Natalizumab (Tysabri®) for the Treatment of Adults with Highly Active Relapsing Remitting Multiple Sclerosis ADDENDUM 22-12-06

Biogen Idec Single Technology Appraisal (STA) Submission to The National Institute for Health and Clinical Excellence

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Confidential Information:	Note that all confidential information within the submission has been removed

1 Executive summary

A new Markov model, based on the previous School of Health and Related Research (ScHARR) model commissioned by the National Institute for Health and Clinical Excellence (NICE), reviewed by recognised experts in the field of health economics in multiple sclerosis, and validated against the previous model, demonstrated that **the incremental cost-effectiveness ratio (ICER) of natalizumab compared with any active comparator in the rapidly evolving severe subgroup is below the acceptable published threshold of £36 000 in all decision problems (see section 6).**

Natalizumab uptake at forecast levels represents a modest budget impact in England and Wales (maximum forecast total incremental discounted cost in year 5 of £15.5 million).

Multiple sclerosis is a devastating disease that creates a burden on the health care system in the UK (see section 4)

In the large majority of patients multiple sclerosis is a relentlessly progressive chronic disease. Multiple sclerosis is the most common disabling neurological condition affecting young adults. Multiple sclerosis adversely impacts the lives of patients, caregivers and other stakeholders in many ways:

- multiple sclerosis can devastate the quality of life of the individual with the disease, and may lead to a state worse than death in late stages of the disease
- multiple sclerosis necessitates the support of friends and family
- multiple sclerosis impairs the quality of life of caregivers
- multiple sclerosis leads to an increased burden on caregivers
- multiple sclerosis leads to high unemployment
- multiple sclerosis patients require increased nursing care and home help
- multiple sclerosis has a high personal financial cost to sufferers and carers

Highly active relapsing remitting multiple sclerosis patients relapse more frequently and progress more rapidly to severe disability than a relapsing remitting multiple sclerosis population and therefore one would expect the above consequences to have even greater impact for this group of patients.

There are currently no other treatments that are licensed specifically for patients with highly active relapsing remitting multiple sclerosis and no clear guidelines on initiation of therapy in this patient group, or guidance on what to do in the event of a sub optimal response to current therapy.

It is notable that there are no specific guidelines for patients with highly active relapsing remitting multiple sclerosis. This provides a unique opportunity for NICE to be the first authoritative body to provide much-needed clarity by recognising natalizumab as the most appropriate treatment for highly active relapsing remitting multiple sclerosis patients.

Natalizumab is a significant clinical advance in the treatment of highly active relapsing remitting multiple sclerosis (see sections 2 and 5)

There are currently no other therapies licensed specifically for people with highly active relapsing remitting multiple sclerosis. Highly active relapsing remitting multiple sclerosis patients have more frequent relapses and progress more rapidly to severe disability than the relapsing remitting multiple sclerosis population. The active comparators within this submission are interferon beta and glatiramer acetate. Best supportive care is also considered as a comparator.

Natalizumab is the first in a new class of drug for the treatment of highly active relapsing remitting multiple sclerosis. It is a selective adhesion-molecule inhibitor. Natalizumab has a unique and specific mechanism of action, which prevents white blood cells, the mediators of inflammation in multiple sclerosis, from entering the brain.

Natalizumab is licensed for the treatment of highly active relapsing remitting multiple sclerosis. These patients fall into two subgroups:

Rapidly evolving severe subgroup defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium-enhancing lesions on brain Magnetic Resonance Image (MRI) or a significant increase in T2 lesion load as compared to a previous MRI.

Sub optimally treated subgroup defined as patients who have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in brain MRI or at least 1 Gadolinium-enhancing lesion.

Methodology

The AFFIRM and SENTINEL pivotal studies, upon which the licensed indications of natalizumab are based, are the largest prospective, interventional studies to be conducted in relapsing remitting multiple sclerosis to date.

Critical appraisal based upon the key components of the CONSORT statement indicates that the natalizumab pivotal studies were generally better conducted and better reported than equivalent studies of comparator treatments.

Efficacy results of natalizumab pivotal studies:

All clinical and surrogate primary and secondary endpoints, for both AFFIRM and SENTINEL, showed a clinical and statistically significant benefit in favour of natalizumab treated patients.

These benefits were seen early, were sustained throughout the duration of treatment and were typically superior to those observed in clinical studies of other disease modifying therapies in the treatment of relapsing remitting multiple sclerosis. At 2 years within AFFIRM, compared to placebo natalizumab treated patients experienced a:

68% reduction in annualised relapse rate ($p < 0.001$)

54% reduction in the hazard ratio for disability progression ($p < 0.001$)

81% reduction in annualised relapse rate in the rapidly evolving severe subgroup
($p < 0.001$)

64% reduction in the hazard ratio for disability progression in the rapidly evolving severe subgroup ($p = 0.008$)

A large effect on lesions identified by magnetic resonance imaging (MRI) was observed:

92% reduction in the mean number of Gd+ lesions ($p < 0.001$)

83% reduction in the mean number of new or enlarging T2 hyperintense lesions ($p < 0.001$)

76% reduction in the mean number T1 hypointense lesions ($p < 0.001$)

Nearly a third of patients treated with natalizumab remained disease free at 2 years:

28% of people were free of all measures of disease activity (disability progression, relapses, Gd+ lesions, new or enlarging T2 lesions or new T1 lesions)

In a 1-year open label extension study, the three-year annualised relapse rate for patients was 0.23. This was consistent with the 0.23 annualised relapse rate seen in the natalizumab arm of the two-year AFFIRM study.

Safety results of natalizumab pivotal studies

All common adverse events, except for fatigue and allergic reaction, were not significantly different from placebo.

The rates of serious adverse events were equivalent to placebo.

A risk of Progressive Multifocal Leukoencephalopathy associated with natalizumab monotherapy cannot be excluded. Progressive Multifocal Leukoencephalopathy has not been reported in patients with multiple sclerosis receiving natalizumab monotherapy.

Indirect comparison:

No head to head trials of natalizumab and the active comparators have been conducted. An indirect comparison of efficacy and safety outcomes from available clinical trials of disease modifying therapies, using placebo as the common comparator, demonstrated a consistent beneficial effect of natalizumab compared with both interferon beta and glatiramer acetate for disability progression and relapse frequency.

A superior adverse event profile compared to interferon beta and an equivalent profile to glatiramer acetate (except for patterned reaction, which has not been reported in natalizumab treated patients but has a relative risk of 3.29 in patients treated with glatiramer acetate compared with placebo).

Evidence from non-randomised controlled trials shows that:

Highly active relapsing remitting multiple sclerosis patients experience more rapid disability progression and higher relapse frequency than a relapsing remitting multiple sclerosis population, as evidenced by published natural history studies and a new multi state model constructed for this submission. The multi state model estimates that disability progresses approximately twice as fast in an untreated rapidly evolving severe subgroup compared with a relapsing remitting multiple sclerosis population (mean change in Expanded Disability Status Scale (EDSS) of 0.46 and 0.27 respectively over two years).

The standardised mortality rate for people with multiple sclerosis is worse than the general population and increases with disability. Given that disability progresses faster in patients with highly active relapsing remitting multiple

sclerosis, it is probable that the standardised mortality rate in highly active relapsing remitting multiple sclerosis patients is higher than the broad population of relapsing remitting multiple sclerosis patients.

In 2005, evidence from the largest population based survey of multiple sclerosis patients conducted in the UK provided information on the effect of multiple sclerosis on:

- Direct and indirect resource consumption (resource consumption was directly associated with level of disability).
- Utility was inversely associated with disability until a state worse than death was reached in the most severe disability states.

Caregiver disutility is believed to be correlated with disease severity. We estimate that the disutility of being a caregiver reaches a maximum of 0.14 at an EDSS score of 9.

It is probable that compliance with natalizumab will be better than the current disease modifying therapies because natalizumab is dosed less frequently than the current drugs and is delivered in an outpatient setting rather than at home.

Natalizumab in highly active relapsing remitting multiple sclerosis is an acceptable use of NHS resources (see section 6)

Unlike any other medical technology in England and Wales, an acceptable cost-effectiveness threshold has been established for disease modifying treatments for multiple sclerosis of £36 000 per QALY gained.

The ICER for natalizumab compared with either active comparator in the rapidly evolving severe subgroup is below this acceptable threshold for all evaluated decision problems. For natalizumab compared with interferon beta the ICER is £32 000 per QALY gained. Compared with glatiramer acetate the ICER is £34 600 in the same subgroup.

By comparison, using conservative values for key uncertain parameters, when natalizumab is compared with interferon beta in the sub optimally treated subgroup the ICER is £43 400 per QALY gained. When natalizumab is compared with glatiramer acetate and best supportive care in the sub optimally treated subgroup, the ICER is £44 300 and £56 100 respectively.

Given the threshold of £36 000 per QALY gained, the probabilistic sensitivity analysis resulted in a 59% probability of natalizumab being cost-effective in people with rapidly evolving severe multiple sclerosis compared with interferon beta. The result for the comparison with glatiramer acetate in the same subgroup was found to be 48%. If an alternative (societal) perspective is chosen, these values increase to 83% and 80% respectively.

The key parameters that affect the ICER the most are patient baseline characteristics, natural history, efficacy, cost, perspective chosen and time horizon. Safety and tolerability, discount rate and utility parameters have a marginal effect on the ICER. There is a higher degree of certainty in the rapidly evolving severe subgroup economic evaluation than in the evaluation of the sub optimally treated subgroup.

Despite every effort to source appropriate data for all components of the model, sufficient uncertainty exists in some of the input data for the sub optimally treated subgroup evaluation that the cost-effectiveness could be considered artificially pessimistic.

- The absence of natural history data in the sub optimally treated subgroup and the decision to use data from the intention-to-treat placebo arm of the phase III natalizumab registration study (AFFIRM)

(rather than data from the rapidly evolving severe subgroup) could be considered overly conservative.

The absence of specific efficacy data in the sub optimally treated subgroup and the assumption used to apply a relative risk of disability progression and relapse frequency from a broad relapsing remitting multiple sclerosis population from the intention-to-treat analysis in AFFIRM (rather than data from the rapidly evolving severe subgroup) could also be considered overly conservative.

Using the less conservative, but arguably more realistic assumption that the sub optimally treated subgroup is equivalent to the rapidly evolving severe subgroup in all aspects except for a previous decision to treat with a comparator disease modifying treatment, then the cost-effectiveness of natalizumab in the sub optimally treated subgroup would become very similar to that of the rapidly evolving severe subgroup (at £32.0K, £34.6K and £44.6K per QALY compared with interferon beta and glatiramer acetate and best supportive care respectively).

A new Markov model (based on the ScHARR model previously commissioned by NICE) was developed for the submission since there are no relevant published, economic evaluations in the literature.

This highly active relapsing remitting multiple sclerosis specific model adopted the reference case approach specified by NICE.

Natural history data was sourced from the well-recognised London Ontario dataset, combined with a new multi state model based on the placebo arm of the AFFIRM study.

Clinical effects were based on meta-analyses of relevant available data for both natalizumab and the comparators.

The utility of treatment was taken from the largest survey of utility and resources ever conducted in multiple sclerosis in the UK (UK multiple sclerosis Survey 2005), supplemented by analyses of data from AFFIRM and previously published sources.

The UK multiple sclerosis Survey 2005 provided resource consumption data and unit costs were sourced from recognised UK sources

All of the nine published flaws identified by Claxton of previous models submitted to NICE have been addressed within this model

Recognised experts in the economics of multiple sclerosis have critically appraised the methods and assumptions used in the model and confirmed that: it has high external validity compared with the previous model commissioned by NICE. In addition, the Scottish Medicines Consortium critical appraisal of the model concluded that, 'good internal and external validation information was provided'

Model validation showed that the model was able to reproduce very similar ICERs to the previous NICE model for interferon beta and glatiramer acetate compared with best supportive care. The ICERs we generate for interferon beta and glatiramer acetate respectively of £55.2k and £102.2k per QALY compare well with the reported ICERS of £42-72k and £98k per QALY respectively.

Natalizumab is a new class of drug for the treatment of highly active relapsing remitting multiple sclerosis (see sections 2 and 4)

The UK approved name for natalizumab is Tysabri®. Natalizumab received marketing authorisation on 27 June 2006.

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4 subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule 1, and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment 1. Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressing cell adhesion molecule 1. Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4 expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

Natalizumab is available in single vials of 300 mg concentrate for solution for infusion. Each vial is for single use only. Natalizumab is administered once every 4 weeks. The price per vial is £1130.

Natalizumab uptake at forecast levels represents a modest budget impact in England and Wales (see section 7)

The maximum forecast total incremental discounted cost of natalizumab in year 5 is £15.5 million.

Rapidly evolving severe:

The budget impact in the rapidly evolving severe subgroup is forecast to be £0.8 million in year 1, rising to £4.4 million in year 5.

Sub optimally treated:

The budget impact in the sub optimally treated subgroup is forecast to be £0.3 million in year 1, rising to £11.1 million in year 5.

Large cost offsets of approximately half the acquisition cost of natalizumab may be realised due to a reduction in use in interferon beta and glatiramer acetate.

The budget impact model does not include costs associated with disability progression and is likely overestimate the incremental cost of natalizumab introduction.

The forecast is based on Biogen Idec estimates of market penetration.

Changes made to model since previous version

The three potential errors identified by PENTAG were investigated and confirmed. In brief the corrections were:

- Correction to disability progression to EDSS 7 in RES subgroup
- Correction to discounting formula
- Correction to cost of relapse

During test 37 described below we also identified an incorrect formula (worksheet 'INPUT AEs', cell reference 'L12'). The corrected formula results in an inconsequential change to the ICERs of approximately -£3. The error was an overestimate of the number of people requiring NAB tests and has now been corrected.

The results presented in the addendum reflect the effect of these changes.

Note that the executive summary for section 6 has not been included since the text also appears in the main executive summary in section 1 (above).

5.8.3 Estimating transition probabilities in RES and SOT subgroups

(Updated Table 42)

Table 42 Median time to disability progression derived from MSM

	From EDSS 1 to EDSS 3	From EDSS 1 to EDSS 4	From EDSS 1 to EDSS 6	From EDSS 1 to EDSS 7	From EDSS 3 to EDSS 8
London Ontario Data	11-12 yrs	14-15 yrs	18-19 yrs	22-23 yrs	13-14 yrs
ITT population (AFFIRM)	3-4 yrs	6-7 yrs	10-11 yrs	14-15 yrs	16-17 yrs
RES subgroup (AFFIRM)	2-3 yrs	4-5 yrs	9-10 yrs	13-14 yrs	15-16 yrs

6.2.12.3 Validity

We report an additional verification check (number 37) to check for any formulae within the model that reference empty cells (see Table 81).

Table 81 Test conducted on model as part of the model verification and internal validation

Index	Test	Expected effect	Observed Effect	Action Taken
37	Replace all blank cells within active area of workbook with text string	No change to any results	As expected	None required

6.3 Results

6.3.1 Base-case analysis

6.3.1.1 What were the results of the base-case analysis?

The results of the base case analysis are presented in Table 83. The ICER for natalizumab compared with an active comparator in the RES subgroup is approximately £32-35K per QALY gained (approximately £45K compared with BSC). The equivalent result in the SOT subgroup is £44K - £45K for an active comparator.

Table 83 Results for base-case analysis over a 20-year time horizon

RES Subgroup					
Comparison	**Cost per patient (£K) (natalizumab)**	**QALYs per patient (natalizumab)**	**Cost per patient (£K) (comparator)**	**QALYs per patient (comparator)**	**Incremental cost per QALY gained (£K)**
NAT vs. IFN-beta	162.0	7.51	122.3	6.27	32.0
NAT vs. GA	162.0	7.51	110.0	6.01	34.6
NAT vs. BSC	162.0	7.51	84.7	5.78	44.6
SOT Subgroup					
Comparison	**Cost per patient (£K) (natalizumab)**	**QALYs per patient (natalizumab)**	**Cost per patient (£K) (comparator)**	**QALYs per patient (comparator)**	**Incremental cost per QALY gained (£K)**
NAT vs. IFN-beta	159.5	7.58	119.2	6.65	43.4
NAT vs. GA	159.5	7.58	106.2	6.38	44.3
NAT vs. BSC	159.5	7.58	79.2	6.15	56.1

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, NAT = natalizumab

Health and PSS perspective, costs and benefits discounted at 3.5%, 20-year time horizon. These results are based on mean values.

The absolute gain in QALYs between natalizumab and the comparators is substantial (> 1 QALY for 5/6 decision problems). The QALY gains in the RES subgroup are 1.73, 1.50 and 1.24 for natalizumab compared with BSC, GA and IFN-beta respectively. The equivalent QALY gains in the SOT subgroup are 1.43, 1.20 and 0.93 for natalizumab compared with BSC, GA and IFN-beta respectively.

The clear effect of natalizumab on other NHS and PSS costs is shown in Table 84. Cost savings in other NHS and PSS budgets offsets a large proportion of the treatment cost of natalizumab.

Table 84: Disaggregated discounted costs per patient from the base case over a 20-year time horizon

	SOT Subgroup			RES Subgroup		
Comparison	**Treatment costs (£K)**	**Other NHS & PSS costs (£K)**	**Total costs (£K)**	**Treatment costs (£K)**	**Other NHS & PSS costs (£K)**	**Total costs (£K)**
NAT	100.2	59.3	159.5	102.4	59.6	162.0
IFN-beta	50.8	68.4	119.2	48.8	73.5	122.3
GA	31.2	75.0	106.2	29.8	80.2	110.0
BSC	0.0	79.2	79.2	0.0	84.7	84.7

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, NAT = natalizumab

6.3.2 Subgroup analysis

6.3.2.1 What were the results of the subgroup analysis / analyses if conducted?

No additional subgroup analyses were conducted over and above the two licensed subgroups (RES and SOT).

6.3.3 Sensitivity analyses

Uncertainty is ubiquitous in all economic models. The impact of uncertainty on the estimates of incremental costs and QALYs has been assessed through a process of comprehensive sensitivity analysis.

One-/multi-way sensitivity analysis and probabilistic sensitivity analysis (PSA) have been undertaken for each of the 6 decision problems in order to elucidate the effect of key parameters on the ICER. The one-way and multi-way sensitivity analyses are presented in section 6.3.3.1 in Table 85. The PSAs are presented in section 6.3.3.2 as cost-effectiveness acceptability curves (CEAC) in Figure 16 to Figure 26. Scatter diagrams that plot the results of the PSA simulation on the cost-effectiveness plane are also shown.

6.3.3.1 What were the main findings of the univariate sensitivity analyses?

The results of the one-way and multi-way sensitivity analysis are reported in Table 85 as change in £'000 per QALY. The results for all 6 decision problems appear in 6 columns to the right of the table and are represented as the difference from the base case. In the discussion of the sensitivity analysis we present changes to the ICER in italics as *-£XX* for favourable changes and *+£XX* for unfavourable changes. Absolute results are presented in standard font. For example, the base case for natalizumab compared with IFN-beta in RES is £32 000; taking a societal perspective for the analysis would change the base case cost-effectiveness estimate by *-£20 600*, to £11 400 per QALY.

The parameters that have the greatest impact upon the ICER are the baseline characteristics of the model population, the natural history, the efficacy of the disease-modifying therapies, cost, the health economic perspective chosen and time horizon over which costs and outcomes are evaluated. Safety and tolerability, discount rate and utility parameters have only a marginal effect on the ICER. There is a greater degree of overall certainty surrounding the costs and effects of natalizumab in the RES subgroup economic evaluation than in the evaluation of the SOT subgroup.

The sensitivity analysis of baseline characteristics indicates that natalizumab appears to be

more cost-effective compared with all comparators in all decision problems in younger patients, although the effect of age on the ICER is marginal for patients up to 46 years old. The cost-effectiveness does not appear to be greatly altered by the initial severity of disability of patients in the RES subgroup although the influence of disability is slightly more pronounced in the SOT subgroup.

Safety and tolerability parameters have little impact on the ICERs for all comparisons in all decision problems.

The uncertainty in the natural history of HARRMS (or RRMS) has to our knowledge never been explored in depth in previous economic models. Varying censoring assumptions in the MSM had a marginal effect on the ICER of between *0K* and *+1.5K* (see scenarios 4.4 to 4.7). Treating a broad RRMS population (which is outside the license for natalizumab), applying only disability progression rates from the London Ontario dataset, results in a large unfavourable impact on the cost-effectiveness, confirming that natalizumab is most cost-effective within its licensed indications (see scenario 4.8).

The uncertainty in the effect of natalizumab and the comparators on relapse rate has a marginal effect on the ICERs (see scenarios 5.4a to 5.5b and 5.8a to 5.9b), although the impact of uncertainty in disability progression is more pronounced.

Discounting both costs and benefits under previously specified rates (i.e. costs at 6% and benefits at 1.5%) has a large favourable effect on the ICER (e.g. scenario 6.3 demonstrates that the ICER would be less than £25K for all active comparator RES subgroup decision problems had the previous rates been used, and as low as £22.6K for the comparison with IFN-beta).

Varying the assumptions related to utilities and disutilities had little effect on any ICER, except for uncertainty regarding caregiver disutility, which changed the ICER by between *-£2.7K* and *+£6.4K* per QALY.

Uncertainties in cost estimates have an impact on the ICER of between *-£15.5K* and *+£15.6K* in the SOT subgroup decision problems. The effect is less pronounced in the RES subgroup decision problems (*-£12.8K* to *+£11.2K*).

The chosen perspective for the economic evaluation has a considerable impact on the ICER, with broader governmental and societal perspectives changing the relative cost-effectiveness of natalizumab by as much as *-£8.5K* and *-£24.0K* respectively.

The ICERs are also sensitive to the time horizon chosen, with large improvements in the relative cost-effectiveness noted for natalizumab compared with all comparators as the horizon is extended. If costs and benefits were extended to 30 years for example, the ICER for natalizumab in the RES subgroup would reduce to between £25.3K per QALY (compared with GA) and £32.3K per QALY (compared with BSC). If the time horizon was extended to 50 years, as recommended by Richards et al, (29) the ICERs would become as low as £22.8K per QALY for the comparison with GA for the RES subgroup and £28.8K for the same comparison in the SOT subgroup.

Table 85 Results of the univariate sensitivity analysis

Scenario		Parameter	RES BSC (£K)	RES IFN-beta (£K)	RES GA (£K)	SOT BSC (£K)	SOT IFN-beta (£K)	SOT GA (£K)
		Base case	**44.6**	**32.0**	**34.6**	**56.1**	**43.4**	**44.3**
Baseline Characteristics	1.1	Mean age at baseline = -10 years	-0.9	-0.5	-0.7	-1.0	-0.6	-0.8
	1.2	Mean age at baseline = +10 years	2.3	1.3	1.8	2.6	1.4	2.0
	1.3	Mean age at baseline = +20 years	8.1	4.6	6.3	9.2	4.9	7.1
	2.1	EDSS at baseline = 0	-0.6	-0.8	-0.8	3.0	1.3	1.7
	2.2	EDSS at baseline = 1	-0.2	-0.3	-0.4	2.6	1.3	1.6
	2.3	EDSS at baseline = 2	2.4	1.4	1.7	3.7	2.1	2.5
	2.4	EDSS at baseline = 3	0.6	0.5	0.7	-1.2	-0.5	-0.5
	2.5	EDSS at baseline = 4	-3.4	-1.9	-2.2	-7.1	-4.0	-4.9
Safety & Tolerability	3.1	Natalizumab withdrawal rate = 50%	-1.0	-4.8	-3.3	-1.3	-5.9	-4.1
	3.2	Natalizumab withdrawal rate = -50%	1.2	4.1	3.1	1.6	4.9	3.9
	3.3	IFN-beta/GA withdrawal rate = +50%	0.0	2.4	1.4	0.0	2.9	1.8
	3.4	IFN-beta/GA withdrawal rate = -50%	0.0	-3.1	-1.7	0.0	-4.1	-2.2
	3.5	PML effect = worst case scenario	0.2	0.0	0.0	0.4	0.3	0.2
	3.6	NABs = 100% people tested	0.3	0.4	0.3	0.3	0.5	0.4
Natural History	4.1	Relapse rate	0.8	0.7	0.5	0.0	0.0	0.0
	4.2	Relapse duration +50%	-0.4	-0.3	-0.2	-0.3	-0.3	-0.2
	4.3	Relapse duration –50%	0.2	0.2	0.1	0.1	0.1	0.1
	4.4	Progression data from AFFIRM	0.7	0.4	0.5	1.5	0.8	1.0
	4.5	Progression data from AFFIRM	0.7	0.4	0.4	1.5	0.8	1.0
	4.6	Progression data from AFFIRM	0.9	0.6	0.6	1.0	0.6	0.7
	4.7	Progression data from AFFIRM	0.5	0.0	0.3	1.5	0.4	1.0
	4.8	Progression data from London Ontario data *	23.2	10.3	15.9	27.8	11.9	19.3
	4.9	No effect of tx. on transition from RRMS to SPMS	9.9	2.3	5.2	13.1	3.8	7.6
	4.10	Full effect of tx. on transition from RRMS to SPMS	-7.1	-2.1	-4.0	-9.5	-3.6	-5.9
Efficacy	5.1	Disease progression 12 week definition **	10.2	10.8	9.1	17.5	24.9	17.1
	5.2a	NAT effectiveness (progression) lower SE (SOT)	-	-	-	10.6	13.9	10.1
	5.2b	NAT effectiveness (progression) upper SE (SOT)	-	-	-	-7.0	-7.5	-6.2
	5.3a	NAT effectiveness (progression) lower SE (RES)	17.7	20.6	16.3	-	-	-
	5.3b	NAT effectiveness (progression) upper SE (RES)	-7.2	-6.4	-6.0	-	-	-
	5.4a	NAT effectiveness (relapse) lower SE (SOT)	-	-	-	0.3	0.3	0.3
	5.4b	NAT effectiveness (relapse) upper SE (SOT)	-	-	-	-0.2	-0.3	-0.2
	5.5a	NAT effectiveness (relapse) lower SE (RES)	0.2	0.2	0.2	-	-	-
	5.5b	NAT effectiveness (relapse) upper SE (RES)	-0.2	-0.2	-0.1	-	-	-
	5.6a	IFN-beta effectiveness (progression) lower SE	-	-5.5	-	-	-9.4	-
	5.6b	IFN-beta effectiveness (progression) upper SE	-	7.3	-	-	14.4	-
	5.7a	GA effectiveness (progression) lower SE ***	-	-	-6.5	-	-	-9.8
	5.7b	GA effectiveness (progression) upper SE	-	-	26.8	-	-	53.1
	5.8a	IFN-beta effectiveness (relapse) lower SE	-	-0.2	-	-	-0.1	-
	5.8b	IFN-beta effectiveness (relapse) upper SE	-	0.2	-	-	0.1	-
	5.9a	GA effectiveness (relapse) lower SE	-	-	-0.7	-	-	-0.4
	5.9b	GA effectiveness (relapse) upper SE	-	-	0.5	-	-	0.3
	5.10	GA progression including Bornstien 1987	-	-	16.5	-	-	29.9
Disc	6.1	Costs = 6%	-4.8	-4.0	-4.0	-6.4	-5.6	-5.3
	6.2	Benefits = 1.5%	-9.3	-6.2	-7.1	-11.9	-8.2	-9.2
	6.3	Costs = 6% and benefits = 1.5%	-13.2	-9.4	-10.3	-16.9	-12.7	-13.4
Utility	7.1a	Utility by EDSS – Upper 95% limit	12.0	5.4	8.8	16.8	9.5	9.9
	7.1b	Utility by EDSS – Lower 95% limit	-7.8	-4.3	-5.9	-10.7	-7.1	-8.1
	7.2	No variation in relapse effect by EDSS	-0.5	-0.2	-0.3	-0.3	-0.1	-0.2
	7.3a	Disutility of adverse events – Upper 95% limit	0.3	2.9	0.4	0.6	7.9	0.9
	7.3b	Disutility of adverse events – Lower 95% limit	-1.0	-5.3	-2.2	-1.5	-7.3	-3.7
	7.4	Literature derived relapse disutility	-1.2	-0.7	-0.8	-0.8	-0.5	-0.6
	7.5	Disutility of AEs for natalizumab = half	0.0	0.0	0.0	0.0	0.0	0.0
	7.6	Disutility of AEs for natalizumab = double	0.0	0.0	0.0	0.0	0.1	0.0
	7.7	Disutility of caregivers = +50%	-2.2	-1.2	-1.6	-2.7	-1.5	-2.0
	7.8	Disutility of caregivers = + 0	5.2	2.8	3.8	6.4	3.3	4.7
Cost	8.1a	Costs of resources and IFN-beta/GA – Upper 95% limit	3.2	7.9	11.2	3.6	15.6	14.0
	8.1b	Costs of resources and IFN-beta/GA – Lower 95% limit	-3.5	-12.8	-12.6	-3.9	-14.3	-15.5
Prsp	9.1	Societal perspective	-22.9	-20.6	-23.4	-23.3	-19.8	-24.0
	9.2	Government costs perspective	-8.5	-6.9	-8.1	-8.3	-6.2	-8.0
Time	10.1	10 years	53.3	23.2	37.6	66.9	26.4	46.4
	10.2	30 years	-12.3	-7.4	-9.3	-15.6	-9.2	-11.9
	10.3	40 years	-15.2	-9.4	-11.6	-19.7	-12.1	-15.1
	10.4	50 years	-15.6	-9.6	-11.8	-20.3	-12.6	-15.5

* Patients in EDSS 0 added to EDSS 1 as London Ontario dataset does not include progression to or from EDSS 0,
** Only efficacy for natalizumab changed

*** The relative risk is capped at 1.0 for GA, despite the 95% CI resulting in 1.11.

- = no sensitivity analysis possible, AE = adverse event, IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, NAT = natalizumab, NAB = Neutralising Antibody, PML = Progressive Multifocal Leukoencephalopathy, RES = rapidly evolving severe RRMS, RRMS = relapsing remitting multiple sclerosis, SOT = sub optimal treatment RRMS.

We also present two scenarios that do not appear in Table 85 to further investigate the uncertainty in the SOT subgroup.

Firstly, we explore the uncertainty in the rate of disability progression in the SOT subgroup by applying a more rapid rate of disability progression, which is in line with the estimated natural history of the RES subgroup. If this assumption is correct, it would be plausible that the underlying effect of natalizumab on disability progression would be in line with the efficacy observed in the RES subgroup.

Secondly, we explore alternative efficacy assumptions for IFN-beta and GA in the SOT subgroup, since there is very limited evidence for the effect of either comparator in this subgroup.

Uncertainty in progression rate and natalizumab efficacy in the SOT Subgroup

In section 6.2.11.1 we suggested that it is plausible that the SOT subgroup merely represent the RES subgroup at a later point in time, after they have experienced suboptimal treatment with IFN-beta or GA. Table 86 presents the effect of altering the efficacy and disability progression rates to those of the RES subgroup and assuming that the population is five years older (at 41 years). Altering individual assumptions, results in a more favourable ICER. Recalculation of the ICER applying the RES disability progression rates and efficacy to the SOT population gives cost effectiveness values of £32.0K, £34.6K, and £44.6K per QALY for comparison with IFN-beta, GA and BSC respectively.

Table 86 Exploration of the uncertainty of progression and efficacy rates in the SOT subgroup

	RES subgroup efficacy		RES subgroup progression rates		RES subgroup efficacy + progression rates	
	ICER (£K)	Change from base case (£K)	ICER (£K)	Change from base case (£K)	ICER (£K)	Change from base case (£K)
IFN-beta	33.0	-10.9	43.4	-0.5	32.6	-11.4
GA	35.9	-9.3	44.5	-0.7	35.3	-9.9

IFN-beta = Interferon beta, GA = glatiramer acetate; base-case refers to base-case with initial average age of cohort is greater by 5 years (i.e. base case for IFN-beta = £44.0K; for GA = £45.1K)

Effect of alternative efficacy assumptions for comparators

The effect of increased relative risks for disability progression for IFN-beta and GA in this subgroup is explored in Table 87. A reduced efficacy assumption was not reported in the base case for the SOT subgroup, but is plausible based on the findings from the QUASIMS study, where the effect of switching between current DMTs failed to offer additional efficacy. (75) Reducing the effect on disability progression of each active comparator changes the ICER by up to *-£20.7K*.

Table 87 Impact of reduction in efficacy of IFN-beta and GA on the ICER

	Relative risk of progression	ICER £K	Change from base case (£K)
IFN-beta	0.7 *	43.4	-
	0.8	33.2	-10.2
	0.9	26.9	-16.5
	1.0	22.7	-20.7
GA	0.88 *	44.3	-
	0.9	42.3	-2.0
	1.0	34.5	-9.8

* base case. IFN-beta = interferon beta, GA = glatiramer acetate.

6.3.3.2 What were the main findings of the PSA?

The results from the PSA analysis are presented in this sub-section. The results shown are the cost-effectiveness (CE) planes and cost-effectiveness acceptability curves (CEAC) for the 6 decision problems.

- RES subgroup comparisons
  - Natalizumab vs. IFN-beta (page 17)
  - Natalizumab vs. GA (page 18)
  - Natalizumab vs. BSC (page 19)
- SOT subgroup comparisons
  - Natalizumab vs. IFN-beta (page 20)
  - Natalizumab vs. GA (page 21)
  - Natalizumab vs. BSC (page 22)

Table 88 contains a summary of the results from the CEACs generated, giving the probability of cost-effectiveness at different willingness-to-pay thresholds for the decision problems using a NHS & PSS perspective. Unlike any other medical technology in England and Wales, an acceptable cost-effectiveness threshold has been established for disease modifying treatments (DMT) for multiple sclerosis (MS) of £36 000 per quality adjusted life year (QALY) gained. (51) Table 88 includes an estimate of the probability of cost-effectiveness at this threshold and also at thresholds of £30 000 and £40 000.

Table 88: Probability of acceptability at different threshold values for the six baseline scenarios (NHS & PSS perspective)

Comparison		Willingness to pay threshold		
		£30 000	**£36 000**	**£40 000**
RES subgroup	BSC	3%	18%	31%
	IFN-beta	42%	59%	66%
	GA	32%	48%	56%
SOT subgroup	BSC	0%	1%	3%
	IFN-beta	18%	32%	43%
	GA	15%	29%	38%

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, RES = rapidly evolving severe subgroup, SOT = sub optimally treated subgroup

We also present summaries of the probability of acceptability using societal and governmental perspectives in Table 89 and Table 90. No CEACs or CE planes are shown for these perspectives.

Table 89: Probability of acceptability at different threshold values for the six baseline scenarios (societal perspective)

Comparison		Willingness to pay threshold		
		£30 000	£36 000	£40 000
RES subgroup	BSC	71%	80%	84%
	IFN-beta	79%	83%	85%
	GA	75%	80%	82%
SOT subgroup	BSC	38%	61%	72%
	IFN-beta	63%	71%	75%
	GA	63%	69%	73%

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, RES = rapidly evolving severe subgroup, SOT = sub optimally treated subgroup

There is greater than a 70% probability of natalizumab being cost-effective in all RES subgroup decision problems, if society is willing to pay £30 000 per QALY gained, generated by the PSA from a societal perspective.

Results for the SOT subgroup societal perspective analysis also indicate a considerably greater probability of natalizumab being cost-effective compared with a health and PSS perspective, if society is willing to pay £30 000 per QALY gained.

Table 90: Probability of acceptability at different threshold values for the six baseline scenarios (governmental perspective)

Comparison		Willingness to pay threshold		
		£30 000	£36 000	£40 000
RES subgroup	BSC	25%	48%	61%
	IFN-beta	61%	71%	76%
	GA	53%	64%	70%
SOT subgroup	BSC	1%	9%	20%
	IFN-beta	34%	48%	56%
	GA	34%	47%	55%

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, RES = rapidly evolving severe subgroup, SOT = sub optimally treated subgroup

The PSA results from a governmental perspective follow a similar trend. A probability in excess of 53% of natalizumab being cost-effective is noted in active comparator RES subgroup decision problems if society is willing to pay £30 000 per QALY gained.

Figure 15 C-E plane for natalizumab vs. IFN-beta for RES subgroup

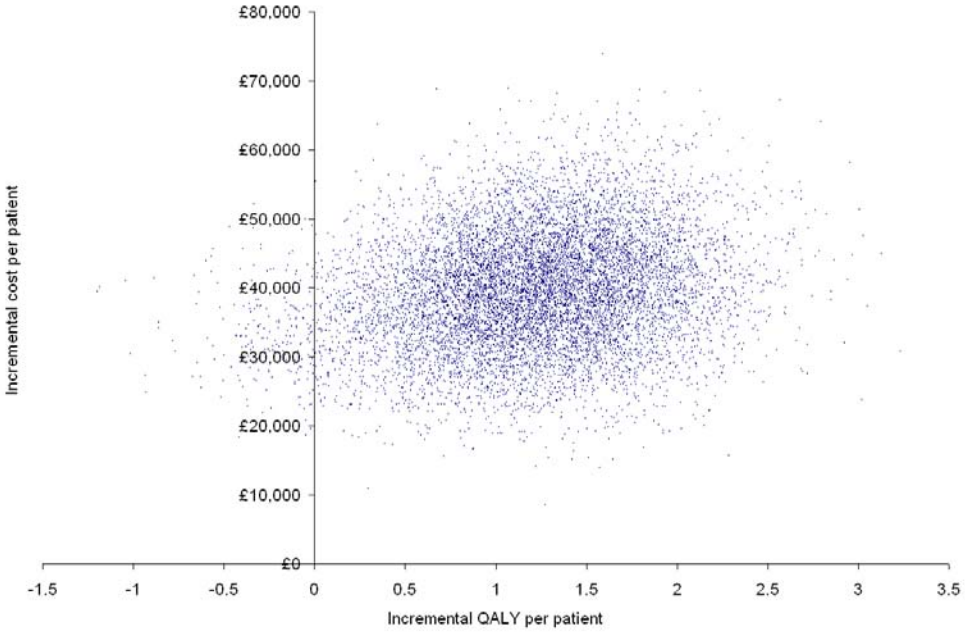

Figure 16 CEAC for natalizumab vs. IFN-beta for RES subgroup

Figure 17 C-E plane for natalizumab vs. GA for RES subgroup

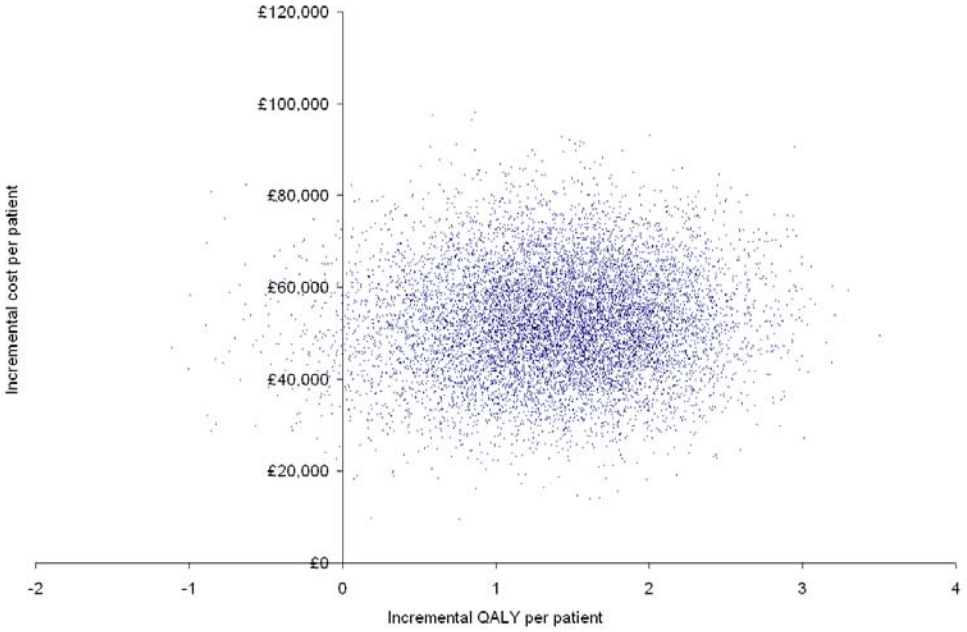

Figure 18 CEAC for natalizumab vs. GA for RES subgroup

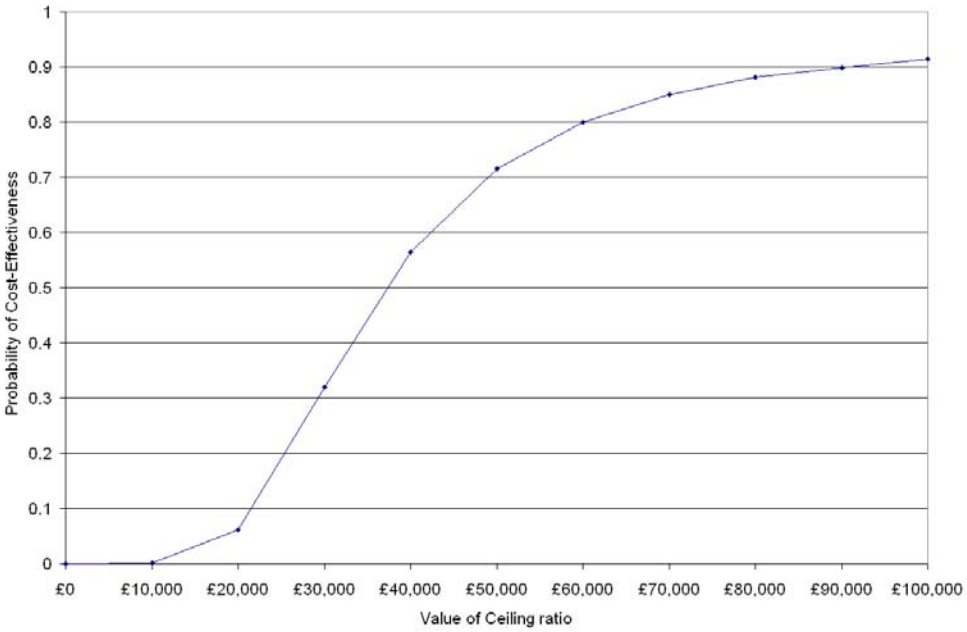

Figure 19 C-E plane for natalizumab vs. BSC for RES subgroup

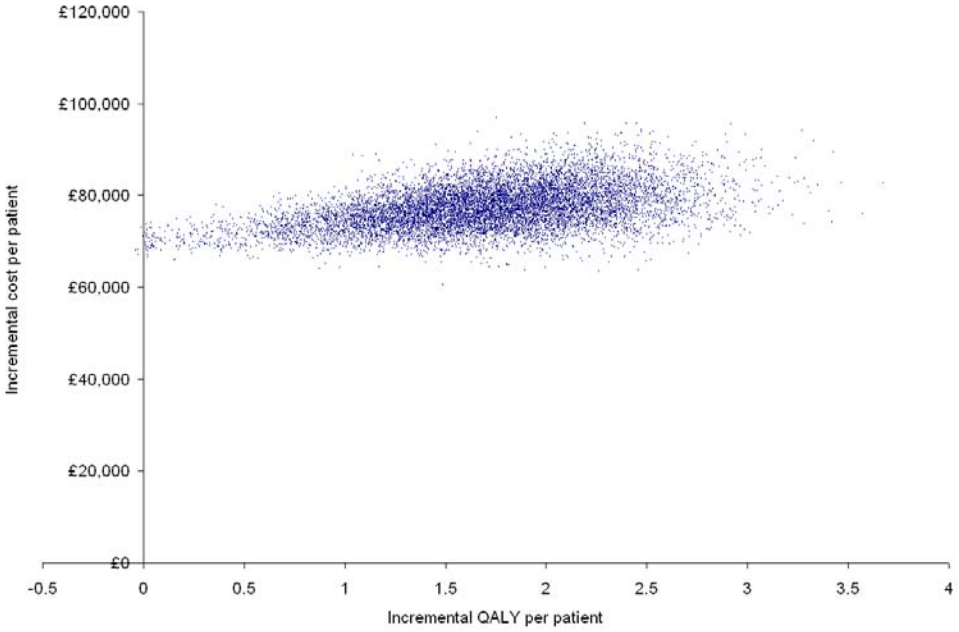

Figure 20 CEAC for natalizumab vs. BSC for RES subgroup

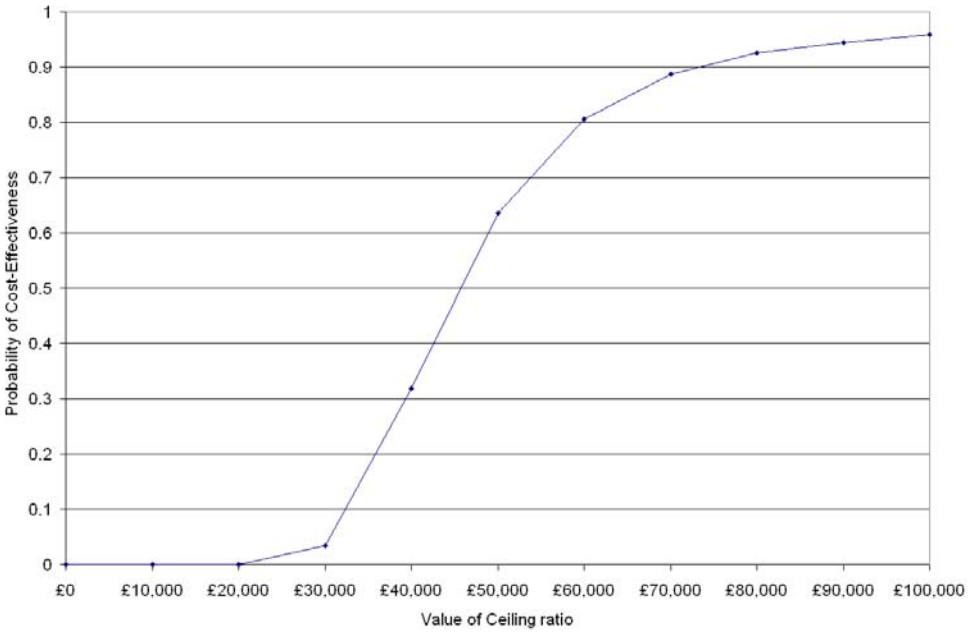

Figure 21 C-E plane for natalizumab vs. IFN-beta for SOT subgroup

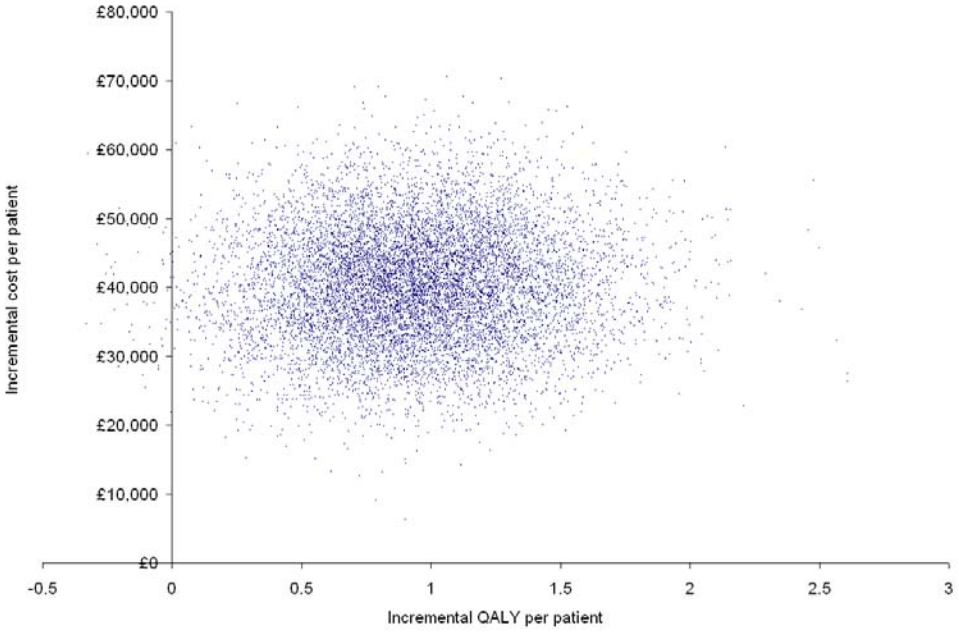

Figure 22 CEAC for natalizumab vs. IFN-beta for SOT subgroup

Figure 23 C-E plane for natalizumab vs. GA for SOT subgroup

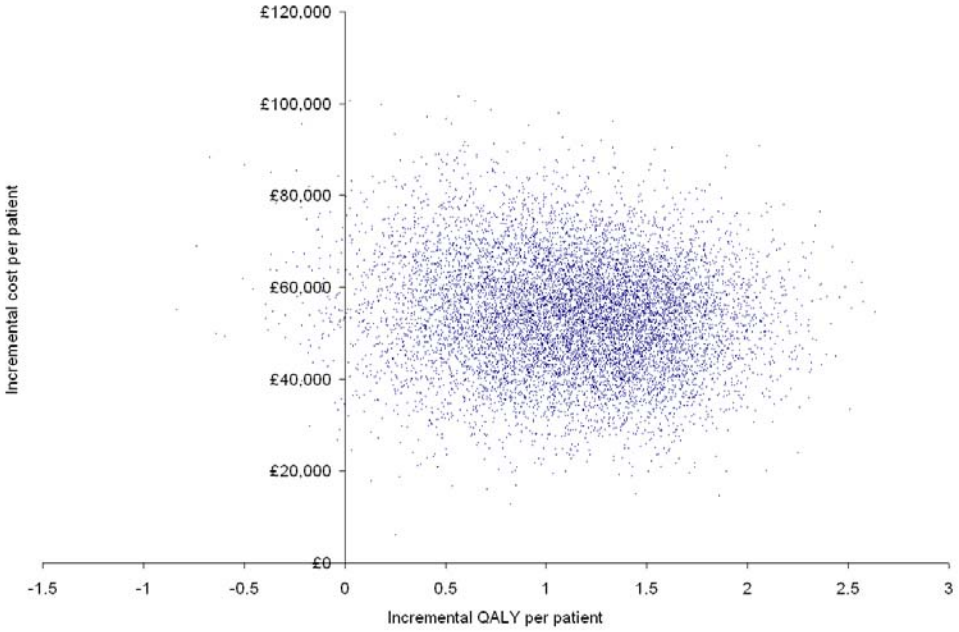

Figure 24 CEAC for natalizumab vs. GA for SOT subgroup

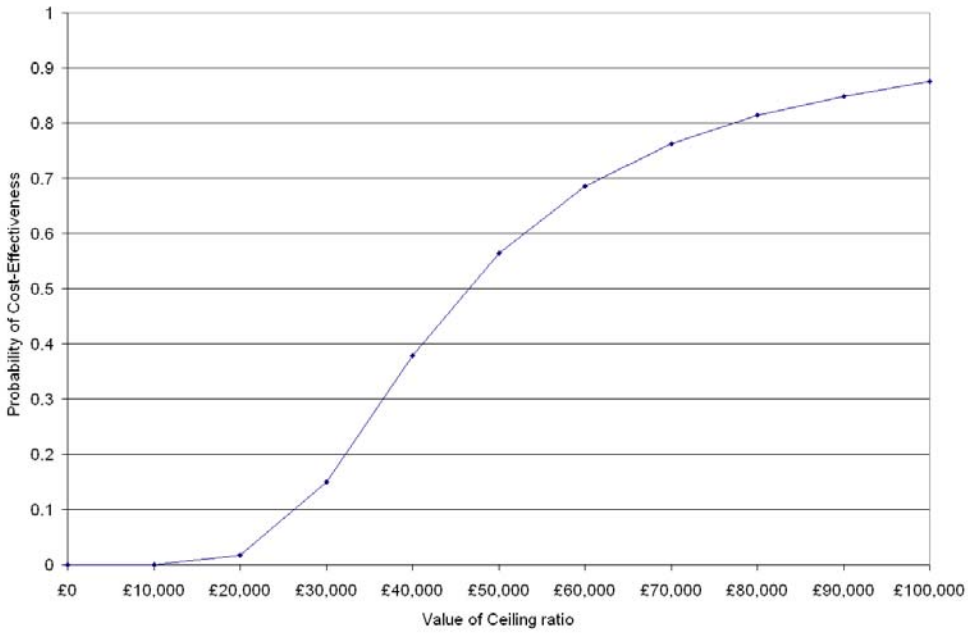

Figure 25 C-E plane for natalizumab vs. BSC for SOT subgroup

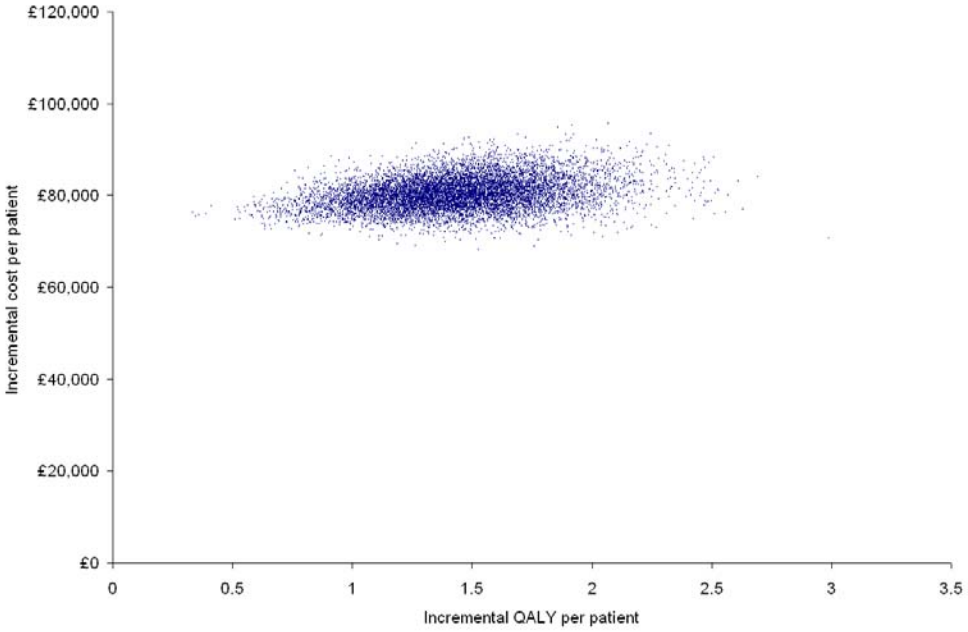

Figure 26 CEAC for natalizumab vs. BSC for SOT subgroup

6.3.4 Interpretation of economic evidence

6.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

To our knowledge, no previous economic evaluations within the HARRMS population have been published, which makes it impossible to directly compare the results of this evaluation with an alternative analysis. However, we concluded in the sub-section entitled, '4. Can the model predict the findings of other studies', on page 153 that a re-parameterised model was able to generate similar results to the ScHARR model previously commissioned by NICE:

> The ICERs we generate for IFN-beta of £55.2K per QALY and for GA of £102.2K per QALY compare well with the values quoted by Tappenden 2001 of £42-72K per QALY for IFN-beta and £98K per QALY for GA (vs. best supportive care).

This finding gives additional credence to the results for the HARRMS evaluations presented in this submission.