Response to question from PenTAG

Section A: Clinical evidence

A1. Please provide details of the results of disability progression in the AFFIRM trial as measured by the MS functional composite scale.

An analysis of the MS functional composite (MSFC) scores for the ITT population in the AFFIRM study is provided below in Table 1. A similar analysis for the RES subgroup is provided below in Table 2.

Table 1: MSFC Z-Score: Changes From Baseline to Two Years - ITT Population

	Placebo	Natalizumab	p-value (a)
Number of subjects randomized	315	627	
25-Foot Walk Z-Score			
n	315	627	
Mean	-0.50	-0.20	<0.001
s.d.	1.730	1.908	
Median	-0.15	-0.05	
Min.,Max.	-18.4,1.1	-32.7,8.5	
9 HPT Z-Score			
n	315	627	
Mean	-0.12515	0.09371	<0.001
s.d.	0.713875	0.610562	
Median	-0.02946	0.12884	
Min.,Max.	-3.7510,2.5308	-3.4245,1.9266	
PASAT 3 Z-Score			
n	315	627	
Mean	0.13	0.22	0.005
s.d.	0.629	0.532	
Median	0.10	0.10	
Min.,Max.	-1.9,3.2	-2.5,2.7	
MSFC Composite Z-Score			
n	315	627	
Mean	-0.16	0.04	<0.001
s.d.	0.717	0.714	
Median	-0.04	0.09	
Min.,Max.	-5.9,1.0	-10.9,2.3	

NOTE: Z-scores were calculated based on a reference population mean of 5.328 and a standard deviation of 2.005 for the 25-foot Walk, a mean of 0.050 and a standard deviation of 0.010 for the 9 Hole Peg Test, and a mean of 50.824 and a standard deviation of 10.304 for the PASAT 3.

(a) P-value for comparison between the treated and placebo groups, based on Friedmans analysis of covariance (ranked data), adjusted for the baseline MSFC corresponding component score.

Table 2: MSFC Z-Score: Change From Baseline to Two Years - Subjects with at least 2 relapses prior to study and at least 1 Gd Lesion at baseline

	Placebo	Natalizumab	p-value (a)
Number of subjects randomized	61	148	
25-Foot Walk Z-Score			
n	61	148	
Mean	-0.74	-0.24	<0.001
s.d.	2.193	1.891	
Median	-0.25	-0.05	
Min.,Max.	-12.5,1.1	-20.8,2.4	
9 HPT Z-Score			
n	61	148	
Mean	-0.06414	0.16340	0.040
s.d.	0.671043	0.662596	
Median	0.06381	0.14793	
Min.,Max.	-1.8635,2.5308	-3.4245,1.9266	
PASAT 3 Z-Score			
n	61	148	
Mean	0.03	0.19	0.106
s.d.	0.515	0.510	
Median	0.00	0.10	
Min.,Max.	-1.8,1.1	-1.4,2.0	
MSFC Composite Z-Score			
n	61	148	
Mean	-0.26	0.04	<0.001
s.d.	0.865	0.727	
Median	-0.09	0.08	
Min.,Max.	-4.0,1.0	-6.8,1.4	

NOTE: Z-scores were calculated based on a reference population mean of 5.328 and a standard deviation of 2.005 for the 25-foot Walk, a mean of 0.050 and a standard deviation of 0.010 for the 9 Hole Peg Test, and a mean of 50.824 and a standard deviation of 10.304 for the PASAT 3.

(a) P-value for comparison between the treated and placebo groups, based on Friedmans analysis of covariance (ranked data), adjusted for the baseline MSFC corresponding component score.

A2. Please provide data on the number of relapses per year seen in Table 2 for the combined group of people with two, and people with more than two relapses in the year prior to screening.

The addition to Table 2 in the original submission document is provided in Table 3 in this document (below).

Table 3: academic / commercial in confidence information removed

A3. Please provide any interim data available about adverse events with natalizumab from the 101-MS-321/322 and TYGRIS 101-MS-403 trials described in Table 4.

There is no interim analysis of safety data available for these studies.

A4. Please provide more detail about how and why the adverse event data for natalizumab was pooled (page 89).

Background

The data used to inform the AE indirect comparisons were taken from three trials of natalizumab vs placebo (AFFIRM, MS 201 and MS 231). We chose to pool all available adverse event data for natalizumab to maximise the amount of information available for the indirect comparison.

Natalizumab vs placebo

The AE data extracted from the natalizumab studies are shown in Table 2.

Table 1: AE data extracted from natalizumab studies

Outcome	Study	Treatment group n/N (%)	Control group n/N (%)
Influenza like illness			
	AFFIRM	41/627 (7%)	26/312 (8%)
	MS201	2/37 (5%)	2/35 (6%)
Pyrexia			
	AFFIRM	29/627 (5%)	16/312 (5%)
	MS231	9/142 (6%)	1/71 (1%)
Myalgia			
	AFFIRM	30/627 (5%)	19/312 (6%)
	MS231	4/142 (3%)	1/71 (1%)
Athralgia			
	AFFIRM	117/627 (19%)	45/312 (14%)

Outcome	Study	Treatment group n/N (%)	Control group n/N (%)
	MS231	15/142 (11%)	7/71 (10%)
Fatigue			
	AFFIRM	168/627 (27%)	65/312 (21%)
	MS201	12/37 (32%)	4/35 (11%)
Nausea			
	AFFIRM	85/627 (14%)	42/312 (13%)
	MS201	1/37 (3%)	4/35 (11%)
	MS231	14/142 (10%)	15/71 (21%)
Vomiting			
	AFFIRM	38/627 (6%)	29/312 (9%)
	MS231	4/142 (3%)	3/71 (4%)
Headache			
	AFFIRM	220/627 (35%)	96/312 (31%)
	MS201	13/37 (35%)	11/35 (31%)
	MS231	54/142 (38%)	31/71 (44%)
Psychiatric disorders			
	AFFIRM	8/627 (1%)	7/312 (2%)
Suicidal ideation			
	AFFIRM	2/627 (0%)	0/312 (0%)
Infusion site swelling			
	AFFIRM	3/627 (0%)	0/312 (0%)
	MS231	1/142 (1%)	1/71 (1%)
Infusion site pain			
	AFFIRM	6/627 (1%)	0/312 (0%)
	MS231	2/142 (1%)	1/71 (1%)
Convulsions			
	AFFIRM	2/627 (0%)	2/312 (1%)
	MS231	1/142 (1%)	0/71 (0%)
Dyspnoea			
	AFFIRM	13/627 (2%)	5/312 (2%)
	MS231	3/142 (2%)	2/71 (3%)
Anxiety			
	AFFIRM	37/627 (6%)	27/312 (9%)
	MS231	4/142 (3%)	2/71 (3%)
Syncope			
	AFFIRM	10/627 (2%)	4/312 (1%)
	MS231	2/142 (1%)	3/71 (4%)
Rash NOS			
	AFFIRM	50/627 (8%)	23/312 (7%)
	MS231	21/142 (15%)	6/71 (8%)
Muscle contraction involuntary			
	AFFIRM	1/627 (0%)	0/312 (0%)
	MS231	1/142 (1%)	1/71 (1%)
Joint stiffness			
	AFFIRM	5/627 (1%)	3/312
Constipation			
	AFFIRM	43/627 (7%)	24/312 (8%)
	MS201	3/37 (8%)	0/35 (0%)
	MS231	11/142 (8%)	8/71 (11%)

Outcome	Study	Treatment group n/N (%)	Control group n/N (%)
Abdominal discomfort			
	AFFIRM	2/627 (0%)	0/312 (0%)
	MS231	1/142 (1%)	0/71 (0%)
AEs causing treatment withdrawal			
	AFFIRM	39/627 (6%)	11/312 (4%)
	MS201	0/37 (0%)	1/35 (3%)
	MS231	4/142 (3%)	2/71 (3%)
Infusion site erythema			
	AFFIRM	3/627 (0%)	1/312 (0%)
Infusion site pruritus			
	AFFIRM	2/627 (0%)	1/312 (0%)
Somnolence			
	AFFIRM	11/627 (2%)	2/312 (1%)
	MS231	1/142 (1%)	0/71 (0%)
Appetite decreased NOS			
	AFFIRM	4/627 (1%)	4/312 (1%)
Infusion site reaction			
	AFFIRM	9/627 (1%)	2/312 (1%)
	MS231	2/142 (1%)	0/71 (0%)
Dizziness			
	AFFIRM	67/627 (11%)	35/312 (11%)
	MS201	1/37 (3%)	3/35 (9%)
	MS231	18/142 (13%)	9/71 (13%)
Alopecia			
	AFFIRM	22/627 (4%)	9/312 (3%)
	MS231	5/142 (4%)	0/71 (0%)
Myalgia or arthralgia			
	AFFIRM	137/627 (22%)	54/312 (17%)
Nausea or vomiting			
	AFFIRM	106/627 (17%)	56/312 (18%)
Amenorrhoea NOS			
	AFFIRM	11/627 (2%)	3/312 (1%)
Urinary tract infection NOS			
	AFFIRM	84/627 (13%)	38/312 (12%)
	MS201	4/37 (11%)	5/35 (14%)
Phlebitis			
	AFFIRM	5/627 (1%)	0/312 (0%)

A6. Please provide the data from the meta-analyses that were used to inform the indirect comparisons. We note that the Cochrane review presents a 'best' and 'worst scenario' for individual comparisons. Please provide indirect comparisons that use these sensitivity analyses.

Background

Data used to inform the efficacy indirect comparisons were taken from three sources: (i)

trials of natalizumab vs placebo (AFFIRM, MS 201 and MS 231), (ii) a Cochrane review, Rice 2002 (reference 73), of the efficacy of recombinant interferons in adults with RRMS, and (iii) a Cochrane review, Munari 2004 (reference 70) of glatiramer acetate in patients with MS.

The indirect relative risks, confidence intervals and p-values were calculated using a random effects model following the method of Song (references 125 and 126). The variance of the log relative risk for natalizumab vs IFN-beta was calculated as the sum of the variance of the log relative risk for IFN-beta vs placebo and the variance of the log relative risk for natalizumab vs placebo.

Natalizumab vs placebo

Efficacy data at two years was available only from the AFFIRM natalizumab trial and not from MS 201 or MS 231. This is summarized in Table 3 below.

Table 2: Natalizumab efficacy data

Outcome	Population	Treatment group n/N (%)	Control group n/N (%)
Disability progression at 12 weeks			
	Whole ITT population	104/627 (17%)	84/315 (27%)
	RES subgroup	20/148 (14%)	16/61 (26%)
Disability progression at 24 weeks			
	Whole ITT population	68/627 (11%)	68/315 (22%)
	RES subgroup	14/148 (9%)	14/61 (23%)
Relapse			
	Whole ITT population	173/627 (28%)	169/315 (54%)
	RES subgroup	42/148 (28%)	44/61 (72%)

Glatiramer acetate scenarios

Munari 2004 did not present 'best' and 'worst' scenarios. Bornstein 1991 was excluded from our analysis of efficacy outcomes because it considered chronic-progressive rather than relapsing-remitting patients.

Table 3: Efficacy data from the glatiramer acetate studies in Munari 2004

Outcome	Study	Treatment group n/N (%)	Control group n/N (%)
Patients with at least one exacerbation at 2 years of follow-up			
	Bornstein 1987	11/25 (44%)	17/25 (68%)
	Johnson 1995	83/125 (66%)	92/126 (73%)
Patients who progressed at 2 years			
	Bornstein 1987	5/25 (20%)	11/25 (44%)
	Johnson 1995	27/125 (22%)	31/126 (25%)

IFN-beta vs placebo scenarios

Rice 2002 (reference 73) was a Cochrane review of the efficacy of recombinant interferons in adults with RRMS, which considered trials of both alpha- and beta-recombinant interferons. The alpha-interferon studies of Durelli 1994 and Myhr 1999 were excluded from our analysis, because these were not relevant to the decision problem. In the two efficacy outcomes reported in our submission, patients with at least one exacerbation at 2 years and patients who progressed at 2 years, the review presented 'intermediate', `best'

and 'worst' case scenarios. The review authors stated:

'The best case scenario (with regards to treatment) assumed that none of the patients who were excluded from the analysis in the interferon-treated group had the outcome of interest, while all those excluded from the control group did and visa versa for the worst case scenario.'

The indirect comparisons we presented in Table 30 of the submission relied on the 'intermediate' scenario data. Data from all three scenarios for both outcomes are presented below in Table 5.

Table 4: Efficacy data from the beta-interferon studies in Rice 2002

Outcome Study	`Intermediate' scenario		`Best' scenario		`Worst' scenario	
	Treatment group n/N	Control group n/N	Treatment group n/N	Control group n/N	Treatment group n/N	Control group n/N
Patients with at least one exacerbation at 2 years						
IFNB MS Group 1993	79/124 (64%)	94/123 (76%)	79/124 (64%)	105/123 (85%)	88/124 (71%)	94/123 (76%)
The MSCRG 1996	53/158 (34%)	64/143 (45%)	53/158 (34%)	120/143 (84%)	126/158 (80%)	64/143 (45%)
The PRISMS 1998	125/184 (68%)	157/187 (84%)	125/184 (68%)	167/187 (89%)	130/184 (71%)	157/187 (84%)
Patients who progressed at 2 years						
IFNB MS Group 1993	25/124 (20%)	34/123 (28%)	25/124 (20%)	45/123 (37%)	34/124 (27%)	34/123 (28%)
The MSCRG 1996	18/158 (11%)	29/143 (20%)	18/158 (11%)	85/143 (59%)	91/158 (58%)	29/143 (20%)
The PRISMS 1998	49/184 (27%)	68/187 (36%)	49/184 (27%)	77/187 (41%)	54/184 (29%)	68/187 (36%)

We have recalculated the indirect comparison of natalizumab vs IFN-beta using the 'best' and 'worst' scenario data, as requested, in Table 6 and Table 7 respectively. This supplements the original 'intermediate' scenario analysis presented in Table 30 of our submission.

In the original submission we chose not to undertake indirect comparisons with the 'best' or 'worst' case scenarios. Please review the criticism of the 'best' and 'worst' case scenarios that followed the publication of the Cochrane review (see page 55 of the original submission).

Table 5: academic / commercial in confidence information removed

Table 6: academic / commercial in confidence information removed

A7. Please provide details of the patient baseline characteristics and clinical results from the SENTINEL trial.

Baseline characteristics for the SENTINEL trial are provided in Table 8 below and can also be found in Table 1 of Rudick 2006, which is included in the accompanying files and denoted as reference 3 in main submission document.

Table 7: Baseline characteristics of the patients in SENTINEL (Rudick 2006)

Characteristic	Interferon Beta-1a plus Natalizumab (N=589)	Interferon Beta-1a Alone (N=582)	Total (N=1171)
Age — yr			
Mean ±SD	38.8±7.7	39.1±7.6	38.9±7.7
Range	18–55	19–55	18–55
Sex — no. of patients (%)			
Male	147 (25)	162 (28)	309 (26)
Female	442 (75)	420 (72)	862 (74)
Race— no. of patients (%)†			
White	550 (93)	542 (93)	1092 (93)
Other	39 (7)	40 (7)	79 (7)
Duration of disease — yr			
Median	7.0†	8.0	7.0
Range	1–34	1–34	1–34
No. of relapses in previous 1 yr — no. of patients (%)			
0	0	1 (<1)	1 (<1)
1	390 (66)	357 (61)	747 (64)
2	153 (26)	174 (30)	327 (28)
≥3	44 (7)	50 (9)	94 (8)
Missing data	2 (<1)	0	2 (<1)
No. of relapses in previous 1 yr			
Mean ±SD	1.44±0.75	1.49±0.72	1.47±0.73
Range	1–7	0–5	0–7
EDSS score — no. of patients (%)§			
0	24 (4)	19 (3)	43 (4)
1.0–1.5	145 (25)	143 (25)	288 (25)
2.0–2.5	214 (36)	203 (35)	417 (36)
3.0–3.5	125 (21)	126 (22)	251 (21)
4.0–4.5	68 (12)	72 (12)	140 (12)
5.0	12 (2)	16 (3)	28 (2)
≥5.5	1 (<1)	3 (<1)	4 (<1)
EDSS score			
Mean ±SD	2.4±1.1	2.5±1.1	2.4±1.1
Range	0–6.0	0–5.5	0–6.0

Section B: Cost Effectiveness

B1. Please provide the "in press" UK MS survey by Orme et al (reference 14).

Response already supplied (See previous email sent 21/12/06)

B2. Please provide a copy of the cost data by disease severity from Tyas et al (reference 143).

Response already supplied (See previous email sent 21/12/06)

B3. Please provide the London Ontario dataset used in the model.

Response already supplied (See previous email sent 21/12/06)

B4. Given the use of AFFIRM to model the natural history of MS in the model, please explain why the treatment arm was not used to derive transition probabilities for the natalizumab group.

The active treatment arm from AFFIRM was not used to derive transition probabilities for natalizumab for three reasons:

Paucity of comparator data

Equivalent data is not available for the other active comparators and this would have added to the uncertainty within the model had natalizumab transition probabilities been used. As the underlying transition probabilities in our model were the same for all comparisons, we were able to apply the published relative risks of progression consistently across all arms. If they were not, we would have been applying different measures of progression to the different transition probabilities.

Transition data from AFFIRM limited to RRMS and early / moderate states of disability

Data for an untreated cohort was available from the London Ontario dataset for both RRMS disease at high EDSS and SPMS at all EDSS states. No such data was available for any treated cohort.

RRMS to SPMS transition implementation

During any given year a proportion of patients will progress from being RRMS to SPMS. We apply the relative risk of progression at a rate of 0.5 of the value applied to other RRMS patients on treatment. This is done to reflect the average time of transition from RRMS to SPMS as being half-way through the year. This would not be possible using transition probabilities calculated from the natalizumab arm of the AFFIRM study as transition from RRMS to SPMS was not recorded during the AFFIRM study.

Therefore by using a single set of transition probabilities for all comparisons and consistently applying the same measure of DMT efficacy, we avoid additional uncertainty in transition probabilities and inconsistencies in the application of the effects of the DMTs on progression.

B5. Please explain why your indirect comparison data is not used in the model.

Progression

Two measures of the relative risks of progression are employed in the submission. These are the hazard ratio and the risk ratio.

- The hazard ratio is a comparison of the average level of hazard in one treatment arm compared to another and is typically calculated after applying the Cox proportional hazards model. This measure is often used in clinical trials, where individual level data is available and the proportionality assumption underlying the Cox model can be assessed.
- The risk ratio is a comparison of risk between two treatment arms (i.e. proportion of patients experiencing an event).

In the economic model we use the hazard ratio as a measure of relative risk for natalizumab in order to capture as much information from the AFFIRM study as possible. It was not possible to calculate the hazard ratio for progression rates for IFN-beta and GA, since only endpoint data was available. Instead, the risk ratio of disability progression has been calculated for IFN-beta and GA as part of the meta-analysis using data from the Cochrane reviews and used in the model.

The risk ratio is often used where no patient level data is available and only aggregate measures can be calculated from results presented. The risk ratio does not take account of differences in the timing of events between arms or of differences in rates of censoring. To ensure consistency with the dichotomous results reported in the Cochrane reviews and therefore perform the indirect analysis, we converted the hazard ratios reported in the natalizumab studies to risk ratios (see section 5.3.1, pg. 82 of the original submission document). These risk ratios were then used to derive the relative benefits of natalizumab over IFN-beta and GA that are reported.

In the absence of censoring and with equality in the timing of events, the risk ratio and hazard ratio produce similar values. However, the hazard ratio is a more robust measurement of relative risk than the risk ratio. Lyman 2005 describe the hazard ratio as a more robust measure of relative risk as it is 'particularly designed for comparing two survival curves by allowing for both censoring and time to an event'. Therefore, the preferred measure of relative risk, the hazard ratio, is used for progression of natalizumab in the model, and the risk ratio is used out of necessity in the indirect analysis.

Relapse Rates

Data for relapses used in the indirect comparison specifically refer to patients with at least one exacerbation at 2 years, and were taken from the Cochrane reviews. The economic model required the relapse rates per year, to derive the actual number of relapses per patient. As the relapse rates were not available for IFN-beta and GA, these were calculated from the values taken from the Cochrane reviews.

B6. In the listing of the one-way sensitivity analyses on page 158, it is unclear how progression data has been altered. Please provide more detail on this.

As part of the sensitivity analysis (scenarios 4.4 to 4.6), three additional transition matrices were generated where the EDSS scores recorded within either 1, 3 or 6 months of a relapse respectively, were replaced by the value of the next subsequent recording. This was intended to remove the effect of relapses on EDSS score by replacing observations over a given period until that effect of the relapse had diminished. However, this method may result in an apparently faster progressing population, as we are bringing back future observations.

By contrast, to generate the transition matrix for the base case we simply remove the unscheduled visit (i.e. the EDSS recording taken approximately 5 days after a patient has a relapse), and we make no assumption about the effect of the relapse on subsequent recordings.

In scenario 4.7, the data used to generate the transition matrix was the same as the base case except that unscheduled visits were included in the analysis to generate the transition matrix.

In scenario 4.8 the transition matrices were derived entirely from the London Ontario dataset.

For each of scenarios 4.4 to 4.7, the transition matrices generated for the SOT and RES subgroups replaced the appropriate transition matrix for the base case.

B7. Please confirm whether one-way sensitivity analyses were carried out on costs of natalizumab and death rates, as they do not appear to be reported.

We can confirm that one-way sensitivity analysis was not carried out on the cost of natalizumab. One-way sensitivity analysis was not explicitly carried out on death rates, though the number of deaths may vary indirectly as a result to changes in other parameters in the model.

Table 9 shows the effect on the ICERs of varying the multiplier on the standard mortality rate (SMR) (see Table 67 in original submission for the values of the SMR multiplier). When the multiplier on the SMR is increased (i.e. the death rate for MS becomes more severe), the cost-effectiveness of natalizumab decreases. Conversely, when the multiplier is decreased, natalizumab becomes more cost-effective.

If the SMR is set to 1 (i.e. the same as the underlying population), the ICER for natalizumab improves by up to £1.1K.

Table 8: Changes to ICERs for the base case as a result of changes to the multiplier on the standard mortality rate (change in £'000s)

Change to SMR MS multiplier	RES BSC	RES IFN-beta	RES GA	SOT BSC	SOT IFN-beta	SOT GA
+10%	0.2	0.1	0.1	0.2	0.1	0.1
-10%	-0.2	-0.1	-0.1	-0.2	-0.1	-0.1
Multiplier = 1	-1.0	-0.7	-0.9	-1.1	-0.6	-0.9

RES = Rapidly evolving severe; SOT – Sub-optimally treated; BSC = Best supportive care; INF-beta = interferon beta; GA = glatiramer acetate; SMR = Standard mortality rate

B8. Please provide the results of multi-way sensitivity analyses that you suggest on page 156 – 6.3.3.1 first sentence – are included in table 85 but do not seem to be included.

The reference to multi-way sensitivity analysis in this sentence refers to scenarios where a

number of parameters are varied simultaneously. These scenarios are:

- 7.1a and 7.1b where the coefficients for individual utilities in worksheet 'CALC Utilities' cells J24:J37 are varied simultaneously
- 7.3a and 7.3b where the treatment disutilities in worksheet 'Treatment Effects' cells L62:M62 are varied simultaneously
- 8.1a and 8.1b where the coefficients for costs in worksheet 'Cost Coeffs' cells C129:C177 are varied simultaneously.

Section C: Textual Clarifications and additional points

C1. Please explain what the asterisk in the key under Table 8 refers to.

The following pieces of text in the footnote to Table 8 are redundant and may be ignored:

'* P < 0.01. Reference case (refers to the reference case in the economic evaluation presented in Section 6).'

'DMG = Direct Medical cost funded by Government. DNMG = Direct Non-Medical cost funded by Government. The table reports the profile of the direct costs of managing MS in the UK.'

C2. Please check whether there is a mistake in Table 27 on page 78. Should the correct figures read 79/124 for IFNB MS Group and 257/466 in the total column underneath? Please confirm whether or not these are mistakes and whether this has affected any calculations.

The correct figure should be 79/124 for IFNB MS Group and the total should be 257/466. This is does not affect any of the calculations.

C3. Please explain the meaning of "a high proportion of data in early EDSS states has been imputed" (Academic in Confidence, penultimate paragraph, page 94).

The imputed data at early states of EDSS was discussed during a teleconference with one of the principal investigators for the London Ontario dataset. Essentially, the year of first symptoms within the dataset was estimated by the participant during the first visit to an investigator and is subject to significant recall bias. To our knowledge this issue has not been published and should be treated as academic in confidence.

C4. Page 101 states that the questionnaire for the MS survey is provided in Appendix J but this appears to be missing. Please provide this appendix.

A copy of the questionnaire has been supplied (see accompanying file 'UK MS Survey 2005 Questionnaire.pdf')

C5. Some data in the model are labeled as being informed by the "1801 trial". Please clarify whether this is the AFFIRM trial.

I can confirm that any data in the model labeled '1801 trial' is from the AFFIRM trial.

C6. Please provide a list of the external experts and how they contributed to the submission, and outline the contractual agreements made.

In addition to the external experts already described in section 6.2.12.3 (page 149) of the original submission, the following clinical advisors were consulted during the project:

- Professor Ron Akehurst, Professor of Health Economics, Sheffield (health economics advice)
- Professor David Bates, Consultant Neurologist, Newcastle (clinical advice)
- Professor Nick Bosanquet, Professor of Health Policy, London (health policy advice)
- Professor Martin Buxton, Professor of Health Economics, Uxbridge (health policy advice)
- Professor Gavin Giovannoni, Consultant Neurologist, London (clinical advice)
- Professor Clive Hawkins, Consultant Neurologist, London (clinical advice)
- Dr Michael Johnson, Consultant Neurologist, London (clinical advice)
- Dr Matthew McGlennon, Independent Consultant, Binley's (health policy advice)
- Mr Neil Snee, Independent Consultant, Essex (health policy advice)

All advisors were contracted to Heron Evidence Development Ltd either individually or as a representative of their employer. Non-disclosure agreements are in place.