Natalizumab in highly active relapsing-remitting multiple sclerosis

Manufacturer (Biogen Idec) Response to ACD

The purpose of this document is to address comments within the NICE pre-meeting briefing document, the Appraisal Consultation Document and Evidence Review Group report.

23/04/2007

All sections underlined red are commercial or academic in confidence

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Executive Summary

Further to the appraisal consultation document (ACD) dated 22 March 2007, we are pleased at the opportunity to clarify the misinterpretation within the ACD. This Executive Summary directly addresses the three headings described within the email from Laura Bridgman. The main body of the document provides evidence to support the statements within the Executive Summary.

Do you consider that all of the relevant evidence has been taken into account?

No.

1. The ACD has failed to consider a wide body of evidence from multiple sources showing that:

a) best supportive care is <u>not</u> a relevant comparator in highly active relapsing remitting multiple sclerosis;

b) current disease modifying treatments <u>are</u> the most appropriate comparators as evidenced by:

- the inclusion of active disease modifying treatments in the final scope (section 0)
- the statement from professional/ patient groups and nominated experts in the NICE pre-meeting briefing (section 1.2.2)
- the MS treatment pathway produced by the ERG (section 1.2.3)
- current clinical opinion (section 1.2.4.1)
- current clinical practice (section 1.2.4.2)
- controlled trial evidence (section 1.2.4.3)

2. The ACD has failed to consider the high unmet need in people with highly active relapsing multiple sclerosis (section 2)

Do you consider that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence, and the preliminary views of the resource impact and implications to the NHS are appropriate?

No.

<u>1. Clinical Effectiveness</u>

We agree with the committee's conclusion that, 'natalizumab is clinically effective in the [rapidly evolving severe relapsing-remitting multiple sclerosis] group'.

We believe that insufficient consideration was given to the sub optimal therapy subgroup. The committee failed to recognise the subset of rapidly evolving

severe patients who happen to be receiving a disease modifying treatment (i.e. those experiencing 2 or more relapse in the prior year) and therefore a subset of the sub optimal treatment group. (section 3)

2. Cost Effectiveness

The Committee should recognise the appropriateness of the active comparators in the rapidly evolving severe subgroup (as outlined above). With this conclusion, natalizumab must be considered a cost-effective use of NHS resources for the treatment of the high unmet medical need in this subgroup.

3. NHS Resources & Implications

The committee made no specific statement about the resource implications of natalizumab use within either subgroup. If natalizumab was adopted for the treatment of rapidly evolving severe multiple sclerosis the net impact on NHS resources would be negligible compared with an NHS drug budget of £94 billion in 2005 (less than £1 million in year 1 rising to approximately than £5 million in year 5). (see original submission section 7)

Do you consider that the provisional recommendations of the appraisal committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

No.

The provisional recommendations are based on an unfounded conclusion that is not evidence-based.

Having addressed the misinterpretations within the ACD, one must conclude that…

There is compelling evidence to support a decision to recommend that all eligible patients that fulfil the rapidly evolving severe relapsing-remitting multiple sclerosis indication, those naïve to treatment and the rapidly evolving severe subset of those receiving a current DMT, should be treated with natalizumab, funded by the NHS.

Document overview

We address the Committee's specific questions in the Executive Summary.

Section 1: Contains Biogen Idec's substantive comments on statements within the Appraisal Consultation Document (ACD) and Evidence Review Group (ERG) report.

Section 2: Provides a summary of relapsing-remitting multiple sclerosis (RRMS) and the high unmet need in people with highly active disease.

Section 3: Presents the rationale to include the subset of sub optimal therapy patients that experience 2 or more relapses per year while already receiving a current disease modifying therapy within the rapidly evolving severe definition.

Section 4: Provides a discussion and conclusion that:

There is compelling evidence to support a decision to recommend that all eligible patients that fulfil the rapidly evolving severe relapsing-remitting multiple sclerosis indication, those naïve to treatment and the rapidly evolving severe subset of those receiving a current DMT, should be treated with natalizumab, funded by the NHS.

1 Substantive Comments

1.1 Related guidance & acceptable cost-effectiveness threshold

ACD Section 4.6 p.10:

'The Committee noted that beta interferon and glatiramer acetate were not recommended by NICE for the treatment of multiple sclerosis on the basis of their cost effectiveness, as described in NICE technology appraisal 32'.

ACD Section 7 p.13:

'Related Guidance'.

Biogen Idec's Response:

Despite the previous NICE recommendation in appraisal 32, the DoH subsequently established a Risk Sharing Scheme in recognition that active disease modifying treatments (DMTs) were appropriate for the treatment of RRMS. (1) Since the scheme 'follows on from' NICE technology appraisal 32 and 'NICE has welcomed the scheme', the most contemporary guidance for use of the current DMTs should be the Risk Sharing Scheme, not NICE technology appraisal 32. (2)

We consider that the Risk Sharing Scheme should be included as Related Guidance (Section 7 of the ACD), as it is clearly related and would minimise confusion for NHS stakeholders.

The Risk Sharing Scheme is important not only because it represents contemporary guidance to the NHS in the treatment of multiple sclerosis but, unlike any other guidance on the cost-effectiveness of medical technology in England and Wales, it also establishes an acceptable cost-effectiveness threshold for disease modifying treatments in multiple sclerosis of £36 000 per QALY gained. The associated Health Service Circular (HSC 2002/004) states:

'A number of 'special factors' which might be considered to be relevant to the cost-effectiveness of MS have been put to us [DoH] in discussion. The FAD [NICE appraisal 32] has specifically referred to two unquantified factors:

1. The impact of treatment on the severity (independent of the frequency) of relapses, and
2. Possible cost offsets from the avoidance of severe levels of disability requiring intervention by the Personal Social Services'

Given the consequential benefit of the enhanced effectiveness of natalizumab on these two 'special factors', the threshold of £36 000 is even more relevant for this appraisal.

There is compelling evidence to support a decision to recommend that all eligible patients that fulfil the rapidly evolving severe relapsing-remitting multiple sclerosis indication, those naïve to treatment and the rapidly evolving severe subset of those receiving a current DMT, should be treated with natalizumab, funded by the NHS.

1.2 Active disease modifying treatments are the most appropriate comparators

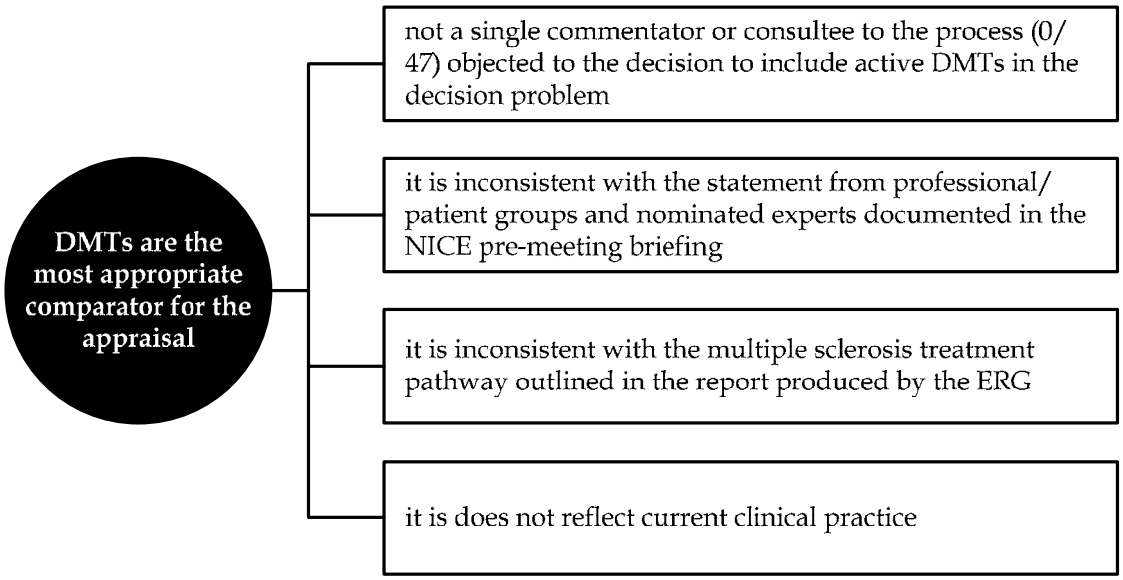
ACD Section 4.8 p11:

'For the RES group, the Committee accepted that natalizumab is clinically effective compared with placebo. The Committee also concluded that for this subgroup the appropriate comparator in current UK practice is best supportive care.'

Biogen Idec's Response:

The Committee's conclusion that the only appropriate comparator for the RES subgroup is best supportive care (no treatment), is unsound.

This conclusion is flawed on 4 counts (see below and also sections 1.2.1 to 1.2.4.):



1.2.1 Active disease modifying treatments formed part of the scope of the appraisal

IFN-beta and glatiramer acetate were both recognised as appropriate comparators in the definition of the decision problem for this appraisal. Not a single commentator or consultee to the process (0/47) objected to the decision to include active DMTs in the appraisal. (3)

1.2.2 DMTs are the most appropriate comparators as this is consistent with the statement from professional/ patient groups and nominated experts in the NICE pre-meeting briefing

ACD Section 4.6 p11:

'It also heard from the clinical experts that, for people with highly active disease, beta interferon is not generally considered to be effective and is consequently not used as a long-term treatment. The Committee was persuaded, therefore, that in the RES group the most appropriate comparator is best supportive care and that use of other currently licensed disease-modifying drugs is of unproven effectiveness'.

Biogen Idec's Response:

The Committee has misinterpreted the views of the clinical experts and failed to make the distinction between 'not adequately effective to suppress disease progression' and 'ineffective'.

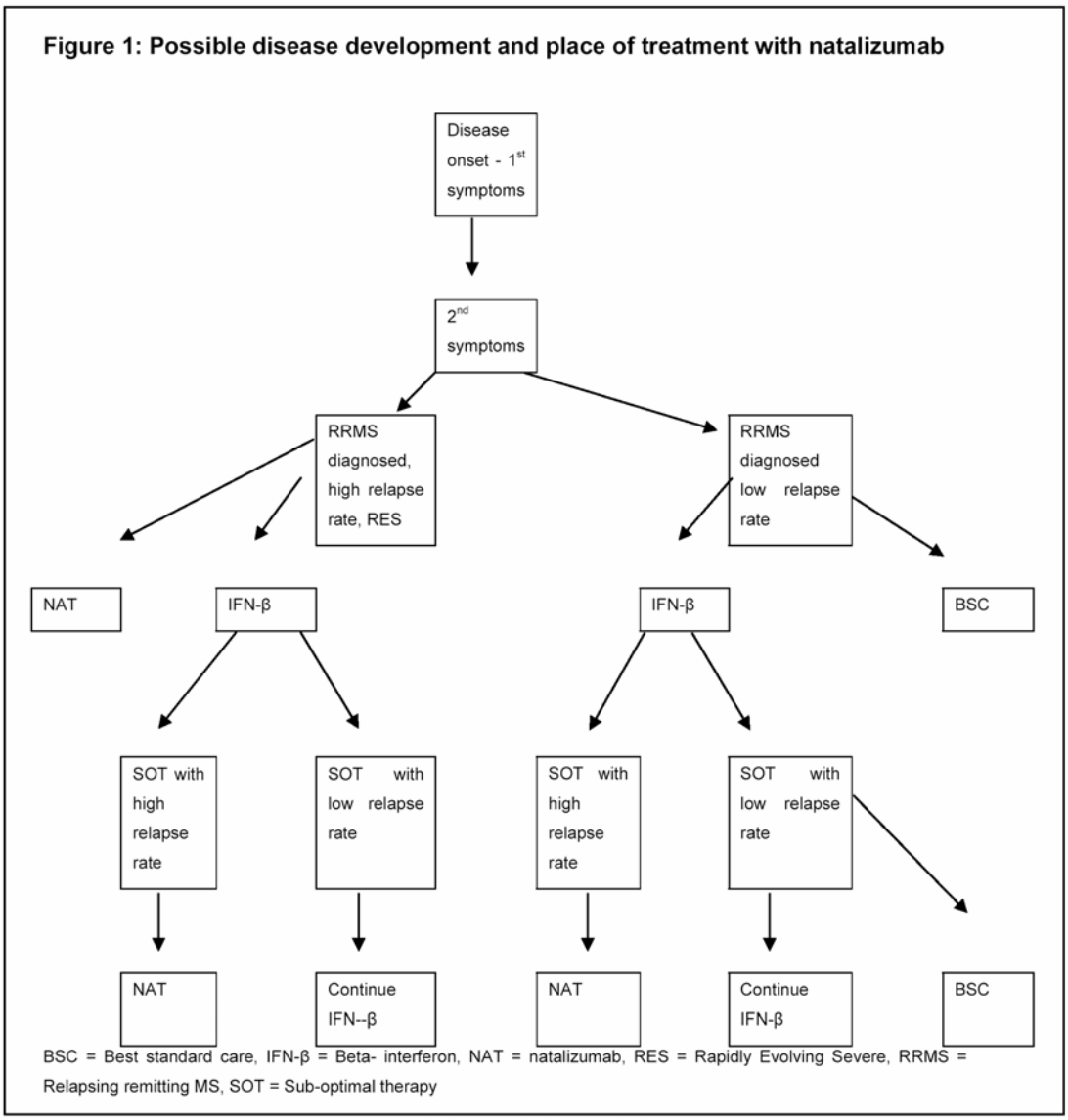
In the pre-meeting briefing notes entitled, 'Multiple Sclerosis: natalizumab: March 2007', produced on behalf of the NICE appraisal committee, it was agreed and acknowledged by the clinical specialists and patient experts that the decision problem was well defined and the place of natalizumab in the treatment pathway was clear. 'There was general agreement that IFN-beta was the most commonly used comparator, followed by glatiramer acetate'. (4)

Clearly the existing DMTs have an important clinical effect, which is explained in section 1.2.4.2.

1.2.3 DMTs are the most appropriate comparators as this is consistent with the MS treatment pathway produced by the ERG

Figure 1 taken from page 18 of the ERG report is reproduced below. (5) The ERG recognised that only active treatments should be used for people diagnosed with RRMS and presenting with a high relapse rate (RES). It should also be noted that best supportive care does <u>not</u> feature at any point in the RES component of the treatment pathway.

Figure 1 Possible disease development and place of treatment with natalizumab, ERG Report (5)



1.2.4 DMTs are the most appropriate comparators as this reflects current clinical practice in the UK

We provide evidence for this statement under 3 sub-headings: Clinical opinion (Section 1.2.4.1); clinical practice (Section 1.2.4.2); and controlled trial evidence (Section 1.2.4.3).

1.2.4.1 Clinical opinion

In this subsection we use clinical opinion to support that DMTs are the most appropriate comparators, since this reflects current clinical practice in the UK.

The Committee will be aware that a letter sent to Andrew Dillon CBE, signed by over 60 neurologists specialising in the management of multiple sclerosis in the UK, refutes the conclusion that best supportive care is the most appropriate comparator in this highly vulnerable group of patients. (data on file) The following statements are extracts from this letter:

- '[the conclusion] demonstrates a lack of understanding of this specialist disease area'
- 'best supportive care essentially means no treatment, and it is inconceivable that patients with the most active multiple sclerosis should receive no treatment at all'
- 'to deny effective treatment to patients with the most active disease flies in the face of current clinical practice' (section 1.2.4.2)
- 'it is clear that natalizumab… has been rejected purely on an economic evaluation based on a flawed comparison with no treatment'
- 'the fair and clinically correct comparison is with the four licensed disease modifying therapies'

The letter was sent to over 100 neurologists specialising in the management of multiple sclerosis in the UK and more than 70 responded, with only 1 person in disagreement.

These experts in the management of multiple sclerosis concluded that NICE 'must reverse, on both clinical and ethical grounds, the decision that best supportive care is the most appropriate comparator for patients with rapidly evolving severe multiple sclerosis'.

1.2.4.2 Clinical Practice

In this subsection we use evidence from clinical practice to support that DMTs are the most appropriate comparators as this reflects current UK practice. This is further broken down in three areas:

- Treatment effect of current DMTs
- Initiation of treatment with current DMTs
- Continuation of therapy with current DMTs.

Treatment Effect of Current DMTs

The Association of British Neurologists acknowledges the importance of even a small treatment effect within their guidelines 'Guidelines for Treatment of Multiple Sclerosis with Beta Interferon and Glatiramer Acetate on page 4: (6)

'It is almost impossible in individual patients to conclude that treatment is providing no benefit and the problem of discontinuation is compounded by the fact that there are few alternative options for disease moderation. It is not feasible to have mandatory stopping criteria that apply in all cases'.

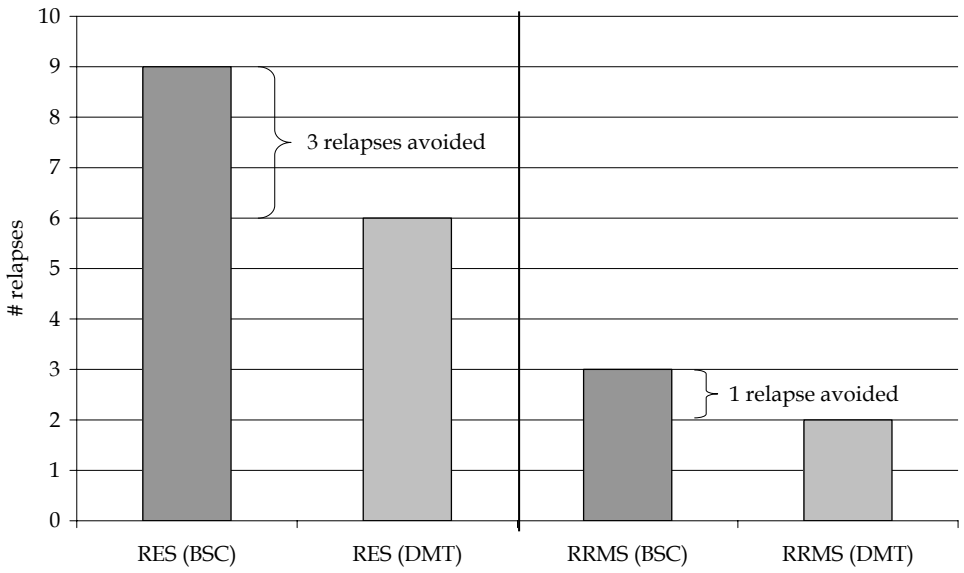
In absolute terms RES patients are likely to derive the most clinical benefit from therapy. The currently available disease modifying therapies, IFN-beta and glatiramer acetate, are only moderately effective, producing about a 30% reduction in relapse rate. For this reason, in patients with the most active disease the modest effect does not completely abolish disease activity. However, this does not equate to lack of clinical effect.

This point is reinforced in the letter from the UK neurologists specialising in the management of multiple sclerosis, sent to Andrew Dillon CBE, which states that, 'although these patients may continue to experience clinically apparent disease activity, such as relapses, whilst on currently licensed disease modifying therapies, this does not mean that these therapies are having no clinical benefit at all'.

To illustrate this point, consider the following (see also Figure 2):

- In a RES patient that is experiencing 3 relapses per year, the currently available DMT would be expected to reduce this rate to approximately 2 relapses per year. The result being an absolute clinical benefit of 3 relapses avoided over 3 years.
- Compare this with a patient that is experiencing one relapse per year. Treatment with the currently available DMTs would reduce this to 2 relapses in 3 years. This equates to an absolute clinical benefit of 1 relapse avoided over 3 years.
- It is evident that the RES patient has derived the most clinical benefit in absolute terms.

Figure 2 Absolute effect on relapse of 3 years treatment with current disease modifying therapies compared with best supportive care for a hypothetical person with rapidly evolving severe RRMS and RRMS



BSC = best supportive care; DMT = disease modifying treatment (IFN-beta or glatiramer acetate); RES = rapidly evolving severe RRMS; RRMS = relapsing remitting multiple sclerosis

Data from the Risk Sharing Scheme also show that relapse frequency falls in RES patients that commence the currently available DMTs, confirming that they do have a clinically relevant effect. In the tables taken from the ScHARR final report on the Risk Sharing Scheme (7) (see Table 5.9 and Figure 5.13 below), it can be seen that, of the 24% of patients that had experienced 4 or more relapses in the 2 years prior to baseline, only 9% (40/431) of these patients experience 4 or more relapses in the 2 years after commencing DMTs. This demonstrates that this highly vulnerable group of patients derive some clinically meaningful benefit from current DMTs.

Initiation of Treatment with Current DMTs

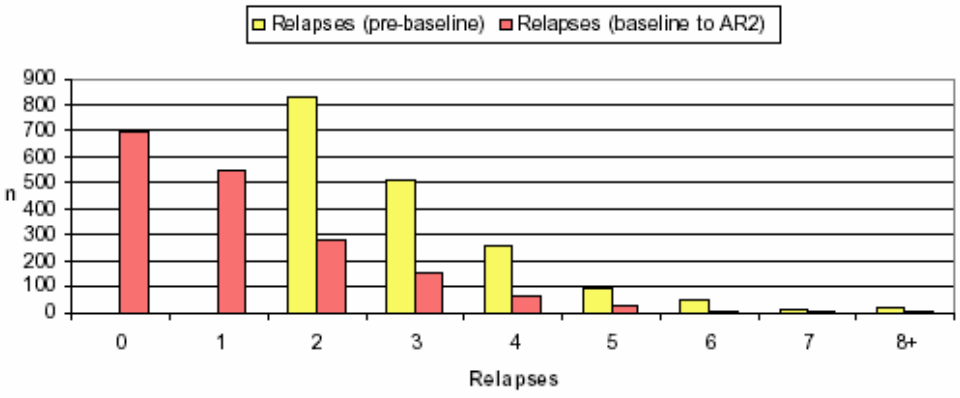
Current clinical practice is best reflected by data from the Risk Sharing Scheme, which clearly shows that patients with a high relapse frequency are prescribed both IFN-beta and glatiramer acetate (see Figure 3 below which reproduces Table 5.9 and Figure 5.13 from the ScHARR final report on the Risk Sharing Scheme). (7)

Figure 3 UK patients with a high relapse rate receive current DMTs, ScHARR final report on Risk Sharing Scheme (7)

Table 5.9 Number of relapses (two years prior to baseline / between baseline and second annual review)

Relapses (pre-baseline)	Relapses (baseline to AR2)									
	0	1	2	3	4	5	6	7	8+	Total
0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	0
2	381	241	120	52	20	9	3	1	1	828
3	191	164	87	45	18	5	1	0	1	512
4	74	89	44	30	12	1	2	2	0	254
5	26	21	20	18	5	5	0	0	1	96
6	17	20	7	4	2	0	0	0	0	50
7	2	2	1	3	2	2	0	0	2	14
8+	4	7	1	1	2	1	0	1	0	17
Total	695	544	280	153	61	23	6	4	5	1771

Figure 5.13 Number of relapses (two years prior to baseline / between baseline and second annual review)



Note, the numbering in the titles is taken directly from this report to assist with cross-referencing and the red dashed line has been added to highlight the relevant data.

RES patients have two or more relapses per year. This broadly equates to the patients in the Risk Sharing Scheme that had suffered four or more relapses in the two years prior to baseline. A total of 431/1771 (24%) patients fulfil this criterion. A similar proportion of patients in the AFFIRM study (22%) formed the RES subgroup. (8) Reconciling the data from the Scheme with that from the AFFIRM study, it is clear that the majority of RES patients are initiated on therapy with the currently available DMTs.

Continuation of Therapy with Current DMTs

Data from the ScHARR final report on the Risk Sharing Scheme shows that about 4.7% of patients discontinue therapy each year (See Figure 4 below that reproduces Table 5.12 and Figure 5.14 from the ScHARR final report on the Risk Sharing Scheme). (7) This is in line with the 5.5% discontinuation rate for IFN-beta treated patients that we used in the model. Therefore, not only do RES patients commence treatment with a disease modifying therapy, but a high proportion of these remain on treatment each year.

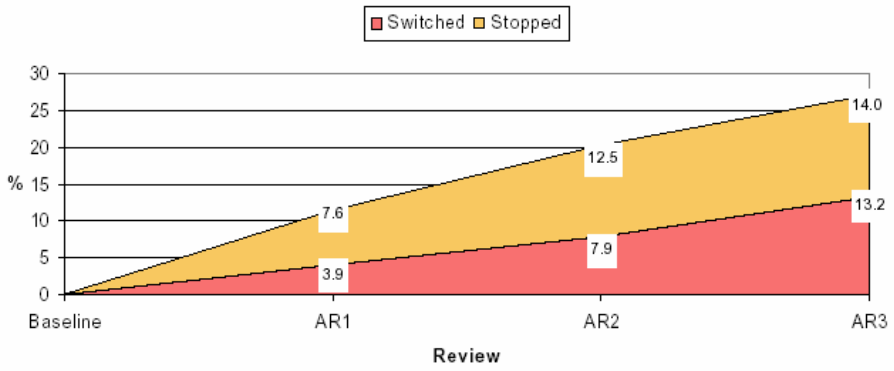
We know from observational data that the most common reason for switching therapy is lack of efficacy. (9) It is clear from the Risk Sharing Scheme that patients are just as likely to switch between therapies as they are to discontinue therapy (Figure 4). This underlines the importance of remaining on an active treatment even in the face of continuing disease activity, supporting clinical practice.

Figure 4 Patient discontinuations and switches on current DMTs, ScHARR final report on Risk Sharing Scheme (7)

Table 5.12 DMT change between baseline and third annual review

DMT following baseline	DMT following AR3												Switched	
	Q		R		S		T		Stopped		Total			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Q	47	(68.1)	4	(5.8)	1	(1.4)	3	(4.3)	14	(20.3)	69	(25.4)	8	(11.6)
R	0	(0.0)	37	(72.5)	7	(13.7)	5	(9.8)	2	(3.9)	51	(18.8)	12	(23.5)
S	2	(1.8)	4	(3.5)	86	(75.4)	7	(6.1)	15	(13.2)	114	(41.9)	13	(11.4)
T	1	(2.6)	1	(2.6)	1	(2.6)	28	(73.7)	7	(18.4)	38	(14.0)	3	(7.9)
Total	50	(18.4)	46	(16.9)	95	(34.9)	43	(15.8)	38	(14.0)	272		36	(13.2)

Figure 5.14 Switchers and stoppers at each annual review



Conclusion

Best supportive care equates to providing no therapeutic intervention. As RES patients have the most active disease and the worse prognosis, this approach is inconceivable and unethical. The multiple sources of data outlined above confirm that:

- the currently available DMTs do have an important clinical effect in RES patients

- the majority of RES patients do receive treatment with current DMTs due to a lack of more effective NICE recommended alternatives
- once initiated on therapy a high proportion of these patients remain on treatment, but switch between available DMTs seeking greater efficacy

1.2.4.3 Controlled Trial Evidence

In this subsection we use additional evidence from controlled trials to support that DMTs are the most appropriate comparators.

The rationale for continuing treatment with DMTs in people who continue to experience disease activity whilst on treatment is supported by data from SENTINEL and AFFIRM.

These studies were conducted in a similar patient population with similar inclusion criteria and baseline characteristics. The notable differences were that patients in SENTINEL were on IFN-beta at baseline and were approximately 3 years older than patients in AFFIRM.

Since the patients in these two studies were identical in every respect apart from the factors stated above, one would expect any difference in the reduction in disability progression between these studies to be largely the result of the effect of the IFN-beta. If IFN-beta was having no clinical effect then the difference should be small.

In the AFFIRM study natalizumab treatment resulted in a 54% reduction in disability progression; in the SENTINEL study this was 18%. Clearly IFN-beta was still having a clinically significant effect in the SENTINEL study, despite the fact that at entry to the study, patients were continuing to experience disease activity whilst on IFN-beta.

1.2.5 Conclusion

IFN-beta and glatiramer acetate are the most appropriate comparators in the RES subgroup. Best supportive care is an inappropriate comparator.

1.3 Modelling of disability progression is appropriate

ACD Section 3.11 p.8:

'The ERG was concerned that the transition probabilities appeared high… The model appeared to predict a higher rate of disability progression than that observed in AFFIRM'.

ACD Section 4.5 p.10:

'…the Committee was concerned about the ERG's opinion that the model predicted greater disability progression than suggested by the trial data, which could lead to an overestimate of the treatment benefit for natalizumab and an underestimate of the ICER'.

ERG Section 5.3.2 p.64:

'Whilst the manufacturer submission has considered model validity, we have undertaken analysis which indicates that the model is predicting a different rate of disability progression to that reported in the AFFIRM trial. Our analysis (see section 5.3.4) also indicates that the model leads to a much greater treatment effect than that reported in the AFFIRM trial, through the use of relative risks/hazard ratios to modify the underlying model of disability progression. We believe that the use of data from the AFFIRM trial to derive transition matrices (for RRMS EDSS states 0-6) may lead to some asymmetry between the model predictions and the outcomes reported in AFFIRM'.

Biogen Idec's Response:

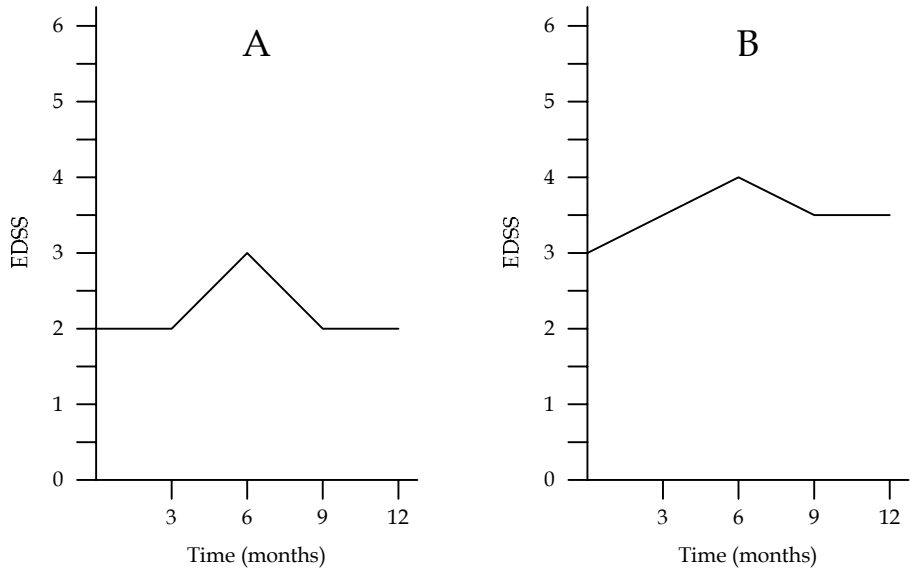
The criticism of our analysis is simply one of definition. Our model requires an estimate of average disability progression for the cohort; the AFFIRM study endpoint requires a definition of sustained disability progression (mandated by the regulators). These definitions are not comparable. We believe that the ERG compared average progression from our model with sustained progression reported in Polman. (10) Average progression has never been reported, so the ERG was unable perform the appropriate comparison.

For example, by only including data from patients that experience sustained disability progression, the ERG analysis actually underestimates average disability progression and therefore disutility. This results in an underestimate of cost effectiveness. Sustained disability progression excludes data from patients that occupy a higher EDSS state for less than the 12 week (or 24 week) definition of sustained progression. However, these patients would still experience the disutility associated with an increase of EDSS state for however long they remain in that state. Failure to include their data will therefore underestimate average disability progression and disutility.

Consider scenario A below (Figure 5) where a patient progresses from EDSS 2 to EDSS 3, but that progression is not maintained beyond 12 weeks. If we only include 'sustained' disability progression, relevant data for this patient will be excluded because the increase in disability observed has not been sustained. Therefore the disutility associated with the change in EDSS (from EDSS 2 to

EDSS 3) for nearly 3 months will not be included. For this patient, our model calculates a probability of progression as follows:

Figure 5 EDSS profile of 2 hypothetical patients with RRMS



Our model constructs a probability of progression based on a weighted average of each patient's discrete EDSS states over time and the length of time spent in each EDSS state. This prevents overestimation of average disability progression.

Scenario A

Probability of Progression (derived from average progression)	= (0 + 1 + 0 + 0)/4	= 0.25
Probability of Sustained Progression		= 0

Consider scenario B (Figure 5) where a patient progress from EDSS 3 to EDSS 3.5, with an interim period at EDSS 4. Again, this patient would not be considered to experience sustained progression. However, the probability of progression will be:

Scenario B

Probability of Progression (derived from average progression)	= (0.5+ 1 + 0.5 + 0.5)/4	= 0.625
Probability of Sustained Progression		= 0

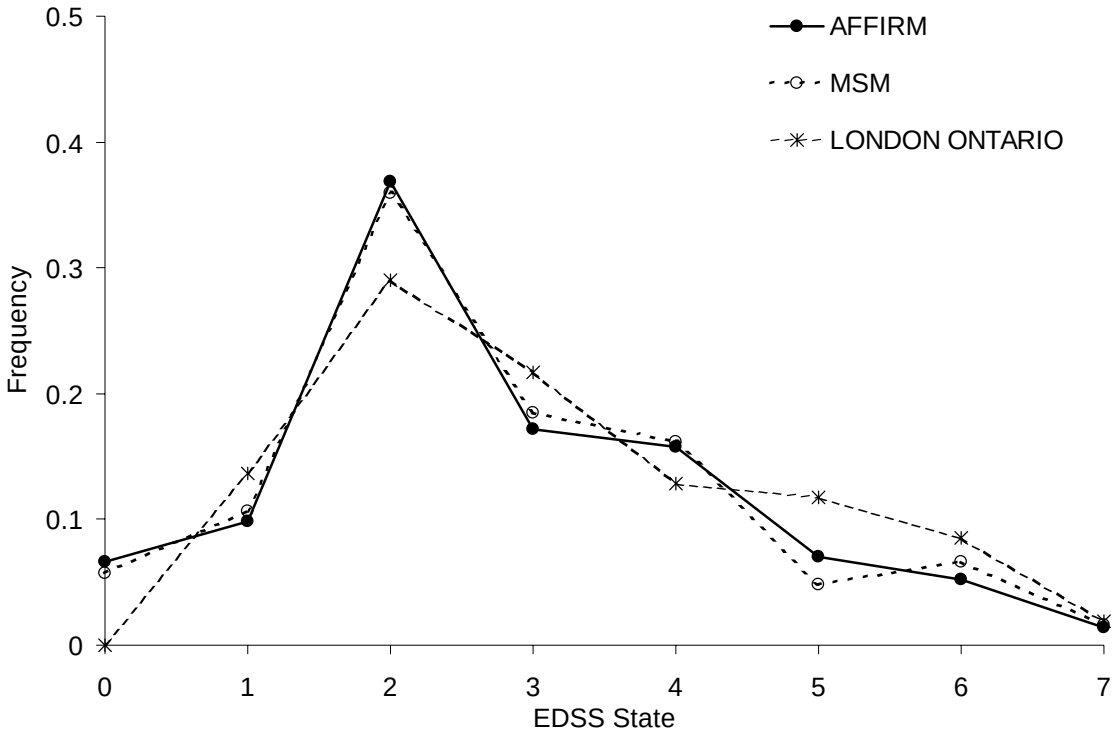
In addition, our model, in line with what has been observed in clinical practice (see section 1.4), allows for patients' disability to improve as well as deteriorate from one cycle to the next, thereby providing an additional protection against overestimation of disability progression over time.

Our model accurately reflects average disability progression i.e. neither

overestimates nor underestimates progression. Average disability progression is an accurate reflection of the RRMS disease process in a real world setting; i.e., reflecting that RRMS patients may cycle between disease progression (deterioration), arrested progression (staying in the same EDSS state) or disease retrogression (reduced EDSS scores), as the case may be.

The acid test of our multi state model is its ability to predict the distribution of patients at the AFFIRM endpoint (i.e. at 2 years) using data from the placebo arm. This is reproduced from the original submission in Figure 6. The actual endpoint profile of EDSS and the modelled profile are very similar, which indicates that the predictive power of the MSM model is high. The standard deviation of the error between the endpoint data from the AFFIRM study and the projections from the MSM fitted to the data is very good at 0.9%. (11)

Figure 6 Comparison between the endpoint data from the ITT population in the AFFIRM study with predictions by EDSS state based on the MSM applied to the AFFIRM data and transition probabilities derived from the London Ontario dataset



Note that no transition probabilities were available for the London Ontario dataset from EDSS 0 so here in the initial conditions EDSS 0 was pooled with EDSS 1

1.4 UK MS Survey 2005 is the most appropriate source of data in people with highly active RRMS

ACD Section 3.9 p.7:

'The ERG also expressed concern that the utility and cost data, which were based on the MS UK survey, were not exclusively derived from people with highly active relapsing–remitting multiple sclerosis'.

ERG Section 5.3.3 p.72:

'Whilst the UK MS Survey 2005 provides additional useful information to the sparse literature on MS, we have concerns over the use of the data from the UK MS Survey due to the potential for selection bias, and the issue of generalisability of data from the study to the broader MS treatment population and specifically to the CEA for the RES and SOT subgroups'.

Biogen Idec's Response:

The concern over generalisability is only important if 'highly active RRMS' is a significant, independent, negative predictive variable for utility and cost. It is unlikely that this parameter would have a tangible impact, given the high relapse frequency in this population that is accounted for within the model already, and the marginal rate of change between RRMS and highly active disease within a Markov model with a 1-year cycle time. It is also extremely unlikely that the parameter would be negative.

It should be noted that the utility data collected within the earlier ScHARR model produced for NICE is comparable with the utility used within the model presented for this submission, giving added confidence in the estimates derived from the UK MS Survey 2005.

ACD Section 3.9 p.7:

'The survey may not have been representative given the low response rate'.

ERG Section 5.3.3 p.72:

'Although the sample size appears large (n=2048), the response rate for the MS Survey, at only 16%, is low. The response rate may introduce selection bias, and… a possible 'volunteer effect'. The diagnosis of MS type and relapse status was made by the respondent and not based on a confirmed clinical diagnosis'.

Biogen Idec's Response:

The UK MS Survey 2005 was the largest of its kind ever conducted in the UK and the concern about response rates are normally only associated with small surveys. (12) Factors associated with response rate and the 'volunteer effect' are:

- study design (postal survey, no telephone follow-up)
- educational status

There is little difference in the profile of respondents to the UK survey compared with participants in Belgium, Germany and the Netherlands where a different study methodology was used (clinic recruitment). (13) Patients recruited in neurology clinics tended to have a shorter disease duration and less permanent disability (lower mean EDSS scores) than patients recruited by patient associations. In contrast, patients recruited by neurology clinics had a higher number of relapses'. This provides assurance that any selection bias or 'volunteer effect' was minimal.

The survey may have been biased to the better educated, and these people have a higher utility than people with less education. Adjusting for the educational status of the average highly active RRMS person will probably have a negligible effect on the cost-effectiveness; the model is mainly driven by differential utility between EDSS states and there is no reason to expect an uneven distribution of well educated people at any particular part of the EDSS scale.

The survey represents by far the best source of contemporary evidence available on the variation in costs and utility in UK people with MS.

ACD Section 3.10 p.8:

'The ERG expressed concern about the extrapolation of data collected on costs and utilities from the UK MS survey'.

Biogen Idec's Response:

The UK-specific questionnaire used in the survey was based upon an established tool developed by Kobelt et al., which has formed the basis of previous cost-of-illness studies and includes a comprehensive range of resource use to estimate both direct and indirect costs. A version of this questionnaire was verified against the medical records of a subset of respondents (n = 202) in an earlier study. (14) This provides assurance that the data from the survey is robust.

ERG Section 5.1 p.51:

'No separate literature searches are reported for quality of life, or resource use and costs. Despite the paucity of evidence for the intervention it would be expected that a broader systematic search should be run for the population group as a whole, within the multiple sclerosis literature, to retrieve suitable model parameters'.

Biogen Idec's Response:

In the utility and cost publications that reported the results from the UK MS Survey 2005 we describe the paucity of evidence in these areas as a rationale for the survey. (12;15) The available literature, identified through a quasi-systematic search, is summarised in these publications.

1.5 Natural history – EDSS improvement and worsening (bi-directional transits)

ACD Section 3.11 p.8:

'The ERG was concerned that, unlike in the ScHARR model, the manufacturer's analysis allowed EDSS scores to improve'.

ERG Section 5.3.2 p.65:

'As discussed above, unlike the ScHARR model, one structural assumption in the model is the use of transition probabilities that permit backward transitions to improved EDSS health states, when people are in RRMS health states of EDSS 0-6. This is based on EDSS data from the AFFIRM trial. However the manufacturer submission does not discuss the rationale for the difference in modelling approach in any detail'.

ERG Section 5.3.3 p.68:

'We have concerns that in some instances these 'improvement' transits appear high. We have discussed the fact that the current model allows people to transit backwards to improved EDSS health states. The ScHARR model assumes disability progression is 'uni-directional' with no backward (improving) disability movement possible, given that this is 'the current understanding of the disease'.

Biogen Idec's Response:

Uni-directional disability progression was current thinking in 2001. Scientific opinion has changed since then and bi-directional progression has now been accepted. This is evidenced by data from both the AFFIRM study and the ScHARR Report from the Risk Sharing Scheme (see Figure 7). (7;16)

The importance of backward transitions is confirmed by the observation that the best fit of our model to the data is produced when both forward and backward transits are included.

Despite the occurrence of backward transits, it should be noted that the underlying trend for all people with RRMS is an increase in disability over time.

Figure 7 Bi-directional disability progression, ScHARR final report on Risk Sharing Scheme (7)

Figure 5.7 EDSS score change (baseline to first annual review)

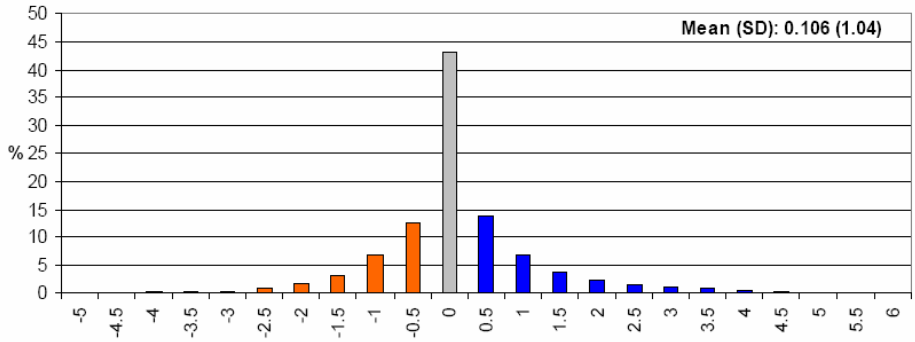


Figure 5.8 EDSS score change (baseline to second annual review)

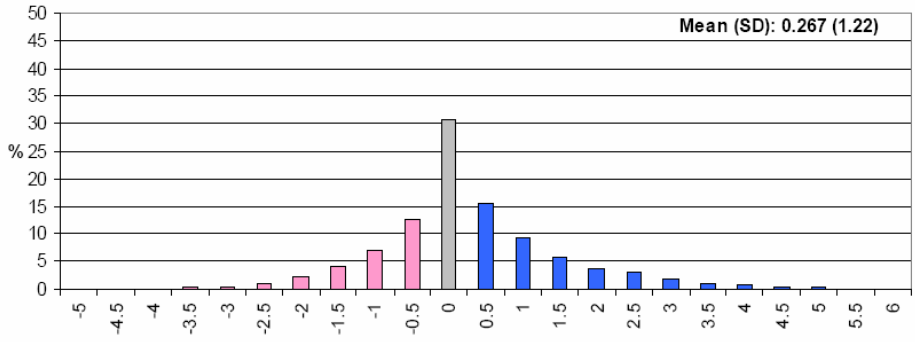
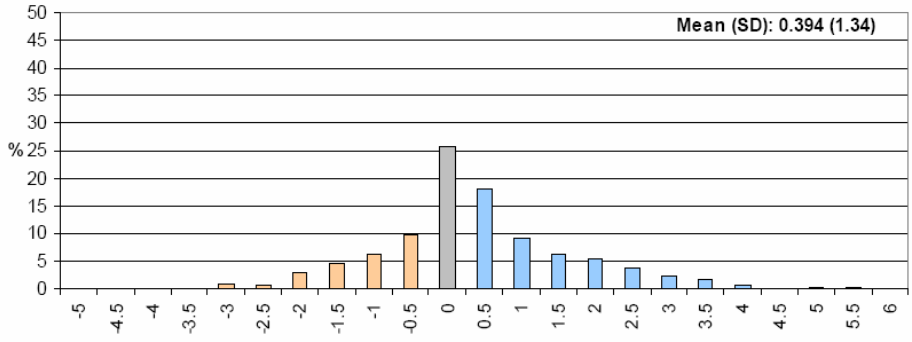


Figure 5.9 EDSS score change (baseline to third annual review)



1.6 Efficacy of Natalizumab

ACD Section 4.2 p.9:

'The Committee concluded that the clinical effectiveness of natalizumab in the suboptimal therapy group has not therefore been established'.

Biogen Idec's Response:

The EMEA concluded that :

'The overall efficacy data suggest that efficacy in C-1802 [SENTINEL] is mainly driven by natalizumab and not by Avonex [IFN-beta], since Avonex by definition was not sufficiently active. Therefore, the efficacy database is considered sufficient to support efficacy in patients being treated in case of failure of beta interferon. The other potential alternatives in the indication wording, (e.g. failure of glatiramer acetate) for the SPC are not represented in this C-1802 population, however, are relevant from a clinical perspective, and it can be assumed that natalizumab will be efficacious'. (8)

In addition, we have demonstrated that the unmet need in this group is very high and alternative licensed active treatments confer no additional benefit. (9)

ERG Section 3.1 p.19:

'The basis for granting marketing license in this group in the European Medicine Agency's (EMEA) Public Assessment Report was:

> *Overall efficacy data suggest that efficacy in SENTINEL is mainly driven by natalizumab and not by Avonex [IFN-β] since Avonex by definition was not sufficiently active (p.30 of the EMEA scientific discussion, quoted on p.22 of submission).*

This statement therefore assumes that monotherapy with natalizumab is equivalent to combination therapy in this population'.

Biogen Idec's Response:

The final sentence in this statement is not accurate. Efficacy in the combination is 'mainly', not exclusively driven by natalizumab. SENTINEL concluded that 'combination therapy has significant benefits when compared with interferon beta-1a alone'. (17) The EMEA does not report that monotherapy is equivalent to combination therapy.

ERG Section 3.5 p.22:

'It is known that natalizumab effectiveness decreases if persistent antibodies develop although it is not yet known whether the incidence of antibodies will increase over time with natalizumab as it does with IFN-beta'.

Biogen Idec's Response:

Data from the 120-week AFFIRM and SENTINEL studies demonstrates that it is highly unlikely that the incidence of persistent NABs will increase over time:

1. The development of NABs occurred exclusively in the first 6 months of the SENTINEL study
2. In the AFFIRM study, NABs occurred predominantly within the first 6 months (95%); exclusively within the first 14 months

This provides evidence that the incidence of NABs may actually reduce over time.

ERG Section 4.2.1 p.39:

'SMC note that the clinical meaning of a mean difference of 0.37 EDSS points is unclear'.

Biogen Idec's Response:

We believe that there has been some misinterpretation concerning the impact of natalizumab on disability progression as measured by EDSS. The SMC stated in its advice that, 'a [mean] difference of 0.37 is unclear.' This statement referred to data from the ITT population from the phase 3 AFFIRM trial. This population is not the same as the licensed population.

The SMC did not consider the greater treatment effect in the licensed, highly active RRMS population that formed the basis of the submission. For the RES population this results in a mean EDSS difference at 2 years for natalizumab compared with placebo of -0.72 (approximately twice the benefit cited by the SMC). For the patients with confirmed disability progression the mean difference was -0.94. (data on file)

ERG Section 4.2.1 p.39:

'The AFFIRM trial suggests that without natalizumab treatment, someone with MS would experience one additional relapse over 16-18 months'.

Biogen Idec's Response:

The above statement refers to the ITT population in the AFFIRM study, not the impact seen in RES patients, where the baseline risk and impact of natalizumab appears to be greater.

We discuss this in two parts:

1. Relapse rates of individual RES patients
2. Proportion of patients relapse free

Relapse rates of individual RES patients

Untreated ITT patients in the AFFIRM study have 1 relapse every 16 months (i.e. 1 every 1/0.73 = 1.37 years). Patients treated with natalizumab in AFFIRM experience 1 relapse every 4.2 years (i.e. 1 every 1/0.24 = 4.17 years).

For the untreated RES group, this is 1 relapse every 8 months and for patients treated with natalizumab this would be 1 relapse every 3.5 years.

These are summarised with relapse rates, 'average relapse-free days per year' and '% time relapse free' in Table 1.

Table 1: Summary of relapse rate data, data on file, AFFIRM

Population	ITT		RES	
Treatment arm	PBO	NAT	PBO	NAT
Relapse rate per year*	0.73	0.24	1.46	0.28
Average time from start of relapse to start of next relapse (years)	1.4	4.3	0.7	3.5
Average relapse-free days per year (assumed length of relapse = 46 days)**	332	354	298	352
Average % of time relapse free ***	91%	97%	82%	96%

* AFFIRM data; **Average relapse-free days = days per year – relapse rate × length of relapse; *** Average relapse free days per year/days per year. ITT = Intention to Treat from AFFIRM; RES = Rapidly Evolving Severe from AFFIRM; PBO = placebo; NAT = natalizumab

Proportion of RES patients relapse free

In the AFFIRM study, 68% of RES patients treated with natalizumab remained relapse free over the 2-year study duration, compared with only 23% of patients treated with placebo (see Figure 8 and Figure 9).

Figure 8 Proportion of RES patients receiving placebo that are relapse free over 2 years, data on file, AFFIRM

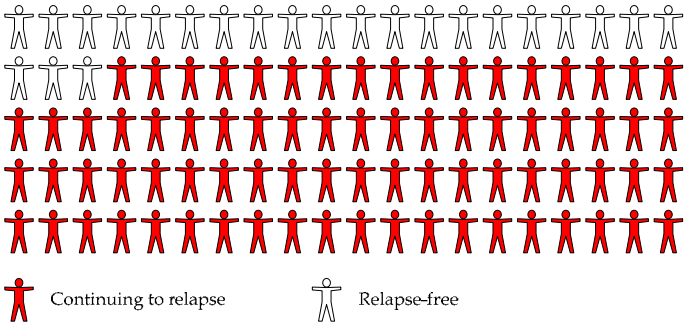
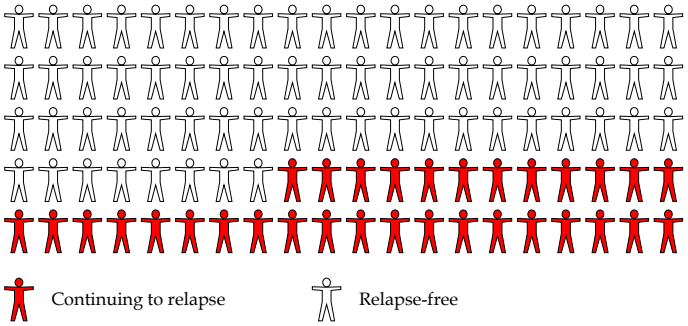


Figure 9 Proportion of RES patients receiving natalizumab that are relapse free over 2 years, data on file, AFFIRM



2 Unmet clinical need is substantial in highly active RRMS

ERG Section 2.1 p.15:

'The beginning of Chapter 4 (p.32 of the submission) is headed as describing the condition but this is presented as a short bullet pointed list which, although it briefly outlines the impact of disease and its prevalence, does not provide details about aetiology, epidemiology, prognosis or symptoms'.

Biogen Idec's Response:

Highly active RRMS is characterised by 2 or more relapses in a year and the disability in these people progresses twice as fast as a broad RRMS population. [1] Retrospective analysis of data from the placebo arm of the AFFIRM study shows that highly active patients who continued to experience one or more relapses over the duration of the study, had a mean progression in disability of 1.9 EDSS points (95% CI 1.58, 2.22). (data on file) This rate of progression means that someone with no disability today would be restricted to a wheelchair within 7 years.

Not only do patients with highly active RRMS experience rapid disability progression, but they also suffer from frequent exacerbations of their underlying disability as a consequence of frequent relapses. The highly active RRMS patient that experiences 2 relapses per year will spend approximately 3 months of each year in relapse (mean length of relapse = 46 days from the original ScHARR model). Patients with more active disease would spend even longer.

In view of this rapid progression and high relapse frequency, highly active RRMS patients have the highest unmet need.

MS not only affects the life of the individual suffering with the disease it also adversely affects the lives of loved ones, families and carers in many ways:

- MS devastates the quality of life of the individual with the disease, leading to a state worse than death in late stages of the disease
- MS necessitates the support of friends and family

---

[1] Multiple sclerosis (MS) is a neurological disease characterised by areas of demyelination (lesions) within the central nervous system. These lesions affect the normal functioning of the nerves involved and an accumulation of MS lesions over time results in irreversible physical and neurological impairment.

MS is common in young and middle-aged adults and thus can strike during a person's most economically productive and active years and during the period when major life decisions are made (i.e. in 20 – 40 years).

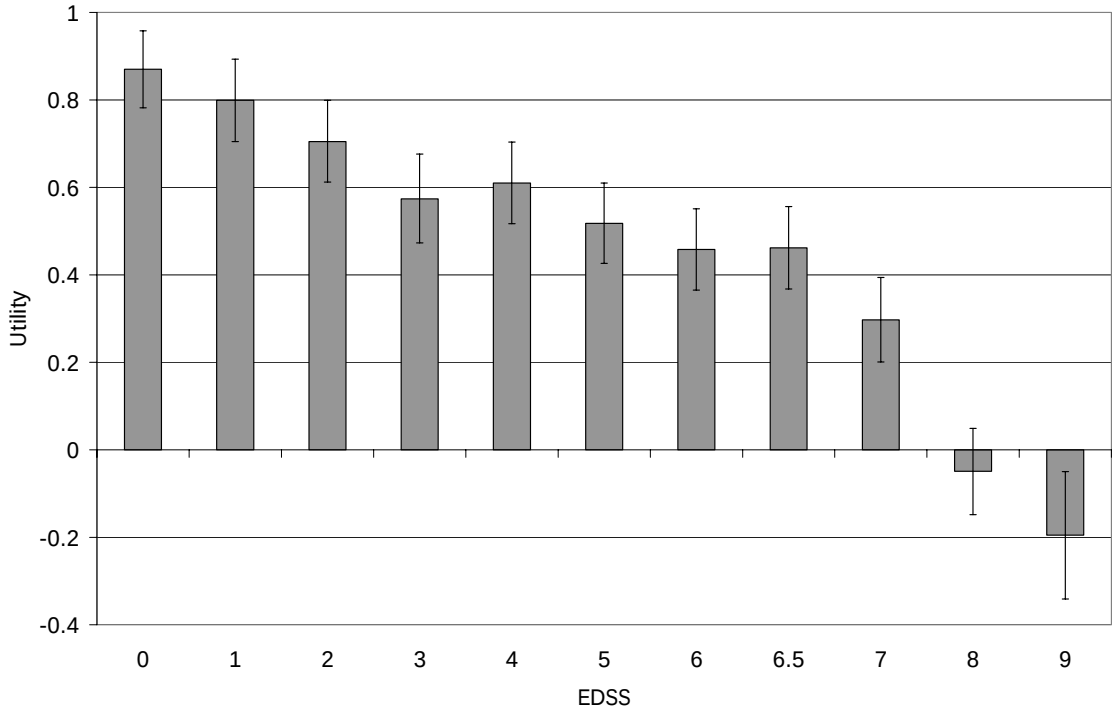
The disease is twice as common in women as in men and, given the age of onset, has a potentially catastrophic impact on the family.

People with MS that experience acute exacerbations of symptoms with periods of stable disease in between are classified as relapsing-remitting MS (RRMS).

Approximately 1 in 5 people diagnosed with RRMS have a highly active form of the disease (rapidly evolving severe RRMS).

- MS impairs the quality of life of caregivers
- MS leads to an increased burden on caregivers
- MS leads to high unemployment
- MS patients require increased nursing care and home help

Figure 10 The effect of MS on quality of life, UK MS Survey 2005, Orme 2007



Orme et al note that, 'the average utility of people with MS as measured in this study appears to be worse than all but one of the most prevalent conditions assessed by Currie et al in a [UK] hospital setting (people with other rheumatoid arthritis attending a hospital outpatient department)' (Table 2 below). (12;18)

Table 2 A comparison of the utility of people with MS and other prevalent conditions, UK MS Survey 2005

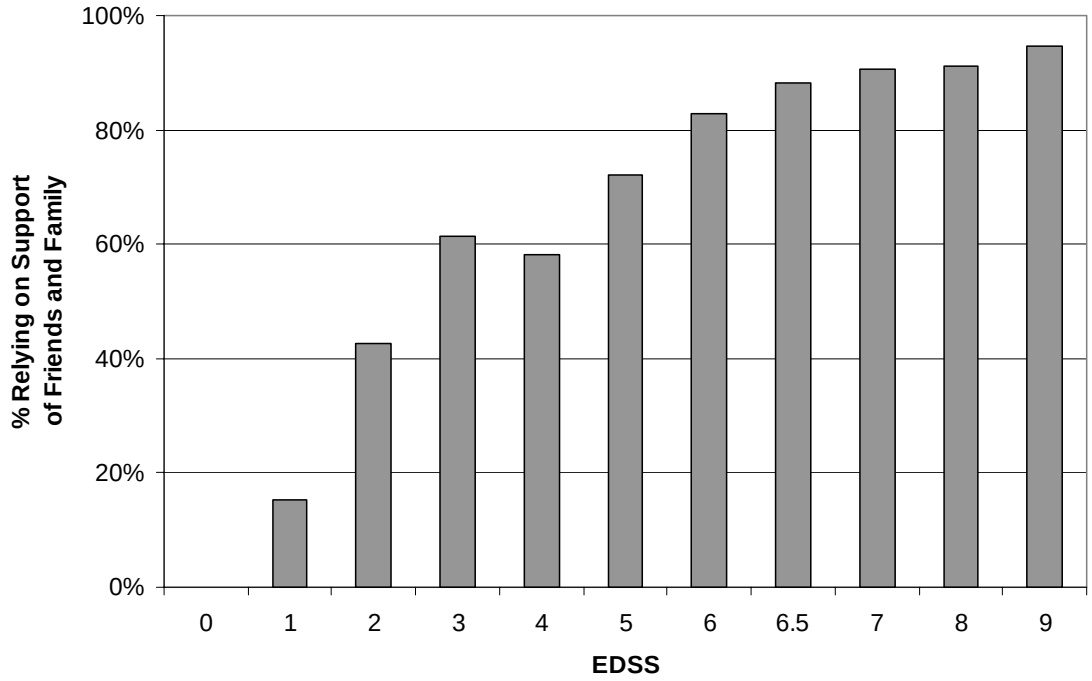
ICD10	Disease	Mean	SD	N	Setting
N92	Excessive, frequent and irregular menstruation	0.804	0.250	116	OP
K51	Ulcerative colitis	0.787	0.235	61	OP
C44	Other malignant neoplasms of skin	0.726	0.267	273	IP
C61	Malignant neoplasm of prostate	0.718	0.278	83	OP
K80	Cholelithiasis	0.709	0.305	192	IP
N95	Menopausal and other perimenopausal disorders	0.703	0.317	103	OP
I10	Essential (primary) hypertension	0.694	0.306	82	OP
K50	Crohn's disease [regional enteritis]	0.692	0.293	73	OP
E11	Non-insulin-dependent diabetes mellitus	0.674	0.287	159	OP
H26	Other cataract	0.672	0.286	748	IP
K21	Gastro-oesophageal reflux disease	0.671	0.301	216	IP
R10	Abdominal and pelvic pain	0.670	0.325	337	IP
I25	Chronic ischemic heart disease	0.636	0.293	789	IP
I48	Atrial fibrillation and flutter	0.614	0.316	189	IP
I21	Acute myocardial infarction	0.610	0.336	251	IP
R07	Pain in throat and chest	0.589	0.346	472	IP
R10	Abdominal and pelvic pain	0.576	0.350	74	OP
I20	Angina pectoris	0.576	0.306	284	IP
I25	Chronic ischemic heart disease	0.558	0.317	146	OP
-	**Multiple sclerosis (PPMS, RRMS & SPMS)**	**0.491**	**0.320**	**2408**	**-**
M06	Other rheumatoid arthritis	0.432	0.310	120	OP

All conditions other than MS adapted from Currie CJ, McEwan P, Peters JR, et al. The Routine Collation of Health Outcomes Data from Hospital Treated Subjects in the Health Outcomes Data Repository (HODaR): Descriptive Analysis from the First 20,000 Subjects. Value in Health 2005;8:586 (Tables 5 & 6). (18) IP = Inpatient, OP = Outpatient

By the time someone reaches EDSS 3, 61% of people with MS rely on help from family and friends (Figure 11); by the time the person is unable to walk this increases to 83%. The magnitude of this help varies from a few hours per month to full-time, round the clock care.

It should be noted that even at EDSS 3 (commonly recognised as a mild disability state), over 60% of patients rely on the support of friends and family.

Figure 11 The impact of MS on friends and family, UK MS Survey 2005

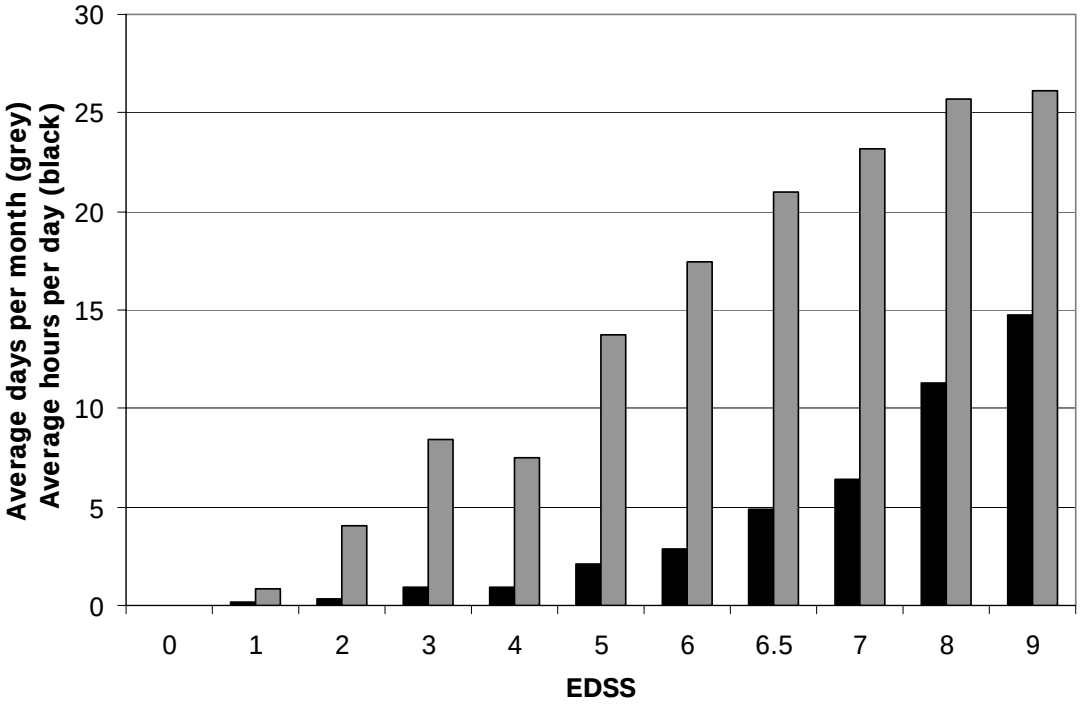


The graph presents the proportion of people with MS relying on the support of friends and family by level of disability. Respondents completed a question about their employment status in the UK MS Survey 2005

Figure 12 presents data on caregiver burden collected during the UK MS Survey 2005. It shows an inexorable increase in reliance on the support from friends and family as disability increases, both in terms of hours per day and days per month.

Figure 12 Burden to the caregiver of looking after someone with MS, UK MS Survey 2005

Data presented shows the caregiver burden in mean number of hours per day and mean number of days per



month of all respondents who reported that they received care from the UK MS Survey 2005

3 Rationale to recommend treatment with natalizumab for the subset of SOT patients that experience 2 or more relapses per year while already receiving a current DMT

The ERG concluded that there is insufficient evidence on the cost effectiveness of natalizumab monotherapy in patients that have a suboptimal treatment effect whilst being treated with IFN-beta (SOT patients) to recommend use. This is based on the SENTINEL study, which did not include a natalizumab monotherapy arm.

There is no scientific or theoretical basis upon which to conclude that patients that are relapsing whilst on a DMT are not RES (at later point in time after they have commenced therapy) and are therefore less likely to respond to natalizumab than treatment naïve patients. The important variable is the fact that they have experienced 2 relapses in the prior year, and these patients should therefore be considered as having rapidly evolving severe disease (RES).

> The ERG has acknowledged (within their treatment pathway on page 18) our assertion that the subset of SOT patients that experience 2 or more relapses per year are actually RES patients at a slightly later point in time, after they have already been commenced on treatment with one of the other DMTs.
>
> The clinical effectiveness of natalizumab in preventing disability progression and relapses in patients experiencing 2 or more relapses in the past year has been accepted by the committee.

Given that best supportive care has been shown to be inappropriate, we believe that NICE should recommend natalizumab as a cost effective therapy for highly active RRMS patients that have had two or more relapses in the prior year, irrespective of whether they are currently on treatment or not.

> It is recognised that current DMTs are not sufficiently effective in suppressing disease activity to a level where disability progression is adequately attenuated.
>
> Failure to include patients that experience 2 or more relapses per year whilst on DMT therapy within NICE's treatment recommendation will condemn these patients to continued rapid progression of disability, frequent relapses and deterioration in quality of life.

This high unmet clinical need is demonstrated by data from the SENTINEL study, which shows that patients who experienced one or more relapses (over the 2 year study duration) whilst on IFN-beta monotherapy (i.e. IFN-beta plus placebo) progressed by a mean of 1.68 EDSS points (95% CI 1.46-1.90) over the

two years of the study. (data on file) This means that if they had perfect mobility at the start of the study, they would be in a wheelchair within 7 years. The rate of progression in this group of patients is twice as fast as that of patients with less active disease.

4 Discussion and Conclusions

The unmet need in people with relapsing-remitting multiple sclerosis is high. For people with highly active disease, the need is far greater; these people experience twice the rate of disability progression compared with less active disease. This inevitably leads to a far more rapid effect on mobility, morbidity, quality of life and constrained NHS, personal and societal finances. A person presenting today with highly active relapsing-remitting multiple sclerosis, and who continues to experience frequent relapses, could expect to be in a wheelchair within 6 or 7 years.

Best supportive care (i.e. no treatment) is not an appropriate comparator to natalizumab for people with highly active disease. Multiple sources of evidence demonstrate that NICE's contrasting conclusion within the ACD is unfounded. In addition, more than 60 neurologists specialising in the management of multiple sclerosis have written to NICE in this respect. The following are extracts from this letter:

- '[the conclusion] demonstrates a lack of understanding of this specialist disease area'
- 'best supportive care essentially means no treatment, and it is inconceivable that patients with the most active multiple sclerosis should receive no treatment at all'
- 'to deny effective treatment to patients with the most active disease flies in the face of current clinical practice'
- 'the fair and clinically correct comparison is with the four licensed disease modifying therapies'

IFN-beta and glatiramer acetate are the most appropriate comparators for this appraisal since a high proportion of people in the UK with highly active disease receive these treatments within the Risk Sharing Scheme. However, despite experiencing some clinically meaningful benefit from the currently available disease modifying therapies, people with highly active disease still need additional efficacy to prevent rapid disability progression. Natalizumab therefore addresses a high unmet clinical need in this group.

We have presented a robust, pragmatic and valid economic evaluation of natalizumab in patients with highly active disease. The model addresses criticisms of previous models in MS and adopts contemporary evidence on the speed and 'bi-directional' nature of disability progression observed in the eligible treatment population.

The cost and utility data within the model were collected from the largest ever UK survey of its kind and has been published in one of the most respected peer reviewed health economic journals (Value in Health).

The Risk Sharing Scheme cited above is important not only because it represents contemporary guidance to the NHS in the treatment of multiple sclerosis, but also because it establishes an acceptable cost-effectiveness threshold for disease

modifying treatments in multiple sclerosis of £36 000 per QALY gained.

Two 'special factors' (impact on relapse severity and Personal Social Services cost offsets) were cited as a rationale for this threshold. Given the consequential benefit of the enhanced effectiveness of natalizumab on these two 'special factors', the threshold of £36 000 per QALY gained is even more relevant for this appraisal. [2]

We have demonstrated that, for patients with rapidly evolving severe relapsing-remitting multiple sclerosis, natalizumab is cost-effective compared with all active disease modifying treatments at this threshold. The incremental cost-effectiveness ratio (£ per QALY gained) for natalizumab compared with IFN-beta is £32.0K and for glatiramer acetate is £34.6K.

There is compelling evidence to support a decision to recommend that all eligible patients that fulfil the rapidly evolving severe relapsing-remitting multiple sclerosis indication, those naïve to treatment and the rapidly evolving severe subset of those receiving a current DMT, should be treated with natalizumab, funded by the NHS.

The consequences of a recommendation to use natalizumab in all eligible patients that fulfil the rapidly evolving severe relapsing-remitting multiple sclerosis indication are:

- to provide much-needed slowing of disability progression by approximately 64%, which equates to years of greater mobility, quality of life and the opportunity to provide a greater contribution to family, social and work life
- to reduce the average time per year within an acute relapse from 67 days to 7
- equitable with the recommendations of the Risk Sharing Scheme and will reduce inequities in access to natalizumab based on ability to pay
- affordable for the NHS with an estimated net annual impact of less than £1 million in the first year increasing to approximately £5 million in 5 years time
- based on a robust, valid economic evaluation that has demonstrated acceptable cost-effectiveness from a NHS and Personal and Social Services perspective (with even greater cost-effectiveness when societal costs are factored in)

The consequences of denying NHS funding for natalizumab in all eligible patients that fulfil the rapidly evolving severe relapsing-remitting multiple sclerosis indication are:

- to condemn the most needy people with MS to a rapid worsening of disability such that the majority will be confined to a wheelchair within 7 years

[2] It should be noted that this willingness-to-pay threshold was established in 2002. If this were inflated to 2007, using the appropriate discount rate of 3.5% it would equate to £42 800 per QALY gained.

- to acknowledge that it is acceptable to live for an average of 67 days per year in a state of acute relapse
- to accept the continued usage of existing disease modifying treatments in a highly active subgroup for which additional effect is needed and sought by patients

There is compelling evidence to support a decision to recommend that all eligible patients that fulfil the rapidly evolving severe relapsing-remitting multiple sclerosis indication, those naïve to treatment and the rapidly evolving severe subset of those receiving a current DMT, should be treated with natalizumab, funded by the NHS.

Appendix A Other Comments

A.1 ACD Document

ACD Section 3.3 p.5:

'Natalizumab significantly improves health-related quality of life when measured with the SF-36 instrument, but not when the MSQLI instrument was used'. Also, ERG Section 4.2.1 p40 *['No significant effect was seen on the MS Quality of Life Inventory (MSQLI)']*.

Biogen Idec's Response:

This is perhaps not surprising since MSQLI was only available in the English language and therefore the MSQLI data was from a small subset of the overall AFFIRM population.

ACD Section 3.10 p.8:

'The ERG expressed concern about the extrapolation of 2-year data from the AFFIRM trial to a 20-year time horizon'.

Also, ERG Section 5.4 p.88:

'The model applies a constant treatment effect over the 20-year time horizon and there is an absence of evidence to support this assumption'.

Biogen Idec's Response:

As is the case with all newly licensed products, there is a lack of data concerning magnitude of treatment effect over the long term. Therefore we modelled an assumption that the relative treatment effect remains stable between the different comparators over the 20 year time horizon. This assumption is identical to that used by ScHARR in their model and is reasonable; and probably conservative as outlined below.

In the absence of specific data it is helpful to examine other indicators to determine whether the product is likely to remain effective in the long term.

As the natural history of MS is one of progressive disability, the relationship between baseline disability and the efficacy of natalizumab at preventing further disability progression is likely to be a good indicator of whether the benefits of natalizumab will be maintained in the 20 year time horizon:

- Baseline EDSS was pre-specified as a covariate in the statistical analysis plan of the AFFIRM study. (10) When the covariate analysis was performed there was no significant relationship (p=0.87) between baseline EDSS and disability progression. (19) Only age at baseline had a significant effect on disability progression and was included in the final model. (19)

- In addition, natalizumab-treated patients had a highly significant reduction (compared with placebo) in the probability of reaching the pre-specified tertiary endpoints, EDSS ≥ 4 (hazard ratio = 0.33, $p < 0.001$) and EDSS ≥ 6 (hazard ratio = 0.30, $p = 0.002$). (19) EDSS 4 signifies that the patient is experiencing significant limitation in walking ability and EDSS 6 means that the patient can only walk with assistance.
- These data therefore show that natalizumab continues to reduce disability progression across the whole range of relevant EDSS scores and this in turn supports the continued effectiveness of natalizumab over time.

In clinical practice, when a reduction in efficacy is seen in individual patients receiving DMTs, the main contributor is the development of neutralising antibodies (NABs).

In the natalizumab studies no NABs occurred after week 60. Hence any reduction in efficacy is likely to occur early rather than late and, because treatment pathways include testing for NABs if reduction in treatment effect is observed, emergence of antibodies will be rapidly detected and the affected patients' removed from therapy.

This contrasts with the case of IFN-beta where NABs tend to occur late. In a sample of patients on IFN-beta, Sorensen demonstrated that 33% of patients were persistently antibody positive after 24 months treatment (37% after 60 months). (20)Herndon et al showed that, over 6 years of follow-up, the incidence of NABs rose over the first 18 months of therapy and then reached a plateau. (21)

This aspect of IFN-beta treatment probably contributes to the diminishing efficacy results demonstrated in the second years of multi-year studies for interferons. This is in contrast with natalizumab, where the treatment effect is greater in year 2.

Importantly, routine screening for NABs to IFN-beta is not recommended in the UK, so it is probable that these patients will remain on therapy despite attenuated treatment effect. This is supported by UK market research data showing that 40% of patients on IFN-beta and glatiramer acetate are on their 2nd, 3rd, or 4th line of treatment. Mainly they switch because the original treatment was not controlling their MS disease activity. (9) Rather than discontinue treatment, these patients continue to try different DMTs in the hope that one of these treatments will work better for them. However data also demonstrates that there is no clinical benefit from switching therapies. (9)

It is plausible that the effect of natalizumab would improve over time compared with IFN-beta and glatiramer acetate, as those for whom treatment is not working are identified early (due to specific recommendation to test for NABs) and withdrawn. This is not the case for IFN-beta.

A.2 ERG Document

ERG Section 1.4.3 p.14:

'Underlying disease progression in the model is based on data from the AFFIRM trial and should be treated with caution'.

Biogen Idec's Response:

AFFIRM data was the only source of data available for highly active RRMS. Most transition probabilities within the model are based on London Ontario data, however, and AFFIRM data only supplements this in RRMS at mild and moderate states of disability.

ERG Section 3.3 p.21:

'IFN-β reduces disability progression by about 30% (RR 0.69, 95% CI 0.55, 0.87; p=0.002) compared to placebo over two years of treatment'.

Biogen Idec's Response:

This should read, 'IFN-β reduces *relapse frequency* by about 30% (RR 0.69, 95% CI 0.55, 0.87; p=0.002) compared to placebo over two years of treatment'.

ERG Section 3.3 p.21:

'The Biogen submission further includes data from the MS survey (2005, n=2048) showing that of the 288 people with RRMS in the UK who were taking DMT, none were taking MTX'.

Biogen Idec's Response:

This should read '…of the 288 people with RRMS in *the UK MS Survey 2005* who were taking DMT, none were taking MTX'.

ERG Section 3.4 p.22:

'As there are no formal inclusion and exclusion criteria for trials discussed in the manufacturer's submission, no outcomes are specified as criteria for inclusion'.

Biogen Idec's Response:

We chose not to report inclusion/exclusion criteria since we stated that we updated reviews by Cochrane. Please refer to the criteria employed in the Cochrane reviews.

ERG Section 4.2.1 p.40:

'Relative risk of disability progression at two years is 0.19 (95% CI 0.30, 0.12)'.

Biogen Idec's Response:

Should read, 'Relative risk of *relapse* at two years is 0.19 (95% CI *0.12, 0.30*)'.

ERG Section 4.2.1 p.42:

'The submission does pool information from AFFIRM, MS201 and MS231 on safety. As the length of follow-up in these three trials is different (2 years, 12 weeks and 24 weeks) it may have been more appropriate to use rate ratios, rather than the risk ratios used in the submission. Given the shorter follow up period in MS231 and MS201, it is possible that these trials may bias the results in favour of natalizumab, as there may be less adverse effects with less exposure to the drug'.

Biogen Idec's Response:

We chose to pool adverse events from all available sources since this would maximise the likelihood of highlighting a significant difference in an adverse event not identified in AFFIRM. Had relative rates been chosen as the summary statistic an indirect comparison with other DMTs would not have been possible.

ERG Section 4.2.1 p.43:

'The submission argues that RES patients are less likely to respond to IFN-β because the mode of action in MS is unknown, making it is reasonable for them to assume that impact in RRMS is the same as RES'.

Biogen Idec's Response:

We do not state that RES patients are less likely to respond to IFN-beta. Page 80 of the submission states that, 'in the absence of evidence to the contrary, it was assumed that there was no difference in efficacy for IFN-beta or glatiramer acetate between an ITT population (i.e. a RRMS population) and the RES subgroup'.

ERG Section 5.1.1 p.52:

'No patients are withdrawn from natalizumab treatment in the model due to PML or NAB'.

Biogen Idec's Response:

Withdrawals due to PML and NAB were included in the annual withdrawal rate of 6.4% used in the model.

ERG Section 5.2.1 p.60 Table 11:

'Care giver disutility included in base case analysis for NHS & PSS perspective, this may not be appropriate for NICE reference case'.

Biogen Idec's Response:

This was added to the reference case at the suggestion of NICE on 17 October 2006 during a meeting to discuss the decision problem, and is based on the conclusion that care giver utility was considered relevant to Appraisal 111 (Alzheimer's - donepezil, galantamine, rivastigmine (review) and memantine). (22)

ERG Section 5.3.2 p.65:

'A further structural assumption is the adjustment of the probability of people moving from RRMS to SPMS at each 1-year cycle. The model applies a relative risk reduction parameter to modify the risk of transition from RRMS to SPMS in each cycle. An assumption is made to use 50% of the risk reduction seen in the RRMS strata of the model. This assumption is based on a fitting of the model and trial data (discussed in Section 6.2.12.3 of the manufacturer submission). However, the rationale for this assumption is not clearly stated'.

Biogen Idec's Response:

This rationale is stated in our original submission (at the end of section 6.2.6.2 (i) 'Impact of DMT on progression').

ERG Section 5.3.3 p.68:

'Whilst the London Ontario dataset has been used widely in the analysis of the natural history of MS, it is taken from a long term observational dataset largely comprising untreated MS patients, and it may not reflect the HARRMS patient group relevant for the current appraisal (CEA)'.

Biogen Idec's Response:

The London Ontario dataset: i) was the only data available for a complete analysis; ii) probably results in a conservative estimate of cost-effectiveness since highly active patients progress more rapidly than people within less active multiple sclerosis.

ERG Section 5.3.3 p.69:

'In the AFFIRM trial the mean annual relapse rate at 2-years was 1.46 for the RES placebo group, whilst the model uses rates ranging from 0.972 to 1.448 (see submission Table 48). For the SOT subgroup the model uses relapse rates ranging from 0.490 to 0.729, compared to an annual relapse rate in the AFFIRM ITT group (SOT proxy) of 0.73'.

Biogen Idec's Response:

If we increase the relapse rates in the RES group and the SOT groups to 1.46 and 0.73 per year respectively this has a beneficial effect on the ICERs.

ERG Section 5.3.3 p.73:

'We note that the utility differences associated with administration favour the use of natalizumab (with a relatively big difference between natalizumab and other treatments), and that there are a number of concerns with the treatment disutility estimates used… further research is required in this area'.

Biogen Idec's Response:

Additional research is needed in this area and we have endeavoured to make logical assumptions about disutility associated with treatment using the sparse data available. The average annual disutility associated with treatment with IFN-beta, glatiramer acetate and natalizumab is 0.047, 0.013 and 0.008; the magnitude of the difference is not big, particularly between glatiramer acetate and natalizumab.

ERG Section 5.3.3 p.74:

'These [standardised mortality rate] data are from a Canadian study addressing the relationship between MS severity and life-expectancy in 2,348 patients followed in MS clinics during 1972-1985'.

Biogen Idec's Response:

The study was Danish, not Canadian.

ERG Section 5.3.3 p.76:

'The submission cites the unpublished manuscript by Tyas and colleagues to support the use of the cost estimates presented by EDSS state. However we have not been able to reconcile the cost estimates in these two sources, especially for the NHS and PSS perspective'.

Biogen Idec's Response:

The coefficients differ because we removed parameters not relevant to the decision problem (e.g. educational status) and re-ran the analyses.

ERG Section 5.3.3 p.78:

'A further issue related to concerns over PML is that, in practice, all patients treated with natalizumab may undergo a baseline MRI scan, in order to consider any future concern over PML. This cost is not presently included in the analysis for all patients'.

Biogen Idec's Response:

An MRI scan is indicated for both natalizumab and current DMT groups at baseline irrespective of the PML risk.

ERG Section 5.3.5 p.84:

'For sensitivity analysis against the use of the London Ontario data for progression parameters we find quite different results, especially so in the comparison of natalizumab and BSC'.

Biogen Idec's Response:

We believe that this is an oversight by the ERG. The London Ontario data does not have transition probabilities to or from EDSS 0. Therefore, for this simulation, the patients in EDSS 0 and EDSS 1 are pooled into EDSS 1. This is stated in the footnote to the Table 85 in the main submission and results in the sensitivity analysis that we produced.

ERG Appendix 4 p.115:

'Characteristics of included trials not reported'.

Biogen Idec's Response:

These were reported in Appendix C of the original Biogen Idec submission.

There is compelling evidence to support a decision to recommend that all eligible patients that fulfil the rapidly evolving severe relapsing-remitting multiple sclerosis indication, those naïve to treatment and the rapidly evolving severe subset of those receiving a current DMT, should be treated with natalizumab, funded by the NHS.

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