission). 31% of patients receiving VR-CAP induction, receive a treatment from category 2 at second or subsequent treatment-line, while 34% of patients receiving R-CHOP induction are treated with this type of therapy at second or subsequent-line. Therefore no difference in PPS is expected between the two arms of the trial. The base case assumption is further justified by Figure 2; the PPS curves for VR-CAP and R-CHOP are very similar. PPS is slightly worse for R-CHOP than for VR-CAP, suggesting that the assumption that PPS is equal in both arms may be conservative.

C4. **Priority request:** The relative treatment effectiveness (of VR-CAP versus R-CHOP) seems to be less for patients treated in the European Union/North America versus the rest of the world (company submission Figure 8).[1] Please provide the results of an updated economic analysis while applying a hazard ratio to PFS, OS and TFI to reflect the relative effectiveness (of VR-CAP versus R-CHOP) for European Union/North America.

As presented in Table 2, HRs for the EU subgroup for PFS and TFI are very similar to those of the overall population and therefore applying a HR for this subgroup versus all patients for

these outcomes would not be expected to have a major impact on the model outcomes. As outlined in response to question C1, in the EU subpopulation there are marked imbalances between the treatment arms in important prognostic factors. Furthermore, the small size of the EU, or indeed the EU/North America subpopulation, would introduce unnecessary uncertainty given that the LYM-3002 study was not powered for subgroup analysis.

C5. The treatment-free interval (TFI) is derived from the safety population, which includes all patients who received at least one dose of drug. As a result, TFI also includes patients without progression who did not receive any additional treatment, while in the model second-line treatment is only applicable for patients with progression. It is expected that the inclusion of patients without progression overestimates the TFI since these patients would probably not have received any second-line treatment. Please report the TFI restricted to patients with progression and include these estimates in the cost-effectiveness analysis instead of the current TFI estimates.

TFI in the model is applied only to those patients that have already progressed, however it has been taken into account that the TFI measured also included patients that had not yet progressed by dividing the proportion of patients that would start second-line treatment based on the TFI curves by the proportion of patients that have progressed. In the model this is calculated on the patient flow sheets in column U; the part of the formula that addresses this adaptation is (example cell U13) "/(SUM(H$12:H12)/SUM(G$12/H12))".

C6. In the base-case analysis, the TFI begins after 18 cycles (=considered the average treatment duration). Please justify why TFI begins after 18 cycles rather than with the start of the TFI at time of progression, since it can be assumed that initial treatment is stopped at time of progression.

TFI in the trial is measured from end of first-line treatment to the start date of the new treatment. On average first-line treatment was stopped after 18 weeks (18 model cycles). This was calculated within the patient flow sheet and then applied to the model. Starting TFI at time of progression would be more appropriate if patients were treated until progression and end of treatment was more directly related to the time of progression. However, VR-CAP and R-CHOP are both given for a fixed treatment duration of up to six treatment cycles (or eight for patients with a response first documented at cycle 6) at which time the majority of patients have not yet progressed. Therefore starting the TFI at time of progression would largely underestimate the number of patients commencing second-line treatment.

<u>Health related quality of life</u>

C7. Please clarify which tariff was used to calculate the EQ5D utilities.

The UK tariff was used to calculate EQ-5D utilities.

C8. **Priority request:** Different questions arise from the utility values chosen for progressed from first-line treatment, progressed from second-line treatment and for progression-free survival from second-line treatment in the base case and scenario analysis:

a. Please explain why a utility value of 0.693 is chosen for progressed from first-line treatment in the base case analysis. This value seems to be an overestimation as this utility is measured while patients were on treatment (page 124), while probably not all patients in the progressed health state in the model are on treatment. Please confirm if alternative utility values identified in the literature?
b. Please explain why a utility value of 0.45 is chosen for progressed from second-line treatment for the base case analysis. This utility value is very different from

0.693 that is used for progressed from first-line treatment. In table 47 it is stated that the value is derived from the most robust evidence available (Doornduijn et al. 2014).[1,6] However, this evidence is only based on 13 observations, and based on a different patient population.

c. The 0.45 value (Doornduijn et al. 2014) is calculated as the average of the utilities for 0-1 and 2-3 on the age adjusted Prognostic Index (aaPI) while the distribution of aaPI within the patient population of the LYM-3002 trial is unknown.[6] What was the rationale for assuming that 50% of the patients in the LYM-trial are classified aaPI 0-1 and 50% as 2-3?
d. A utility value of 0.764 is assumed for progression-free survival from second-line treatment in the base case analysis. Please explain the rationale behind assuming a similar utility (0.764) for progression-free survival from first- and second- line treatment.
e. A utility value of 0.693 was used in the scenario analysis for progression-free survival from second-line treatment. Please provide more justification of using a utility of 0.693 for the scenario analysis. What was the rationale for assuming progression-free survival from second line treatment has similar utility as progressed from first line treatment? Please clarify if any other values were identified in the literature review?

a.

There are indeed some limitations to the trial-based utility data. However systematic searching of the literature identified no alternative sources for MCL utilities, and few data that would be appropriate for a similarly aggressive type of NHL (Table 44 of the company submission). Many of the cost-effectiveness analyses identified in the systematic literature review used a utility value of 0.618 for progressed patients with follicular lymphoma.[13] Several others used the utility values reported by Doorduijn et al.

It should be noted that patients do not spend a long period of time in the progressed from first-line treatment health state as the vast majority of patients in this state receive further treatment. As presented in table 67 of the company submission, 2% of the incremental QALY gain is achieved in the progressed from first line treatment health state.

Using the 0.618 value for progressed patients in a scenario analysis results in an ICER of £20,455 compared to £20,362 in the base case. Using 0.45, as calculated directly from Doorduijn et al[16], generates an ICER of £20,655.

b.

At the advisory board meeting it was stated by clinical experts that patients that have progressed from second-line treatment have a worse quality of life than patients who have progressed from first-line treatment because they have limited treatment options still available and, moreover, their disease and symptoms will have worsened over time.[5] Therefore the utility for this health state was believed to be substantially lower than for patients who have progressed from first-line treatment.

The estimate of 0.45 by Doorduijn et al, was seen as a sensible estimate.128 patients with non-Hodgkin's lymphoma (NHL) were included in this quality of life study, however it is acknowledged there were only 13 observations at the time of progression. No utility data are available in patients with MCL, and even in patients with aggressive NHL, studies that report utilities are rare. Therefore qualitatively weaker data were used with clinical advice guiding the selection of a sensible utility. Importantly however, post progression survival is assumed to be the same for all treatments limiting the impact of assumptions outside of the observed

EQ-5D data in the trial and numerous scenario analyses have been performed around the quality of life assumptions.

c.

As the ERG notes, the aaPI was not collected for patients in LYM-3002 and the distribution is therefore unknown. In LYM-3002, patients were stratified by the International Prognostic Index (IPI). The IPI is a prognostic marker that predicts the prognosis of patients with aggressive NHL by assigning points for known risk factors including as age, disease stage, extranodal site involvement, LDH and performance status (as described in section 4.3 of the submission). Thus the IPI is slightly different to the aaPI; the latter being based only on a subgroup of these risk factors (disease stage, performance status and LDH).[17] We also note that the aaPI applied in the Doorduijn analysis used the WHO performance status score whereas the IPI in LYM-3002 scored performance status using ECOG.

Despite these differences, a broad comparison can be made based on categorisation of risk level as defined by Shipp et al (Table 10).[17] The distribution across aaPI 0-1 and 2-3 is close to 50% in each category and the assumption applied to the calculation of the base case analysis utility value is therefore sound. Applying the more precise distributions in Table 10 would have a negligible impact on the utility (0.451 vs 0.450) and was therefore considered unnecessary.

Table 10: Categorisation of risk level

Risk group[17]	**aaPI: No. of risk factors**	**IPI: No. of risk factors**	**LYM-3002 (n=487)**
Low/low intermediate	0-1	0-2	222 (46.6%)
High intermediate/high	2-3	3-5	265 (54.4%)

d.

Based on discussion with clinical experts it was considered that, in very general terms, patients feel worse when they experience disease progression and then feel somewhat better once further treatment is initiated which successfully manages disease and relieves associated symptoms. Thus, health related quality of life being similar to having disease controlled by initial treatment.[5] As there was no utility value for progression-free survival from second-line treatment available from the LYM-3002 trial, assumptions had to be made for the quality of life in this health state. In the base case as many utility values from the trial as could be justified were used for improved internal consistency. Therefore the utility was assumed to be equal to that for progression-free survival from first-line treatment.

e.

This scenario analysis was included in order to test the model using utility estimated only from the LYM-3002 trial. As there were no utilities measured after the end of treatment visit, no utility value was available for the progressed from second-line treatment visit. Therefore in this scenario analysis the assumption was made that this utility value was equal to that at progression from first-line treatment. Table 44 of the company submission lists all utility values that were found in the literature. No utility value that is specific to progression from second-line treatment was found in the systematic literature review.

C9. It is stated on page 130 that a scenario analysis were conducted using all the utility values reported by Doorduijn et al. 2005.[16] In addition, on page 131 it is stated that utility decrements for progression reported in Hayslip et al. 2008, Soini et al. 2012

and Deconinck et al. 2010 were applied to the utility for the progression-free health state from the LYM-3002 trial in scenario analyses.[13, 18, 19]

a. Please provide a table showing all utility values that were used as inputs for scenario analyses QOL1-QOL8 and clarify how these were incorporated in the economic model.
b. Please clarify why utility decrements for progression in patients with follicular lymphoma (FL; reported in these three studies) are applicable to the progression-free health state of patients with MCL (page 131)?

a.

In Table 11 utility values used in all quality of life scenario analyses are listed and their sources are given.

Table 11: Scenario analyses for quality of life

Scenario	Utility values used in model	Source of utility values used in model
QOL1: Utility for PFS on second-line equal to progressed from first-line	PFS from first-line: 0.764 Progressed from first-line: 0.693 PFS from second-line: 0.693 Progressed from second-line: 0.45	LYM-3002 PFS LYM-3002 progressed LYM-3002 progressed Doorduijn et al, 2005[16]
QOL2: Utility for progressed from second-line equal to progressed from first-line	PFS from first-line: 0.764 Progressed from first-line: 0.693 PFS from second-line: 0.764 Progressed from second-line: 0.693	LYM-3002 PFS LYM-3002 progressed LYM-3002 PFS LYM-3002 progressed
QOL3: Doorduijn et al utility values	PFS from first-line: 0.61 Progressed from first-line: 0.45 PFS from second-line: 0.61 Progressed from second-line: 0.45	Doorduijn et al, 2005[16] Doorduijn et al, 2005[16] Doorduijn et al, 2005[16] Doorduijn et al, 2005[16]
QOL4: Utility decrement for progressing Soini	PFS from first-line: 0.764 Progressed from first-line: 0.604 PFS from second-line: 0.764 Progressed from second-line: 0.45	LYM-3002 PFS Soini et al (2012): 0.764-(0.78-0.62)[19] LYM-3002 progressed Doorduijn et al, 2005[16]
QOL5: Utility decrement for progressing Hayslip	PFS from first-line: 0.764 Progressed from first-line: 0.694 PFS from second-line: 0.764 Progressed from second-line: 0.45	LYM-3002 PFS Hayslip et al (2008): 0.764-(0.73-0.66)[18] LYM-3002 progressed Doorduijn et al, 2005[16]
QOL6: Utility decrement for progressing Deconinck	PFS from first-line: 0.764 Progressed from first-line: 0.577 PFS from second-line: 0.764 Progressed from second-line: 0.45	LYM-3002 PFS Deconinck et al (2010): 0.764-(0.805-0.618)[13] LYM-3002 progressed Doorduijn et al, 2005[16]
QOL7: No utility decrements for AEs	Health state utility values as base case Utility decrements for all adverse events are set to 0	N/A
QOL8: Utility decrements at lower limit of 95% CI	Health state utility values as base case Utility decrements of adverse events are set to the lower limit of the 95% CI	LYM-3002, see Table 47 of company submission for 95% CIs[1]
Key: AE, adverse event; CI, confidence interval; PFS, progression-free survival; QOL, quality of life.		

b.

The difference in utility between progression-free and progressed reported in these three studies were applied to the LYM-3002 PFS from first line utility value to derive a progression from first line utility value for scenario analyses. Utility decrements for progression are not applied to the progression-free health state of patients with MCL.

C10. Table 42 describes the utilities from the LYM-3002 trial. Please provide more details regarding the estimation and validation of the mixed model used to calculate the utilities scores presented in Table 42 of the company submission.[1]

Using the mixed model framework ensured that any correlations between repeated measurements from the same subject were properly taken into account. Therefore, the model accounted for the between- and within-subject variability, while the standard errors of the parameter estimates were estimated. Because mixed models have the ability to deal with missing values, they are preferred over more traditional approaches.

For calculating utility values *proc mixed* code in SAS software was used including progression status as the only covariate in the model, with unstructured covariance matrix and the degrees-of-freedom method.

Utility values were validated by comparing them to values found in the systematic literature review. No utility values for patients with MCL are available in the literature, therefore utilities from the trial were compared to those of patients with NHL.

C11. Table 46 describes utility decrements of adverse events without a reference to the source.
   a. Please provide more details about the utility decrements presented in table 46 (including references)
   b. Please explain why utility decrements can be positive (i.e. 0.010 for anaemia and 0.090 for febrile neutropenia).
   c. Please clarify whether the effect of the disabilities of adverse events was already captured by the quality of life (QoL) measurement of the trial?

a.

Utility decrements associated with AEs were derived from EQ-5D data reported in the LYM-3002 trial. Utility decrements were calculated by subtracting the utility value before developing an AE from the utility value with the AE. These were applied for the duration of the AE.

b.

Utility decrements were most likely positive for some adverse events due to the low number of measurements during these adverse events (Table 12). In light of this, Janssen accepts that these values are not robust and should not have been applied to the model. A scenario analysis where no utility decrements are applied for AEs was included in the company submission (QOL 7 in Table 72) and resulted in an ICER of £20,340; applying utility decrements for adverse events had very little impact on the ICER.

Table 12: Number of EQ-5D measurements utility decrements for AEs are based on

Event	Number of EQ-5D values before AE	Number of EQ-5D values during AE
Neutropenia	361	92
Thrombocytopenia	149	29
Anaemia	62	15
Leukopenia	176	32
Lymphopenia	88	14
Febrile neutropenia	70	4
Pneumonia	28	5
Fatigue	21	8
Diarrhoea	17	0
Peripheral sensory neuropathy	18	13
Sepsis	6	1
Alopecia	6	6

c.

Utility measurements for health states were not corrected for adverse events, and therefore it could be argued that quality of life decrements associated with adverse events are already included in these measurements. In previous health technology assessments for NHL performed by NICE (TA226, TA243, TA147 and TA119) no utility decrements for adverse events were applied. As noted above, scenario analysis where no utility decrements are applied for AEs was included in the company submission (QOL 7 in Table 72) and resulted in an ICER of £20,340; applying utility decrements for adverse events had very little impact on the ICER.

C12. In table 20, utility values for VR-CAP and R-CHOP are presented at baseline, change from baseline (CFB) at cycle 6 and end of treatment (EOT). Different questions arise from this table:

a. Please explain why the utility values of VR-CAP and R-CHOP are assumed to be equal.
b. Please provide utilities for the R-CHOP group and the VR-CAP group separately for the following health states of the economic model; progression-free survival from first-line treatment and progressed from first-line treatment. Please provide an additional analysis of the cost-effectiveness while incorporating these utility values.

a.

There was very little difference (non-significant and numerically small) between utilities of patients treated with VR-CAP and those treated with R-CHOP, therefore, in order to make use of the maximum number of observations in the utility analyses done for the model, utilities for both treatment arms were assumed equal.

b.

Utility values from the LYM-3002 trial by health state by arm are presented in Table 13. These were applied as they were in the base case analysis; PFS from first-line treatment is

also applied to the PFS from second-line treatment health state, utilities from Doorduijn et al (2005) are used for the progressed from second-line treatment health state. Results using these utilities are presented in Table 14 and shows that using utilities by arm has very little impact on the ICER.

Table 13: Utility values by health state by treatment arm

Health state	VR-CAP utility, mean (SE)	R-CHOP utility, mean (SE)
PFS from first-line treatment	0.764 (0.011)	0.763 (0.011)
Progressed from first-line treatment	0.654 (0.036)	0.693 (0.034)
Key: N, number of observations; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.		

Table 14: Results of VR-CAP versus R-CHOP using utilities by trial arm

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
VR-CAP	£45,884	6.44	4.14				
R-CHOP	£29,625	5.69	3.35	£16,259	0.75	0.79	£20,607
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.							

<u>Adverse events</u>

C13. Please clarify and justify why the duration of adverse events is assumed to be treatment dependent in the base case (particularly given the small differences in duration reported in table 45).

At the advisory board meeting it was stated by the clinical experts that adverse event profiles differ across treatment regimens. Therefore adverse event duration was assessed by trial arm. A scenario analysis has been performed in which adverse event duration was not dependent on treatment (EFF18) and this resulted in an ICER of £20,331 compared to the base case of £20,363.

C14. The Company stated that “no AEs for second-line treatment were included as no EQ-5D data were available from the trial to do so”.
   a. Please clarify and justify if an attempt was made to identify these data from the literature.
   b. Please elaborate whether this should be regarded as a conservative assumption.

a.

In the systematic literature review for quality of life in patients with NHL, utilities reported for adverse events were also assessed. No utility data for adverse events associated with second-line treatment were identified in this review. Including adverse events utility decrements already makes very little difference for first-line treatment (see C11), and the impact is therefore expected to be negligible for second-line treatment.

b.

This is a conservative assumption as in the R-CHOP arm patients take up second-line treatment sooner than in the VR-CAP arm. Therefore a greater negative impact of AEs associated with second-line treatment would be expected in the R-CHOP arm.

C15. Please provide the results of an updated economic analysis using the data presented in response to clarification question B4 (including all comparators, also the 'exploratory comparators', described in the scope using the hazard ratios obtained from the indirect treatment comparison).

Model outcomes using HRs and ORs from indirect comparisons for PFS, OS and adverse events for R-FC and R-bendamustine are presented in Table 15. It should be noted that most outcomes from indirect comparisons that were applied were not statistically significant. Furthermore, this analysis does not include safety outcomes from indirect comparison to R-bendamustine as no MCL specific adverse event data were reported in the StiL NHL1 study.

Table 15: Pairwise incremental cost-effectiveness results using the Bucher indirect comparison for PFS, OS and adverse events

	Total			**Incremental**			**ICER (VR-CAP vs comparator)**
	Costs	**Life years**	**QALYs**	**Costs**	**Life years**	**QALYs**	
VR-CAP	£45,884	6.44	4.15				
R-CHOP	£29,625	5.69	3.35	£16,259	0.75	0.80	£20,241
R-FC	£29,736	4.01	2.58	£16,259	2.43	1.56	£10,340

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

C16. Please clarify why the cycle probability of Sepsis grade 4/5 is set to 0.000 (worksheet 'adverse events' cell E75), while this is 0.001 per week in cell I38 (worksheet 'adverse events').

This was an error in the model which can be corrected by copying cell C73 down to C74 and C75. Using the correct cycle probability of Sepsis grade 4/5 results in a base case ICER of £20,421, £59 higher than the previously reported base case ICER.

Resources and costs

C17. **Priority request:** In table 54 of the company's submission the difference between the per protocol dose and the dose received in the LYM-3002 trial is presented.[1] These dose reductions are used in the model to adjust the per protocol dose in the economic model.

a. Please clarify and justify whether the adjusted protocol dose (i.e. the average dose received in the LYM-3002 trial) is more applicable to clinical practice in the UK than the per protocol dose.
b. Please clarify and justify why the dose reductions for Rituximab, Cyclophosphamide and Prednisone are assumed to be treatment dependent (for VR-CAP and R-CHOP).
c. Please provide a scenario analysis using the unadjusted per protocol dose while including all four comparators.

d. No dose reductions were applied for the ‘exploratory comparators’. Please provide a scenario analysis wherein the same dose reductions are applied for the ‘exploratory comparators’ as for VR-CAP.

a.

The adjusted protocol dose is considered more applicable to clinical practice in the UK, than the per protocol dose. The permitted dose adjustments outlined in the study protocol for LYM-3002 were based on the posology modifications for the drugs as used in clinical practice and/or outlined in the Summary of Product Characteristics (SmPC). Dose reductions are specified in the bortezomib SmPC, in light of the findings of the LYM-3002 study, and it is expected that clinical practice will be undertaken in view of the SmPC. The only exception to this is the dose reductions in response to peripheral neuropathy. In UK practice bortezomib is administered subcutaneously, rather than intravenously with an expected reduction in peripheral neuropathy compared to what was observed in LYM-3002. Thus, it is noted that the purpose of dose modifications is to manage toxicity, and both safety and efficacy observed will be influenced by the dose applied. That is, a cost effectiveness scenario applying the costs of the per protocol doses will not accurately reflect the expected associated efficacy and adverse events.

b.

The doses of rituximab, cyclophosphamide and prednisone included in the economic model are included as observed in the LYM-3002 study. That is, these are not assumed values and no assumptions were made about treatment dependence or otherwise. Permitted dose adjustments for each of the drugs were outlined in the protocol of LYM-3002 and were the same for the VR-CAP and the R-CHOP regimens[1]. The observed difference in dose reductions of rituximab, cyclophosphamide and prednisone between these regimens is due to differences in the tolerability profiles of bortezomib and vincristine.

c./d.

In Table 16, model outcomes using the unadjusted per protocol dose for each treatment are presented. In Table 17 model outcomes applying dose reductions to all treatments (dose reductions from the VR-CAP arm are applied to R-FC and R-bendamustine) are presented. Please note that the error identified in C16 has been corrected in these analyses.

As bendamustine and fludarabine are not used in LYM-3002, dose reductions for these drugs are assumed to be the average of that of all drugs in the VR-CAP regimen. Dose reductions for rituximab and cyclophosphamide in R-FC and R-bendamustine are assumed equal to those in VR-CAP.

[1] With the exception of prednisone where no dose adjustments were specified in the protocol.

Table 16: Pairwise incremental cost-effectiveness results using the unadjusted per protocol dose for each treatment

	Total			Incremental			ICER (VR-CAP vs comparator)
	Costs	Life years	QALYs	Costs	Life years	QALYs	
VR-CAP	£48,964	6.44	4.15				
R-CHOP	£29,643	5.69	3.35	£19,321	0.75	0.80	£24,265
R-FC	£31,362	5.69	3.36	£17,601	0.75	0.78	£22,518
R-bendamustine	£35,011	5.69	3.36	£13,952	0.75	0.78	£17,780

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Table 17: Pairwise incremental cost-effectiveness results using the dose reductions for each treatment (dose reductions from VR-CAP applied to R-FC and R-bendamustine)

	Total			Incremental			ICER (VR-CAP vs comparator)
	Costs	Life years	QALYs	Costs	Life years	QALYs	
VR-CAP	£45,884	6.44	4.15				
R-CHOP	£29,625	5.69	3.35	£16,259	0.75	0.80	£20,421
R-FC	£31,198	5.69	3.36	£14,686	0.75	0.78	£18,789
R-bendamustine	£34,660	5.69	3.36	£11,224	0.75	0.78	£14,304

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

C18. The Company stated that "no transfusions or concomitant medication use was assumed for second-line treatment due to the lack of sufficient data".
   a. Please clarify and justify if an attempt was made to identify these data from the literature.
   b. Please elaborate whether this should be regarded as a conservative assumption.

No literature was searched for transfusions or concomitant medication associated with second line treatment, however, this should be regarded as a conservative assumption as in the R-CHOP arm of LYM-3002 patients receive second-line treatment sooner than in the VR-CAP arm. Therefore more transfusions and concomitant medicines would be expected in the R-CHOP arm.

C19. Not all potential stochastic parameters are incorporated as stochastic parameters in the model. As a result these parameters are not considered in the deterministic sensitivity analysis (DSA) and the uncertainty is not reflected in the probabilistic sensitivity analysis (PSA).
   a. Please provide additional DSAs including all potential stochastic parameters reported in tables 50, 53, 54 and 56

b. Please provide additional PSA results while include all potential stochastic parameters reported in tables 50, 53, 54 and 56 as stochastic parameters

In table 50 the number of vials per administration was presented. These were calculated using the method of moments calculation and were based on weight. Weight was included as a stochastic parameter and therefore data in table 50 were included in the sensitivity analyses.

In table 53 the proportion of patients receiving each line of treatment are presented. These were not included as stochastic parameters in the sensitivity analyses, but are included in the following analyses presented in Figure 4 to Figure 6 using the beta distribution.

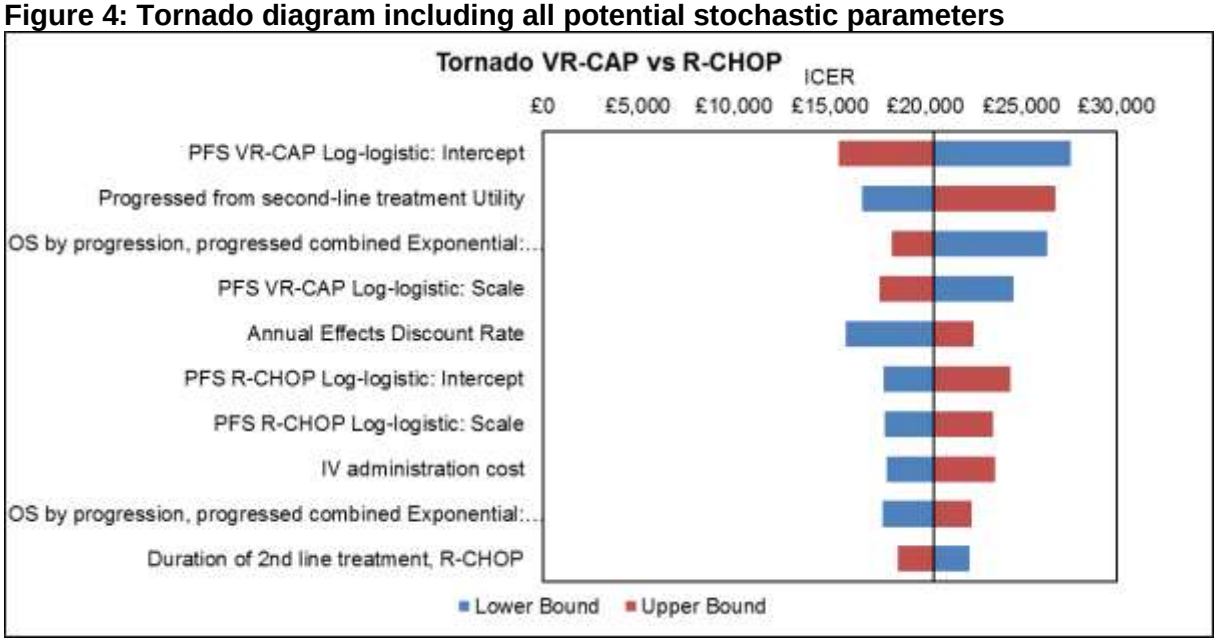
In table 54 dose reductions were presented. These were included as stochastic parameters in sensitivity analyses, and are displayed at rows 145 to 224 of the parameters sheet.

In table 56 the proportion of patients receiving concomitant medications were presented. These were not included as stochastic parameters, but are included in the following analyses presented in Figure 4 to Figure 6 using the beta distribution.

a.

Results of the one-way sensitivity analysis including the additional parameters are presented in the tornado diagram in Figure 4. The outcomes are equal to those without the additional parameters included.

Figure 4: Tornado diagram including all potential stochastic parameters



Key: ICER, incremental cost-effectiveness ratio; IV, intravenous; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

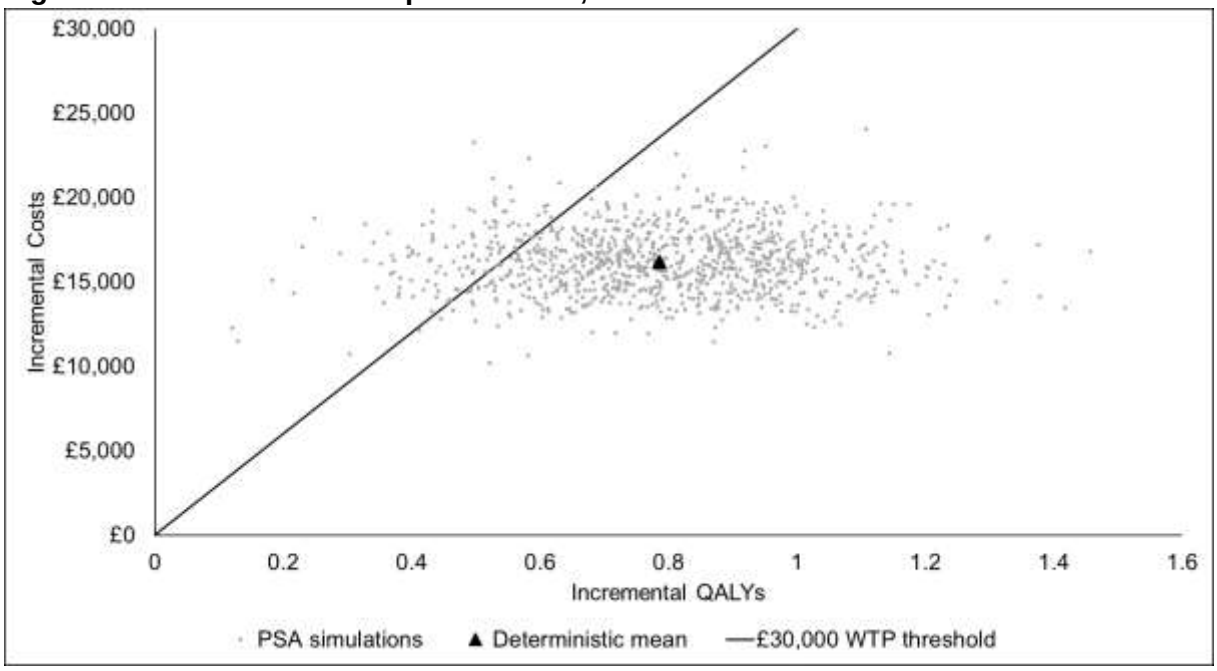
b.

Results from 1,000 probabilistic sensitivity analysis (PSA) iterations of VR-CAP versus R-CHOP are presented in Figure 5. This shows incremental QALYs and costs for VR-CAP versus R-CHOP. Incremental QALYs range from approximately 0.1 to 1.5, while incremental costs are approximately clustered between £10,000 and £24,000. The mean cost difference

is £16,213, and the mean difference in QALYs is 0.79, with a mean probabilistic ICER of £20,642.

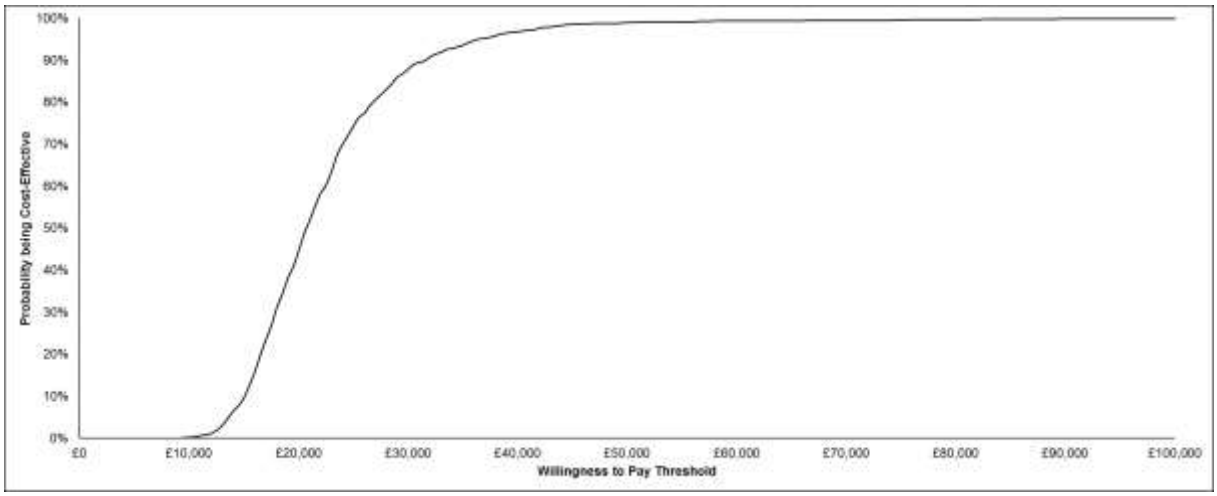
Based on 1,000 PSA iterations, the incremental cost-effectiveness acceptability curve versus R-CHOP (Figure 6) has been constructed. There is a 44.6% likelihood that VR-CAP is cost effective when compared to R-CHOP at a willingness to pay threshold of £20,000. At a threshold of £30,000, the likelihood is 87.9%.

Figure 5: Cost-effectiveness plane from 1,000 PSA iterations



Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 6: Incremental cost-effectiveness acceptability curve for VR-CAP versus R-CHOP



Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

<u>Sensitivity and scenario analyses</u>

C20. On page 179 of the company submission, the potential impact of including rituximab maintenance followed by induction therapy was tested using an hazard ratio of 0.55

for PFS (first-scenario) and hazard ratios of 0.40 for PFS and 0.39 for OS (second-scenario).

a. Please provide details with sources and justify how these model inputs were obtained.
b. On page 27 of the company submission it is stated that: "At the NICE scoping meeting, it was noted that R-maintenance would be considered after any standard induction therapy". Please clarify and justify why rituximab maintenance therapy is only included in the scenario analyses and not in the base case analysis.

a.

Scenario analyses were undertaken to test the impact of including R-maintenance within the model. These analyses should be viewed as purely exploratory as no clinical trial evidence is available assessing the effectiveness of R-maintenance compared to no maintenance therapy after any of the treatments used for MCL.

Two sources of evidence were used to inform the potential effectiveness of MCL as shown in Table 18. There are considerable limitations with both available data sources; however, no more robust data are available for R-maintenance in MCL. The European MCL Elderly Trial was the only relevant source identified in the systematic literature review of clinical effectiveness (described in section 4.1 of the company submission). As NICE had previously assessed rituximab maintenance in other NHLs, a targeted search of NICE Technology Appraisal guidance identified TA226 as an alternative source, given the limitations of the European MCL Elderly trial.

Table 18: Sources of data used for exploratory analysis of impact of inclusion of R-maintenance in the model

Source	NICE TA226[20]	European MCL Elderly trial[6]
Population	Follicular lymphoma	MCL
Comparison	R-maintenance vs observation after induction with rituximab plus chemotherapy	R-CHOP followed by R-maintenance vs R-CHOP followed by interferon
Results	HR 0.55 for PFS No significant effect on OS	HR 0.41 for PFS HR 0.48 for OS (see Appendix 9)
Key advantages	Comparison to no R-maintenance Two year treatment duration	Studied in MCL population Both OS and PFS presented
Key limitations	Not studied in an MCL population Open label OS is too immature as stated in the NICE appraisal Trial stopped early; there may be some bias in the HR for PFS, overestimating the benefit of R-maintenance	Not a comparison to observation Open label Duration of remission assumed equal to PFS R-maintenance given until progression rather than limited to 2 years as per UK practice Imbalanced drop out post randomisation between the arms (14% for IFN, 5% for rituximab) Differing results depending on initial treatment (R-FC vs R-CHOP)
Key: HR, hazard ratio; MCL, mantle cell lymphoma; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; OS, overall survival; R, rituximab; R-CHOP, rituximab with cyclophosphamide,		

doxorubicin, vincristine and prednisone.

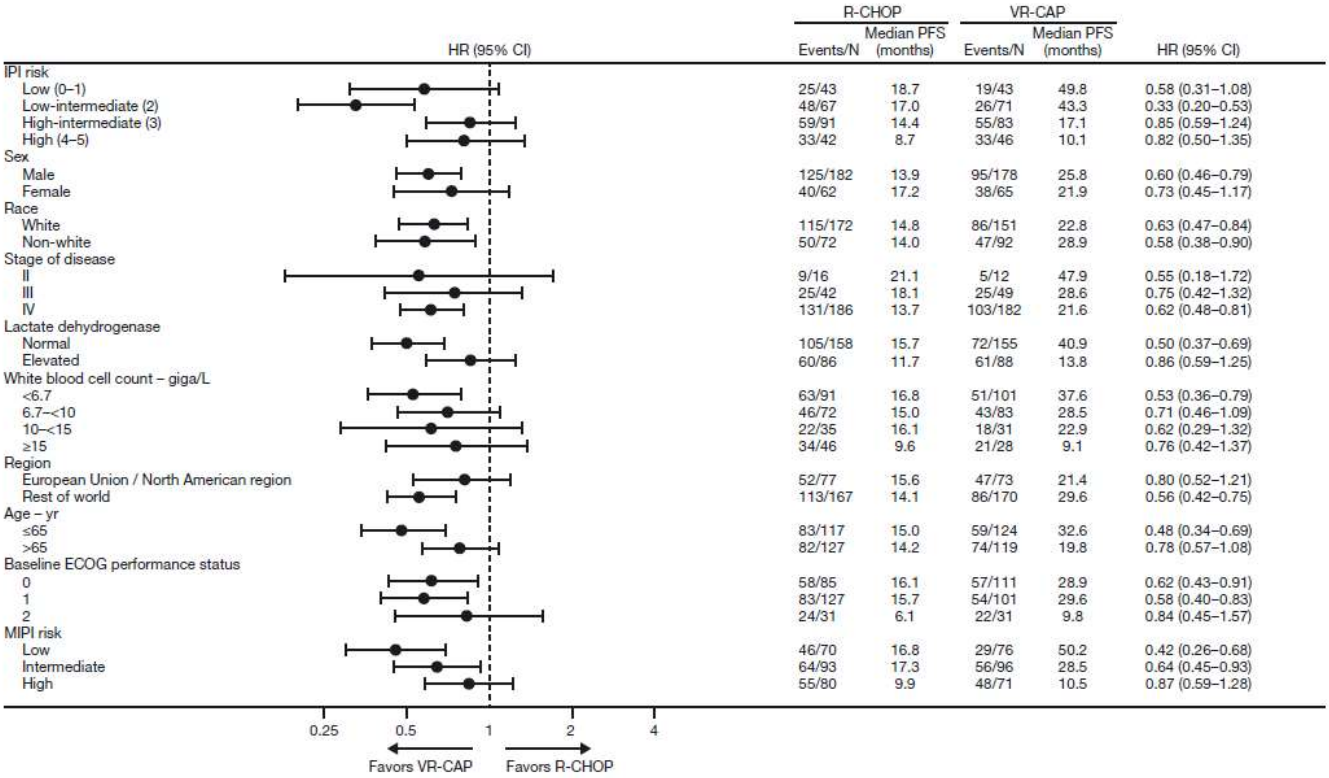
b.

As noted, at the NICE scoping meeting clinical experts considered that R-maintenance would be considered after any standard induction therapy (with the same benefit expected) and would thus not impact the initial treatment decision.[21] The final scope for this appraisal does not specify the inclusion of R-maintenance. In light of the direction from NICE through its scoping workshop and the final scope document, combined with the limitations to the evidence available to model R-maintenance, the inclusion of R-maintenance to an induction regimen of VR-CAP or R-CHOP was presented only as scenario analysis.

Section D: Textual clarifications and additional points

D1. The text in figure 8 is difficult to read because of the poor quality. Please provide a figure of better quality.

Figure 7: PFS subgroup analysis based on IRC assessment, ITT analysis set



	R-CHOP Events/N	R-CHOP Median PFS (months)	VR-CAP Events/N	VR-CAP Median PFS (months)	HR (95% CI)
IPI risk					
Low (0–1)	25/43	18.7	19/43	49.8	0.58 (0.31–1.08)
Low-intermediate (2)	48/67	17.0	26/71	43.3	0.33 (0.20–0.53)
High-intermediate (3)	59/91	14.4	55/83	17.1	0.85 (0.59–1.24)
High (4–5)	33/42	8.7	33/46	10.1	0.82 (0.50–1.35)
Sex					
Male	125/182	13.9	95/178	25.8	0.60 (0.46–0.79)
Female	40/62	17.2	38/65	21.9	0.73 (0.45–1.17)
Race					
White	115/172	14.8	86/151	22.8	0.63 (0.47–0.84)
Non-white	50/72	14.0	47/92	28.9	0.58 (0.38–0.90)
Stage of disease					
II	9/16	21.1	5/12	47.9	0.55 (0.18–1.72)
III	25/42	18.1	25/49	28.6	0.75 (0.42–1.32)
IV	131/186	13.7	103/182	21.6	0.62 (0.48–0.81)
Lactate dehydrogenase					
Normal	105/158	15.7	72/155	40.9	0.50 (0.37–0.69)
Elevated	60/86	11.7	61/88	13.8	0.86 (0.59–1.25)
White blood cell count – giga/L					
<6.7	63/91	16.8	51/101	37.6	0.53 (0.36–0.79)
6.7–<10	46/72	15.0	43/83	28.5	0.71 (0.46–1.09)
10–<15	22/35	16.1	18/31	22.9	0.62 (0.29–1.32)
≥15	34/46	9.6	21/28	9.1	0.76 (0.42–1.37)
Region					
European Union / North American region	52/77	15.6	47/73	21.4	0.80 (0.52–1.21)
Rest of world	113/167	14.1	86/170	29.6	0.56 (0.42–0.75)
Age – yr					
≤65	83/117	15.0	59/124	32.6	0.48 (0.34–0.69)
>65	82/127	14.2	74/119	19.8	0.78 (0.57–1.08)
Baseline ECOG performance status					
0	58/85	16.1	57/111	28.9	0.62 (0.43–0.91)
1	83/127	15.7	54/101	29.6	0.58 (0.40–0.83)
2	24/31	6.1	22/31	9.8	0.84 (0.45–1.57)
MIPI risk					
Low	46/70	16.8	29/76	50.2	0.42 (0.26–0.68)
Intermediate	64/93	17.3	56/96	28.5	0.64 (0.45–0.93)
High	55/80	9.9	48/71	10.5	0.87 (0.59–1.28)

Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPI, International Prognostic Index; IRC, independent review committee; ITT, intent-to-treat; MIPI, MCL International Prognostic Index; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Source: Robak et al. 2015.[22]

D2. Please confirm that the missing reference in the last paragraph on page 120 is referring to table 40 on the following page.

Yes, this should be referring to table 40 on page 121.

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