NOVARTIS

Single Technology Appraisal (STA)

Ranibizumab for the treatment of choroidal neovascularisation associated with pathological myopia [ID555]

Response to ERG queries

17th July 2013

Literature searching

1. Page 48 section 6.1: The submission states that all literature searches were conducted in November 2012. However, in Appendix 10.2.2 all search dates are reported as March/April 2012. Please explain this discrepancy.

All literature searches were initially run in March/April 2012, but updated in November 2012. This is stated in section 6.1 and should also be mentioned in Appendix 10.2.2. This is an error in the Appendix.

2. Page 51, Figure 7: Please clarify and provide references for the RCTs that were excluded because they did not include a ranibizumab arm.

The following are the RCTs that were excluded for this reason:

Fardeau, C., Soubrane, G., and Coscas, G. (1992), 'Photocoagulation de néo–vessaux sous–rétinien compliquant la dégénérescence myopique', Bulletin des Societes d'Ophtalmologie de France 3, 239–42.

Parodi, M. B., et al. (2010), 'Laser photocoagulation, photodynamic therapy, and intravitreal bevacizumab for the treatment of juxtafoveal choroidal neovascularization secondary to pathologic myopia', Arch Ophthalmol, 128 (4), 437-42.

Verteporfin in Photodynamic Therapy Study Group (2001), 'Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial--VIP report no. 1', Ophthalmology, 108 (5), 841-52.

Section A: Clarification on effectiveness data

A1. Please provide the breakdown of the number of participants by geographical location of centre (i.e. country) for each arm of the Novartis Phase III trial.

Table 1 summarises the number of patients from each country included in the Novartis phase III trial.

Table 1 Breakdown by country of participants in the Novartis phase III trial

Country	No. of patients
Austria	3
Canada	1
France	8
Germany	18
Hong Kong	8
Hungary	13
India	27
Italy	28
Japan	51
Korea	18
Lithuania	17
Latvia	14
Poland	3
Portugal	13
Singapore	10
Slovakia	14
Spain	12
Switzerland	5
Turkey	6
UK	8

A2. PRIORITY. Table 3, page 19 /Table 20, page 82: Please present the data for the vPDT/ranibizumab arm for 0-6 months and 0-12 months.

Table 2 summarises the efficacy data for the Novartis phase III trial and includes 0−6 and 0−12 months data for the vPDT/ranibizumab arm. Caution should be taken when interpreting the data for the 0−6 and 0−12 months comparisons due to the crossover post month 3 in the vPDT arm.

Table 2 Summary of efficacy results from the Novartis phase III trial (Full analysis set/mLOCF)

Time[a]	**Months 0−3**			**Months 0−6**			**Months 0−12**		
	Ranibizumab disease activity, N = 116	**Ranibizumab disease stabilisation, N = 105**	**vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**
Primary endpoint: Mean average change in BCVA (letters) from baseline, mean (SD)	10.6 (7.26)***	10.5 (8.16)***	2.2 (9.47)	11.7 (8.24)***	11.9 (8.81)***	4.2 (9.26)	12.5 (8.83)***	12.8 (9.48)***	6.4 (9.55)
Change in BCVA (letters) from baseline, mean (SD)	12.5 (8.81)***	12.1 (10.18)***	1.4 (12.21)	12.7 (11.01)**	13.7 (10.16)***	7.9 (10.37)	14.4 (10.20)**	13.8 (11.42)*	9.3 (11.33)
Gain of ≥ 10 letters, n (%)	76 (65.5)***	65 (61.9)***	15 (27.3)	75 (64.7)	75 (71.4)	25 (45.5)	80 (69.0)	73 (69.5)	27 (49.1)
Gain ≥ 10 letters (versus vPDT), OR (95% CI)	5.07 (2.50–10.27)	4.33 (2.13–8.83)	NA	–	–	–	–	–	–
Gain ≥ 10 letters (versus vPDT), RR (95% CI)	2.40 (1.53–3.77)	2.27 (1.44–3.58)	NA	–	–	–	–	–	–
Gain of ≥ 15	50 (43.1)**	40 (38.1)**	8	52 (44.8)	49 (46.7)	15 (27.3)	60 (51.7)	56 (53.3)	18 (32.7)

letters, n (%)			(14.5)						
Gain ≥ 15 letters (versus vPDT), OR (95% CI)	4.45 (1.93–10.26)	3.62 (1.55–8.43)	NA	–	–	–	–	–	–
Gain ≥ 15 letters (versus vPDT), RR (95% CI)	2.96 (1.51–5.81)	2.62 (1.32–5.20)	NA	–	–	–	–	–	–
Change from baseline in CRT (µm), mean (SD)	-77.6 (102.25)***	-61.0 (67.46)***	-12.0 (65.84)	-74.8 (97.05)	-66.1 (73.63)	-51.5 (79.98)	-71.3 (100.91)	-66.6 (82.63)	-60.8 (80.04)
No. of ranibizumab injections, mean (SD)	1.8 (0.8)	2.5 (0.6)	0 (0.0)	2.5 (1.6)	3.5 (1.5)	1.3 (1.2)	3.5 (2.9)	4.6 (2.6)	2.4 (2.6)
Change from baseline in NEI VFQ-25 composite score, mean (SD)	4.3 (10.09)*	5.3 (13.96)*	0.3 (12.63)	5.1 (14.38)	6.3 (13.98)	2.3 (13.86)	5.1 (15.83)	6.6 (15.66)	4.9 (11.91)

Bandello et al., 2013;[1] Novartis phase III study 12 month CSR[2]
BCVA, best corrected visual acuity; CRT, central retinal thickness; NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; SD, standard deviation; vPDT, verteporfin photodynamic therapy
[a]The mean average change in BCVA is the average change from months 0–3, 0–6 and 0–12 compared with baseline. For all other parameters, the changes and values reported are at month 3, 6 or 12 compared with baseline.
*p < 0.05, **p < 0.005; ***p < 0.0001 vs vPDT

A3. **PRIORITY.** Please provide the equivalent of Table 20, page 82 (including vPDT/ranibizumab results at 0-6 and 0-12 months) for the observed data, which did not include LOCF. Please indicate clearly the N involved in each efficacy result.

Table 3 summarises the efficacy data for the Novartis phase III trial for observed data set.

Table 3 Summary of efficacy results from the Novartis phase III trial (Full analysis set, observed data)

Time[a]	**Months 0−3**			**Months 0−6**			**Months 0−12**		
	Ranibizumab disease activity, N = 116	**Ranibizumab disease stabilisation, N = 105**	**vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**
Mean average change in BCVA (letters) from baseline, mean (SD)	10.6 (7.27)*** (n = 116)	10.5 (8.16)*** (n = 105)	2.2 (9.47) (n = 55)	11.7 (8.23)*** (n = 116)	11.9 (8.82)*** (n = 105)	4.3 (9.26) (n = 55)	12.6 (8.74)*** (n = 116)	12.8 (9.40)*** (n = 105)	6.4 (9.59) (n = 55)
Change in BCVA (letters) from baseline, mean (SD)	12.3 (8.82)*** (n = 113)	12.2 (10.15)*** (n = 104)	1.2 (12.27) (n = 54)	12.6 (11.05)** (n = 115)	14.1 (10.17)*** (n = 101)	7.8 (10.42) (n = 54)	14.6 (10.25)** (n = 112)	14.4 (11.17)** (n = 100)	9.3 (11.33) (n = 55)
Gain of ≥ 10 letters, n (%)	73 (64.6)*** (n = 113)	65 (62.5)*** (n = 104)	15 (27.8) (n = 54)	74 (64.3) (n = 115)	74 (73.3) (n = 101)	24 (44.4) (n = 54)	79 (70.5) (n = 112)	72 (72.0) (n = 100)	27 (49.1) (n = 55)
Gain ≥ 10 letters (versus vPDT), OR (95% CI)	4.75 (2.33–9.65) (n = 113)	4.33 (2.12–8.86) (n = 104)	NA	2.26 (1.17–4.36) (n = 115)	3.43 (1.71–6.86) (n = 101)	NA	2.48 (1.27–4.84) (n = 112)	2.67 (1.34–5.30) (n = 100)	NA
Gain ≥ 10 letters (versus vPDT), RR (95% CI)	2.33 (1.48–3.65) (n = 113)	2.25 (1.43–3.55) (n = 104)	NA	1.45 (1.04–2.01) (n = 115)	1.65 (1.20–2.27) (n = 101)	NA	1.44 (1.07–1.93) (n = 112)	1.47 (1.09–1.97) (n = 100)	NA

Gain of ≥ 15 letters, n (%)	48 (42.5)*** (n = 113)	40 (38.5)** (n = 104)	8 (14.8) (n = 54)	51 (44.3) (n = 115)	49 (48.5) (n = 101)	14 (25.9) (n = 54)	60 (53.6) (n = 112)	56 (56.0) (n = 100)	18 (32.7) (n = 55)
Gain ≥ 15 letters (versus vPDT), OR (95% CI)	4.25 (1.84–9.82) (n = 113)	3.59 (1.54–8.39) (n = 104)	NA	2.28 (1.12–4.64) (n = 115)	2.69 (1.31–5.55) (n = 101)	NA	2.37 (1.21–4.66) (n = 112)	2.62 (1.32–5.20) (n = 100)	NA
Gain ≥ 15 letters (versus vPDT), RR (95% CI)	2.87 (1.46–5.63) (n = 113)	2.60 (1.31–5.15) (n = 104)	NA	1.71 (1.04–2.81) (n = 115)	1.87 (1.14–3.07) (n = 101)	NA	1.64 (1.08–2.48) (n = 112)	1.71 (1.13–2.60) (n = 100)	NA
Change from baseline in CRT (µm), mean (SD)	-76.6 (101.80)*** (n = 101)	-64.9 (66.75)*** (n = 97)	-10.5 (65.59) (n = 53)	-75.4 (99.15) (n = 99)	-72.4 (72.16) (n = 92)	-56.3 (81.62) (n = 50)	-75.8 (100.49) (n = 94)	-72.0 (82.53) (n = 91)	-62.6 (81.39) (n = 51)
Change from baseline in NEI VFQ-25 composite score, mean (SD)	4.3 (10.09)*	5.3 (13.96)*	0.3 (12.63)	5.1 (14.38)	6.3 (14.08)	2.4 (13.97)	4.8 (15.90)	6.8 (15.70)	5.0 (12.00)

Bandello et al., 2013;[1,3] Ohno-Matsui et al., 2013;[4,5] Novartis phase III study 12 month CSR[2]
BCVA, best corrected visual acuity; CI, confidence interval; NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; OR, odds ratio; RR, risk ratio; SD, standard deviation; vPDT, verteporfin photodynamic therapy
[a]The mean average change in BCVA is the average change from months 0–3, 0–6 and 0–12 compared with baseline. For all other parameters, the changes and values reported are at month 3, 6 or 12 compared with baseline.
*p < 0.05, **p < 0.01; ***p < 0.001 vs vPDT

A4. Table 23, page 91: Please provide an explanation as to why the 'Driving' score for the two ranibizumab groups are so different.

There were marked differences in the baseline means between the three treatment arms for the "driving" score. Specifically, the ranibizumab disease stabilisation arm, which showed a large improvement (+14.1) compared to the other two arms (ranibizumab disease activity, −0.2, and vPDT, +2.6), had a substantially lower baseline mean of 48.2 compared to 66.2 and 63.4 for the ranibizumab disease activity and vPDT arms, respectively. As a consequence, patients in the ranibizumab disease stabilisation group experienced greater changes from baseline.

A5. **PRIORITY.** Table 30, page 100 (VIP trial): Please provide the mean change in BCVA (with standard deviation) in each treatment group at 3, 6, 12 and 24 months. In addition please provide the n(%) of patients gaining ≥ 10 letters, ≥ 20 and ≥ 30 letters at each assessment (3, 6, 12 and 24 months). Please provide the equivalent data for a loss of at least 10, 20, and 30 letters.

Table 4 summarises the mean change from baseline in BCVA in the VIP trial.

Table 4 Mean change in BCVA letters from baseline

	Month 3	Month 6	Month 12	Month 24
vPDT	-0.889 (8.471)	-2.911 (11.718)	-2.608 (16.061)	-4.364 (18.779)
Sham	-5.658 (10.743)	-9.167 (11.500)	-8.971 (14.099)	-8.114 (12.651)
Data are presented as mean (SD).				

Table 5 summarises the proportion of patients gaining ≥ 10 letters, ≥ 20 letters, and ≥ 30 letters.Table 6 summarises the proportion of patients losing ≥ 10 letters, ≥ 20 letters, and ≥ 30 letters in the VIP trial.

Table 5 Proportion (n, %) of patients gaining BCVA letters compared with baseline in the VIP trial

		Month 3	Month 6	Month 12	Month 24
vPDT	≥ 10 letters	9 (11.11)	10 (12.66)	16 (20.25)	17 (22.08)
	≥ 20 letters	1 (1.23)	1 (1.27)	4 (5.06)	3 (3.90)
	≥ 30 letters	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Sham	≥ 10 letters	3 (7.89)	2 (5.56)	1 (2.86)	2 (5.71)
	≥ 20 letters	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	≥ 30 letters	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Data are presented as n (%).					

Table 6 Proportion (n, %) of patients losing BCVA letters compared with baseline in the VIP trial

		Month 3	Month 6	Month 12	Month 24
vPDT	≥ 10 letters	13 (16.05)	17 (21.52)	21 (26.58)	24 (31.17)
	≥ 20 letters	1 (1.23)	8 (10.13)	7 (8.86)	14 (18.18)
	≥ 30 letters	0 (0.00)	3 (3.80)	6 (7.59)	9 (11.69)
Sham	≥ 10 letters	16 (42.11)	17 (47.22)	17 (48.57)	15 (42.86)
	≥ 20 letters	3 (7.89)	6 (16.67)	7 (20.00)	7 (20.00)
	≥ 30 letters	1 (2.63)	4 (11.11)	3 (8.57)	3 (8.57)
Data are presented as n (%).					

A6. **PRIORITY.** Please provide the data for the Novartis phase III trial for the number (%) of patients who had 2, 3, 4 and 6 lines of loss (patients losing 10, 15, 20 and 30 ETDRS letters respectively) as well as 4 and 6 lines gain (patients gaining 20 and 30 ETDRS letters) for each of the follow up assessments (3, 6 and 12 months) for each of the three treatment groups.

These dichotomous data both for the Full Analysis Set (modified LOCF) and the observed data for each of the three time-points requested (3, 6, and 12 months) and summarised in Table 7 and Table 8.

Table 7 Summary of dichotomous efficacy results from the Novartis phase III trial (Full analysis set/mLOCF)

Change from baseline	**Month 3**			**Month 6**			**Month 12**		
	Ranibizumab disease activity, N = 116	**Ranibizumab disease stabilisation, N = 105**	**vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**
Gain of ≥ 30 letters, n (%)	5 (4.3)	6 (5.7)	0	8 (6.9)	7 (6.7)	1 (1.8)	9 (7.8)	8 (7.6)	2 (3.6)
Gain of ≥ 20 letters, n (%)	23 (19.8)	21 (20.0)	3 (5.5)	25 (21.6)	26 (24.8)	8 (14.5)	33 (28.4)	32 (30.5)	13 (23.6)
Loss of ≤ 10 letters, n (%)	9 (7.8)	6 (5.7)	18 (32.7)	7 (6.0)	6 (5.7)	12 (21.8)	4 (3.4)	7 (6.7)	8 (14.5)
Loss of ≤ 15 letters, n (%)	9 (7.8)	6 (5.7)	22 (40.0)	9 (7.8)	8 (7.6)	13 (23.6)	5 (4.3)	10 (9.5)	8 (14.5)
Loss of ≤ 20 letters, n (%)	9 (7.8)	6 (5.7)	25 (45.5)	9 (7.8)	8 (7.6)	14 (25.5)	5 (4.3)	11 (10.5)	8 (14.5)
Loss of ≤ 30 letters, n (%)	9 (7.8)	8 (7.6)	25 (45.5)	9 (7.8)	8 (7.6)	14 (25.5)	6 (5.2)	11 (10.5)	10 (18.2)

Bandello et al., 2013;[1] Novartis phase III study 12 month CSR[6]
vPDT, verteporfin photodynamic therapy
*p < 0.05, **p < 0.005; ***p < 0.0001 vs vPDT

Table 8 Summary of dichotomous efficacy results from the Novartis phase III trial (observed data)

Change from baseline	**Month 3**			**Month 6**			**Month 12**		
	Ranibizumab disease activity, N = 116	**Ranibizumab disease stabilisation, N = 105**	**vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**
Gain of ≥ 30 letters, n (%)	5 (4.4)	6 (5.8)	0	8 (7.0)	7 (6.9)	1 (1.9)	9 (8.0)	8 (8.0)	2 (3.6)
Gain of ≥ 20 letters, n (%)	22 (19.5)	21 (20.2)	3 (5.6)	25 (21.7)	26 (25.7)	8 (14.8)	33 (28.4)	32 (30.5)	13 (23.6)
Loss of ≤ 10 letters, n (%)	9 (8.0)	5 (4.8)	18 (33.3)	7 (6.1)	5 (5.0)	12 (22.2)	4 (3.6)	6 (6.0)	8 (14.5)
Loss of ≤ 15 letters, n (%)	9 (8.0)	5 (4.8)	22 (40.7)	9 (7.8)	7 (6.9)	13 (24.1)	5 (4.5)	8 (8.0)	8 (14.5)
Loss of ≤ 20 letters, n (%)	9 (8.0)	5 (4.8)	25 (46.3)	9 (7.8)	7 (6.9)	14 (25.9)	5 (4.5)	9 (9.0)	8 (14.5)
Loss of ≤ 30 letters, n (%)	9 (8.0)	7 (6.7)	25 (46.3)	9 (7.8)	7 (6.9)	14 (25.9)	6 (5.4)	9 (9.0)	10 (18.2)

Bandello et al., 2013;[1] Novartis phase III study 12 month CSR[6]
vPDT, verteporfin photodynamic therapy
*p < 0.05, **p < 0.005; ***p < 0.0001 vs vPDT

A7. The primary outcome of the Novartis phase III trial (mean average change in BCVA from baseline) is measured at 3 months. Please explain the rationale for why a 3 month assessment is considered clinically relevant, rather than a longer time period.

Several publications available at the time the study was designed suggested that patients with CNV secondary to PM treated with intravitreal injection of 0.5 mg ranibizumab have a mean gain of 10 to 15 letters in VA within the first year of treatment with an average of only 1.5 to 3 injections needed. These publications also reveal that patients have a rapid gain of vision, mostly in the first 3 months, and the anatomical changes such as active leakage of the anomalous vasculature, subretinal fluid and haemorrhage disappear at the same proportion as patients gain VA, most of the morphologic improvement occurs also within the first 3 months.[7-9]

Therefore the 3-month comparative endpoint was based on the preliminary available evidence with anti-VEGF treatment, which suggested early efficacy benefit. vPDT (the active comparator arm in the study) was thought to be only able to reduce visual acuity loss compared to placebo and was not able to stabilise the disease. Therefore, ethically, ranibizumab was made available to patients randomised to vPDT by Month 3.

It was therefore considered, based on previous evidence at the time of the study design, that the 3-month period is sufficient to demonstrate the efficacy of ranibizumab. This assumption was confirmed by the study results during the 12 month follow-up, – at Month 3, the average change in BCVA from Baseline was > 80% of that observed at Month 12. Thus patients achieved the majority of their visual acuity benefit by month 3, which further supports that the 3-month endpoint is clinically relevant.

<u>Summary</u>

A primary endpoint at three-months was seen as a minimum but evaluable treatment period to assess the efficacy of ranibizumab compared to vPDT. It was also chosen due to ethical concerns to minimise the time that a potentially beneficial treatment is withheld from patients in the comparator group.

A8. **PRIORITY.** Please provide the number (%) of patients in each treatment group at each assessment (baseline, 3, 6 and 12 months) that showed CRT thickness < 250 microns.

These data are summarised in Table 9.

Table 9 Number (%) of patients with CRT < 250 µm (Full analysis set/LOCF)

Time point	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**
Baseline, n (%)	[redacted]	[redacted]	[redacted]
Month 3, n (%)	[redacted]	[redacted]	[redacted]
Month 6, n (%)	[redacted]	[redacted]	[redacted]
Month 12, n (%)	[redacted]	[redacted]	[redacted]

A9. **PRIORITY.** Page 133 - Table 41: Please provide the safety data for the vPDT/ranibizumab arm of the trial for baseline to 6 months and for baseline to 12 months.

These data are summarised in Table 10.

Table 10 Summary of ocular AEs of the study eye and non-ocular AEs in the Novartis phase III study reported in at least two patients in any treatment group and all AEs related to ocular safety concerns: baseline to months 6 and 12 (Safety set)

	Baseline to month 6				**Baseline to month 12**			
	Ranibizumab disease activity, N = 118	**Ranibizumab disease stabilisation, N = 106**	**vPDT + ranibizumab, N = 34**	**vPDT, N = 19**	**Ranibizumab disease activity, N = 118**	**Ranibizumab disease stabilisation, N = 106**	**vPDT + ranibizumab, N = 38**	**vPDT, N = 15**
Ocular AEs, n (%)[a]								
Any	31 (26.3)	38 (35.8)	10 (29.4)	4 (21.1)	44 (37.3)	46 (43.4)	16 (42.1)	4 (26.7)
Severe	1 (0.8)	0	0	0	1 (0.8)	1 (0.9)	0	0
Conjunctival haemorrhage	11 (9.3)	10 (9.4)	0	0	12 (10.2)	12 (11.3)	2 (5.3)	0
Punctate keratitis	3 (2.5)	6 (5.7)	1 (2.9)	1 (5.3)	3 (2.5)	8 (7.5)	2 (5.3)	0
Intraocular pressure increased	3 (2.5)	2 (1.9)	2 (5.9)	0	7 (5.9)	3 (2.8)	4 (10.5)	0
Eye pain	3 (2.5)	3 (2.8)	0	0	4 (3.4)	4 (3.8)	1 (2.6)	1 (6.7)
Dry eye	0	4 (3.8)	0	0	2 (1.7)	4 (3.8)	0	1 (6.7)
Injection site haemorrhage	3 (2.5)	3 (2.8)	2 (5.9)	0	3 (2.5)	3 (2.8)	2 (5.3)	0
Vitreous floaters	1 (0.8)	3 (2.8)	0	0	1 (0.8)	5 (4.7)	0	0
Retinal tear	0	2 (1.9)	0	0	1 (0.8)	2 (1.9)	0	0
Conjunctivitis allergic	2 (1.7)	0	0	0	5 (4.2)	1 (0.9)	1 (2.6)	0
Metamorphopsia	2 (1.7)	0	0	0	3 (2.5)	0	0	0
Retinal haemorrhage	2 (1.7)	0	0	0	3 (2.5)	1 (0.9)	0	0
Blepharitis	0	0	0	0	2 (1.7)	2 (1.9)	0	0
Conjunctivitis	0	0	0	0	1 (0.8)	2 (1.9)	0	0
Eyelid oedema	0	0	0	0	0	2 (1.9)	0	0

Cataract	0	2 (1.9)	0	0	2 (1.7)	1 (0.9)	0	1 (6.7)
Ocular hyperaemia	0	0	0	0	2 (1.7)	1 (0.9)	1 (2.6)	0
Visual impairment	0	0	1 (2.9)	0	0	0	2 (5.3)	0
Ocular AEs related to study medication or ocular injection, or both, n (%)								
Any, n (%)	19 (16.1)	21 (19.8)	4 (11.8)	2 (10.5)	24 (20.3)	26 (24.5)	8 (21.1)	2 (13.3)
Conjunctival haemorrhage	9 (7.6)	8 (7.5)	0	0	10 (8.5)	10 (9.4)	2 (5.3)	0
Punctate keratitis	2 (1.7)	3 (2.8)	1 (2.9)	1 (5.3)	2 (1.7)	5 (4.7)	2 (5.3)	0
Eye pain	3 (2.5)	2 (1.9)	0	0	3 (2.5)	3 (2.8)	1 (2.6)	0
Intraocular pressure increased	1 (0.8)	2 (1.9)	1 (2.9)	0	5 (4.2)	3 (2.8)	2 (5.3)	0
Conjunctival oedema	0	1 (0.9)	0	0	0	1 (0.9)	0	0
Corneal erosion	1 (0.8)	1 (0.9)	0	0	1 (0.8)	1 (0.9)	0	0
Retinal tear	0	1 (0.9)	0	0	0	1 (0.9)	0	0
Vitreous floaters	1 (0.8)	1 (0.9)	0	0	1 (0.8)	1 (0.9)	0	0
Vitreous prolapse	0	1 (0.9)	0	0	0	1 (0.9)	0	0
Conjunctival hyperaemia	0	0	0	1 (5.3)	0	0	0	1 (6.7)
Injection site haemorrhage	3 (2.5)	3 (2.8)	2 (5.9)	0	3 (2.5)	3 (2.8)	2 (5.3)	0
Intracranial pressure increased	0	1 (0.9)	0	0	0	1 (0.9)	0	0
Uveitis	1 (0.8)	1 (0.9)	0	0	1 (0.8)	1 (0.9)	0	0
Ocular hyperaemia	0	1 (0.9)	0	0	1 (0.8)	1 (0.9)	1 (2.6)	0
Iridocyclitis	1 (0.8)	0	0	0	1 (0.8)	0	0	0
Drug hypersensitivity	0	0	0	0	0	1 (0.9)	0	0

Injection site pain	0	0	0	0	0	1 (0.9)	0	0
Adenoviral conjunctivitis	0	0	0	0	1 (0.8)	0	0	0
Eye irritation	0	0	0	0	1 (0.8)	0	0	0
Metamorphopsia	0	0	0	0	1 (0.8)	0	0	0
Cataract	0	0	0	0	0	0	0	1 (6.7)
Visual impairment	0	0	1 (2.9)	0	0	0	2 (5.3)	0
Non-ocular AEs, n (%)[b]								
Any	42 (35.6)	38 (35.8)	5 (14.7)	5 (26.3)	51 (43.2)	48 (45.3)	19 (50.0)	5 (33.3)
Severe	3 (2.5)	1 (0.9)	0	0	6 (5.1)	3 (2.8)	0	0
Nasopharyngitis	7 (5.9)	7 (6.6)	0	1 (5.3)	12 (10.2)	12 (11.3)	1 (2.6)	2 (13.3)
Headache	7 (5.9)	6 (5.7)	0	0	11 (9.3)	8 (7.5)	1 (2.6)	0
Intervertebral disc protrusion	0	2 (1.9)	0	0	0	2 (1.9)	0	0
Pharyngitis	0	2 (1.9)	0	0	0	2 (1.9)	0	0
Upper respiratory tract infection	4 (3.4)	1 (0.9)	0	0	4 (3.4)	3 (2.8)	1 (2.6)	0
Back pain	3 (2.5)	1 (0.9)	0	0	4 (3.4)	2 (1.9)	0	0
Hypertension	3 (2.5)	2 (1.9)	1 (2.9)	0	5 (4.2)	3 (2.8)	3 (7.9)	0
Fatigue	2 (1.7)	0	0	0	2 (1.7)	0	0	0
Haemorrhoids	2 (1.7)	0	0	0	2 (1.7)	0	0	0
Tooth disorder	2 (1.7)	0	0	0	2 (1.7)	0	0	0
Migraine	0	2 (1.9)	0	0	1 (0.8)	2 (1.9)	1 (2.6)	0
Pain in extremity	0	2 (1.9)	0	0	1 (0.8)	2 (1.9)	0	1 (6.7)
Hypercholesterolaemia	2 (1.7)	1 (0.9)	0	0	2 (1.7)	1 (0.9)	0	0

Urinary tract infection	4 (3.4)	1 (0.9)	0	0	3 (2.5)	3 (2.8)	0	0
Bronchitis	2 (1.7)	1 (0.9)	0	0	4 (3.4)	1 (0.9)	1 (2.6)	0
Influenza	2 (1.7)	0	0	0	4 (3.4)	2 (1.9)	1 (2.6)	0
Tendonitis	2 (1.7)	0	0	0	2 (1.7)	1 (0.9)	0	0
Abdominal pain	0	0	0	0	1 (0.8)	3 (2.8)	0	0
Bacteriuria	0	0	0	0	0	2 (1.9)	0	0
Diabetes mellitus	0	0	0	0	1 (0.8)	2 (1.9)	1 (2.6)	0
Nausea	0	0	1 (2.9)	0	1 (0.8)	2 (1.9)	1 (2.6)	0
Osteoporosis	0	0	0	0	0	2 (1.9)	0	0
Toothache	0	0	0	0	1 (0.8)	2 (1.9)	0	0
Vomiting	0	0	0	0	1 (0.8)	2 (1.9)	0	0
Arthralgia	0	0	0	0	2 (1.7)	1 (0.9)	0	0
Cough	0	0	0	1 (5.3)	2 (1.7)	1 (0.9)	1 (2.6)	0
Cystitis	0	0	0	0	1 (0.8)	1 (0.9)	2 (5.3)	0
Sciatica	0	0	0	0	2 (1.7)	1 (0.9)	0	0
Dental caries	0	0	0	0	2 (1.7)	0	0	1 (6.7)
Hyperglycaemia	0	0	0	0	2 (1.7)	0	0	0
Hyperlipidaemia	0	0	0	0	2 (1.7)	0	0	0
Seasonal allergy	0	0	0	0	2 (1.7)	0	0	0
Tinnitus	0	0	0	1 (5.3)	2 (1.7)	0	0	1 (6.7)
Urticaria	0	0	0	0	2 (1.7)	0	0	0
Serious AEs, n (%)	**2 (1.7)**	**3 (2.8)**	**0**	**0**	**6 (5.1)**	**7 (6.6)**	**0**	**0**

Bandello et al., 2013;[1,3] Novartis phase III 12 month CSR[6]
[a]Reported in at least 2 patients in any treatment group and all AEs related to ocular safety concerns; [b]Reported in at least 2 patients in any treatment group.

A10. PRIORITY. Ranibizumab is known to accelerate retinal pigment epithelium atrophy. Atrophy is a major issue in myopia. The manufacturer submission, however, does not include atrophy in the adverse events section. Would you please provide the rationale for this omission and clarify whether atrophy was measured in the Novartis phase III trial?

We fully agree, atrophy, in particular of the retinal pigment epithelium (RPE) is indeed an important and clinically relevant factor in pathologic myopia (PM), and one of the characteristics and diagnostic criteria of pathologic myopia. However, we disagree with the statement that ranibizumab is known to accelerate RPE atrophy, for the reasons described below.

Pathologic myopia and atrophy
The most commonly used definition for PM includes an abnormal elongation of the axial length of the eyeball (more than 26 mm) associated with high myopia (refractive errors greater than -6.0 Diopters) and the clinical characteristics mostly accompanied by anatomical changes of the posterior pole of the eye, especially with choroidal atrophy but also atrophy of the retina, beyond other findings.[10,11] The thinning of the choroids, lacquer cracks, stretching of the retina as well as development of atrophy are considered the main mechanisms of CNV formation in pathologic myopia.[12,13]

In the Novartis phase III study at time of enrolment into the study, 213 (76.9%) patients presented with chorioretinal atrophy and 115 (41.5%) patients with mottling of RPE, as part of the list of features confirming myopic abnormalities.

In a previous observational (i.e. non-treatment) retrospective study with 81 eyes, factors influencing the development of chorioretinal atrophy − the main cause of long-term visual decrease in myopic choroidal CNV – have been evaluated. Seventy-seven of 81 eyes (95.1%) developed chorioretinal atrophy around myopic CNV during the follow-up period of 3 years during the natural course of the disease. CNV size was the only factor to influence the development of chorioretinal atrophy in the patients younger than 40 years, whereas age was an influencing factor in those older than 40 years.[14] Thus treating CNV early in PM patients (e.g. with ranibizumab) may even prevent the development of atrophy in those patients.

A prospective clinical study following the natural history of highly myopic patients showed that in patients who developed CNV, macular atrophy developed after CNV-onset.[15] Thus as proposed already above, preventing expansion of CNV may even prevent the development of further atrophy in myopic CNV.

Ranibizumab in patients with myopic CNV (Novartis phase III trial)
The Novartis phase III trial assessed the effect of ranibizumab on the visual acuity and morphologic features of patients with CNV due to PM.

Per protocol, although areas of RPE atrophy were not specifically measured during the course of the trial, at every scheduled visit after the baseline visit, analysis by indirect ophthalmoscopy of the posterior pole of the study eye was performed with careful examination of the peripheral retina to look for degenerative/atrophic changes. Additionally, study investigators examined fluorescein angiographies, colour fundus photographs and OCT images of the patients and provided them to the Bern Photographic Reading Centre, a specialised and experienced retina imaging centre, for further evaluation of the anatomical changes.

In none of the assessments was atrophy reported as a morphological finding. Per protocol, any worsening of a clinical sign/ feature, including RPE atrophy, after starting the study drug had to be recorded as an adverse event (AE). However, no AEs of RPE atrophy were reported in this trial. Similarly, only 2 of the 262 patients (0.8%) in all three treatment arms who received any ranibizumab during the 12-month study period reported visual impairment as an AE, and only 6 of the 212 patients (2.8%) who received ranibizumab alone during the study lost at least 10-letters of visual acuity by month 12. Therefore, there were only a small number of cases of clinically relevant visual impairment after ranibizumab treatment in the study, and none of them were accompanied with AEs like atrophic changes.

[redacted]

Summary

In summary, atrophy is a feature of PM which can get worse over time as a nature of the disease itself. All reported clinical findings and the extensive analysis of morphologic changes in colour fundus and OCT images in the Novartis phase III study gave no hint to suggest that atrophy occurs during the treatment with ranibizumab. The major effect of ranibizumab is a regression or prevention of CNV, which was associated in the phase III study with clinically significant increases in BCVA, the primary objective of our study. Therefore in the absence of relevant signals for induction of atrophy, atrophy data were not assessed.

Further evaluation of the long-term efficacy and safety in subjects with CNV secondary to PM is planned in a 3-year observational study including at least 300 subjects. The study protocol will be submitted in Q1 2014.

A11. PRIORITY. Please provide, in tabular format, the data that have been used to generate the graphs for the network analyses reported on pages 308-310 of the submission.

[redacted]

[redacted]

[redacted]

Section B: Clarification on cost-effectiveness data

B1. Retinal tears are not considered in the economic model as they happened in less than 5% of patients. However, a retinal tear may cause a retinal detachment which if untreated may lead to permanent visual loss. In the Novartis phase III trial, 1%-2% of patients had retinal tears. Please explain why this was not taken into consideration in the economic model.

The criteria for selecting adverse events for the NICE economic model (see page 156 of the submission, section 7.3.1) was "events that occurred in at least five patients, and the AEs that are suspected to be related to the study drug and/or ocular injection." Please note that the criteria did not include 5% as suggested in the question.

Patients with pathologic myopia have a higher risk of retinal tears and retinal detachments, independent of an ocular procedure.

There were no cases of "retinal detachment" reported. Three events reported by the investigators as "retinal hole", "retinal break" and "retinal tears with operculum" were coded (according to MedDRA) with the preferred term "retinal tear" and reported for 2 (1.9%) patients in Group I (ranibizumab disease stabilisation) and 1 (0.8%) patient in Group II (the licensed posology – ranibizumab disease activity). All AEs were of mild intensity.

In Group II (the licensed posology – ranibizumab disease activity), one patient was reported with an AE of retinal tear (with operculum), which occurred 357 days after the patient's first dose of ranibizumab and 10 months after their last (3rd) dose of ranibizumab. This 41-year-old patient had a history of keratomileusis laser surgery in both eyes nine years ago. **The retinal tear was assessed as not suspected to be related to either ocular injection or study drug** and resolved within 1 day following barrage laser therapy. The economic model specifically evaluates the cost effectiveness of the licensed posology in this indication (ranibizumab – Group II) and thus this AE did not meet the criteria for inclusion.

A retinal hole was reported in one patient in Group I as an AE on Day 21 after the patient's first injection of ranibizumab. This patient had a medical history of glaucoma and pseudophakia (preferred term "intraocular lens implant"). The retinal hole resolved after 7 days and was assessed as suspected to be related to ocular injection by the reporting Investigator. The other AE in Group I was a retinal break which occurred 49 days after the patient's 4th injection of ranibizumab. The patient was reported with a medical history of keratoconjunctivitis sicca (preferred term "dry eye"). The retinal break was assessed as not suspected to be related to either ocular injection or study drug. The AE was of mild intensity, did not require treatment and continued until the final ophthalmological examination.

B2. Page 183: the submission states that ranibizumab and vPDT both incur administration costs each time the patient receives treatment. The administration

costs for ranibizumab was assumed to consist of the cost of the OCT and the injection visit whereas that for vPDT was assumed to consist of OCT plus an ophthalmologist consultation visit. Please explain why an ophthalmologist consultation visit was considered for vPDT but not for ranibizumab.

Ranibizumab-treated patients receive an intravitreal injection and thus the injection visit code accurately represents the activity. For vPDT, the patient receives an IV injection, and then a laser is flashed in the patient's eye to activate the treatment. Since the ophthalmological expertise was related to the laser activation, the ophthalmologist consultation code was felt to more accurately represent this activity.

There is a small additional cost with the ophthalmologist consultation visit, and it was felt that this was commensurate with the additional time spent for the vPDT procedure (IV injection and laser activation) compared to an intravitreal injection procedure which is estimated to last around 15 minutes.

B3. **PRIORITY.** Please provide the baseline distribution of patient numbers for the subgroup of those who were treated in their WSE at baseline. Please provide absolute patient numbers rather than percentages (see suggested layout below)

These data are provided in Table 11 below.

Table 11 BCVA distribution for patients treated in WSE at baseline

		BSE BCVA (untreated eye)							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
WSE BCVA	86-100	0	0	0	0	0	0	0	0
	76-85	2	3	0	0	0	0	0	0
	66-75	8	23	6	0	0	0	0	0
	56-65	13	28	27	7	0	0	0	0
	46-55	5	18	12	7	0	0	0	0
	36-45	3	8	13	5	2	1	0	0
	26-35	1	5	4	7	2	1	1	0
	<25	0	1	0	0	0	1	0	0

B4. **PRIORITY.** Please provide the baseline distribution of patient numbers for the subgroup of those who were treated in their BSE at baseline. Please provide absolute patient numbers rather than percentages (see suggested layout below).

These data are provided in Table 12 below.

Table 12 BCVA distribution for patients treated in BSE at baseline

		BSE BCVA (treated eye)							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
WSE BCVA	86-100	0	0	0	0	0	0	0	0
	76-85	0	0	3	1	0	1	1	0
	66-75	0	0	3	3	2	6	2	2
	56-65	0	0	0	3	3	5	4	3
	46-55	0	0	0	0	2	7	4	0
	36-45	0	0	0	0	0	4	1	0
	26-35	0	0	0	0	0	0	0	3
	<25	0	0	0	0	0	0	0	0

B5. **PRIORITY.** Please provide the baseline distribution of patient numbers for the subgroup for whom the treated eye and the untreated eye had the same BCVA at baseline. Please provide absolute patient numbers rather than percentages (see suggested layout below).

These data are provided in Table 13 below.

Table 13 BCVA distribution of patients for whom the treated and untreated eye had the same BCVA at baseline

	Treated eye BCVA and untreated eye BCVA							
	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
Number	0	0	0	0	0	0	0	0

No patients had the same BCVA at baseline in their treated and untreated eye.

B6. **PRIORITY.** Please provide the patient numbers underlying the cells C63:U105 of the *All Patients* worksheet, and for each of these the number that were inferred from adjacent time points, the number that were LOCF and the number that were observed.

Ranibizumab

0 to 3m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	4	0	0	0	0	0
	76-85	0	3	15	9	2	0	0	0
	66-75	0	0	5**	24**	5	3	4	0
	56-65	0	0	0	5*	8	5	3	0
	46-55	0	0	0	2	5*	5	0	0
	36-45	0	0	0	0	1	2*	2	0
	26-35	0	0	0	0	0	0	0	0
	0-25	0	0	0	0	0	0	0	0

*Value includes one LOCF patient record
**One value from inferred from adjacent time points (2006_00001 (VA 66) from screening visit, 702_00004 (VA 61) from unscheduled visit one day after baseline)

3m to 6m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	3	3	0	0	0	0	0	0
	76-85	1	21	8	1	1	0	0	0
	66-75	0	4	23	6	0	0	0	0
	56-65	0	0	6	12*	6	0	0	0
	46-55	0	0	0	1	8*	1	0	0
	36-45	0	1	0	2	0	1*	0	0
	26-35	0	0	0	0	0	1	2	0
	0-25	0	0	0	0	0	0	0	0

*Value includes one LOCF patient record

6m to 9m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	4*	0	0	0	0	0	0	0
	76-85	1	23	4	2*	0	0	0	0
	66-75	1	8	25	5	0	0	0	0
	56-65	0	1	4	14	1	0	0	0
	46-55	0	0	0	3	9*	2	0	0
	36-45	0	0	0	0	0	2*	1	0
	26-35	0	0	0	0	0	0	2	0
	0-25	0	0	0	0	0	0	0	0

*Value includes one LOCF patient record

9m to 12m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	4*	4	0	0	0	0	0	0
	76-85	0	23	12	1	0	0	0	0
	66-75	0	3	26	5	1	0	0	0
	56-65	0	0	1	13	5*	0	0	0
	46-55	0	0	0	1	7	1*	0	0
	36-45	0	0	0	0	1	1	1	0
	26-35	0	0	0	0	0	1	1	0
	0-25	0	0	0	0	0	0	0	0
*Value includes one LOCF patient record									

vPDT

0 to 3m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	1	0	0	0	0	0
	76-85	0	0	2	1	0	0	0	0
	66-75	0	2	4	6	0	0	0	0
	56-65	0	0	3	5	5	2	0	0
	46-55	0	0	0	6	2	0	0	0
	36-45	0	0	0	1	1	7	2	0
	26-35	0	1	0	0	1	1	2	0
	0-25	0	0	0	0	0	0	0	1*
*Value includes one LOCF patient record									

3m to 6m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	0	0	0	0	0	0
	76-85	0	0	3	1	0	0	0	0
	66-75	0	2	15	4	0	0	0	0
	56-65	0	0	8	17**	2	0	0	0
	46-55	0	0	1	3	15	1	0	0
	36-45	0	0	1	0	3	2*	0	0
	26-35	0	1	0	0	1	1	0	0
	0-25	0	0	0	0	0	1	0	0
*Value includes one LOCF patient record **Value includes two LOCF patient records									

6m to 9m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	0	0	0	0	0	0
	76-85	0	3	3	1	0	0	0	0
	66-75	0	1	13	4	1	0	0	0
	56-65	0	0	5	17**	7	1	0	0
	46-55	0	0	0	4	9	1	1	0
	36-45	0	0	0	1	2	4*	1	1
	26-35	0	0	0	0	0	0	1	0
	0-25	0	0	0	0	1	0	0	0

*Value includes one LOCF patient record
**Value includes three LOCF patient records

9m to 12m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	0	0	0	0	0	0
	76-85	0	5	4	0	0	0	0	0
	66-75	0	2	14	8*	0	0	0	0
	56-65	0	0	1	16**	4	0	0	0
	46-55	0	0	0	5	7	3	0	0
	36-45	0	0	0	0	4	3*	1	0
	26-35	0	0	0	1	0	1	0	0
	0-25	0	0	0	0	0	2	0	1

*Value includes one LOCF patient record
**Value includes two LOCF patient records

B7. **PRIORITY.** Please provide the patient numbers for the corollary of the cells C85:K94 of the *All Patients* worksheet for the vPDT arm of the VIP trial.

vPDT (VIP)

0 to 3m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	0	0	0	0	0	0
	76-85	0	0	2	1	0	0	0	0
	66-75	0	0	13	12	3	0	0	0
	56-65	0	1	7	17	0	0	0	0
	46-55	0	0	2	12	7	0	0	0
	36-45	0	0	0	2	3	0	0	0
	26-35	0	0	0	0	0	0	0	0
	0-25	0	0	0	0	0	0	0	0

B8. Please provide the patient numbers that would underlie the corollary of cells C85:U105 of the *All Patients* worksheet for the control arm of the VIP trial.

Sham (VIP)

0 to 3m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	0	0	0	0	0	0
	76-85	0	1	3	0	0	0	0	0
	66-75	0	0	1	3	0	0	0	0
	56-65	0	1	2	4	2	0	0	0
	46-55	0	0	1	2	5	0	0	0
	36-45	0	0	0	5	5	0	0	0
	26-35	0	0	0	1	1	0	0	0
	0-25	0	0	0	0	1	0	0	0

3m to 6m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	0	0	0	0	0	0
	76-85	0	2	1	0	0	0	0	0
	66-75	0	0	3	4	0	0	0	0
	56-65	0	0	2	6	4	0	0	0
	46-55	0	0	0	4	6	0	0	0
	36-45	0	0	0	1	2	0	0	0
	26-35	0	0	1	0	2	0	0	0
	0-25	0	0	0	0	0	0	0	0

6m to 9m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	0	0	0	0	0	0
	76-85	0	1	1	0	0	0	0	0
	66-75	0	2	1	3	0	1	0	0
	56-65	0	0	0	5	3	1	0	0
	46-55	0	0	0	1	2	1	0	0
	36-45	0	0	0	0	4	3	1	0
	26-35	0	0	0	1	0	4	1	1
	0-25	0	0	0	0	0	0	0	1

9m to 12m		**Before**							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	0-25
After	86-100	0	0	0	0	0	0	0	0
	76-85	0	1	2	0	0	0	0	0
	66-75	0	0	3	2	0	0	0	0
	56-65	0	1	2	5	0	1	0	0
	46-55	0	0	0	1	2	2	0	0
	36-45	0	0	0	1	2	3	2	0
	26-35	0	0	0	0	0	2	5	0
	0-25	0	0	0	0	0	0	0	1

B9. **PRIORITY.** Please provide the baseline distribution of patient numbers with bilateral involvement at baseline. Please provide absolute patient numbers rather than percentages (see suggested layout below).

These data are provided in Table 14 below.

Table 14 BCVA distribution of patients with bilateral involvement at baseline

	Treated eye BCVA							
	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
Bilateral	0	0	0	0	0	0	0	0

In the Novartis phase III trial, data were not collected for those patients who had bilateral involvement.

B10. Please provide the baseline mean values to which the NEI VFQ-25 changes of tables 23, 24 and 25 relate to, in the same format as tables 23, 24 and 25.

These data are provided in Table 15 below.

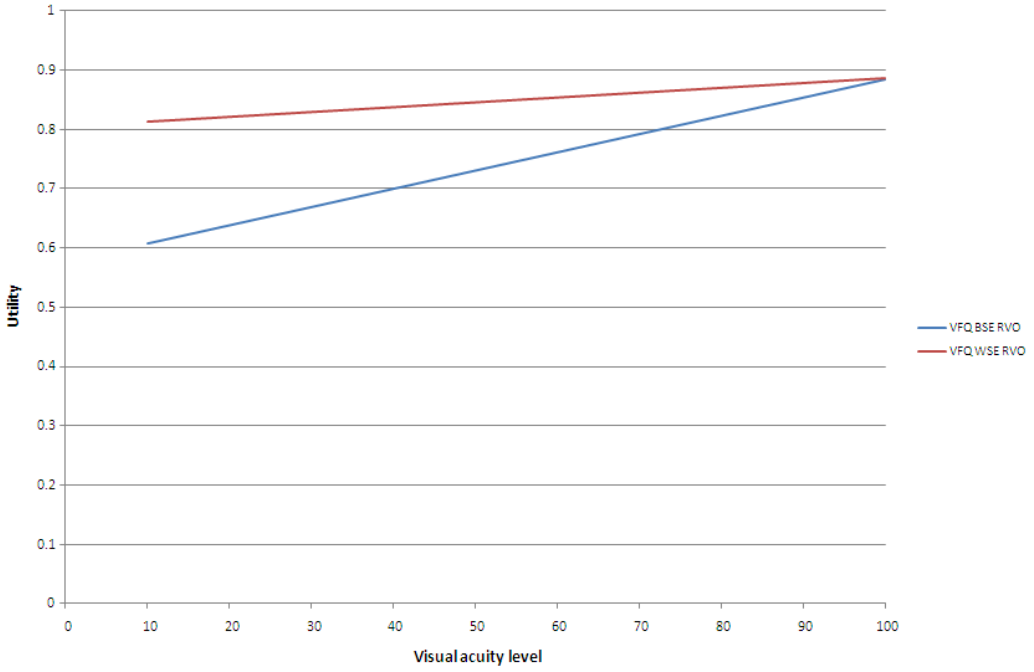
Table 15 Baseline NEI VFQ-25 values for all treatment groups

NEI VFQ-25 score	Ranibizumab disease activity (N = 101)	Ranibizumab disease stabilisation (N = 111)	vPDT (N = 51)
Composite	**69.37 (17.78)**	**71.31 (17.45)**	**71.84 (17.89)**
General health	49.43 (23.05)	49.49 (21.53)	53.33 (24.77)
General vision	52.36 (17.71)	54.69 (16.63)	59.56 (14.45)
Ocular pain	84.27 (17.12)	77.81 (20.11)	80.28 (16.96)
Near activities	61.89 (24.29)	66.96 (22.89)	65.37 (22.82)
Mental health	59.43 (25.21)	60.20 (23.61)	63.89 (23.57)
Dependency	78.28 (28.80)	80.44 (26.19)	83.89 (22.92)
Distance activities	64.42 (24.18)	68.49 (22.64)	65.00 (23.00)
Driving	47.06 (35.65)	64.07 (30.09)	60.21 (35.78)
Social functioning	77.95 (23.84)	82.65 (22.32)	80.28 (22.85)
Roles difficulties	63.34 (27.81)	61.61 (28.56)	61.11 (28.23)
Colour vision	92.33 (15.33)	90.56 (15.45)	86.67 (18.92)
Peripheral vision	71.91 (24.37)	73.72 (25.22)	77.27 (23.39)
NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; vPDT, verteporfin photodynamic therapy All data are mean (SD)			

B11. The *QoL* worksheet cell G10 permits the WSE utility function *VFQ25 mapping (WSE)* to be selected. Please provide details of the VFQ25 data feeding into each of the 8 utilities, its standard deviations, the number of patients this relates to and the mapping function employed (Payakatchat 2009?). Please also provide the corollary of this VFQ25 data for the 8 health states of the BSE.

VFQ-25 scores from the BRAVO and CRUISE trials for retinal vein occlusion (RVO) were converted to utility values using a mapping equation from the RESTORE trial. This exercise was undertaken by Novartis for the ranibizumab submission for RVO. The mapping exercise only predicted 25% of EQ-5D utilities in RESTORE, which suggests that the mapping equation from the VFQ-25 was not sensitive enough to predict utilities. In the RVO studies, a significant number of patients were predicted to have a utility value of 1.0, suggesting a lack of sensitivity of the mapped utilities and a likely lower slope as a greater number of patients accumulate at value 1. The results of the mapping analysis are showing below in Figure 1.

Figure 1 Mapping analysis of VFQ-25 utility scores from BRAVO and CRUISE in patients with RVO



A standard linear regression was undertaken, and covariance between visual acuity in each eye was not accounted for.

The mean utility value for each health state based on the worst-seeing eye (WSE) is shown in Table 16.

Table 16 Utility values for WSE according to BCVA

	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
Mean	-	0.91100	0.87591	0.84570	0.84571	0.83709	0.82947	0.83739
S.D	-	0.27168	0.08760	0.10077	0.09619	0.10232	0.10539	0.10577
N	0	6	618	1230	953	602	479	202

A standard linear regression provided the equation for predicting utility values based on VA in the WSE:

$$Y = 0.0008294x + 0.80440781$$

The mean utility value for each health state based on the best-seeing eye (BSE) is shown in Table 17.

Table 17 Utility values for BSE according to BCVA

	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
Mean	-	-	0.79876	0.75904	0.72832	0.71164	0.69253	-
S.D	-	-	0.13155	0.12708	0.11036	0.08564	0.06481	-
N	0	0	54	95	35	34	6	0

A standard linear regression provided the equation for predicting utility values based on VA in the BSE:

$$Y = 0.00306776x + 0.57786753$$

B12. PRIORITY. The NICE methods guide is explicit about the preference for EQ-5D HRQoL data valued using the UK social tariff for the reference case, and Novartis has used EQ-5D HRQoL data valued using the UK social tariff for previous ranibizumab submissions to NICE. Please present the mean value, standard deviation of the sample and number of observations by arm at baseline, 1 month, 3 months, 6 months, 9 months and 12 months, or by the schedule of the EQ-5D measurements if this differed (see suggested layout below).

These data are reported in Table 18 below.

Table 18 EQ-5D scores in patients treated with ranibizumab or vPDT

		EQ-5D data valued using UK social tariff					
		Month 0	Month 3	Month 6	Month 7	Month 10	Month 12
Ranibizumab	Mean	0.81104	0.85582	0.82805	0.84800	0.77900	0.85539
	SD	0.20814	0.15472	0.21342	-	-	0.18593
	N	118	118	118	1	1	118
vPDT	Mean	0.83248	0.83149	0.85532	-	-	0.86196
	SD	0.19608	0.19442	0.19902	-	-	0.15653
	N	52	53	53	-	-	53

B13. PRIORITY. Please also present the EQ-5D HRQoL data valued using the social tariff pooled across arms and time points in the following format. Note that this does not need to take into account whether the treated eye is or was the BSE or the WSE and relates solely to binocular vision states (see suggested layout below).

These data are reported in Table 19 below.

Table 19 Distribution of EQ-5D data according to BCVA

			BSE BCVA							
			86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
WSE BCVA	86-100	μ SD n	0.9873 0.0510 16							
	76-85	μ SD n	0.9330 0.1032 30	0.8853 0.1780 64						
	66-75	μ SD n	0.9475 0.0917 22	0.8856 0.1554 72	0.8533 0.1120 35					
	56-65	μ SD n	0.9158 0.1371 19	0.8290 0.1751 51	0.8408 0.1402 65	0.7889 0.2221 22				
	46-55	μ SD n	0.9320 0.1038 8	0.8339 0.2339 31	0.7828 0.2026 37	0.6545 0.2489 15	0.7500 0.1699 4			
	36-45	μ SD n	0.6270 0.4092 7	0.8717 0.1703 20	0.8418 0.1930 32	0.8142 0.1903 19	0.7086 0.2497 16	0.8438 0.1547 12		
	26-35	μ SD n	1.000 - 1	0.8082 0.1434 5	0.8136 0.1032 14	0.6617 0.3391 13	0.7020 0.2417 9	0.7925 0.2934 2	0.9380 0.1074 3	
	<25	μ SD n	0.5445 0.2199 2	0.8875 0.0912 6	0.8010 0.1494 5	0.8214 0.1540 7	0.5430 0.3804 3	0.6900 0.0606 3	0.673 0.1078 4	- - 0

B14. Please provide more detail of the source and calculation of the all-cause mortality data in cells D12:D112 of the *Mortality* worksheet; e.g. gender averaging.

The mortality data in the model is based on the interim life tables for England and Wales published by the Office of National Statistics (http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-274529). Rates were calculated using q_x, the mortality rate between age x and x+1 (the probability that a person aged x exactly will die before reaching age x+1), and were equally averaged across genders (that is, a 50-50 split between the male and female rates. Rates are based on the 2007-2009 period; however more recent data has been published for the 2009-2011 period. Mortality rates have fallen in the 2009-2011 period by a small amount for 96% of the age categories. Updating the mortality rates in the model has a very small impact on the results – the incremental cost increases, resulting in a larger net benefit of £11,461.23 (compared with £11,389.92).

B15. **PRIORITY.** Please outline the number of vPDT doses in months 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-21 and 21-24 in the vPDT arm of the VIP trial; i.e. each quarter, coupled with the number of patients remaining in the vPDT arm of the VIP trial for these periods.

The number of patients on study and receiving treatment at each visit are summarised in Table 20.

Table 20 Patients on study and the number who received treatment at each visit in the VIP trial

Visit	**Patients on study, n (%)**		**Patients receiving treatment, n (%)**	
	vPDT, N = 81	Placebo, N = 39	vPDT, N = 81	Placebo, N = 39
Month 0	81 (100.0)	39 (100.0)	81 (100.0)	39 (100.0)
Month 3	81 (100.0)	39 (100.0)	74 (91.4)	31 (79.5)
Month 6	79 (97.5)	38 (97.4)	64 (79.0)	29 (74.4)
Month 9	79 (97.5)	37 (94.9)	56 (69.1)	25 (64.1)
Month 12	79 (97.5)	37 (94.9)	46 (56.8)	20 (51.3)
Month 15	78 (96.3)	37 (94.9)	41 (50.6)	13 (33.3)
Month 18	78 (96.3)	36 (92.3)	30 (37.0	12 (30.8)
Month 21	78 (96.3)	36 (92.3)	23 (28.4)	9 (23.1)
Month 24	78 (96.3)	36 (92.3)		

B16. **PRIORITY.** Please submit the model validation report of the external expert health economist at Oxford University referred to on page 220.
The report is attached.

B17. **PRIORITY.** The reason for dividing (1 minus the monthly rate) by 3 in the equation *Probability = 1 – exp(ln[1 – rate] / 3)* to arrive at the quarterly probability is not understood by the ERG. At face value it also appears to result in counterintuitive values within table 51, such as the monthly rate for Yoshida being 0.8% but the quarterly rate being only 0.3%. This may be a misinterpretation of the underlying data on the part of the ERG, but it would seem more intuitive to multiply (1 minus the monthly rate) by 3. Some further explanation of this calculation, its data inputs, the intuition underlying it and its results would be much appreciated.

The equations for converting rates to probabilities are taken from a paper Fleurence et al 2007.[16] However there appears to be an error converting the monthly rate to a three-monthly probability. The correct equation should be *Probability = 1 – exp(– rate*3).* This has a small impact on the results: the incremental number of QALYs with the amendment is 0.36 (instead of 0.43), the incremental cost is -£3,806.68 (instead of -£2,750.73), and the resulting net benefit is £10,984.65 (instead of £11,389.92).

B18. It appears that the annual costs of recurrence may not have been divided by 4 to give quarterly amounts. Please clarify if this requires amendment.

The recurrence costs should not be divided by four – the rate of recurrence refers to the *incidence* rate, and the patients in this state represent the new cases of recurrence rather than the total number of patients (i.e. prevalence) who are having a recurrence during that cycle.

B19. The adverse event costs appear to be limited to the first year. Is this correct, and if so what is the justification for this? Recurrence also appears to not include adverse event costs. Is this correct, and if so what is the justification for this?

The rates of adverse events were taken from the clinical study report, and apply to the entire trial period. Thus when the rates are applied to the relevant population, the patients experiencing an adverse event are the total number of patients who will experience an adverse event over the treatment period.

Adverse events are not considered when a patient experiences a recurrence. Recurrence applies to a small number of patients (with an annual rate of 6%, around 15 patients per cycle experience a recurrence). Applying the adverse event rates to these patients will have a negligible impact on the costs as very few patients will be affected.

B20. The calculation of QALYs appears to mix patient numbers that have half cycle correction applied to them with patient numbers which have not had half cycle correction applied to them, and also to possibly confuse cycles. For instance, cell D12 of the *Tx_QALYs* worksheet relies upon cell D11 and cell BM11 of the *Calculations* worksheet. Cell D11 of the *Calculations* worksheet appears to have half cycle correction while cell BM11 of the *Calculations* worksheet appears not to have half cycle correction. Cell D12 of the *Tx_QALYs* worksheet also relates to the 2nd cycle of the model while cell BM11 of the *Calculations* worksheet relates to the 1st cycle of the model. Are these errors, and if they are what is the effect of them upon results?

The calculation of QALYs does mix patient numbers that have half cycle correction applied to them with patient numbers which have not had half cycle correction applied to them. If this error is corrected by applying half-cycle correction to the number of patients with the study eye as the best-seeing eye (cells BM:BT on the *Calculations* worksheet), the impact on the results is minimal – there is no impact on the total incremental cost, and the total incremental QALYs is 0.4322 (compared with 0.4320). Net benefit is increased from £11,389.92 in the analysis with the error to £11,393.86.

In the *Calculations* worksheet, cells D11:K11 have had half-cycle correction applied to them, and these cells refer to the mid-cycle estimate of the number of patients between Month 0 and Month 3, (cells D12:K12 refer to the patients between month 3 and Month 6).

Cells D12:K12 of the *Tx_QALYs* worksheet refer to the costs borne in the first three months of the model, and so the mid-cycle estimate of patients between Month 0 and Month 3 is applied, rather than the patients between Month 3 and Month 6.

B21. The assumed 15% rate of bilateral involvement appears to only impact the first two years of the model. Is it assumed that there is no further development of bilateral involvement subsequent to baseline?

Bilateral involvement is only considered during the initial treatment period (two years). No further development of bilateral involvement is assumed subsequent to baseline.

The baseline 15% value refers to the prevalence of bilateral disease and represents the level of bilateral disease in the population for a given time period. There is an absence of evidence for the number of patients who develop bilateral disease over the time-frames considered in the analysis (i.e. the incidence rate). Without knowing how to apply this incidence rate, the application of this in addition to the baseline rate over the model's 40-year time-horizon would lead to high levels of bilateral disease which would not be supported by any evidence.

B22. PRIORITY. Page 315: The submission provides an estimate of the cost effectiveness of ranibizumab relative to bevacizumab of £21,922 per QALY. Please tabulate the assumptions and data inputs underlying this estimate, including the transition probability matrices or the data underlying them. Please also clarify the status of this estimate.

As per Section 2.7, it is clearly stated that bevacizumab has not been considered as a comparator to ranibizumab in this single technology appraisal. The use of unlicensed bevacizumab is not considered as established practice across the NHS, according to clinical experts at NICE scoping meetings for technology appraisals in this indication. Furthermore, given the absence of approval for bevacizumab, it cannot be considered best practice.

The use of intravitreal bevacizumab represents the use of a product that does not have regulatory approval for any ocular indications, is not presented in a licensed formulation for administration in the eye and does not have approval for compounding into smaller doses for ocular use. Potential systemic and ocular safety signals for bevacizumab mean that it is inappropriate to include this intervention in an appraisal before safety and quality have been assessed by the regulatory authorities.[17-19] The implications of these safety signals are a need for a large pharmacovigilance programme, as identified by stakeholders during the exploratory work by NICE regarding the feasibility of an appraisal of bevacizumab for eye conditions.[20] There are also liability consequences of unlicensed use. The uncertain costs of these activities cannot be incorporated adequately into an economic analysis using the existing NICE guidance for technology appraisal. Finally, General Medical Council (GMC) guidance is clear that use of an unlincensed medicine might be reasonable when there is no licensed alternative available; however the situation will be entirely different the moment the new medicine receives its marketing authorisation and is available to the NHS. GMC prescribing advice would then support use of the licensed medicine and the use of the unlicensed medicine only in exceptional circumstances where that would serve an individual patient's need. Therefore inclusion of unlicensed bevacizumab as a comparator to ranibizumab in this submission is considered inappropriate and implausible.

Furthermore, there is a lack of reliable and robust efficacy and safety data for bevacizumab in the treatment of CNV secondary to PM as there are only two small head to head trials comparing ranibizumab and bevacizumab,[21,22] which have considerable methodological weaknesses. Gharbiya 2010[21] is unclear with respect to how randomisation and allocation concealment were performed. It is also unclear whether patients were similar at baseline in terms of prognostic factors and whether the treating investigator(s) and outcomes assessors were blinded to treatment. Finally, it is not reported if an intention-to-treat approach was used for the analyses. The lack of rigour associated with this study was further ratified by the critical appraisal within the bevacizumab in eye conditions NICE DSU report by Poku et al 2013.[23] The second trial, by Iacono 2012,[22] is an explorative study and was not designed to produce comparative results. Multiple testing was not accounted for even though there are three defined primary variables and further comparisons between and within groups. The analyses are reported as intent-to-treat but elsewhere the manuscript stated that the analyses excluded "patients who did not complete all visits." Therefore the analyses are inconsistent with the

standard intent-to-treat approach. Finally, there are inconsistencies in the reporting of the results as well as limited safety data presented.

Section C: Textual clarifications and additional points

C1. Table 20, page 82: Please indicate whether the change in BCVA from baseline compared to vPDT is statistically significant (line 2 of the table).

The difference in mean average change from baseline (primary endpoint) and the mean change from baseline for both ranibizumab groups was statistically compared with vPDT at 3 months and compared with vPDT/ranibizumab at 6 and 12 months as summarised in

Table 21.

Table 21 Summary of mean average change from baseline (primary endpoint) and the mean change from baseline in the Novartis phase III trial.

Time[a]	**Months 0−3**			**Months 0−6**			**Months 0−12**		
	Ranibizumab disease activity, N = 116	**Ranibizumab disease stabilisation, N = 105**	**vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**
Primary endpoint: Mean average change in BCVA (letters) from baseline, mean (SD)	10.6 (7.26)***	10.5 (8.16)***	2.2 (9.47)	11.7 (8.24)***	11.9 (8.81)***	4.2 (9.26)	12.5 (8.83)***	12.8 (9.48)***	6.4 (9.55)
Change in BCVA (letters) from baseline, mean (SD)	12.5 (8.81)***	12.1 (10.18)***	1.4 (12.21)	12.7 (11.01)**	13.7 (10.16)***	7.9 (10.37)	14.4 (10.20)**	13.8 (11.42)*	9.3 (11.33)

[a]The mean average change in BCVA is the average change from months 0–3, 0–6 and 0–12 compared with baseline. For all other parameters, the changes and values reported are at month 3, 6 or 12 compared with baseline.
*p < 0.05, **p < 0.005; ***p < 0.0001 vs baseline

C2. Table 20, page 82: Please indicate whether the change in CRT from baseline compared to vPDT is statistically significant.
The difference in change from baseline in CRT for both ranibizumab groups was statistically significant compared with the vPDT at 3 months but not compared to vPDT/ranibizumab at 6 and 12 months as summarised in Table 22.

Table 22 Summary of change from baseline in CRT in the Novartis phase III trial

Change from baseline	**Month 3**			**Month 6**			**Month 12**		
	Ranibizumab disease activity, N = 116	**Ranibizumab disease stabilisation, N = 105**	**vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**	**Ranibizumab disease activity, N = 116**	**Ranibizumab disease stabilisation, N = 105**	**Ranibizumab/ vPDT, N = 55**
Change from baseline in CRT (µm), mean (SD)	-77.6 (102.25)***	-61.0 (67.46)***	-12.0 (65.84)	-74.8 (97.05)	-66.1 (73.63)	-51.5 (79.98)	-71.3 (100.91)	-66.6 (82.63)	-60.8 (80.04)
*p < 0.05, **p < 0.005; ***p < 0.0001 vs baseline									

C3. What data has been redacted from Figure 10, page 317 of the submission, and what were the reasons for the redaction?

The version of figure 10 included on page 317 of the submission is a redacted version of that included on page 85 of the submission. The 12 month data are redacted because they are AIC.

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