NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL-

Dimethyl fumarate
for the treatment of adult patients with relapsing remitting multiple sclerosis

July 2013

Biogen Idec Clarifications and Responses to NICE

(Full response document)

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Executive summary

Overview

Biogen Idec would like to thank the National Institute for Clinical Excellence (NICE) and the Evidence Review Group (ERG) at the University of York for its review of the submission for dimethyl fumarate for the treatment of adult patients with relapsing remitting multiple sclerosis. In this document Biogen Idec provides NICE and the ERG with clarifications as requested. In particular, we provide:

1. An item by item response to clarification questions asked by NICE/ Evidence Review Group (ERG). These responses are based on the originally submitted economic model and are presented in sections A and B according to NICE's question numbering;

2. Revised annual discontinuation risk table presented in the submission, shown in section A8

The revised results presented in this document should be considered as a replacement to the results presented in and with the original submission.

Section summary

For section A (clarification of the effectiveness data), five of the questions were highlighted as priorities by NICE/ERG. These included:

1. List of studies excluded from Mixed Treatment Comparison (MTC) analysis (A5);
2. Explanation on the adjustment of G matrix (A6);
3. Explanation of SAS code used in MTC and use of either risk or hazard ratio in the model (A7);
4. Expanded explanation on the difference in the results of the analysis with and without the use of covariates. In addition, MTC results for comparison of the included interventions relative to placebo were added and data for annual discontinuation risk used in the model were revised (A8);
5. Explanation on the specification of the covariates used in the MTC model (A9).

For section B (clarification of the cost-effectiveness data), five of the questions were highlighted as priorities by NICE/ERG. These were:

1. provide the model code and the model output for the seemingly unrelated regressions (SUR) (B5)
2. Clarify the reference for resource use (B6)
3. State how the costs were adjusted to be consistent with a 12 month cycle (B7);
4. Present mean incremental cost-effectiveness ratios (ICERs) from the PSA using 10,000 iterations and explain any significant differences between the PSA and the deterministic results (B8);
5. Confirm what distributional assumptions were made for the probabilistic sensitivity analysis (PSA) (B9).

Section A: Clarifications of the effectiveness data

Search strategy

A1. On page 37 of the manufacturer's submission (MS) and Appendix 2 (page 291 of the MS) it lists the databases searched, please state the service providers used for each database.

Biogen Idec response:
A list of service providers used for each database is provided in Table 1.

Table 1: Databases examined for the systematic review and the service provider used

Data source	Service Provider
MEDLINE®	Embase.com; http://www.embase.com/
Embase®	
MEDLINE® In-process	PubMed®(in-process citations); http://www.ncbi.nlm.nih.gov/sites/entrez
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane library; http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html

Embase®: Excerpta Medica Database; MEDLINE®: Medical Literature Analysis and Retrieval System Online

A2. Section 10.2.5 (page 294 of the MS) summarises the additional searches carried out by the manufacturer for the evidence presented in Section 6.1 of the MS. Please provide details of search terms (if any) used for searching Clinicaltrials.gov, metaRegister of Controlled Trials, and the NICE website.

Biogen Idec response:
The keyword 'Multiple Sclerosis' was used to search trials in progress in both clinicaltrials.gov and metaRegister of Controlled Trials. The clinicaltrials.gov search was further restricted using the following filters available on the website:

- Search by Topic: Condition - Multiple sclerosis;
- Study type – Interventional

The search terms and results are summarised in Table 2.

Table 2: Trials in progress search (searches conducted on 05 April 2012)

#	Search terms	Number of results
	metaRegister search run	
1	(Interferon or avonex or rebif or betaferon or betaseron or 'glatiramer acetate' or copaxone or BG00012)	105
2	'multiple sclerosis'	90
3	#1 AND #2	9
	clinicaltrials.gov search	
1	Avonex [ALL-FIELDS] OR Rebif [ALL-FIELDS] OR interferon beta-1a [ALL-FIELDS] OR Betaseron [ALL-FIELDS] OR Betaferon [ALL-FIELDS] OR interferon beta-1b [ALL-FIELDS] OR Glatiramer acetate [ALL-FIELDS] OR Copaxone [ALL-FIELDS] OR fingolimod [ALL-FIELDS] OR natalizumab [ALL-FIELDS] OR tysabri [ALL-FIELDS] OR BG [ALL-FIELDS]	1662
2	multiple sclerosis [ALL-FIELDS]	861
3	#1 AND #2	359

A3. Page 37 of the MS suggests that a number of conference proceedings were searched for the evidence presented in Section 6.1 of the MS. Please clarify how each of the named conferences were searched. Please confirm whether they were searched using a website – (if so, what search terms were used), or hand searched as paper copies (if so, what volumes were used).

Biogen Idec response:
The following conferences were searched via their websites using a combination of disease and treatment terms (Table 3):

Table 3: Databases examined for the systematic review and the service provider used

Conference	Dates	Website
European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS)	2009 - 2012	http://www.ectrims.eu/
Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)	2009 - 2012	http://annualmeeting.mscare.org/
American Academy of Neurology (AAN)	2009 - 2012	http://www.aan.com/
American Neurological Association (ANA)	2009 - 2012	http://www.aneuroa.org/i4a/pages/index.cfm?pageid=1
European Federation of Neurological Societies (EFNS)	2009 - 2012	http://www.efns.org/Congresses-Meetings.8.0.html

The following keywords were used to search each website:

- Disease terms: RRMS, RMS, MS, multiple sclerosis
- Intervention terms: interferon, avonex, rebif, beta?eron, extavia, glatiramer, copaxone, fingolimod, FTY720, gilenya, natalizumab, tysabri, bg00012, dimethyl fumarate, teriflunomide, aubagio

A4. Section 6.8 (and Appendix 6, page 302 of the MS) provides details of the additional searches carried out for non-RCT evidence. Please state how each of the named conferences were searched. Please confirm whether they were searched using a website – (if so, what search terms were used), or hand searched as paper copies (if so, what volumes were used).

Biogen Idec response:
The searches were conducted on 24th December 2012 via OVID using the search strings in Table 4 from 2010–2012.

Table 4: Search strings for conference proceedings

#	Searches	Results
1	("relapsing remitting multiple sclerosis" or "RRMS").af.	4132
2	((secondary or chronic) adj progressive multiple sclerosis).af.	815
3	1 or 2	4771
4	("American Academy of Neurology" or "AAN").cf,cg,so,in.	3249
5	neurology.jn.	36918
6	(conference or conference proceeding or conference proceeding article or conference proceeding conference paper or conference proceeding editorial or conference proceeding note or "conference proceeding review" or journal conference abstract or journal conference paper or "journal conference review" or proceeding).pt.	1629860
7	5 and 6	2944

#	Searches	Results
8	4 or 7	3711
9	("Americas Committee for Treatment and Research in Multiple Sclerosis" or "ACTRIMS").cg,cf,in,so.	76
10	("European Committee for Treatment and Research in Multiple Sclerosis" or "ECTRIMS").cg,cf,in,so.	1870
11	"Multiple Sclerosis".jn.	5443
12	6 and 11	3326
13	9 or 10 or 12	3432
14	"EUROPEAN CHARCOT FOUNDATION".af.	68
15	8 or 13 or 14	7203
16	3 and 15	852
17	limit 16 to yr="2010 -Current"	627

Mixed Treatment Comparison

A5. Priority Question: Please provide a list of studies excluded from the review of RCTs for the mixed treatment comparison (MTC) together with reasons for exclusion.

Biogen Idec response:
A total of seven studies were excluded from MTC analysis. A list of these excluded studies together with the reason for exclusion for each study is shown in Table 5.

Table 5: List of studies excluded from MTC analysis

Study	Reason for exclusion	Title	Authors	Publication date	Journal name	Volume (Issue)	Pages
CARE-MS I trial	Alemtuzumab-not an approved multiple sclerosis treatment	Alemtuzumab for relapsing-remitting multiple sclerosis: CARE-MS I baseline demographics and disease characteristics	Havrdova,E.; Coles,A.; Cohen,J.; Confavreaux,C.; Fox,E.; Hartung,H.-P.; Selmaj,K.; Weiner,H.; Lake,S.; Moran,S.; Margolin,D.; Compston,A.	2010	Multiple Sclerosis	16 (10)	S151
CARE-MS II trial	Alemtuzumab-not an approved MS treatment	Efficacy of alemtuzumab in relapsing-remitting multiple sclerosis patients who relapsed on prior therapy (CARE-MS-II): subgroup analyses by previous DMT use	Freedman,M.S.; Arnold,D.L.; Cohen,J.; Confavreux,C.; Fox,E.J.; Hartung,H.-P.; Havrdova,E.; Selmaj,K.; Weiner,H.; Miller,T.; Twyman,C.L.; Vallee,M.; Margolin,D.H.; Panzara,M.; Compston,D.A.S.	2012	ECTRIMS		

Study	Reason for exclusion	Title	Authors	Publication date	Journal name	Volume (Issue)	Pages
CAMMS223 trial	Alemtuzumab-not an approved MS treatment	Alemtuzumab vs. interferon beta-1a in early multiple sclerosis	Coles,A.J.; Compston,D.A.S.; Selmaj,K.W.; Lake,S.L.; Moran,S.; Margolin,D.H.; Norris,K.; Tandon,P.K.	2008	New England Journal of Medicine	359 (17)	1786-1801
REMAIN trial	Comparator not of interest (No therapy was compared to interferon)	Treatment de-escalation after mitoxantrone therapy: First results of a phase IV, multicentre, open-label, randomised study of subcutaneous interferon beta-1a, 44 mcg three times weekly, in patients with relapsing multiple sclerosis	Gold,R.; Heidenreich,F.; Rieckmann,P.; Sailer,M.; Zettl,U.; Zessack,N.	2010	Multiple Sclerosis	16 (10)	S308
EUSPMS trial	Disease not within scope	Final analysis of the European multicenter trial on IFN(beta)-1b in secondary-progressive MS	Kappos,L.; Polman,C.; Pozzilli,C.; Thompson,A.; Beckmann,K.; Dahlke,F.	2001	Neurology	57 (11)	1969-1975
SPECTRIMS trial	Disease not within scope	Randomised controlled trial of interferon-beta-1a in secondary progressive MS: Clinical results	Francis,G.	2001	Neurology	56 (11)	1496-1504
Kappos 2008	Unlicensed dose of BG00012	Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study	Kappos,L.; Gold,R.; Miller,D.H.; MacManus,D.G.; Havrdova,E.; Limmroth,V.; Polman,C.H.; Schmierer,K.; Yousry,T.A.; Yang,M.; Eraksoy,M.; Meluzinova,E.; Rektor,I.; Dawson,K.T.; Sandrock,A.W.; O`Neill,G.N.	2008	The Lancet	372 (9648)	1463-1472

Abbreviations: DMT, Disease Modifying Therapy; MTC, Mixed Treatment Comparison

A6. Priority Question: The description for the SAS code for the MTCs with binomial outcomes, page 343 of the MS, states that adjustment may have been made for the G matrix. Please clarify if this was done for every analysis with a binomial outcome. If not, please clarify for which analyses it was done.

Biogen Idec response:
Adjustment for G-matrix in SAS code was only conducted for outcomes where the G-matrix was not positive definite; namely, discontinuations due to death and AV block.

A7. Priority Question: The outcomes of the MTC and the effectiveness data use in the economic model are not clear. Specifically:

a) The use of the logit function in the SAS code for the MTCs with binomial outcomes, pages 342 to 343 of the MS, suggests that the results of the analyses would be odds ratios. The results of the MTCs, pages 139 to 152 of the MS, indicate that a risk ratio was the outcome for binomial outcomes. Please state:

i. what the outcomes of the binomial analyses were (odds ratios/risk ratios); and,

ii. if relative risk outcomes were derived, please explain how they were derived.

Biogen Idec response:
Risk ratios were estimated for the binomial outcomes. The model has been incorrectly specified in the text on pages 342 to 343; please see the revised model for PROC GLIMMIX:

The indicative SAS code (PROC GLIMMIX) suitable for binomial MTC is provided below (note, r = number of patients with the outcome and n = total number of patients in that study or treatment arm).

```
proc glimmix data = Relapse_data;

class treatment study;

model r/n = treatment / noint link = log solution cl;

random intercept / subject = study solution;

estimate "trt-a vs trt-b" trt 1 – 1 0 0 … / exp cl;
```

Please note that the analyses were re-run with hazard ratios (see A7b, below) for disability progression.

a) The effectiveness outcome for disability progression used in the economic model is not clear. Firstly, the transition probabilities are converted to rates and adjusted by applying a disability progression rate relative to placebo. This rate ratio appears to be the same as the risk ratio in Table 50, page 180 of the MS. Secondly, in Section 7.6.3, page 216 of the MS, it states that hazard ratios were used for disability progression. Please explain:

i. whether you intended to use rate ratios or risk ratios in the model;

ii. if you intended to use risk ratios, what the rationale was (as opposed to using a hazard ratio);

iii. if you intended to use rate ratios, how these were derived; and

iv. if the model has been incorrectly specified, please correct it and report the corrected results.

Biogen Idec response:
Confirmed disability progression naturally lends itself to a survival analysis-type endpoint; however, after exploring the evidence base, we determined that the most consistent reporting of this data was estimated proportion of patients with a confirmed disability progression. Thus, we elected to analyse confirmed disability progression as a binomial outcome in order to maximise the number of contributing trials within the analysis using risk ratios as effect estimates.

However, following comments from NICE it has been determined that risk ratio is not the most suitable output for confirmed disability progression. A revised model has been performed using PROC GLIMMIX to produce hazard ratios.

The indicative SAS code (PROC GLIMMIX) suitable for binomial MTC for hazards ratios is provided below**:**

```
proc glimmix data =progression_free;

class treatment Study;

y = progression_free/N;

x = 0.5*(log(1/y));

model x = treatment / noint link = log solution cl;

random intercept / subject=Study solution;
```

The revised base case results from the model are detailed below, with reference to the corresponding section in the submission document. Corresponding table numbers from the submission document are also given. The revised hazard ratio values are shown in Table 37.

b) (NEW QUESTION FROM NICE ON 3RD JULY) We appreciate that in undertaking a re-analysis for disability progression using hazard ratios the manufacturer have provided several amended tables. However there are some tables/figure relevant to our appraisal that have not been resubmitted which are affected by the new analysis:

- the new network figures for disability progression (the manufacturer's comments suggest that some trials may have been lost from the network as a result of using HR.
- the HR for disability progression for dimethyl fumarate versus the active comparators (i.e. figures 28 and 29 in the submission)

Biogen Idec response:

Due to change in HR in the MTC analysis of the disability progression, the following tables and figures were revised (figure 1, figure 2, figure 3, figure 4, figure 5, figure 6, table 1, table 6).

Figure 1: Results of the MTC for confirmed disability progression sustained for 3 months (Figure 28 in the submission document)

HR <1 indicates better efficacy of intervention; Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; HR, Hazard Ratio; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; tid, three times daily; tiw, three times weekly

Figure 2: Results of the MTC for confirmed disability progression sustained for 6 months (Figure 29 in the submission document)

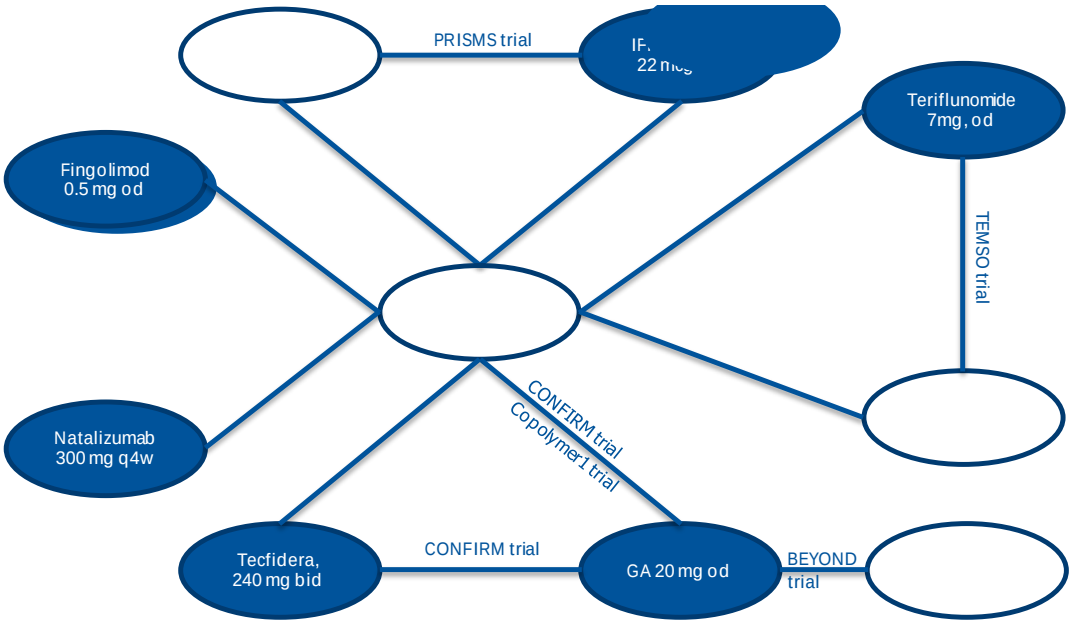
HR <1 indicates better efficacy of intervention; Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; HR, Hazard Ratio; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; tid, three times daily; tiw, three times weekly

Table 6: List of outcomes and analytic approach (Table 33 in the submission document)

Outcomes	Type of data	Information needed	Output statistics of mixed treatment comparison
Efficacy outcomes			
ARR	Poisson	Total number of relapses, person-years	ARR ratio, 95% CI of estimate
Annualised steroid-treated relapse rate			
Change in EDSS score from baseline at 24 months	Continuous	Evaluable N, Mean/median and SD/SE/CI/p value	Median absolute difference, 95% CI of estimate
Confirmed disability progression sustained for 3 months at 24 months	Binomial	Number of patients free from disability (n) ITT Number (N)	HR, 95% CI of estimate
Confirmed disability progression sustained for 6 months at 24 months			
Proportion of patients with relapse at 12 and 24 months		Number of patients with outcome (n) ITT Number (N)	RR, 95% CI of estimate
Proportion of patients relapse free at 12 and 24 months			
Safety outcomes			
Any AEs	Binomial	Number of patients with outcome (n) evaluable/ITT number (N)	HR, 95% CI of estimate
Any SAEs			
Any GI disorder			
Abdominal pain			
Upper abdominal pain			
ALT increase			
Arthralgia			
Back pain			
Depression			
Diarrhoea			
Fatigue			
Flu-like symptoms			
Flushing			
Influenza			
Headache			
Leukopenia			
Nausea			
Pain in extremity			
Pruritus			
Rash			
Urinary tract infection			
Tolerability outcomes			
Discontinuation due to any cause	Binomial	Number of patients with	RR, 95% CI of estimate

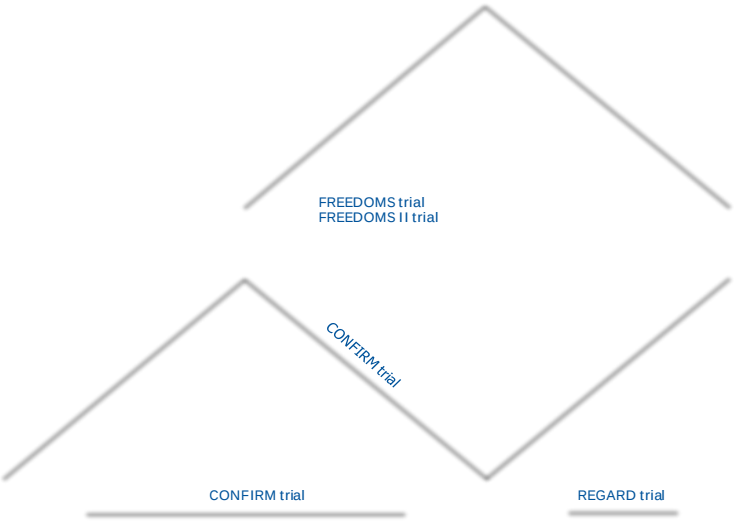
Outcomes	Type of data	Information needed	Output statistics of mixed treatment comparison
Discontinuation due to adverse events		outcome (n) ITT number (N)	
Discontinuation due to death			

Figure 3: Network diagram of trials providing data for analyses of confirmed disability progression sustained for 3 months (Figure 56 in the submission document)



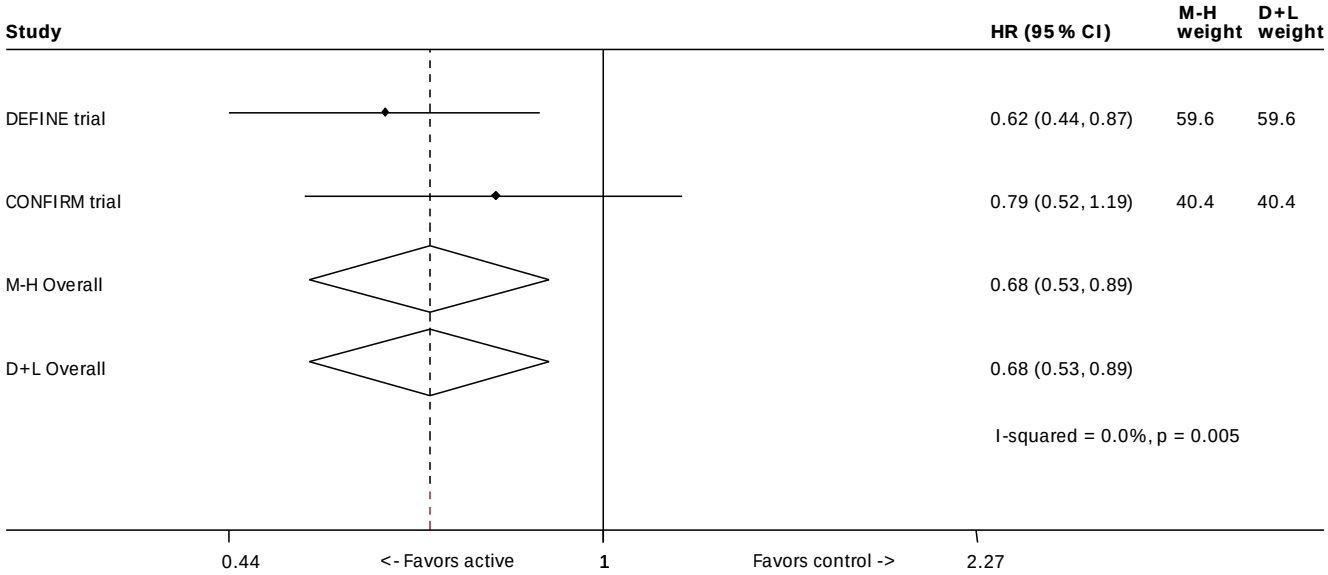
Abbreviations: bid, twice weekly; EOD, every other day; od, once daily; q4w, every four weeks; tiw, three times weekly.

Figure 4: Network diagram of trials providing data for analyses of confirmed disability progression sustained for 6 months (Figure 56 in the submission document)



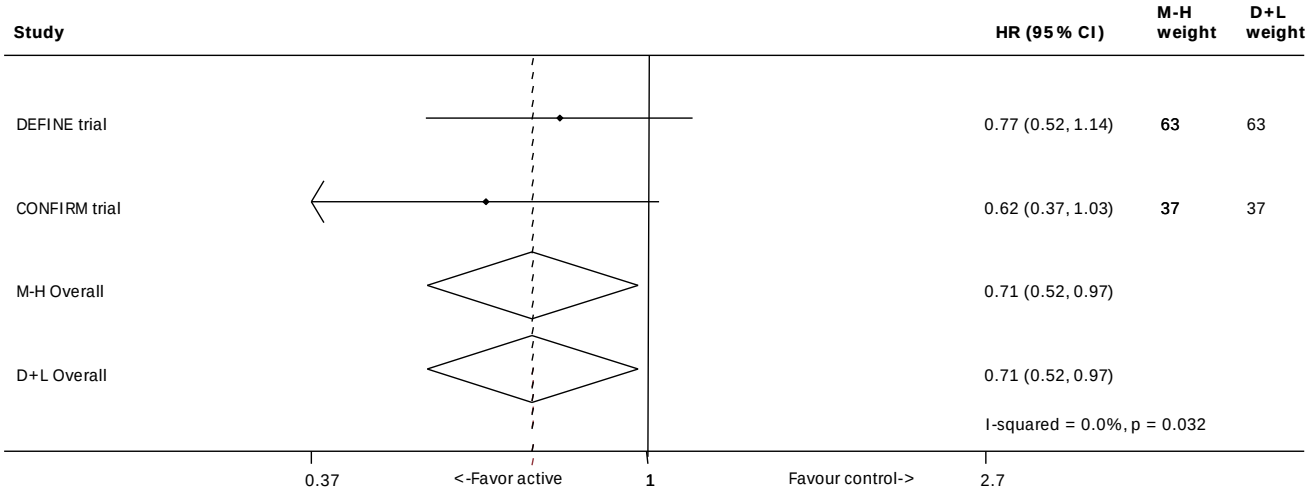
Abbreviations: bid, twice weekly; EOD, every other day; od, once daily; tiw, three times weekly.

Figure 5: Forest plot depicting the meta-analysis results for disability progression sustained for 3 months with dimethyl fumarate BID compared to placebo (Figure 19 in the submission)



Hazard ratio <1 indicates better efficacy of intervention; Abbreviations: BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; M-H, Mantel–Haenszel, indicates fixed effect model; HR, Hazard Ratio

Figure 6: Forest plot depicting the meta-analysis results for disability progression sustained for 3 months with dimethyl fumarate BID compared to placebo (Figure 20 in the submission)



Hazard ratio <1 indicates better efficacy of intervention; Abbreviations: BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; M-H, Mantel–Haenszel, indicates fixed effect model; HR, Hazard Ratio

Section 7.7.1 in the submission document:

The revised tables are given below (Table 7, Table 8, and Table 9). The EDSS distributions observed for the placebo arm did not change when the model was updated with hazard ratios.

Table 7: Actual and predicted baseline, year 1, and year 2 EDSS distributions for the placebo population (Table 77 in the submission document)

RRMS EDSS state	Baseline	Year 1 comparison		Year 2 comparison	
	Baseline, n (%)	DEFINE and CONFIRM week 48, n (%)	Model year 1, n (%)	DEFINE and CONFIRM week 96, n (%)	Model year 2, n (%)
0	34 (4.4)	31 (4.7)	41 (5.9)	37 (6.3)	41 (6.7)
1	63 (8.2)	62 (9.5)	69 (10.0)	46 (7.8)	66 (10.7)
2	265 (34.4)	219 (33.5)	228 (33.3)	179 (30.2)	204 (33.2)
3	181 (23.5)	141 (21.6)	153 (22.3)	139 (23.5)	131 (21.3)
4	161 (20.9)	128 (19.6)	128 (18.6)	127 (21.5)	106 (17.2)
5	66 (8.6)	48 (7.3)	39 (5.7)	27 (4.6)	34 (5.5)
6	1 (0.1)	20 (3.1)	19 (2.7)	24 (4.1)	19 (3.1)
7	0 (0.0)	4 (0.6)	6 (0.9)	11 (1.9)	8 (1.3)
8	0 (0.0)	1 (0.2)	3 (0.4)	1 (0.2)	6 (1.0)
9	0 (0.0)	31 (4.7)	0 (0.0)	1 (0.2)	0 (0.0)
Total RRMS	**771**	**654**	**686**	**592**	**615**

Table 8: Actual and predicted baseline, year 1, and year 2 EDSS distributions for the dimethyl fumarate population (Table 78 in the submission document)

RRMS EDSS state	Baseline	Year 1 comparison		Year 2 comparison	
	Baseline, n (%)	DEFINE and CONFIRM week 48, n (%)	Model year 1, n (%)	DEFINE and CONFIRM week 96, n (%)	Model year 2, n (%)
0	44 (5.7)	43 (6.7)	48 (8.1)	43 (7.2)	48 (10.0)
1	69 (9.0)	73 (11.4)	71 (11.9)	67 (11.2)	65 (13.7)
2	260 (33.9)	207 (32.3)	214 (35.6)	208 (34.7)	174 (36.6)
3	172 (22.4)	119 (18.6)	125 (20.8)	110 (18.3)	92 (19.3)
4	155 (20.2)	140 (21.8)	96 (16.0)	114 (19.0)	64 (13.4)
5	66 (8.6)	38 (5.9)	30 (5.0)	29 (4.8)	19 (3.9)
6	1 (0.1)	17 (2.7)	10 (1.7)	22 (3.7)	9 (1.9)
7	1 (0.1)	3 (0.5)	4 (0.6)	5 (0.8)	3 (0.7)
8	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.5)
9	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)
Total RRMS	**768**	**641**	**600**	**600**	**476**

Table 9: Actual and predicted baseline, year 1, and year 2 EDSS distributions for the dimethyl fumarate population with transfer to SPMS turned off (Table 79 in the submission document)

RRMS EDSS state	Baseline	Year 1 comparison		Year 2 comparison	
	Baseline, n (%)	DEFINE and CONFIRM week 48, n (%)	Model year 1, n (%)	DEFINE and CONFIRM week 96, n (%)	Model year 2, n (%)
0	44 (5.7)	43 (6.7)	49 (7.3)	43 (7.2)	50 (8.6)
1	69 (9.0)	73 (11.4)	74 (11.0)	67 (11.2)	71 (12.1)
2	260 (33.9)	207 (32.3)	227 (33.9)	208 (34.7)	199 (34.1)
3	172 (22.4)	119 (18.6)	142 (21.2)	110 (18.3)	117 (20.0)
4	155 (20.2)	140 (21.8)	117 (17.5)	114 (19.0)	92 (15.7)
5	66 (8.6)	38 (5.9)	40 (6.0)	29 (4.8)	31 (5.3)
6	1 (0.1)	17 (2.7)	14 (2.1)	22 (3.7)	15 (2.6)
7	1 (0.1)	3 (0.5)	5 (0.7)	5 (0.8)	6 (1.0)
8	0 (0.0)	1 (0.2)	2 (0.3)	0 (0.0)	4 (0.7)
9	0 (0.0)	0 (0.0)	0 (0)	2 (0.3)	0 (0)
Total RRMS	**768**	**641**	**671**	**600**	**586**

Section 7.7.3 in the submission document:

The revised tables are given below (Table 10, Table 11, Table 12 and Table 13).

Table 10: QALYs accrued per year in EDSS states (dimethyl fumarate) (cohort of 1,000 patients) (Table 80 in the submission document)

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total undiscounted QALYs (EDSS states)
	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	
1	50.6	77.5	253.9	144.1	109.4	35.6	3.9	0.9	0.0	0.0	0.0	0.0	0.1	3.5	7.6	10.6	5.2	0.0	0.0	0.0	703.0
2	60.5	85.5	234.4	120.2	81.2	21.5	7.5	1.9	0.0	0.0	0.0	0.0	0.3	8.9	18.4	27.4	15.5	1.5	-0.1	-0.1	684.5
3	62.5	83.9	214.3	103.9	66.4	17.0	7.4	2.1	-0.1	0.0	0.0	0.0	0.4	11.8	22.6	36.8	25.7	5.0	-0.4	-0.3	659.0
4	59.2	78.1	195.2	93.2	58.6	14.9	6.9	2.1	-0.1	0.0	0.0	0.0	0.5	13.2	23.7	41.8	35.4	9.2	-0.9	-0.7	630.2
5	54.6	71.5	177.7	84.6	53.0	13.4	6.3	1.9	-0.1	0.0	0.0	0.0	0.5	13.5	23.6	44.0	43.7	14.0	-1.5	-1.4	599.3
6	48.5	64.3	161.1	77.6	48.9	12.4	5.9	1.8	-0.1	0.0	0.0	0.0	0.5	13.3	22.7	44.5	50.3	18.9	-2.3	-2.4	566.0
7	42.3	57.2	145.8	71.6	45.7	11.7	5.5	1.8	-0.1	0.0	0.0	0.0	0.5	12.7	21.6	43.8	55.1	23.7	-3.2	-3.7	531.9
8	37.3	51.0	131.6	65.5	42.3	10.9	5.2	1.7	-0.1	0.0	0.0	0.0	0.5	12.0	20.3	42.5	58.3	28.1	-4.2	-5.4	497.3
9	33.0	45.5	118.6	59.7	38.9	10.1	4.9	1.6	-0.1	0.0	0.0	0.0	0.4	11.1	19.0	40.6	60.0	32.0	-5.3	-7.4	462.6
10	29.3	40.7	106.8	54.2	35.6	9.4	4.5	1.5	-0.1	0.0	0.0	0.0	0.4	10.2	17.5	38.4	60.5	35.2	-6.4	-9.7	428.0
11	26.0	36.4	96.1	49.2	32.5	8.6	4.2	1.4	-0.1	0.0	0.0	0.0	0.4	9.3	16.1	36.0	59.9	37.8	-7.5	-12.5	393.7
12	23.2	32.6	86.4	44.5	29.6	7.9	3.9	1.3	-0.1	0.0	0.0	0.0	0.3	8.5	14.7	33.5	58.5	39.6	-8.5	-15.5	360.0
13	20.6	29.1	77.6	40.1	26.8	7.2	3.5	1.2	-0.1	0.0	0.0	0.0	0.3	7.7	13.4	30.9	56.5	40.8	-9.6	-18.9	327.1
14	18.4	26.0	69.6	36.2	24.3	6.5	3.2	1.1	-0.1	0.0	0.0	0.0	0.3	6.9	12.1	28.4	53.9	41.3	-10.5	-22.5	295.2
15	16.4	23.3	62.5	32.6	21.9	5.9	2.9	1.0	-0.1	0.0	0.0	0.0	0.2	6.2	10.9	25.9	51.0	41.3	-11.3	-26.3	264.4
16	14.6	20.8	56.0	29.3	19.8	5.4	2.7	0.9	-0.1	0.0	0.0	0.0	0.2	5.6	9.9	23.6	47.8	40.7	-12.0	-30.3	234.9
17	13.0	18.6	50.2	26.3	17.8	4.8	2.4	0.8	-0.1	0.0	0.0	0.0	0.2	5.0	8.9	21.4	44.6	39.7	-12.6	-34.4	206.8
18	11.6	16.6	44.9	23.6	16.0	4.4	2.2	0.7	-0.1	0.0	0.0	0.0	0.2	4.5	8.0	19.4	41.3	38.4	-13.1	-38.5	180.1
19	10.3	14.8	40.1	21.2	14.4	3.9	2.0	0.7	-0.1	0.0	0.0	0.0	0.2	4.0	7.2	17.5	38.0	36.7	-13.4	-42.5	155.1
20	9.2	13.2	35.9	19.0	12.9	3.5	1.8	0.6	-0.1	0.0	0.0	0.0	0.1	3.6	6.4	15.7	34.9	34.9	-13.6	-46.5	131.6
21	8.2	11.8	32.0	17.0	11.6	3.2	1.6	0.5	-0.1	0.0	0.0	0.0	0.1	3.2	5.8	14.1	31.8	32.9	-13.7	-50.3	109.8
22	7.3	10.5	28.6	15.2	10.4	2.8	1.4	0.5	-0.1	0.0	0.0	0.0	0.1	2.9	5.2	12.7	29.0	30.8	-13.6	-53.9	89.7

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total
23	6.5	9.4	25.5	13.6	9.3	2.5	1.3	0.4	-0.1	0.0	0.0	0.0	0.1	2.6	4.6	11.4	26.2	28.6	-13.5	-57.2	71.2
24	5.8	8.3	22.7	12.1	8.3	2.3	1.1	0.4	0.0	0.0	0.0	0.0	0.1	2.3	4.1	10.2	23.7	26.5	-13.2	-60.1	54.4
25	5.1	7.4	20.2	10.8	7.4	2.0	1.0	0.3	0.0	0.0	0.0	0.0	0.1	2.0	3.7	9.1	21.3	24.4	-12.9	-62.7	39.2
26	4.5	6.6	18.0	9.6	6.6	1.8	0.9	0.3	0.0	0.0	0.0	0.0	0.1	1.8	3.3	8.1	19.1	22.3	-12.5	-64.8	25.6
27	4.0	5.8	16.0	8.5	5.8	1.6	0.8	0.3	0.0	0.0	0.0	0.0	0.1	1.6	2.9	7.2	17.1	20.3	-12.0	-66.5	13.6
28	3.6	5.2	14.2	7.6	5.2	1.4	0.7	0.2	0.0	0.0	0.0	0.0	0.1	1.4	2.6	6.4	15.3	18.4	-11.4	-67.6	3.2
29	3.2	4.6	12.6	6.7	4.6	1.3	0.6	0.2	0.0	0.0	0.0	0.0	0.0	1.3	2.3	5.7	13.6	16.6	-10.8	-68.1	-5.8
30	2.8	4.1	11.1	5.9	4.1	1.1	0.6	0.2	0.0	0.0	0.0	0.0	0.0	1.1	2.0	5.0	12.1	14.9	-10.1	-68.1	-13.2
31	2.5	3.6	9.8	5.2	3.6	1.0	0.5	0.2	0.0	0.0	0.0	0.0	0.0	1.0	1.8	4.4	10.7	13.3	-9.4	-67.4	-19.3
32	2.2	3.2	8.6	4.6	3.2	0.9	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.9	1.6	3.9	9.4	11.8	-8.7	-66.1	-24.1
33	1.9	2.8	7.6	4.1	2.8	0.8	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.8	1.4	3.4	8.3	10.4	-8.0	-64.1	-27.4
34	1.7	2.4	6.7	3.6	2.4	0.7	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.7	1.2	3.0	7.2	9.1	-7.3	-61.5	-29.6
35	1.5	2.1	5.8	3.1	2.1	0.6	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.6	1.1	2.6	6.3	7.9	-6.6	-58.4	-30.7
36	1.3	1.9	5.1	2.7	1.9	0.5	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.5	0.9	2.3	5.5	6.9	-5.9	-54.8	-30.8
37	1.1	1.6	4.4	2.4	1.6	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.4	0.8	2.0	4.7	5.9	-5.2	-50.7	-30.0
38	1.0	1.4	3.8	2.1	1.4	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.4	0.7	1.7	4.1	5.0	-4.5	-46.1	-28.4
39	0.8	1.2	3.3	1.8	1.2	0.3	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.3	0.6	1.5	3.5	4.3	-3.9	-41.3	-26.1
40	0.7	1.0	2.9	1.5	1.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.5	1.3	3.0	3.6	-3.3	-36.2	-23.2
41	0.6	0.9	2.4	1.3	0.9	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.4	1.1	2.5	3.0	-2.7	-31.1	-20.0
42	0.5	0.8	2.1	1.1	0.8	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.4	0.9	2.1	2.4	-2.2	-26.0	-16.7
43	0.4	0.6	1.7	0.9	0.6	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.8	1.7	2.0	-1.8	-21.1	-13.3
44	0.4	0.5	1.5	0.8	0.5	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.6	1.4	1.5	-1.4	-16.5	-10.0
45	0.3	0.4	1.2	0.6	0.4	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.5	1.1	1.2	-1.0	-12.4	-7.0
46	0.3	0.4	1.0	0.5	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.9	0.9	-0.8	-8.9	-4.5
47	0.2	0.3	0.8	0.4	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.7	0.7	-0.5	-6.1	-2.5
48	0.2	0.2	0.6	0.3	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.5	0.5	-0.4	-3.9	-1.1

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total
49	0.1	0.2	0.5	0.3	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.3	-0.2	-2.3	-0.1
50	0.1	0.1	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.3	0.2	-0.1	-1.3	0.4

Abbreviations: EDSS, expanded disability status scale; QALY, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Table 11: Total and per patient QALYs accrued per year (dimethyl fumarate) (cohort of 1,000 patients) (Table 81 in the submission document)

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
1	703.0	3.3	7.5	692.2	668.8	668.8	0.7
2	684.5	2.5	9.0	673.0	628.2	1297.1	1.3
3	659.0	2.0	11.2	645.8	582.5	1879.6	1.9
4	630.2	1.6	13.9	614.7	535.6	2415.2	2.4
5	599.3	1.3	17.1	580.9	489.1	2904.3	2.9
6	566.0	1.0	20.6	544.4	442.9	3347.2	3.3
7	531.9	0.8	24.4	506.7	398.3	3745.4	3.7
8	497.3	0.7	28.3	468.3	355.7	4101.1	4.1
9	462.6	0.5	32.4	429.6	315.2	4416.3	4.4
10	428.0	0.4	36.6	390.9	277.1	4693.4	4.7
11	393.7	0.3	40.8	352.6	241.5	4934.9	4.9
12	360.0	0.3	44.9	314.8	208.3	5143.2	5.1
13	327.1	0.2	49.0	277.9	177.7	5321.0	5.3
14	295.2	0.2	52.8	242.2	149.6	5470.6	5.5
15	264.4	0.1	56.5	207.8	124.0	5594.6	5.6
16	234.9	0.1	59.9	174.9	100.8	5695.4	5.7

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
17	206.8	0.1	63.1	143.6	80.0	5775.5	5.8
18	180.1	0.1	65.9	114.2	61.5	5836.9	5.8
19	155.1	0.1	68.4	86.7	45.1	5882.0	5.9
20	131.6	0.0	70.5	61.1	30.7	5912.7	5.9
21	109.8	0.0	72.2	37.6	18.2	5931.0	5.9
22	89.7	0.0	73.6	16.1	7.5	5938.5	5.9
23	71.2	0.0	74.6	-3.4	-1.5	5937.0	5.9
24	54.4	0.0	75.1	-20.7	-9.1	5927.9	5.9
25	39.2	0.0	75.2	-36.0	-15.2	5912.7	5.9
26	25.6	0.0	75.0	-49.4	-20.2	5892.5	5.9
27	13.6	0.0	74.3	-60.7	-24.0	5868.5	5.9
28	3.2	0.0	73.2	-70.0	-26.7	5841.8	5.8
29	-5.8	0.0	71.6	-77.4	-28.5	5813.3	5.8
30	-13.2	0.0	69.6	-82.9	-29.5	5783.7	5.8
31	-19.3	0.0	67.2	-86.5	-29.8	5754.0	5.8
32	-24.1	0.0	64.4	-88.4	-29.4	5724.5	5.7
33	-27.4	0.0	61.1	-88.6	-28.5	5696.1	5.7
34	-29.6	0.0	57.5	-87.1	-27.1	5669.0	5.7
35	-30.7	0.0	53.6	-84.4	-25.3	5643.7	5.6
36	-30.8	0.0	49.5	-80.3	-23.3	5620.4	5.6
37	-30.0	0.0	45.1	-75.1	-21.0	5599.4	5.6
38	-28.4	0.0	40.5	-68.9	-18.6	5580.8	5.6
39	-26.1	0.0	35.9	-61.9	-16.2	5564.6	5.6
40	-23.2	0.0	31.1	-54.4	-13.7	5550.8	5.6

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
41	-20.0	0.0	26.5	-46.5	-11.4	5539.5	5.5
42	-16.7	0.0	22.0	-38.7	-9.1	5530.4	5.5
43	-13.3	0.0	17.8	-31.1	-7.1	5523.3	5.5
44	-10.0	0.0	13.9	-23.9	-5.3	5518.0	5.5
45	-7.0	0.0	10.5	-17.5	-3.7	5514.3	5.5
46	-4.5	0.0	7.6	-12.1	-2.5	5511.8	5.5
47	-2.5	0.0	5.2	-7.8	-1.5	5510.3	5.5
48	-1.1	0.0	3.4	-4.5	-0.9	5509.4	5.5
49	-0.1	0.0	2.1	-2.2	-0.4	5509.0	5.5
50	0.4	0.0	1.2	-0.7	-0.1	5508.9	5.5

Table 12: QALYs accrued per year in EDSS states (IM IFNβ-1a 30 µg [Avonex®]) (cohort of 1,000 patients) (Table 82 in the submission document)

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total undiscounted QALYs (EDSS states)
	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	
1	49.3	76.2	251.3	144.0	110.1	35.7	4.3	1.0	0.0	0.0	0.0	0.0	0.1	3.5	7.6	10.6	5.2	0.0	0.0	0.0	699.0
2	57.1	82.3	229.8	121.3	83.6	22.2	8.3	2.2	0.0	0.0	0.0	0.0	0.3	8.8	18.5	27.6	15.5	1.6	-0.1	-0.1	678.9
3	57.8	79.8	209.5	105.3	69.2	18.0	8.1	2.4	-0.1	0.0	0.0	0.0	0.4	11.7	22.8	37.4	26.0	5.1	-0.4	-0.3	652.7
4	54.3	73.8	190.3	94.2	60.9	15.8	7.5	2.3	-0.1	0.0	0.0	0.0	0.5	13.0	24.0	42.7	36.0	9.6	-0.9	-0.8	623.1
5	49.8	67.4	172.7	85.1	54.8	14.3	6.8	2.2	-0.1	0.0	0.0	0.0	0.5	13.3	23.7	45.1	44.7	14.5	-1.6	-1.5	591.5
6	44.4	60.6	156.2	77.6	50.2	13.1	6.3	2.0	-0.1	0.0	0.0	0.0	0.5	13.0	22.8	45.5	51.5	19.5	-2.4	-2.6	558.0
7	39.0	54.0	140.9	71.0	46.3	12.1	5.8	1.9	-0.1	0.0	0.0	0.0	0.5	12.4	21.6	44.7	56.4	24.4	-3.3	-3.9	523.6
8	34.5	48.2	126.9	64.6	42.5	11.2	5.4	1.8	-0.1	0.0	0.0	0.0	0.4	11.6	20.2	43.1	59.6	28.9	-4.4	-5.7	488.7
9	30.7	43.1	114.1	58.6	38.8	10.3	5.0	1.6	-0.1	0.0	0.0	0.0	0.4	10.8	18.7	41.0	61.2	32.9	-5.5	-7.8	453.8
10	27.3	38.5	102.6	53.0	35.3	9.4	4.6	1.5	-0.1	0.0	0.0	0.0	0.4	9.9	17.2	38.6	61.5	36.1	-6.6	-10.2	418.9
11	24.3	34.5	92.2	47.9	32.0	8.6	4.2	1.4	-0.1	0.0	0.0	0.0	0.3	9.0	15.8	36.0	60.7	38.6	-7.7	-13.1	384.6
12	21.7	30.8	82.7	43.2	29.0	7.8	3.9	1.3	-0.1	0.0	0.0	0.0	0.3	8.2	14.3	33.2	59.1	40.4	-8.8	-16.2	350.8
13	19.3	27.6	74.2	38.9	26.2	7.1	3.5	1.2	-0.1	0.0	0.0	0.0	0.3	7.4	13.0	30.6	56.8	41.5	-9.8	-19.7	317.9
14	17.2	24.7	66.6	35.0	23.7	6.4	3.2	1.1	-0.1	0.0	0.0	0.0	0.2	6.6	11.7	27.9	54.0	41.9	-10.7	-23.4	286.1
15	15.4	22.0	59.7	31.4	21.3	5.8	2.9	1.0	-0.1	0.0	0.0	0.0	0.2	6.0	10.6	25.4	50.9	41.8	-11.5	-27.3	255.4
16	13.7	19.7	53.4	28.2	19.2	5.2	2.6	0.9	-0.1	0.0	0.0	0.0	0.2	5.4	9.5	23.1	47.6	41.1	-12.2	-31.3	226.1
17	12.2	17.6	47.8	25.3	17.2	4.7	2.4	0.8	-0.1	0.0	0.0	0.0	0.2	4.8	8.6	20.9	44.2	39.9	-12.8	-35.5	198.3
18	10.9	15.7	42.8	22.7	15.5	4.2	2.1	0.7	-0.1	0.0	0.0	0.0	0.2	4.3	7.7	18.8	40.8	38.5	-13.3	-39.6	171.9
19	9.7	14.0	38.2	20.3	13.9	3.8	1.9	0.6	-0.1	0.0	0.0	0.0	0.1	3.9	6.9	16.9	37.4	36.7	-13.6	-43.7	147.2
20	8.7	12.5	34.2	18.2	12.4	3.4	1.7	0.6	-0.1	0.0	0.0	0.0	0.1	3.5	6.2	15.2	34.2	34.8	-13.7	-47.7	124.1
21	7.7	11.2	30.5	16.2	11.1	3.1	1.5	0.5	-0.1	0.0	0.0	0.0	0.1	3.1	5.5	13.7	31.2	32.7	-13.8	-51.5	102.6

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total
22	6.9	10.0	27.2	14.5	9.9	2.7	1.4	0.5	-0.1	0.0	0.0	0.0	0.1	2.8	4.9	12.2	28.3	30.5	-13.7	-55.1	82.9
23	6.1	8.9	24.2	12.9	8.9	2.4	1.2	0.4	-0.1	0.0	0.0	0.0	0.1	2.5	4.4	10.9	25.5	28.3	-13.6	-58.4	64.8
24	5.4	7.9	21.6	11.5	7.9	2.2	1.1	0.4	0.0	0.0	0.0	0.0	0.1	2.2	3.9	9.8	23.0	26.1	-13.3	-61.4	48.4
25	4.8	7.0	19.2	10.3	7.0	1.9	1.0	0.3	0.0	0.0	0.0	0.0	0.1	1.9	3.5	8.7	20.7	24.0	-12.9	-63.9	33.6
26	4.3	6.2	17.1	9.1	6.3	1.7	0.9	0.3	0.0	0.0	0.0	0.0	0.1	1.7	3.1	7.7	18.5	21.9	-12.5	-66.0	20.5
27	3.8	5.5	15.2	8.1	5.6	1.5	0.8	0.3	0.0	0.0	0.0	0.0	0.1	1.5	2.8	6.9	16.6	19.9	-12.0	-67.6	8.8
28	3.4	4.9	13.4	7.2	4.9	1.4	0.7	0.2	0.0	0.0	0.0	0.0	0.0	1.4	2.4	6.1	14.7	18.0	-11.4	-68.6	-1.2
29	3.0	4.3	11.9	6.4	4.4	1.2	0.6	0.2	0.0	0.0	0.0	0.0	0.0	1.2	2.2	5.4	13.1	16.2	-10.7	-69.1	-9.8
30	2.6	3.8	10.5	5.6	3.9	1.1	0.5	0.2	0.0	0.0	0.0	0.0	0.0	1.1	1.9	4.8	11.6	14.5	-10.1	-69.0	-16.9
31	2.3	3.4	9.3	5.0	3.4	0.9	0.5	0.2	0.0	0.0	0.0	0.0	0.0	0.9	1.7	4.2	10.3	12.9	-9.4	-68.2	-22.6
32	2.1	3.0	8.2	4.4	3.0	0.8	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.8	1.5	3.7	9.0	11.4	-8.7	-66.9	-27.0
33	1.8	2.6	7.2	3.9	2.7	0.7	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.7	1.3	3.3	7.9	10.1	-7.9	-64.8	-30.1
34	1.6	2.3	6.3	3.4	2.3	0.6	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.6	1.1	2.9	6.9	8.8	-7.2	-62.1	-31.9
35	1.4	2.0	5.5	3.0	2.0	0.6	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.6	1.0	2.5	6.0	7.7	-6.5	-58.9	-32.8
36	1.2	1.8	4.8	2.6	1.8	0.5	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.5	0.9	2.2	5.2	6.6	-5.8	-55.2	-32.6
37	1.1	1.5	4.2	2.2	1.5	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.4	0.8	1.9	4.5	5.7	-5.1	-51.0	-31.5
38	0.9	1.3	3.6	1.9	1.3	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.4	0.7	1.6	3.9	4.9	-4.4	-46.4	-29.7
39	0.8	1.2	3.1	1.7	1.2	0.3	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.3	0.6	1.4	3.3	4.1	-3.8	-41.5	-27.2
40	0.7	1.0	2.7	1.4	1.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.5	1.2	2.8	3.4	-3.2	-36.4	-24.2
41	0.6	0.8	2.3	1.2	0.8	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.4	1.0	2.4	2.8	-2.7	-31.2	-20.8
42	0.5	0.7	2.0	1.0	0.7	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.4	0.9	2.0	2.3	-2.2	-26.1	-17.3
43	0.4	0.6	1.7	0.9	0.6	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.7	1.6	1.9	-1.7	-21.2	-13.8
44	0.4	0.5	1.4	0.7	0.5	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.6	1.3	1.5	-1.3	-16.6	-10.4
45	0.3	0.4	1.1	0.6	0.4	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.5	1.1	1.1	-1.0	-12.4	-7.3
46	0.2	0.3	0.9	0.5	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.8	0.9	-0.7	-8.9	-4.8
47	0.2	0.3	0.8	0.4	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.7	0.7	-0.5	-6.1	-2.7

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total
48	0.2	0.2	0.6	0.3	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.5	0.5	-0.3	-3.9	-1.2
49	0.1	0.2	0.5	0.3	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.3	-0.2	-2.3	-0.2
50	0.1	0.1	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.3	0.2	-0.1	-1.3	0.4

Table 13: Total and per patient QALYs accrued per year (IM IFNβ-1a 30 µg [Avonex®]) (cohort of 1,000 patients) (Table 83 in the submission document)

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
1	699.0	16.2	7.6	675.2	652.4	652.4	0.7
2	678.9	12.5	9.2	657.1	613.4	1265.8	1.3
3	652.7	9.8	11.6	631.3	569.4	1835.2	1.8
4	623.1	7.7	14.4	600.9	523.7	2358.9	2.4
5	591.5	6.1	17.7	567.7	478.0	2836.9	2.8
6	558.0	4.9	21.3	531.9	432.7	3269.5	3.3
7	523.6	3.8	25.2	494.6	388.7	3658.2	3.7
8	488.7	3.0	29.2	456.5	346.6	4004.9	4.0
9	453.8	2.4	33.4	418.0	306.7	4311.6	4.3
10	418.9	1.9	37.6	379.4	269.0	4580.5	4.6
11	384.6	1.5	41.9	341.2	233.7	4814.2	4.8
12	350.8	1.2	46.0	303.6	200.9	5015.1	5.0
13	317.9	0.9	50.1	266.9	170.7	5185.8	5.2
14	286.1	0.7	54.0	231.4	142.9	5328.8	5.3
15	255.4	0.6	57.6	197.2	117.7	5446.5	5.4
16	226.1	0.5	61.0	164.6	94.9	5541.4	5.5

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
17	198.3	0.4	64.2	133.7	74.5	5615.9	5.6
18	171.9	0.3	67.0	104.7	56.4	5672.3	5.7
19	147.2	0.2	69.4	77.6	40.3	5712.6	5.7
20	124.1	0.2	71.5	52.4	26.4	5739.0	5.7
21	102.6	0.1	73.2	29.3	14.3	5753.2	5.8
22	82.9	0.1	74.5	8.3	3.9	5757.1	5.8
23	64.8	0.1	75.4	-10.6	-4.8	5752.3	5.8
24	48.4	0.1	75.8	-27.5	-12.0	5740.3	5.7
25	33.6	0.1	75.9	-42.3	-17.9	5722.4	5.7
26	20.5	0.0	75.6	-55.2	-22.6	5699.8	5.7
27	8.8	0.0	74.9	-66.1	-26.1	5673.7	5.7
28	-1.2	0.0	73.7	-74.9	-28.6	5645.1	5.6
29	-9.8	0.0	72.0	-81.8	-30.2	5615.0	5.6
30	-16.9	0.0	70.0	-86.9	-30.9	5584.0	5.6
31	-22.6	0.0	67.5	-90.1	-31.0	5553.0	5.6
32	-27.0	0.0	64.6	-91.6	-30.5	5522.5	5.5
33	-30.1	0.0	61.3	-91.4	-29.4	5493.1	5.5
34	-31.9	0.0	57.6	-89.6	-27.8	5465.3	5.5
35	-32.8	0.0	53.7	-86.5	-25.9	5439.4	5.4
36	-32.6	0.0	49.5	-82.2	-23.8	5415.6	5.4
37	-31.5	0.0	45.1	-76.7	-21.5	5394.1	5.4
38	-29.7	0.0	40.5	-70.2	-19.0	5375.1	5.4
39	-27.2	0.0	35.8	-63.0	-16.5	5358.7	5.4
40	-24.2	0.0	31.1	-55.3	-14.0	5344.7	5.3

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
41	-20.8	0.0	26.4	-47.3	-11.5	5333.2	5.3
42	-17.3	0.0	22.0	-39.3	-9.3	5323.9	5.3
43	-13.8	0.0	17.7	-31.5	-7.2	5316.7	5.3
44	-10.4	0.0	13.9	-24.3	-5.3	5311.4	5.3
45	-7.3	0.0	10.4	-17.8	-3.8	5307.6	5.3
46	-4.8	0.0	7.5	-12.3	-2.5	5305.1	5.3
47	-2.7	0.0	5.2	-7.9	-1.6	5303.5	5.3
48	-1.2	0.0	3.4	-4.6	-0.9	5302.6	5.3
49	-0.2	0.0	2.1	-2.3	-0.4	5302.2	5.3
50	0.4	0.0	1.2	-0.8	-0.1	5302.1	5.3

Section 7.7.4 in the submission document:

The revised table is given below (Table 14).

Table 14: Model outputs by comparator (Table 84 in the submission)

Comparator	LY	QALY	Cost (£)
Dimethyl fumarate (Tecfidera®)			List: £269,240
SC IFNβ-1a 22 µg (Rebif® 22 µg)	17.01	5.50	£233,746
Glatiramer acetate (Copaxone®)	17.00	5.45	£235,283
IM IFNβ-1a 30 µg (Avonex®)	17.02	5.58	£238,325
SC IFNβ-1b 250 µg (Betaferon®/ Extavia®)	17.00	5.40	£240,822
SC IFNβ-1a 44 µg (Rebif® 44 µg)	17.02	5.62	£240,619
Natalizumab (Tysabri®)	17.04	5.89	£284,230
Fingolimod (Gilenya®)	17.01	5.52	£281,933

Abbreviations: ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous.

Section 7.7.5 in the submission document:

The revised tables are given below (Table 15, Table 16, Table 17, Table 18 and Table 19).

Table 15: Summary of QALY gain per patient by comparator (Table 85 in the submission)

Health state	QALY (dimethyl fumarate)	QALY ((IM IFNβ-1a 30 µg (Avonex®))	Increment	Absolute increment	% absolute increment
EDSS health states:	**6.60**	**6.46**	**0.13**	**0.13**	**67.2%**
RRMS, EDSS 0	0.53	0.49	0.04	0.04	17.9%
RRMS, EDSS 1	0.73	0.69	0.04	0.04	17.7%
RRMS, EDSS 2	1.95	1.89	0.06	0.06	29.1%
RRMS, EDSS 3	0.99	0.98	0.01	0.01	4.0%
RRMS, EDSS 4	0.66	0.67	-0.01	0.01	2.8%
RRMS, EDSS 5	0.18	0.18	0.00	0.00	1.7%
RRMS, EDSS 6	0.07	0.07	0.00	0.00	1.7%
RRMS, EDSS 7	0.02	0.02	0.00	0.00	0.7%
RRMS, EDSS 8	0.00	0.00	0.00	0.00	0.0%
RRMS, EDSS 9	0.00	0.00	0.00	0.00	0.0%
SPMS, EDSS 0	0.00	0.00	0.00	0.00	0.0%
SPMS, EDSS 1	0.00	0.00	0.00	0.00	0.0%

Health state	QALY (dimethyl fumarate)	QALY ((IM IFNβ-1a 30 µg (Avonex®))	Increment	Absolute increment	% absolute increment
SPMS, EDSS 2	0.01	0.00	0.00	0.00	0.1%
SPMS, EDSS 3	0.14	0.13	0.00	0.00	1.8%
SPMS, EDSS 4	0.24	0.24	0.00	0.00	1.3%
SPMS, EDSS 5	0.49	0.49	0.00	0.00	0.4%
SPMS, EDSS 6	0.71	0.71	0.00	0.00	1.7%
SPMS, EDSS 7	0.46	0.47	0.00	0.00	2.5%
SPMS, EDSS 8	-0.14	-0.14	0.00	0.00	1.0%
SPMS, EDSS 9	-0.44	-0.45	0.01	0.01	5.9%
Treatment-related adverse events:	**-0.01**	**-0.06**	**0.05**	**0.05**	**25.7%**
Abdominal pain	0.00	0.00	0.00	0.00	0.0%
Abdominal pain upper	0.00	0.00	0.00	0.00	0.0%
ALT increased	0.00	0.00	0.00	0.00	0.0%
Arthralgia	-0.0001	0.00	0.00	0.00	0.1%
Atrioventricular conduction block	0.000	0.000	0.00	0.00	0.0%
Back pain	0.00	0.00	0.00	0.00	0.3%
Bradycardia	0.00	0.00	0.00	0.00	0.0%
Chest pain	0.00	0.00	0.00	0.00	0.1%
Cough	0.00	0.00	0.00	0.00	0.0%
Depression	-0.01	-0.01	0.01	0.01	4.5%
Diarrhoea	0.00	0.00	0.00	0.00	0.0%
Fatigue	0.00	0.00	0.00	0.00	0.0%
Flu-like symptoms	0.00	-0.03	0.03	0.03	16.0%
Flushing	0.00	0.00	0.00	0.00	0.0%
Gastroenteritis	0.00	0.00	0.00	0.00	0.1%
Headache	0.00	0.00	0.00	0.00	0.9%
Influenza	0.00	-0.01	0.01	0.01	4.7%
Leucopoenia	0.00	0.00	0.00	0.00	0.0%
Lower respiratory tract infection	0.00	0.00	0.00	0.00	0.0%
Nausea	0.00	0.00	0.00	0.00	0.0%
Pain in extremity	0.00	0.00	0.00	0.00	0.2%
Pruritus	0.00	0.00	0.00	0.00	0.0%
Rash	0.00	0.00	0.00	0.00	0.0%
Urinary tract infection	0.00	0.00	0.00	0.00	0.1%
Caregiver	-0.80	-0.81	0.01	0.01	7.1%
Total:	**5.784**	**5.584**	**0.200**	**0.200**	**100.00%**

Abbreviations: ALT, alanine transaminase; EDSS, expanded disability status scale; PAS, patient access scheme; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 16: Summary of costs per patient by health state (PAS price) (Table 86 in the submission document)

Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
EDSS health states	**£199,651**	**£204,139**	**-£4,487**	**£4,487**	**47.3%**
RRMS, EDSS 0	£1,793	£1,833	-£40	£40	0.4%
RRMS, EDSS 1	£2,738	£2,848	-£111	£111	1.2%
RRMS, EDSS 2	£7,183	£7,675	-£492	£492	5.2%
RRMS, EDSS 3	£8,652	£9,000	-£347	£347	3.7%
RRMS, EDSS 4	£4,361	£4,710	-£349	£349	3.7%
RRMS, EDSS 5	£1,829	£1,971	-£142	£142	1.5%
RRMS, EDSS 6	£985	£1,058	-£73	£73	0.8%
RRMS, EDSS 7	£869	£922	-£53	£53	0.6%
RRMS, EDSS 8	£4,408	£4,669	-£261	£261	2.8%
RRMS, EDSS 9	£26	£27	-£2	£2	0.0%
SPMS, EDSS 0	£0	£0	£0	£0	0.0%
SPMS, EDSS 1	£0	£0	£0	£0	0.0%
SPMS, EDSS 2	£20	£19	£1	£1	0.0%
SPMS, EDSS 3	£1,590	£1,547	£42	£42	0.4%
SPMS, EDSS 4	£1,820	£1,801	£19	£19	0.2%
SPMS, EDSS 5	£6,041	£6,050	-£9	£9	0.1%
SPMS, EDSS 6	£11,741	£11,798	-£58	£58	0.6%
SPMS, EDSS 7	£20,291	£20,509	-£219	£219	2.3%
SPMS, EDSS 8	£78,910	£80,079	-£1,169	£1,169	12.3%
SPMS, EDSS 9	£46,395	£47,621	-£1,226	£1,226	12.9%
Treatment acquisition costs	**£34,570**	**£30,101**	**£4,469**	**£4,469**	**47.1%**
Treatment administration costs	**£0**	**£85**	**-£85**	**£85**	**0.9%**
Treatment monitoring costs	**£3,209**	**£3,108**	**£101**	**£101**	**1.1%**
Treatment-related adverse events	**£548**	**£893**	**-£346**	**£346**	**3.6%**
Abdominal pain	£10	£0	£10	£10	0.1%
Abdominal pain upper	£10	£0	£10	£10	0.1%
ALT increased	£0	£0	£0	£0	0.0%
Arthralgia	£9	£10	-£1	£1	0.0%
Atrioventricular conduction block	£6	£15	-£9	£9	0.1%

Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
Back pain	£13	£10	£3	£3	0.0%
Bradycardia	£0	£0	£0	£0	0.0%
Chest pain	£12	£0	£12	£12	0.1%
Cough	£0	£0	£0	£0	0.0%
Depression	£37	£117	-£80	£80	0.8%
Diarrhoea	£0	£0	£0	£0	0.0%
Fatigue	£0	£0	£0	£0	0.0%
Flu-like symptoms	£1	£74	-£72	£72	0.8%
Flushing	£0	£0	£0	£0	0.0%
Gastroenteritis	£77	£0	£77	£77	0.8%
Headache	£232	£538	-£306	£306	3.2%
Influenza	£7	£39	-£32	£32	0.3%
Leucopoenia	£0	£0	£0	£0	0.0%
Lower respiratory tract infection	£4	£0	£4	£4	0.0%
Nausea	£0	£0	£0	£0	0.0%
Pain in extremity	£19	£29	-£10	£10	0.1%
Pruritus	£0	£0	£0	£0	0.0%
Rash	£84	£48	£36	£36	0.4%
Urinary tract infection	£25	£14	£11	£11	0.1%
Total:	**£237,977**	**£238,325**	**-£347**	**£9,489**	**100.00%**

Abbreviations: ALT, alanine transaminase; EDSS, expanded disability status scale; PAS, patient access scheme; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 17: Summary of costs per patient by health state (List price) (Table 87 in the submission document)

Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
EDSS health states:	**£199,651**	**£204,139**	**-£4,487**	**£4,487**	**11.0%**
RRMS, EDSS 0	£1,793	£1,833	-£40	£40	0.1%
RRMS, EDSS 1	£2,738	£2,848	-£111	£111	0.3%
RRMS, EDSS 2	£7,183	£7,675	-£492	£492	1.2%
RRMS, EDSS 3	£8,652	£9,000	-£347	£347	0.9%
RRMS, EDSS 4	£4,361	£4,710	-£349	£349	0.9%
RRMS, EDSS 5	£1,829	£1,971	-£142	£142	0.3%
RRMS, EDSS 6	£985	£1,058	-£73	£73	0.2%
RRMS, EDSS 7	£869	£922	-£53	£53	0.1%

Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
RRMS, EDSS 8	£4,408	£4,669	-£261	£261	0.6%
RRMS, EDSS 9	£26	£27	-£2	£2	0.0%
SPMS, EDSS 0	£0	£0	£0	£0	0.0%
SPMS, EDSS 1	£0	£0	£0	£0	0.0%
SPMS, EDSS 2	£20	£19	£1	£1	0.0%
SPMS, EDSS 3	£1,590	£1,547	£42	£42	0.1%
SPMS, EDSS 4	£1,820	£1,801	£19	£19	0.0%
SPMS, EDSS 5	£6,041	£6,050	-£9	£9	0.0%
SPMS, EDSS 6	£11,741	£11,798	-£58	£58	0.1%
SPMS, EDSS 7	£20,291	£20,509	-£219	£219	0.5%
SPMS, EDSS 8	£78,910	£80,079	-£1,169	£1,169	2.9%
SPMS, EDSS 9	£46,395	£47,621	-£1,226	£1,226	3.0%
Treatment acquisition costs	**£65,832**	**£30,101**	**£35,732**	**£35,732**	**87.7%**
Treatment administration costs	**£0**	**£85**	**-£85**	**£85**	**0.2%**
Treatment monitoring costs	**£3,209**	**£3,108**	**£101**	**£101**	**0.2%**
Treatment-related adverse events:	**£548**	**£893**	**-£346**	**£346**	**0.8%**
Abdominal pain	£10	£0	£10	£10	0.0%
Abdominal pain upper	£10	£0	£10	£10	0.0%
ALT increased	£0	£0	£0	£0	0.0%
Arthralgia	£9	£10	-£1	£1	0.0%
Atrioventricular conduction block	£6	£15	-£9	£9	0.0%
Back pain	£13	£10	£3	£3	0.0%
Bradycardia	£0	£0	£0	£0	0.0%
Chest pain	£12	£0	£12	£12	0.0%
Cough	£0	£0	£0	£0	0.0%
Depression	£37	£117	-£80	£80	0.2%
Diarrhoea	£0	£0	£0	£0	0.0%
Fatigue	£0	£0	£0	£0	0.0%
Flu-like symptoms	£1	£74	-£72	£72	0.2%
Flushing	£0	£0	£0	£0	0.0%
Gastroenteritis	£77	£0	£77	£77	0.2%
Headache	£232	£538	-£306	£306	0.8%
Influenza	£7	£39	-£32	£32	0.1%
Leucopoenia	£0	£0	£0	£0	0.0%

Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
Lower respiratory tract infection	£4	£0	£4	£4	0.0%
Nausea	£0	£0	£0	£0	0.0%
Pain in extremity	£19	£29	-£10	£10	0.0%
Pruritus	£0	£0	£0	£0	0.0%
Rash	£84	£48	£36	£36	0.1%
Urinary tract infection	£25	£14	£11	£11	0.0%
Total:	**£269,240**	**£238,325**	**£30,915**	**£40,751**	**100.00%**

Table 18: Summary of predicted resource use per patient by category of cost (PAS price) (Table 88 in the submission document)

EDSS Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
EDSS state costs	199,651	204,139	-4,487	4,487	47.2913%
Treatment cost	34,570	30,101	4,469	4,469	47.1016%
Administration cost	0	85	-85	85	0.8959%
Monitoring cost	3,209	3,108	101	101	1.0645%
Adverse events	548	893	-346	346	3.6467%
Total:	**237,977**	**238,325**	**-347**	**9,488**	**100%**

Abbreviations: EDSS, expanded disability status scale

Table 19: Summary of predicted resource use per patient by category of cost, per patient (list price) (Table 89 in the submission document)

EDSS Health state	Cost intervention (Tecfidera®)	Cost comparator (Avonex®)	Increment	Absolute increment	% absolute increment
EDSS state costs	199,651	204,139	-4,487	4,487	11.0108%
Treatment cost	65,832	30,101	35,732	35,732	87.6837%
Administration cost	0	85	-85	85	0.2086%
Monitoring cost	3,209	3,108	101	101	0.2478%
Adverse events	548	893	-346	346	0.8491%
Total:	**269,240**	**238,325**	**30,915**	**67,179**	**100%**

Abbreviations: EDSS, expanded disability status scale

Section 7.7.6 in the submission document

The revised tables are given below (Table 20, Table 21, Table 22, and Table 23).

Table 20: Base-case results (list price) (Table 90 in the submission document)

Technologies	Total			Incremental (dimethyl fumarate vs comparator)			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Dimethyl fumarate (Tecfidera®)	£269,240	17.03	5.78	-	-	-	-
SC IFNβ-1a 22 µg (Rebif® 22 µg)	£233,746	17.01	5.50	£35,494	0.02	0.29	£124,337
Glatiramer acetate (Copaxone®)	£235,283	17.00	5.45	£33,957	0.03	0.33	£102,830
IM IFNβ-1a 30 µg (Avonex®)	£238,325	17.02	5.58	£30,915	0.01	0.20	£154,781
SC IFNβ-1a 44 µg (Rebif® 44 µg)	£240,619	17.02	5.62	£28,621	0.01	0.16	£175,779
SC IFNβ-1b 250 µg (Betaferon®/Extavia®)	£240,822	17.00	5.40	£28,417	0.03	0.39	£73,724
Fingolimod (Gilenya®)	£281,933	17.01	5.52	-£12,693	0.02	0.26	Dominant
Natalizumab (Tysabri®)	£284,230	17.04	5.89	-£14,990	-0.01	-0.10	£146,300

Abbreviations: ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous.

Table 21: Base-case results (PAS price) (Table 91 in the submission document)

Technologies	Total			Incremental (dimethyl fumarate vs comparator)			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SC IFNβ-1a 22 µg (Rebif® 22 µg)	£233,746	17.01	5.50	£4,232	0.02	0.29	£14,823
Glatiramer acetate (Copaxone®)	£235,283	17.00	5.45	£2,694	0.03	0.33	£8,159
Dimethyl fumarate (Tecfidera®)							-
IM IFNβ-1a 30 µg (Avonex®)							Dominant
SC IFNβ-1a 44 µg (Rebif® 44 µg)	£240,619	17.02	5.62	- £2,642	0.01	0.16	Dominant

Technologies	Total			Incremental (dimethyl fumarate vs comparator)			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SC IFNβ-1b 250 µg (Betaferon®/ Extavia®)	£240,822	17.00	5.40	- £2,845	0.03	0.39	Dominant
Fingolimod (Gilenya®)	£281,933	17.01	5.52	-£43,955	0.02	0.26	Dominant
Natalizumab (Tysabri®)	£284,230	17.04	5.89	-£46,252	-0.01	-0.10	£451,419 (less costly and less effective)

Abbreviations: ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous.

Table 22: Incremental cost-effectiveness analysis (list price) (Table 92 in the submission document)

Treatment	Total cost	Total QALYs	Inc. costs	Inc. QALYs	ICER
SC IFNβ-1a 22 µg (Rebif® 22 µg)	£233,746	5.50	-	-	-
IM IFNβ-1a 30 µg (Avonex®)	£238,325	5.58	£4,579	0.09	£53,410
SC IFNβ-1a 44 µg (Rebif® 44 µg)	£240,619	5.62	£2,294	0.04	£62,158
Dimethyl fumarate (Tecfidera®)	£269,240	5.78	£28,621	0.16	£175,779
Natalizumab (Tysabri®)	£284,230	5.89	£14,990	0.10	£146,300

Glatiramer acetate (Copaxone®), SC IFNβ-1b 250 µg (Betaferon®/ Extavia®), IM IFNβ-1a 30 µg (Avonex®), and Fingolimod (Gilenya®) were all either dominated or extendedly dominated; the results for these treatments are therefore not shown.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SC, subcutaneous.

Table 23: Incremental cost-effectiveness analysis (PAS price) (Table 93 in the submission document)

Treatment	Total cost	Total QALYs	Inc. costs	Inc. QALYs	ICER
SC IFNβ-1a 22 µg (Rebif® 22 µg)	£233,746	5.50	-	-	-
Dimethyl fumarate (Tecfidera®)					£14,823
Natalizumab (Tysabri®)	£284,230	5.89	£46,252	0.10	£451,419

SC IFNβ-1a 44 µg (Rebif®), SC IFNβ-1b 250 µg (Betaferon®/ Extavia®), IM IFNβ-1a 30 µg (Avonex®), and Fingolimod (Gilenya®) were all either dominated or extendedly dominated; the results for these treatments are therefore not shown.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SC, subcutaneous.

Section 7.7.7 in the submission document

The revised tables are given below (Table 24, Table 25, Table 26, Table 27, and Table 28).

Table 24: List price univariate sensitivity analysis results part 1 (Table 94 in the submission document)

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Baseline results	-	-£12,693	0.265	Dominant	£33,957	0.330	£102,830	£30,915	0.200	£154,781	£28,417	0.385	£73,724
EDSS state costs	+ 20%	-£13,694	0.265	Dominant	£32,752	0.330	£99,181	£30,387	0.200	£152,138	£27,123	0.385	£70,366
	- 20%	-£11,692	0.265	Dominant	£35,162	0.330	£106,480	£31,443	0.200	£157,423	£29,712	0.385	£77,081
Relapse costs	+ 20%	-£12,481	0.265	Dominant	£33,849	0.330	£102,505	£30,545	0.200	£152,930	£28,319	0.385	£73,469
	- 20%	-£12,905	0.265	Dominant	£34,064	0.330	£103,156	£31,285	0.200	£156,631	£28,516	0.385	£73,978
Patient utilities	+ 20%	-£12,693	0.311	Dominant	£33,957	0.388	£87,533	£30,915	0.227	£136,437	£28,417	0.447	£63,531
	- 20%	-£12,693	0.218	Dominant	£33,957	0.273	£124,607	£30,915	0.173	£178,822	£28,417	0.324	£87,812
Natural history relapse rates	+ 20%	-£12,481	0.264	Dominant	£33,849	0.331	£102,354	£30,545	0.201	£151,661	£28,319	0.386	£73,384
	- 20%	-£12,905	0.266	Dominant	£34,064	0.330	£103,307	£31,285	0.198	£157,952	£28,516	0.385	£74,063
Dimethyl fumarate relapse rate†	+ 20%	-£11,869	0.261	Dominant	£34,781	0.326	£106,526	£31,739	0.196	£161,923	£29,241	0.382	£76,601
	- 20%	-£13,517	0.268	Dominant	£33,133	0.334	£99,217	£30,091	0.203	£147,900	£27,594	0.389	£70,902
Comparator relapse rate†	+ 20%	-£13,419	0.268	Dominant	£32,923	0.335	£98,310	£29,739	0.205	£145,037	£27,278	0.391	£69,837
	- 20%	-£11,967	0.261	Dominant	£34,990	0.326	£107,480	£32,091	0.194	£165,057	£29,556	0.380	£77,716
Dimethyl fumarate disability progression rate†	+ 20%	-£11,001	0.089	Dominant	£35,648	0.154	£231,076	£32,607	0.024	£1,370,971	£30,109	0.210	£143,713
	- 20%	-£14,441	0.450	Dominant	£32,208	0.515	£62,520	£29,167	0.385	£75,820	£26,669	0.570	£46,754
Comparator disability progression rate†	+ 20%	-£14,610	0.495	Dominant	£30,533	0.564	£54,157	£28,263	0.388	£72,806	£24,828	0.642	£38,681
	- 20%	-£10,698	0.019	Dominant	£37,570	0.080	£467,733	£33,685	0.001	£51,442,926	£32,219	0.109	£294,326
Dimethyl fumarate dropouts	+ 20%	-£18,352	0.215	Dominant	£28,298	0.281	£100,801	£25,256	0.150	£168,103	£22,758	0.336	£67,740
	- 20%	-£5,780	0.322	Dominant	£40,870	0.387	£105,528	£37,828	0.257	£147,304	£35,330	0.443	£79,838

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Comparator dropouts	+ 20%	-£6,707	0.287	Dominant	£35,933	0.348	£103,360	£33,430	0.232	£144,285	£30,544	0.396	£77,080
	- 20%	-£19,783	0.240	Dominant	£31,600	0.311	£101,754	£27,824	0.163	£170,518	£25,945	0.374	£69,449

† Change applied to reduction in relapse rate relative to placebo.
Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 25: List price univariate sensitivity analysis results part 2 (Table 95 in the submission document)

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Baseline results	-	£35,494	0.285	£124,337	£28,621	0.163	£175,779	-£14,990	-0.102	£146,300
EDSS state costs	+ 20%	£34,535	0.285	£120,980	£28,139	0.163	£172,821	-£14,594	-0.102	£142,440
	- 20%	£36,452	0.285	£127,695	£29,102	0.163	£178,737	-£15,385	-0.102	£150,160
Relapse costs	+ 20%	£35,183	0.285	£123,247	£28,371	0.163	£174,248	-£14,664	-0.102	£143,116
	- 20%	£35,805	0.285	£125,428	£28,870	0.163	£177,311	-£15,316	-0.102	£149,483
Patient utilities	+ 20%	£35,494	0.333	£106,747	£28,621	0.187	£153,088	-£14,990	-0.123	£121,949
	- 20%	£35,494	0.238	£148,868	£28,621	0.139	£206,368	-£14,990	-0.082	£182,802
Natural history relapse rates	+ 20%	£35,183	0.287	£122,643	£28,371	0.164	£173,050	-£14,664	-0.104	£141,087
	- 20%	£35,805	0.284	£126,049	£28,870	0.162	£178,547	-£15,316	-0.101	£151,665
Dimethyl fumarate relapse rate†	+ 20%	£36,318	0.282	£128,904	£29,444	0.159	£185,070	-£14,166	-0.106	£133,413
	- 20%	£34,670	0.289	£119,888	£27,797	0.167	£166,904	-£15,814	-0.099	£160,159
Comparator relapse rate†	+ 20%	£34,552	0.290	£119,262	£27,698	0.167	£165,866	-£15,546	-0.100	£155,536
	- 20%	£36,435	0.281	£129,566	£29,543	0.159	£186,213	-£14,434	-0.105	£137,506
Dimethyl fumarate disability progression rate†	+ 20%	£37,185	0.110	£339,551	£30,312	-0.013	Dominated	-£13,298	-0.278	£47,765
	- 20%	£33,745	0.470	£71,736	£26,872	0.348	£77,270	-£16,738	0.082	Dominant

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Comparator disability progression rate†	+ 20%	£32,962	0.453	£72,716	£26,390	0.324	£81,484	-£16,239	0.071	Dominant
	- 20%	£38,135	0.109	£350,565	£30,938	-0.006	Dominated	-£13,710	-0.285	£48,122
Dimethyl fumarate dropouts	+ 20%	£29,835	0.236	£126,434	£22,962	0.113	£202,611	-£20,649	-0.152	£135,890
	- 20%	£42,407	0.343	£123,804	£35,533	0.220	£161,599	-£8,077	-0.045	£177,932
Comparator dropouts	+ 20%	£37,810	0.316	£119,744	£31,687	0.204	£154,952	-£8,019	-0.048	£167,351
	- 20%	£32,559	0.250	£130,270	£24,753	0.114	£217,018	-£23,420	-0.165	£142,063

† Change applied to reduction in relapse rate relative to placebo.
Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 26: PAS price univariate sensitivity analysis results part 1 (Table 96 in the submission document)

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Baseline results	-			Dominant			£8,159			Dominant			Dominant
EDSS state costs	+ 20%			Dominant			£4,510			Dominant			Dominant
	- 20%			Dominant			£11,809			£904			Dominant
Relapse costs	+ 20%			Dominant			£7,834			Dominant			Dominant
	- 20%			Dominant			£8,485			£112			Dominant
Patient utilities	+ 20%			Dominant			£6,946			Dominant			Dominant
	- 20%			Dominant			£9,887			Dominant			Dominant
Natural history relapse rates	+ 20%			Dominant			£7,823			Dominant			Dominant
	- 20%			Dominant			£8,497			£113			Dominant
Dimethyl fumarate relapse rate†	+ 20%			Dominant			£10,776			£2,431			Dominant
	- 20%			Dominant			£5,602			Dominant			Dominant
Comparator	+ 20%			Dominant			£4,959			Dominant			Dominant

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
relapse rate†	- 20%			Dominant			£11,452			£4,261			Dominant
Dimethyl fumarate disability progression rate†	+ 20%			Dominant			£32,906			£85,548			Dominant
	- 20%			Dominant			£426			Dominant			Dominant
Comparator disability progression rate†	+ 20%			Dominant			Dominant			Dominant			Dominant
	- 20%			Dominant			£78,533			£3,699,357			£8,737
Dimethyl fumarate dropouts	+ 20%			Dominant			£511			Dominant			Dominant
	- 20%			Dominant			£15,088			£10,909			£687
Comparator dropouts	+ 20%			Dominant			£13,434			£9,356			Dominant
	- 20%			Dominant			£1,089			Dominant			Dominant

† Change applied to reduction in relapse rate relative to placebo.

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 27: PAS price univariate sensitivity analysis results part 2 (Table 97 in the submission document)

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Baseline results	-			£14,823			Dominant			£451,419
EDSS state costs	+ 20%			£11,466			Dominant			£447,559
	- 20%			£18,181			Dominant			£455,279
Relapse costs	+ 20%			£13,733			Dominant			£448,236
	- 20%			£15,914			Dominant			£454,603
Patient utilities	+ 20%			£12,726			Dominant			£376,283
	- 20%			£17,748			Dominant			£564,049
Natural history relapse rates	+ 20%			£13,666			Dominant			£441,880
	- 20%			£15,993			Dominant			£461,237
Dimethyl fumarate relapse rate†	+ 20%			£17,943			Dominant			£427,835
	- 20%			£11,784			Dominant			£476,781
Comparator relapse rate†	+ 20%			£11,356			Dominant			£468,321
	- 20%			£18,396			Dominant			£435,326
Dimethyl fumarate disability progression rate†	+ 20%			£60,390			£19,790			£157,574
	- 20%			£3,734			Dominant			Dominant
Comparator disability progression rate†	+ 20%			£3,750			Dominant			Dominant
	- 20%			£63,176			£52,726			£157,849
Dimethyl fumarate dropouts	+ 20%			£7,122			Dominant			£321,174
	- 20%			£21,547			£2,306			£949,536
Comparator dropouts	+ 20%			£20,736			£2,074			£819,789
	- 20%			£5,187			Dominant			£331,692

† Change applied to reduction in relapse rate relative to placebo.
Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 28: Two-way sensitivity analysis results (Table 98 in the submission document)

Comparison	Analysis	Change	Dimethyl fumarate	Comparator	List price			PAS price		
					Incr. Cost	Incr. QALY	ICER	Incr. Cost	Incr. QALY	ICER
vs fingolimod	**Base case**				-£12,693	0.265	Dominant			Dominant
	Treatment effect on relapse rate	Lower confidence interval	0.45	0.36	-£12,589	0.264	Dominant			Dominant
		Upper confidence interval	0.62	0.5	-£12,397	0.263	Dominant			Dominant
	Treatment effect on disability progression rate	Lower confidence interval	0.43	0.63	-£13,100	0.273	Dominant			Dominant
		Upper confidence interval	0.84	1.01	-£11,924	0.226	Dominant			Dominant
	Drop outs	+ 20%	15.1%	12.8%	-£12,366	0.237	Dominant			Dominant
		- 20%	10.0%	8.5%	-£12,870	0.297	Dominant			Dominant
vs glatiramer acetate	**Base case**				£33,957	0.330	£102,830			£8,159
	Treatment effect on relapse rate	Lower confidence interval	0.45	0.59	£33,812	0.331	£102,190			£7,706
		Upper confidence interval	0.62	0.72	£34,100	0.330	£103,465			£8,609
	Treatment effect on disability progression rate	Lower confidence interval	0.43	0.64	£35,737	0.299	£119,660			£11,514
		Upper confidence interval	0.84	1.09	£32,042	0.345	£92,865			£6,101
	Drop outs	+ 20%	15.1%	13.2%	£30,274	0.298	£101,538			£7,108
		- 20%	10.0%	8.8%	£38,513	0.368	£104,763			£9,485
vs IM IFNβ-1a	**Base case**				£30,915	0.200	£154,781			Dominant

Comparison	Analysis	Change	Dimethyl fumarate	Comparator	List price			PAS price		
					Incr. Cost	Incr. QALY	ICER	Incr. Cost	Incr. QALY	ICER
30 µg	Treatment effect on relapse rate	Lower confidence interval	0.45	0.69	£30,972	0.199	£155,262			Dominant
		Upper confidence interval	0.62	0.88	£30,861	0.200	£154,320			Dominant
	Treatment effect on disability progression rate	Lower confidence interval	0.43	0.54	£31,353	0.253	£123,730			Dominant
		Upper confidence interval	0.84	0.87	£30,668	0.111	£275,085			£6,549
	Drop outs	+ 20%	15.1%	15.8%	£27,771	0.182	£152,420			Dominant
		- 20%	10.0%	10.5%	£34,737	0.220	£157,724			Dominant
vs SC IFNβ-1b 250 µg	**Base case**				£28,417	0.385	£73,724			Dominant
	Treatment effect on relapse rate	Lower confidence interval	0.45	0.6	£28,391	0.386	£73,631			Dominant
		Upper confidence interval	0.62	0.76	£28,352	0.386	£73,497			Dominant
	Treatment effect on disability progression rate	Lower confidence interval	0.43	0.55	£33,042	0.129	£255,937			£5,760
		Upper confidence interval	0.84	1.35	£21,895	0.739	£29,639			Dominant
	Drop outs	+ 20%	15.1%	10.7%	£24,885	0.347	£71,763			Dominant
		- 20%	10.0%	7.2%	£32,857	0.431	£76,298			Dominant
vs SC IFNβ-1a 22 µg	**Base case**				£35,494	0.285	£124,337			£14,823
	Treatment effect on relapse rate	Lower confidence interval	0.45	0.62	£35,526	0.285	£124,513			£14,943

Comparison	Analysis	Change	Dimethyl fumarate	Comparator	List price			PAS price		
					Incr. Cost	Incr. QALY	ICER	Incr. Cost	Incr. QALY	ICER
		Upper confidence interval	0.62	0.83	£35,474	0.286	£124,229			£14,750
	Treatment effect on disability progression rate	Lower confidence interval	0.43	0.58	£35,693	0.370	£96,553			£9,182
		Upper confidence interval	0.84	0.92	£35,555	0.160	£221,910			£35,060
	Drop outs	+ 20%	15.1%	21.1%	£32,151	0.266	£120,749			£15,010
		- 20%	10.0%	14.1%	£39,471	0.307	£128,573			£14,480
vs SC IFNβ-1a 44 µg	**Base case**				£28,621	0.163	£175,779			Dominant
	Treatment effect on relapse rate	Lower confidence interval	0.45	0.6	£28,481	0.163	£174,245			Dominant
		Upper confidence interval	0.62	0.74	£28,838	0.162	£178,191			Dominant
	Treatment effect on disability progression rate	Lower confidence interval	0.43	0.50	£28,683	0.241	£119,120			Dominant
		Upper confidence interval	0.84	0.83	£28,781	0.049	£585,120			Dominant
	Drop outs	+ 20%	15.1%	19.4%	£26,028	0.155	£167,919			Dominant
		- 20%	10.0%	12.9%	£31,666	0.171	£185,044			Dominant
vs natalizumab	**Base case**				-£14,990	-0.102	£146,300			£451,419
	Treatment effect on relapse rate	Lower confidence interval	0.45	0.29	-£15,203	-0.101	£149,788			£457,802
		Upper confidence interval	0.62	0.4	-£14,781	-0.103	£142,941			£445,272

Comparison	Analysis	Change	Dimethyl fumarate	Comparator	List price			PAS price		
					Incr. Cost	Incr. QALY	ICER	Incr. Cost	Incr. QALY	ICER
	Treatment effect on disability progression rate	Lower confidence interval	0.43	0.37	-£15,382	-0.139	£110,275			£341,825
		Upper confidence interval	0.84	0.82	-£14,669	-0.036	£410,051			£1,246,897
	Drop outs	+ 20%	15.1%	13.6%	-£13,678	-0.097	£140,416			£429,449
		- 20%	10.0%	9.0%	-£16,508	-0.108	£153,140			£478,075

Section 7.7.8 in the submission document

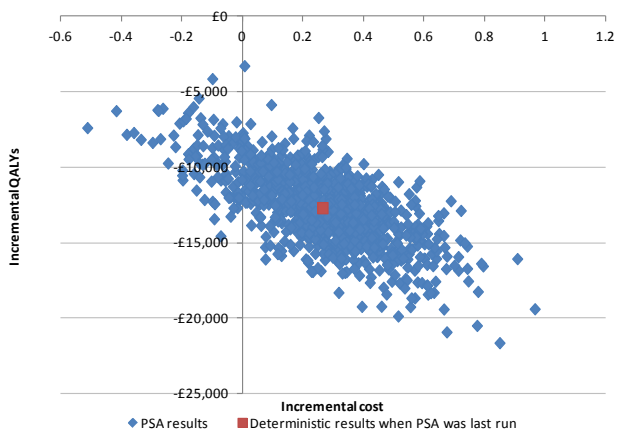
The revised results are given below (Table 29, Figure 7, Figure 8, Figure 9, Figure 10, Table 30, Figure 11, Figure 12 Figure 13, and Figure 14)

Table 29: Incremental cost and QALY range from PSA (list price) (Table 99 in the submission document)

Comparison	Incremental cost range			Incremental QALY range		
Dimethyl fumarate vs fingolimod		Mean	SD		Mean	SD
	Absolute	Min	Max	Absolute	Min	Max
	95% CI	Lower	Upper	95% CI	Lower	Upper
Dimethyl fumarate vs glatiramer acetate		Mean	SD		Mean	SD
	Absolute	Min	Max	Absolute	Min	Max
	95% CI	Lower	Upper	95% CI	Lower	Upper
Dimethyl fumarate vs IM IFNβ-1a 30 µg		Mean	SD		Mean	SD
	Absolute	Min	Max	Absolute	Min	Max
	95% CI	Lower	Upper	95% CI	Lower	Upper
Dimethyl fumarate vs SC IFNβ-1b 250 µg		Mean	SD		Mean	SD
	Absolute	Min	Max	Absolute	Min	Max
	95% CI	Lower	Upper	95% CI	Lower	Upper
Dimethyl fumarate vs SC IFNβ-1a 22 µg		Mean	SD		Mean	SD
	Absolute	Min	Max	Absolute	Min	Max
	95% CI	Lower	Upper	95% CI	Lower	Upper
Dimethyl fumarate vs SC IFNβ-1a 44 µg		Mean	SD		Mean	SD
	Absolute	Min	Max	Absolute	Min	Max
	95% CI	Lower	Upper	95% CI	Lower	Upper
Dimethyl fumarate vs natalizumab		Mean	SD		Mean	SD
	Absolute	Min	Max	Absolute	Min	Max

Comparison	Incremental cost range			Incremental QALY range		
		-£22,520.23	-£5,699.57		-1.0165	0.5979
	95% CI	Lower	Upper	95% CI	Lower	Upper

Figure 7: List price cost-effectiveness planes: dimethyl fumarate vs (1) fingolimod, (2) glatiramer acetate, (3) IM IFNβ-1a 30 µg (Avonex®), and (4) SC IFNβ-1b 250 µg (Betaferon®/Extavia®) (Figure 35 in the submission document)



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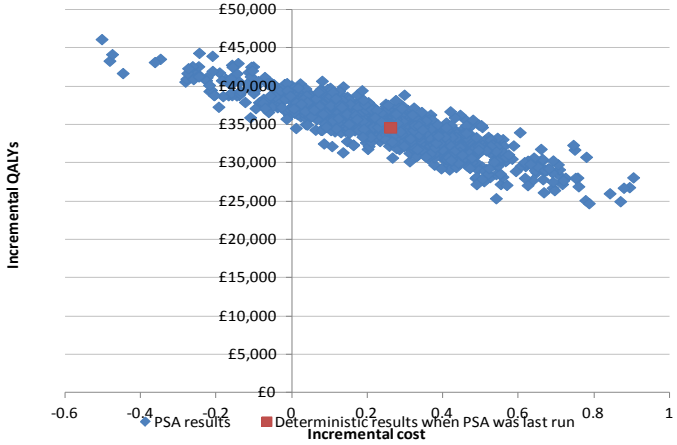

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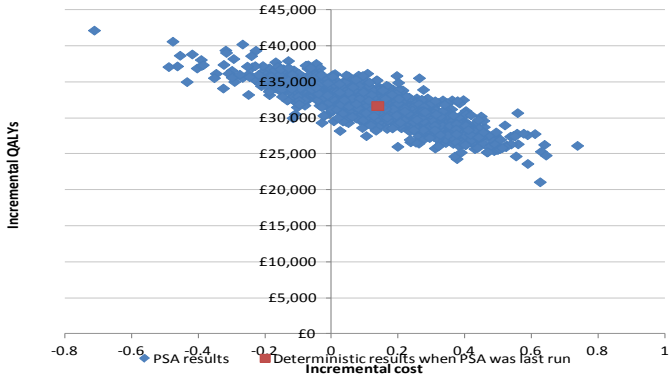

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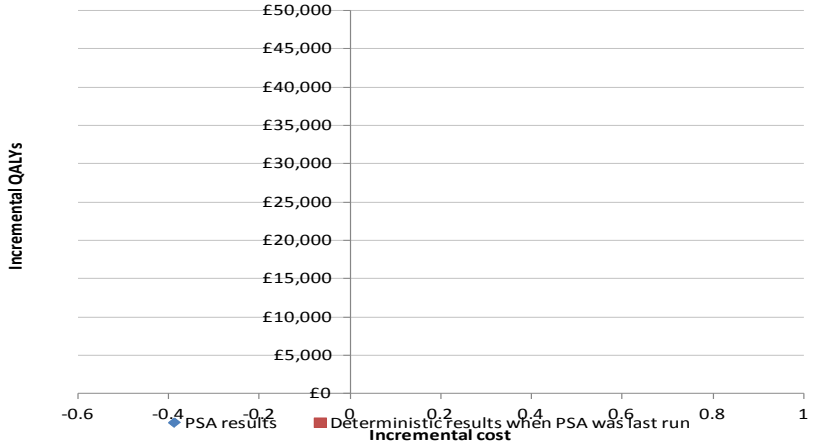
Figure 8: List price cost-effectiveness planes: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab (Figure 36 in the submission document)



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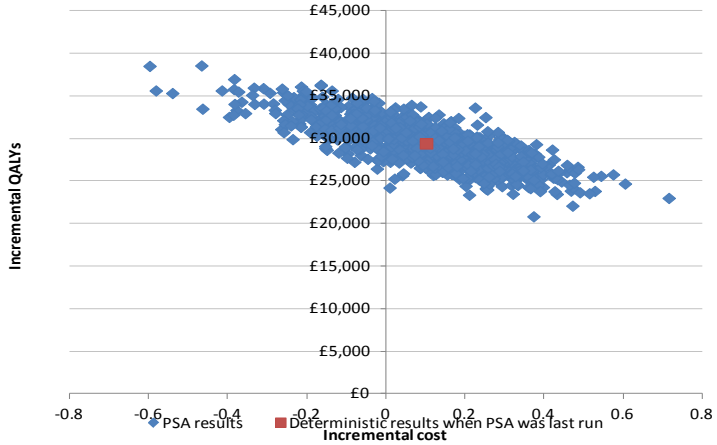

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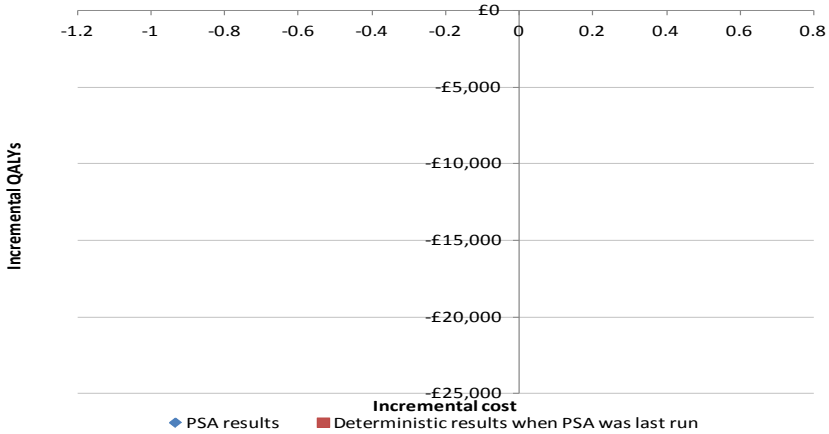

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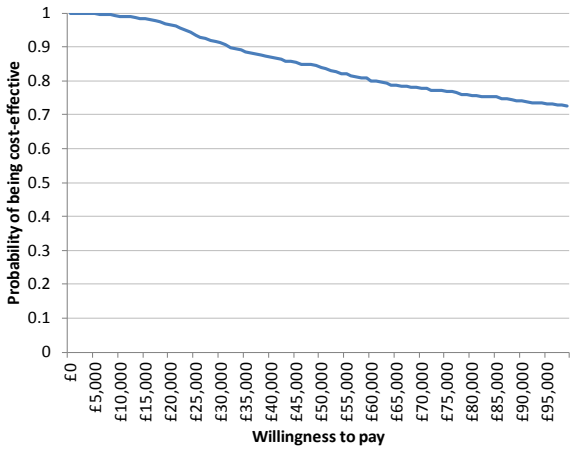
Figure 9: List price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) fingolimod, (2) glatiramer acetate, (3) IM IFNβ-1a 30 µg (Avonex®), and (4) SC IFNβ-1b 250 µg (Betaferon®/Extavia®) (Figure 37 in the submission document)



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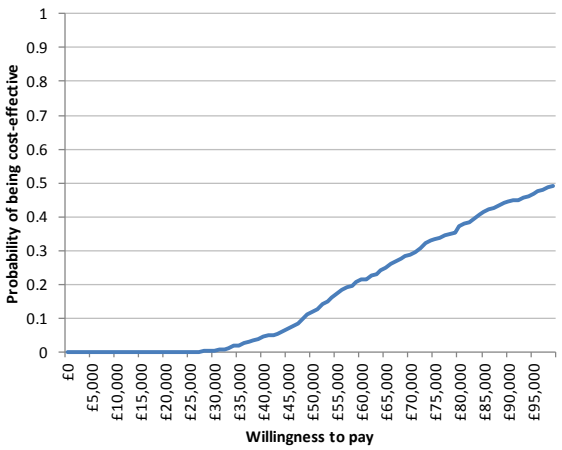

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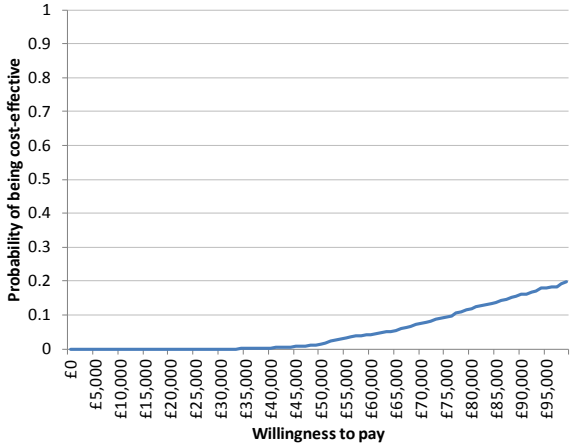

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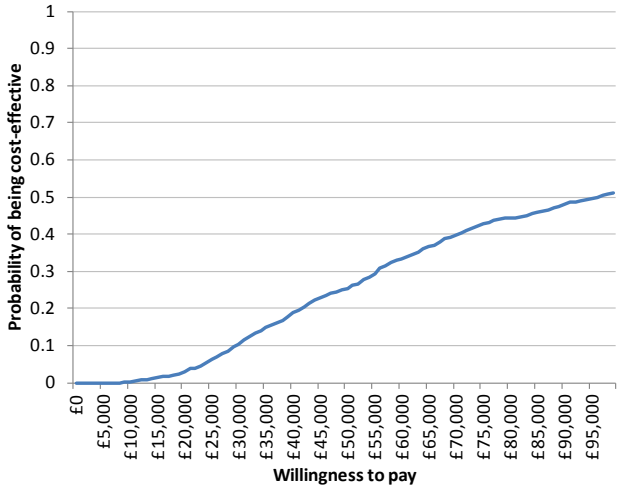

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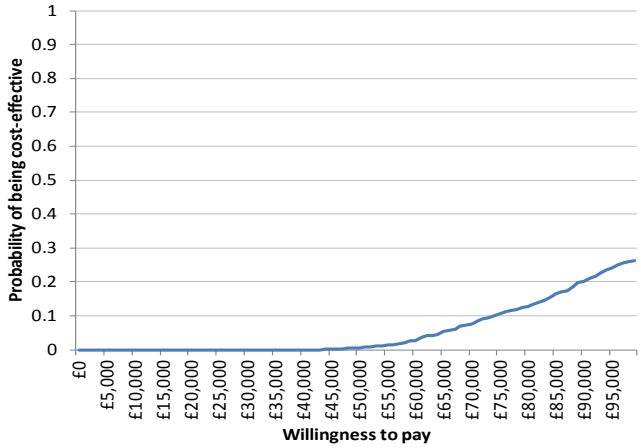
Figure 10: List price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab (Figure 38 in the submission document)



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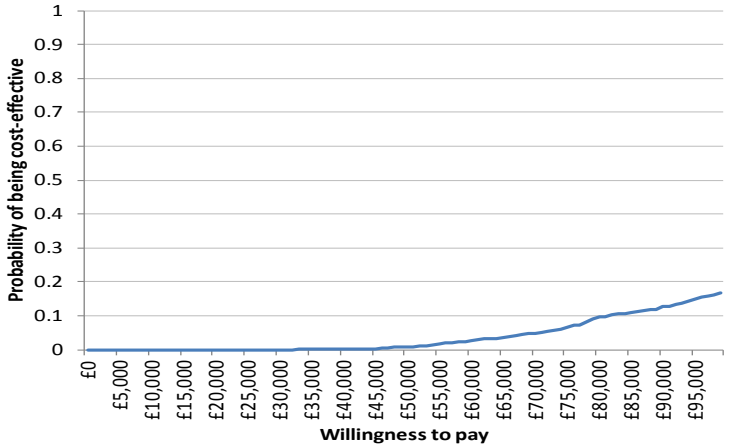

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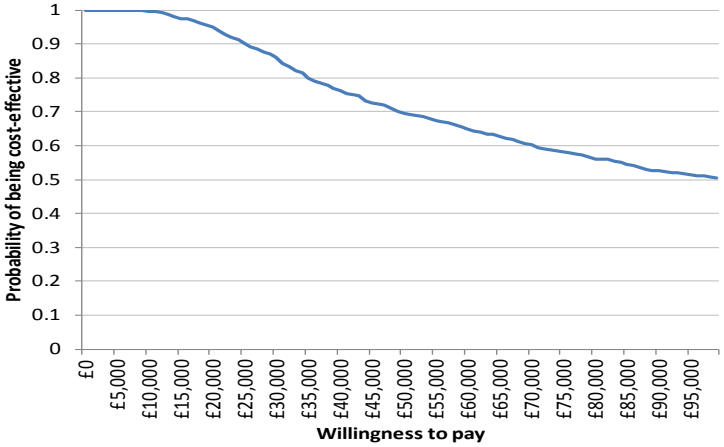

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Table 30: Incremental cost and QALY range from PSA (PAS price) (Table 100 in the submission document)

Comparison	Incremental cost range	Incremental QALY range
Dimethyl fumarate vs fingolimod		
Dimethyl fumarate vs glatiramer acetate		
Dimethyl fumarate vs IM IFNβ-1a 30 µg		
Dimethyl fumarate vs SC IFNβ-1b 250 µg		
Dimethyl fumarate vs SC IFNβ-1a 22 µg		
Dimethyl fumarate vs SC IFNβ-1a 44 µg		
Dimethyl fumarate vs natalizumab		

Figure 11: List price cost-effectiveness planes: dimethyl fumarate vs (1) fingolimod, (2) glatiramer acetate, (3) IM IFNβ-1a 30 µg (Avonex®), and (4) SC IFNβ-1b 250 µg (Betaferon®/Extavia®) (Figure 39 in the submission document)

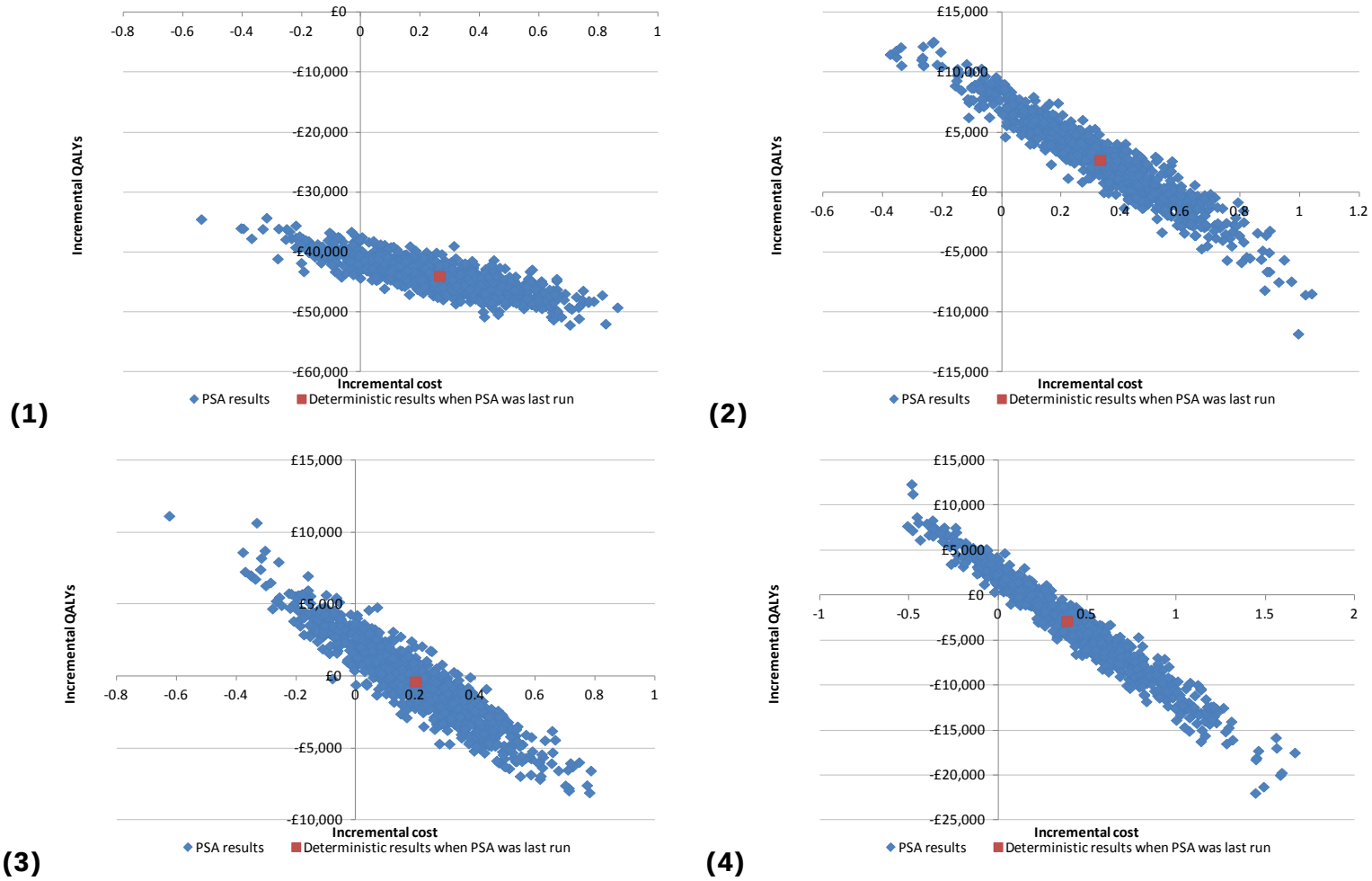
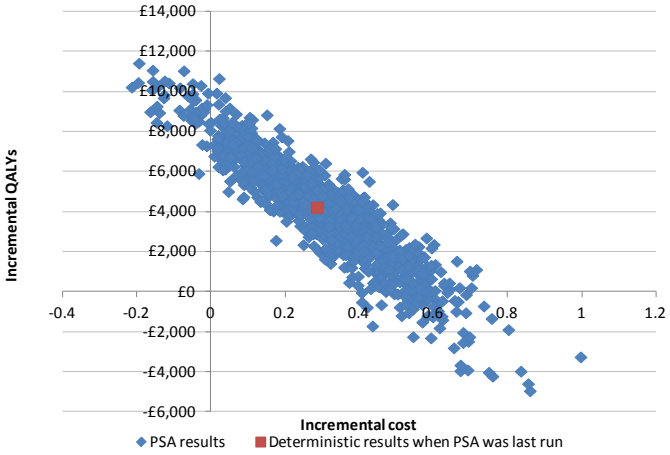


Figure 12: List price cost-effectiveness planes: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab (Figure 40 in the submission document)



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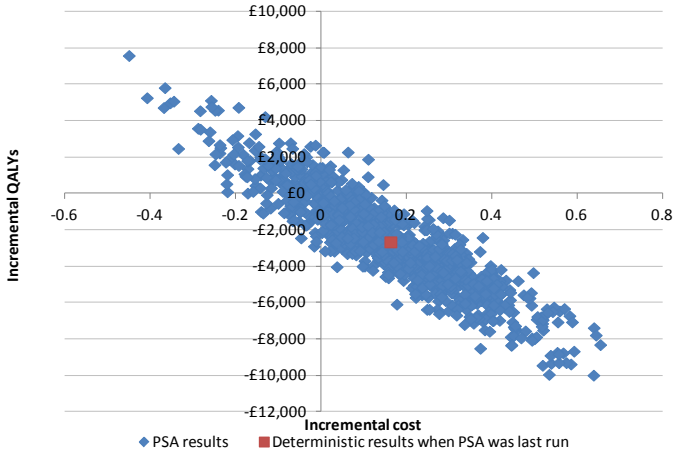

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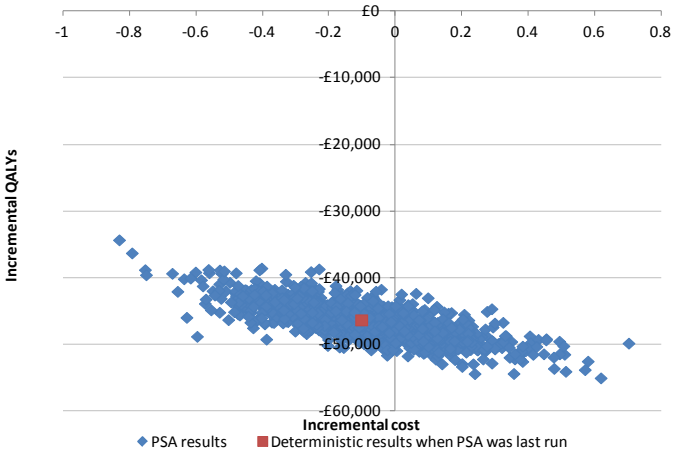

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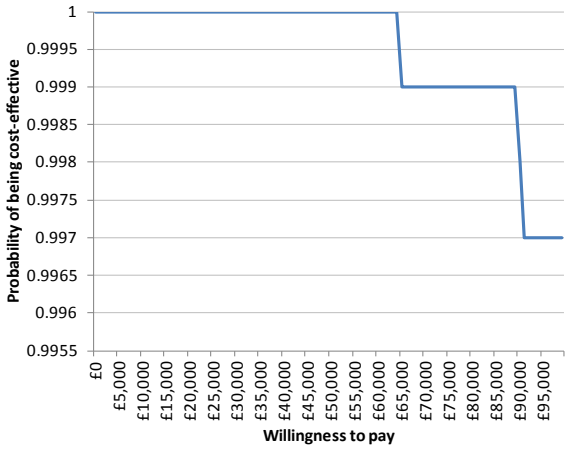
Figure 13: List price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) fingolimod, (2) glatiramer acetate, (3) IM IFNβ-1a 30 µg (Avonex®), and (4) SC IFNβ-1b 250 µg (Betaferon®/Extavia®) (Figure 41 in the submission document)



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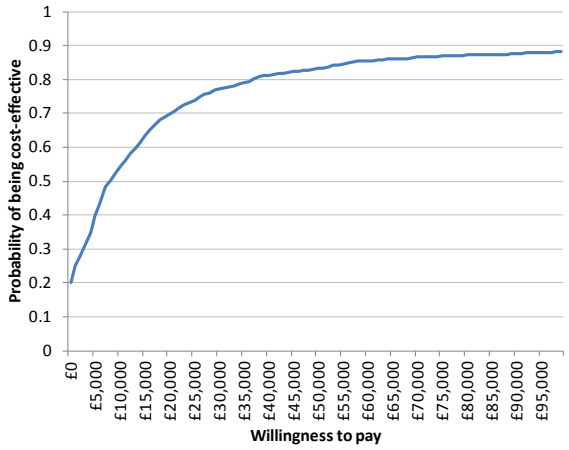

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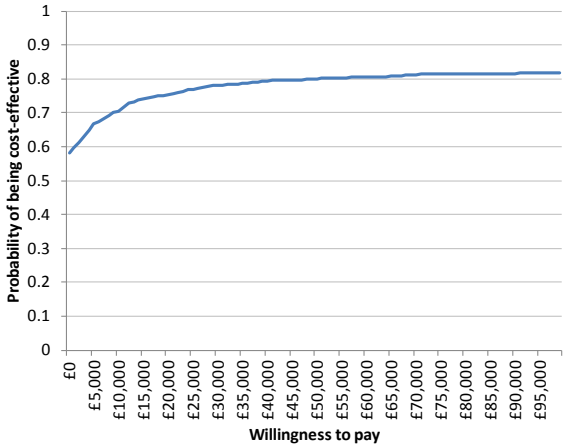

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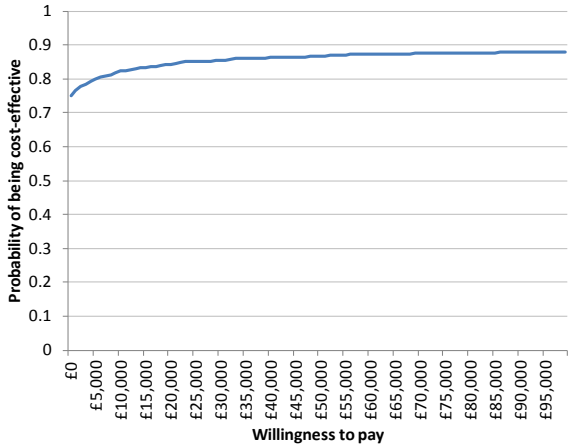

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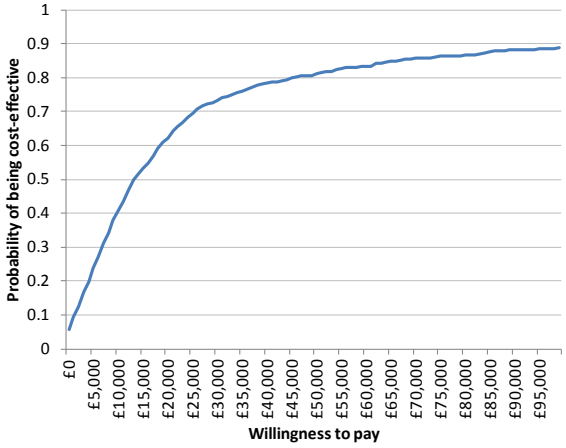
Figure 14: List price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab (Figure 42 in the submission document)



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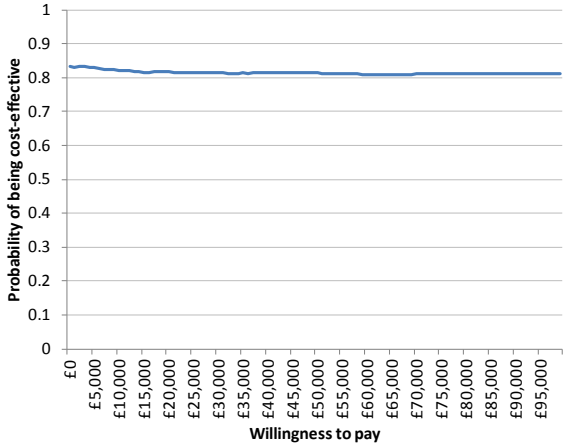

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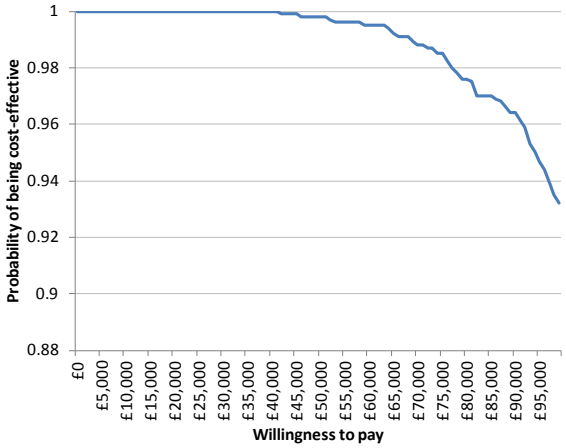


(3)

Section 7.7.9 in the submission document

The revised results are given below (Table 31, Table 32, Table 33, Table 34, and Table 35).

Table 31: Results of fingolimod simulated PAS price scenario analysis (Table 101 in the submission document)

Fingolimod price reduction	Annual fingolimod cost	List price			PAS price		
-5%	£18,217	-£9,011	0.265	Dominant			Dominant
-10%	£17,258	-£5,329	0.265	Dominant			Dominant
-15%	£16,300	-£1,650	0.265	Dominant			Dominant
-20%	£15,341	£2,033	0.265	£7,680			Dominant
-25%	£14,382	£5,716	0.265	£21,591			Dominant
-30%	£13,423	£9,399	0.265	£35,501			Dominant
-35%	£12,464	£13,082	0.265	£49,412			Dominant
-40%	£11,506	£16,761	0.265	£63,308			Dominant
-45%	£10,547	£20,444	0.265	£77,218			Dominant
-50%	£9,588	£24,127	0.265	£91,129			Dominant
-55%	£8,629	£27,810	0.265	£105,039			Dominant
-60%	£7,670	£31,493	0.265	£118,950			£870
-65%	£6,712	£35,172	0.265	£132,846			£14,766
-70%	£5,753	£38,855	0.265	£146,756			£28,676
-75%	£4,794	£42,537	0.265	£160,667			£42,587
-80%	£3,835	£46,220	0.265	£174,577			£56,497
-85%	£2,876	£49,903	0.265	£188,488			£70,408
-90%	£1,918	£53,582	0.265	£202,384			£84,304
-95%	£959	£57,265	0.265	£216,294			£98,214

Please note that Tables 32-35 have been reformatted to improve the clarity of the results relating to the discount rate scenario analyses.

Table 32: Results of scenario analysis part 1 (list price) (Table 102 in the submission document)

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
No waning effect (all set to 100%)	-	-£13,213	0.343	Dominant	£33,256	0.428	£77,698	£30,442	0.253	£120,457	£27,710	0.485	£57,094
Discount rate costs and benefits	0%	-£17,338	0.426	Dominant	£37,253	0.527	£70,654	£35,442	0.297	£119,236	£30,191	0.601	£50,222
Discount rate costs and benefits	6%	-£10,539	0.197	Dominant	£31,700	0.248	£127,968	£28,248	0.158	£178,866	£26,918	0.294	£91,498
Discount rate costs	0%	-£17,338	0.197	Dominant	£37,253	0.248	£150,384	£35,442	0.158	£224,418	£30,191	0.294	£102,623
Discount rate benefits	6%												
Discount rate costs	6%	-£10,539	0.426	Dominant	£31,700	0.527	£60,123	£28,248	0.297	£95,034	£26,918	0.601	£44,778
Discount rate benefits	0%												
Discount rate costs and benefits	1.5%	-£15,045	0.344	Dominant	£35,842	0.427	£83,913	£33,376	0.248	£134,592	£29,516	0.492	£60,010
Discount rate costs	1.5%	-£15,045	0.265	Dominant	£35,842	0.330	£108,539	£33,376	0.200	£167,104	£29,516	0.385	£76,573
Discount rate benefits	3.5%												
Discount rate costs	3.5%	-£12,693	0.344	Dominant	£33,957	0.427	£79,499	£30,915	0.248	£124,666	£28,417	0.492	£57,777
Discount rate benefits	1.5%												
No caregiver utility	-	-£12,693	0.238	Dominant	£33,957	0.298	£114,025	£30,915	0.186	£166,590	£28,417	0.351	£81,050
Time horizon	1 year	-£1,685	0.003	Dominant	£9,570	0.007	£1,469,330	£7,296	0.016	£443,312	£8,499	0.013	£630,698

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
	5 year	-£5,561	0.045	Dominant	£28,234	0.062	£451,982	£23,240	0.067	£344,532	£25,267	0.089	£283,285
	10 year	-£8,695	0.112	Dominant	£34,582	0.145	£237,987	£29,675	0.113	£262,849	£30,174	0.186	£162,519
	20 year	-£11,914	0.219	Dominant	£34,578	0.275	£125,852	£31,098	0.174	£178,973	£29,180	0.327	£89,271
	50 year	-£12,583	0.277	Dominant	£34,113	0.345	£98,941	£30,988	0.207	£149,829	£28,578	0.400	£71,360
Mortality	General population	-£13,336	0.275	Dominant	£33,315	0.342	£97,386	£30,676	0.205	£149,604	£27,701	0.398	£69,552
Annualised relapse rate relative to placebo	Lower 95% CI	-£12,589	0.264	Dominant	£33,812	0.331	£102,190	£30,972	0.199	£155,262	£28,391	0.386	£73,631
	Upper 95% CI	-£13,718	0.269	Dominant	£32,778	0.336	£97,687	£29,540	0.206	£143,432	£27,031	0.392	£69,004
Disability progression rate relative to placebo	Lower 95% CI	-£13,100	0.273	Dominant	£35,737	0.299	£119,660	£31,353	0.253	£123,730	£33,042	0.129	£255,937
	Upper 95% CI	-£11,924	0.226	Dominant	£32,042	0.345	£92,865	£30,668	0.111	£275,085	£21,895	0.739	£29,639
London Ontario transition matrix for RRMS-RRMS transitions EDSS 1 - 9		-£11,875	0.230	Dominant	£31,075	0.287	£108,239	£28,183	0.175	£160,675	£26,165	0.338	£77,495

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 33: Results of scenario analysis part 2 (list price) (Table 103 in the submission document)

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
No waning effect (all set to 100%)	-	£34,440	0.385	£89,551	£28,109	0.224	£125,630	-£14,543	-0.153	£95,087
Discount rate costs and benefit	0%	£40,479	0.452	£89,583	£33,362	0.253	£131,952	-£17,862	-0.171	£104,325
Discount rate costs and benefits	6%	£32,461	0.216	£150,233	£25,893	0.125	£206,789	-£13,370	-0.074	£179,625
Discount rate cost	0%	£40,479	0.216	£187,345	£33,362	0.125	£266,440	-£17,862	-0.074	£239,979
Discount rate benefits	6%									
Discount rate costs	6%	£32,461	0.452	£71,838	£25,893	0.253	£102,411	-£13,370	-0.171	£78,088
Discount rate benefits	0%									
Discount rate costs and benefits	1.5%	£38,235	0.367	£104,125	£31,181	0.207	£150,597	-£16,532	-0.136	£121,535
Discount rate costs	1.5%	£38,235	0.285	£133,939	£31,181	0.163	£191,502	-£16,532	-0.102	£161,351
Discount rate benefits	3.5%									
Discount rate costs	3.5%	£35,494	0.367	£96,661	£28,621	0.207	£138,233	-£14,990	-0.136	£110,198
Discount rate benefits	1.5%									
No caregiver utility	-	£35,494	0.260	£136,640	£28,621	0.150	£190,873	-£14,990	-0.092	£163,117
Time horizon	1 year	£7,882	0.012	£667,591	£5,886	0.011	£552,008	-£2,027	-0.001	£2,795,740
	5 year	£26,374	0.064	£410,268	£20,163	0.045	£449,120	-£9,586	-0.013	£711,889
	10 year	£34,441	0.131	£263,446	£26,874	0.081	£333,679	-£13,712	-0.037	£369,580

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
	20 year	£35,930	0.237	£151,509	£28,776	0.136	£210,990	-£15,075	-0.081	£186,265
	50 year	£35,616	0.299	£119,144	£28,683	0.171	£168,149	-£15,048	-0.109	£138,160
Mortality	General population	£35,014	0.295	£118,685	£28,410	0.168	£169,416	-£14,804	-0.106	£139,207
Annualised relapse rate relative to placebo	Lower 95% CI	£35,526	0.285	£124,513	£28,481	0.163	£174,245	-£15,203	-0.101	£149,788
	Upper 95% CI	£34,153	0.292	£117,153	£27,517	0.168	£163,978	-£16,102	-0.097	£165,259
Disability progression rate relative to placebo	Lower 95% CI	£35,693	0.370	£96,553	£28,683	0.241	£119,120	-£15,382	-0.139	£110,275
	Upper 95% CI	£35,555	0.160	£221,910	£28,781	0.049	£585,120	-£14,669	-0.036	£410,051
London Ontario transition matrix for RRMS-RRMS transitions EDSS 1 - 9		£32,002	0.246	£130,152	£25,775	0.139	£184,854	-£12,973	-0.085	£151,964

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 34: Results of scenario analysis part 1 (PAS price) (Table 104 in the submission document)

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
No waning effect (all set to 100%)				Dominant			£3,062			Dominant			Dominant
Discount rate costs and benefits				Dominant			£1,140			Dominant			Dominant
Discount rate costs and benefits				Dominant			£13,780			Dominant			Dominant
Discount rate costs				Dominant			£2,427			Dominant			Dominant
Discount rate benefits													
Discount rate costs				Dominant			£6,474			Dominant			Dominant
Discount rate benefits													
Discount rate costs and benefits				Dominant			£4,003			Dominant			Dominant
Discount rate costs				Dominant			£5,178			Dominant			Dominant
Discount rate benefits													
Discount rate costs				Dominant			£6,308			Dominant			Dominant
Discount rate benefits													
No caregiver utility				Dominant			£9,048			Dominant			Dominant
Time horizon				Dominant			£350,753			£652			£90,040
				Dominant			£88,363			£7,790			£28,624

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
				Dominant			£38,863			£6,555			£6,672
				Dominant			£12,637			Dominant			Dominant
				Dominant			£8,238			Dominant			Dominant
Mortality				Dominant			£5,776			Dominant			Dominant
Annualised relapse rate relative to placebo				Dominant			£7,706			Dominant			Dominant
				Dominant			£4,518			Dominant			Dominant
Disability progression rate relative to placebo				Dominant			£11,514			Dominant			£5,760
				Dominant			£6,101			£6,549			Dominant
London Ontario transition matrix for RRMS-RRMS transitions EDSS 1 – 9				Dominant			£7,923			Dominant			Dominant

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 35: Results of scenario analysis part 2 (PAS price) (Table 105 in the submission document)

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
No waning effect (all set to 100%)				£6,487			Dominant			£303,960
Discount rate costs and benefits				£8,471			Dominant			£318,396
Discount rate costs and benefits				£19,319			Dominant			£559,663
Discount rate costs				£17,715			Dominant			£732,405
Discount rate benefits										
Discount rate costs				£9,238			Dominant			£243,300
Discount rate benefits										
Discount rate costs and benefits				£11,173			Dominant			£372,458
Discount rate costs				£14,372			Dominant			£494,479
Discount rate benefits										
Discount rate costs				£11,524			Dominant			£340,024
Discount rate benefits										
No caregiver utility				£16,290			Dominant			£503,310
Time horizon				£50,509			Dominant			£12,842,218
				£56,931			Dominant			£2,398,65

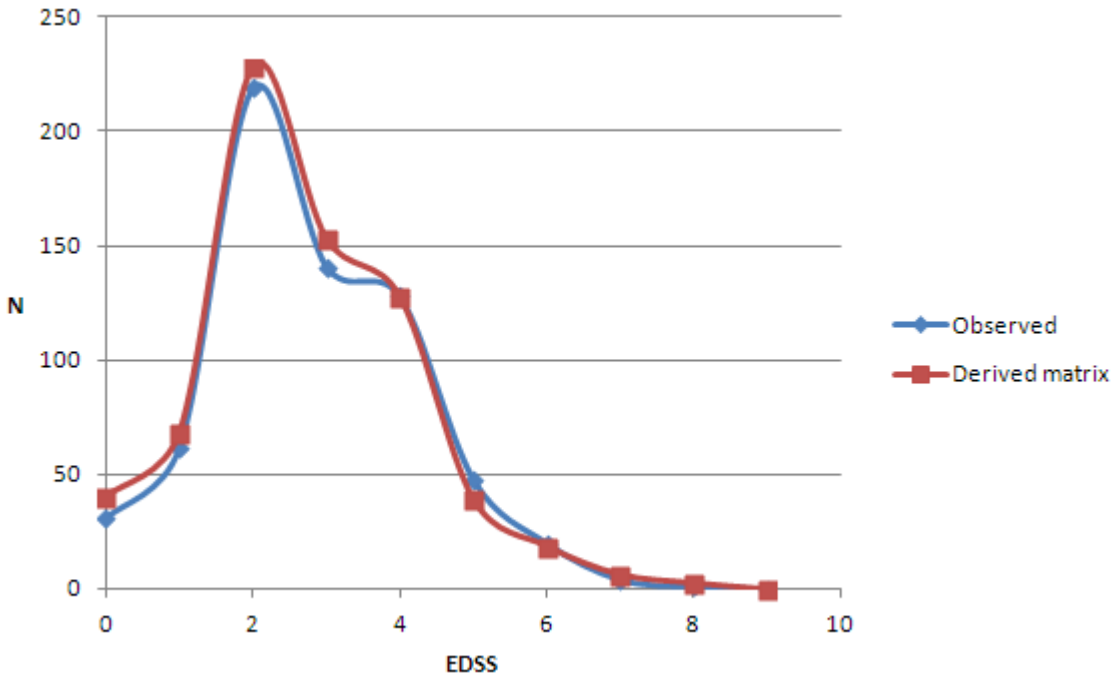
Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
										8
				£42,118			Dominant			£1,149,456
				£20,340			Dominant			£570,617
				£14,529			Dominant			£425,289
Mortality				£12,459			Dominant			£433,898
Annualised relapse rate relative to placebo				£14,943			Dominant			£457,802
				£9,915			Dominant			£486,114
Disability progression rate relative to placebo				£9,182			Dominant			£341,825
				£35,060			Dominant			£1,246,897
London Ontario transition matrix for RRMS-RRMS transitions EDSS 1 - 9				£13,020			Dominant			£489,317

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Section 7.8.1 in the submission document

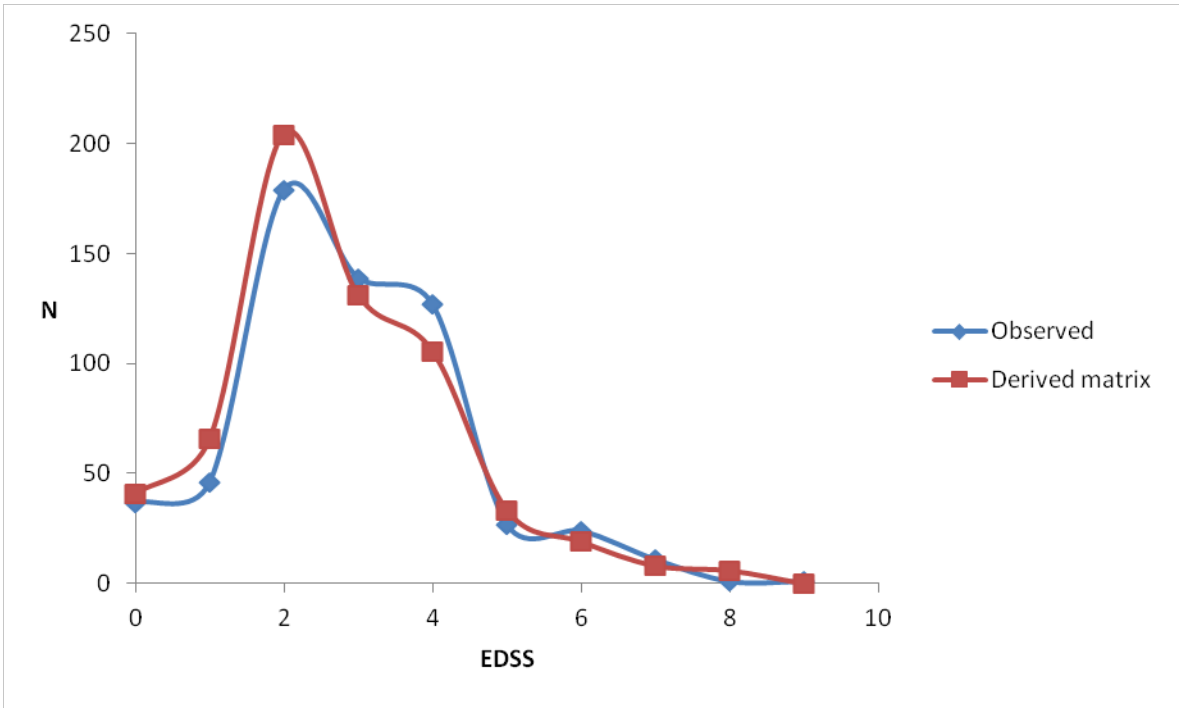
The revised figures are given below (Figure 15, Figure 16, Figure 17, and Figure 18). The EDSS distributions observed for the placebo arm (Figure 15 and Figure 16) did not change when the model was updated with hazard ratios.

Figure 15: Line graph of model EDSS state occupancy at end of year 1 (derived matrix), and observed patient distributions at week 48 in the clinical trial for the placebo population (Figure 43 in the submission document)



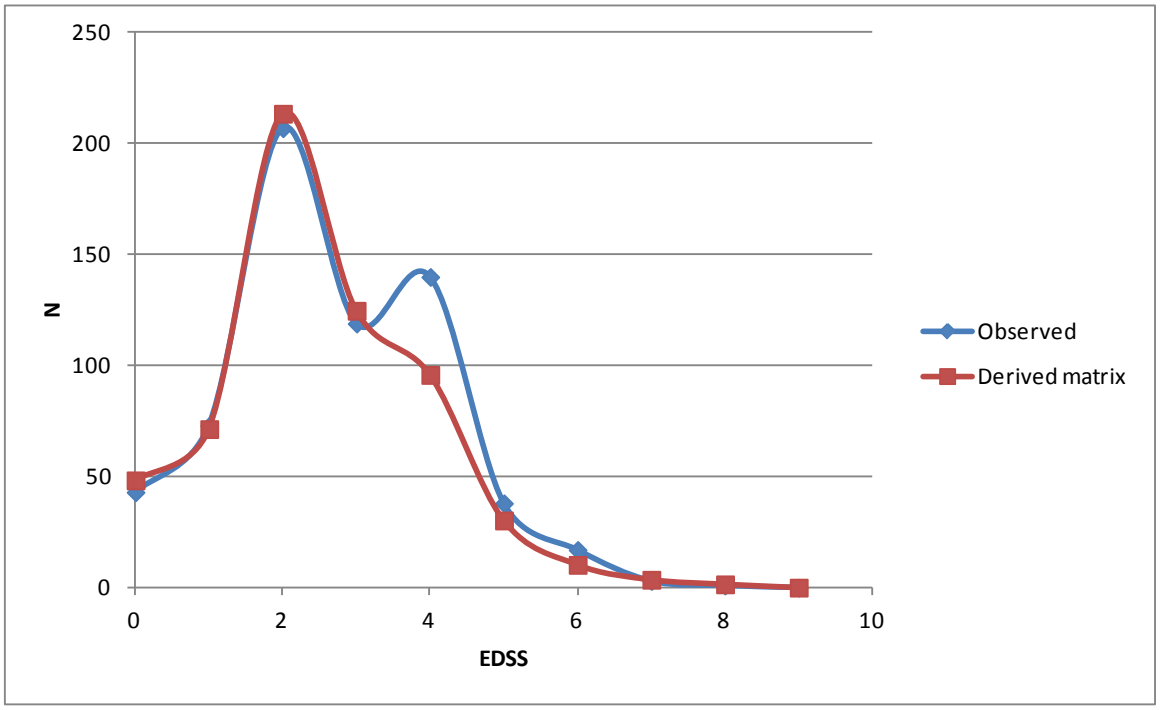
Abbreviations: EDSS, Expanded Disability Status Scale.
Mean square error = 46.2, Root mean square error = 6.8

Figure 16: Line graph of model EDSS state occupancy at end of year 2 (derived matrix), and observed patient distributions at week 96 in the clinical trial for the placebo population (Figure 44 in the submission document)



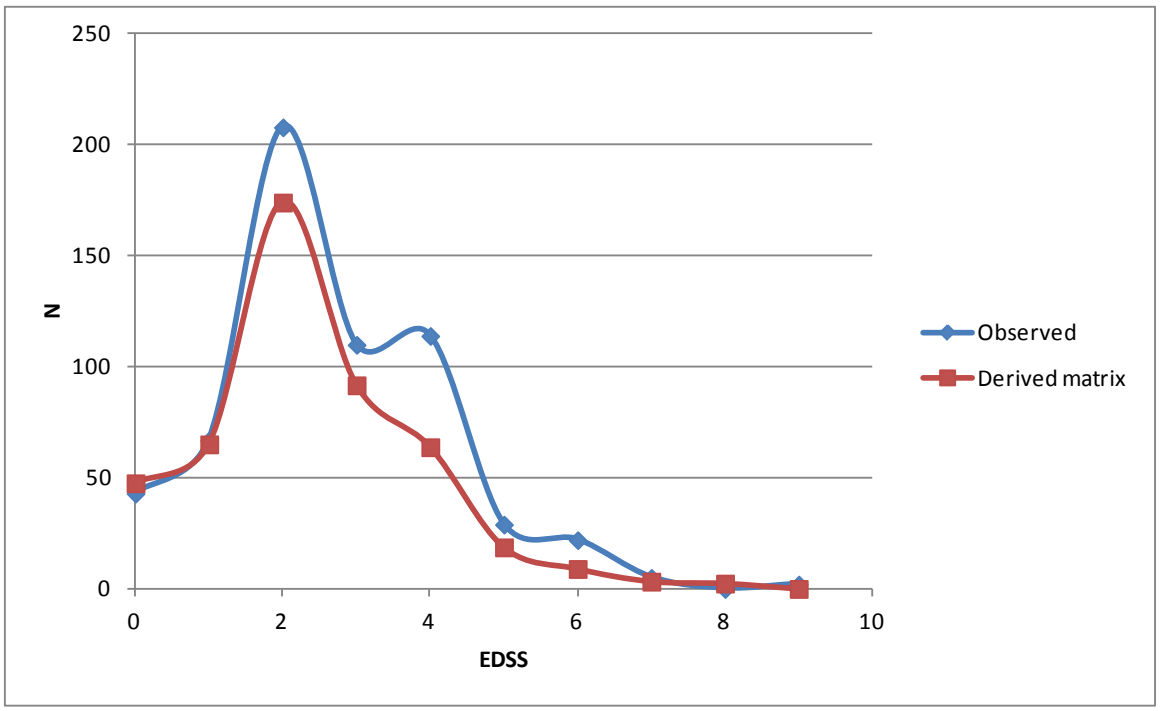
Abbreviations: EDSS, Expanded Disability Status Scale.
Mean square error = 166.1, Root mean square error = 12.89

Figure 17: Line graph of model EDSS state occupancy at end of year 1 (derived matrix), and observed patient distributions at week 48 in the clinical trial for the dimethyl fumarate BID population (Figure 45 in the submission document)



Abbreviations: EDSS, Expanded Disability Status Scale.
Mean square error = 216.1, Root mean square error = 14.70

Figure 18: Line graph of model EDSS state occupancy at end of year 2 (derived matrix), and observed patient distributions at week 96 in the clinical trial for the dimethyl fumarate population (Figure 46 in the submission document)



Abbreviations: EDSS, Expanded Disability Status Scale.
Mean square error = 430.5, Root mean square error = 20.75.

Validation of mortality estimates

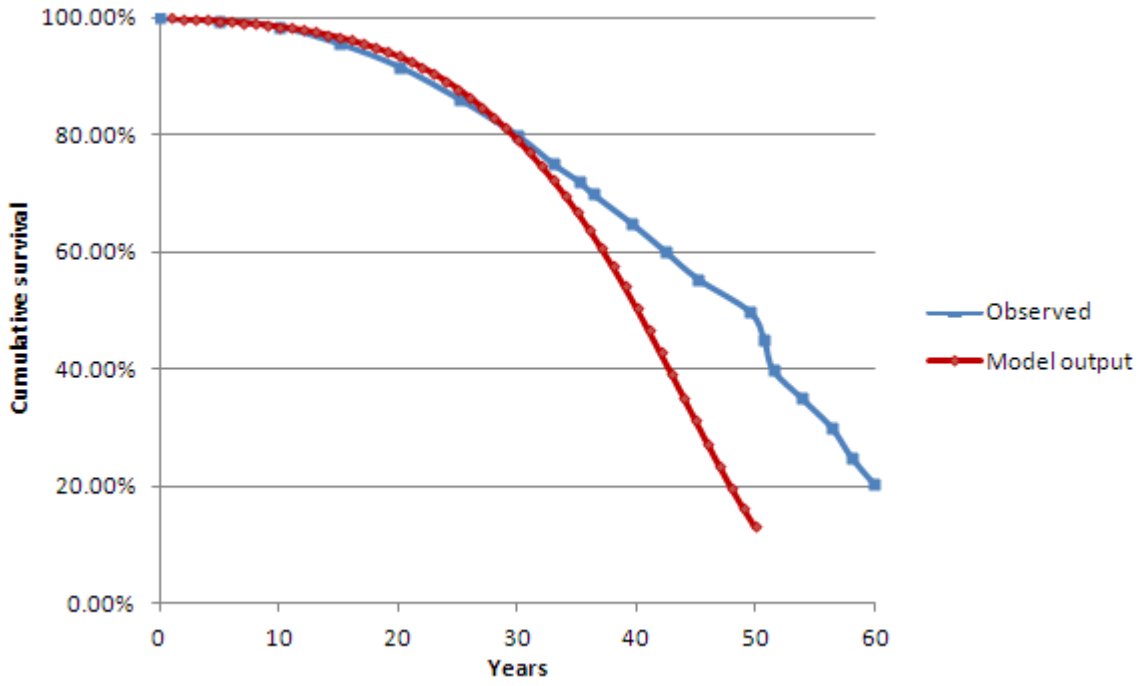
The results of this validation did not change with the updated hazard ratios. The results are shown in Table 36 and Figure 19.

Table 36: Initial patient characteristics for the RRMS population as reported by Kingwell et al (Table 106 in the submission document)

Variable	Input value
Initial cohort size	6172
Median age at onset (starting age)	30 years
Years since diagnosis	0 years (onset at beginning of model)
Female to male ratio	2.9

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis.

Figure 19: Comparison of cumulative survival in the model against observed studies (Figure 47 in the submission document)



Mean square error = 2.45%, Root mean square error = 15.6%
Mean square error until 0 - 35 years: 0.05%, 35 - 50 years: 4.42%

A8 Priority Question: There appears to be some inconsistency between results reported in the submission.

a) Please clarify whether the MTC results reported in pages 139 to 152 of the MS were adjusted for covariates or unadjusted and whether these are the results that are used in the economic model.

Biogen Idec response:
The results reported from pages 139 to 152 are unadjusted results without covariates. Further detail of this is provided in A8b below.

b) If the results on pages 139 to 152 of the MS are the unadjusted results, there appear to be inconsistencies between these results and those reported in Tables 112 to 122, on pages 350 to 356 of the MS. Please clarify the apparent discrepancies between the results.

Biogen Idec response:
The original systematic review was conducted in October 2011. As a part of this review, a covariate analysis was performed - the results from this were robust and showed that there was little or no impact of the covariates on the outcomes of interest.
The systematic review was then updated with new searches in October 2012 to capture the most recent clinical evidence. The updated search included clinical evidence for teriflunomide, which received its marketing authorisation from the FDA in September 2012. All analyses were updated with the new data, which included teriflunomide. However, as there was little impact of covariates on the outcomes in the original analysis, no analysis evaluating the impact of covariates on the new data set was performed.

c) Please present the results of the MTC analyses for all comparators versus placebo as well as versus dimethyl fumarate.

Biogen Idec response:

The MTC results for all the efficacy outcomes are presented in Table 37.

Table 37: MTC results for efficacy outcomes relative to placebo

Comparison	ARR	Steroid treated ARR	Proportion of patients with relapse at 24 months	Proportion of patients with relapse at 12 months	Proportion of relapse free patients at 24 months	Proportion of relapse free patients at 12 months	Confirmed disability progression sustained for 3 months at 24 months	Confirmed disability progression sustained for 6 months at 24 months	Change in EDSS score at 24 Months
BG00012									
IFN beta-1a 30 mcg once weekly									
IFN beta-1b 250 mcg EOD	0.675 (0.601 – 0.758)	0.718 (0.435 – 1.184)	0.824 (0.728 – 0.932)	0.675 (0.007 – 60.39)	1.225 (1.071 – 1.401)	1.129 (0.169 – 7.549)	0.859 (0.545 – 1.352)	0.546 (0.115 – 2.596)	-0.722 (-1.01 - -0.434)
GA 20 mg od	0.653 (0.590 – 0.721)	0.654 (0.534 – 0.801)	0.804 (0.723 – 0.895)	0.689 (0.154 – 3.082)	1.240 (1.124 – 1.369)	1.105 (0.655 – 1.863)	0.832 (0.636 – 1.087)	0.584 (0.170 – 2.007)	-0.169 (-0.364 – 0.027)
IFN beta-1a 22 mcg tiw	0.718 (0.623 – 0.826)	0.739 (0.580 – 0.942)	0.864 (0.767 – 0.973)	0.813 (0.342 – 1.932)	1.254 (0.893 – 1.760)	1.503 (0.218 – 10.37)	0.733 (0.584 – 0.920)	-	-0.271 (-0.582 – 0.041)
IFN beta-1a 44 mcg tiw	0.666 (0.597 – 0.742)	0.606 (0.492 – 0.746)	0.782 (0.696 – 0.878)	0.710 (0.272 – 1.852)	1.336 (1.160 – 1.538)	1.798 (0.306 – 10.56)	0.646 (0.504 – 0.827)	0.538 (0.061 – 4.735)	-0.303 (-0.523 - -0.08)
Teriflunomide 7 mg od	0.687 (0.581 – 0.812)	-	0.827 (0.693 – 0.987)	-	1.757 (1.007 – 1.372)	-	0.765 (0.550 – 1.066)	-	
Teriflunomide 14 mg od	0.681 (0.575 – 0.807)	-	0.772 (0.642 – 0.928)	-	1.233 (1.059 – 1.435)	-	0.716 (0.506 – 1.012)	-	
Fingolimod 0.5 mg od	0.454 (0.399 – 0.516)	0.414 (0.340 – 0.505)	0.537 (0.472 – 0.611)	0.512 (0.061 – 4.316)	1.712 (1.529 – 1.916)	1.795 (0.248 – 13.01)	0.797 (0.631 – 1.007)	0.609 (0.148 – 2.509)	-0.156 (-0.487 – 0.176)

Comparison	ARR	Steroid treated ARR	Proportion of patients with relapse at 24 months	Proportion of patients with relapse at 12 months	Proportion of relapse free patients at 24 months	Proportion of relapse free patients at 12 months	Confirmed disability progression sustained for 3 months at 24 months	Confirmed disability progression sustained for 6 months at 24 months	Change in EDSS score at 24 Months
Natalizumab 300 mg q4w	0.343 (0.294 – 0.400)	0.308 (0.242 – 0.391)	0.513 (0.427 – 0.617)	0.502 (0.133 – 1.897)	1.571 (1.359 – 1.816)	1.335 (0.706 – 2.523)	0.552 (0.373 – 0.818)	-	-0.361 (-0.693 - -0.03)

For annualized relapse rate- rate ratio vs. placebo, and for change in EDSS, absolute difference was reported. For other binomial outcomes, relative risk vs. placebo reported; ARR: Annualised Relapse Rate; EOD: Every Other Day; ES: Effect Size; GA: Glatiramer Acetate; IFN: Interferon; mcg: Microgram; mg: Milligram; MTC: Mixed Treatment Comparison; od: Once Daily; q4w: Every 4 Weeks; tiw: Thrice A Week; ES<1 indicates favourable efficacy of intervention (except in Relapse free, where ES>1 indicates favorable efficacy and ES<0 indicates favorable efficacy in case of EDSS change); Cells highlighted in blue represent significant results

d) In Table 52 (page 183 of the MS) some of the relative risks for intervention versus placebo and annual discontinuation risk values appear inconsistent with each other.

i. Please check all the values in Table 52, page183 of the MS, for consistency and provide correct data if there are errors, and;
ii. ensure that these are derived from the correct MTC results.

Biogen Idec response:
A corrected version of the table is given in Table 38.

Table 38: Annual discontinuation risk used in the model

Treatment	Relative risk vs. placebo	Annual discontinuation risk
Dimethyl fumarate		
Fingolimod	0.74	10.68%
Glatiramer acetate	0.76	10.97%
IM IFNβ-1a 30 µg		
SC IFNβ-1b 250 µg	0.62	8.95%
Natalizumab	0.78	11.26%
Placebo	NA	14.43%
SC IFNβ-1a 22 µg	1.22	17.60%
SC IFNβ-1a 44 µg	1.12	16.16%

Abbreviations: IFN, interferon; IM, intramuscular; SC, subcutaneous.

A9. Priority Question: Please indicate how the covariates included in the MTC covariate analyses (pages 344 to 349 of the MS) were specified as this is unclear for some of the variables. Please clarify whether the covariates were continuous or discrete, and if a variable was discrete please provide details of how it was defined.

Biogen Idec response:
All the variables that were used as covariates in the model were continuous. A list of variables used as covariates is provided in Table 39.

Table 39: List of study and patient characteristics for which covariate analyses were performed

Study and baseline covariates
Study duration in years (mean)
Mean age in years (mean)
Disease duration in years (mean)
Female percentage (%)
Relapse in prior 1 year (mean)
EDSS score at baseline (mean)

Abbreviations: EDSS, Expanded Disability Status Scale

A10. Figure 57, page 360 of the MS, is labelled as “analyses of confirmed disability progression sustained for 3 months at 24 months”. It appears that this may be the network for 6 months sustained disability. Please clarify whether this is correct.

Biogen Idec response:
Figure 57 is incorrectly labelled as “analyses of confirmed disability progression sustained for 3 months at 24 months”. It should state “analyses of confirmed disability progression sustained for 6 months at 24 months”.

A11. Please provide the rationale for including teriflunomide in the MTC to strengthen the placebo arm but not including other interventions such as alemtuzumab and laquinimod.

Biogen Idec response:
Only licensed interventions and their approved doses for the treatment of relapsing remitting multiple sclerosis (RRMS) were included in this review. During the review process, teriflunomide received an FDA approval on 12th September 2012 and was therefore included in the analysis. Alemtuzumab and lacquinimod are not licensed for the treatment of patients included in the decision problem.

Non-RCT evidence

A12. Page 40 of the MS states that two records of non-RCTs were identified and the reader is referred to Section 6.2.7. These are described in Section 6.2.7. and a quality assessment of each is provided in Appendix 7 (page 306 of the MS). However, Section 6.2.7 (page 47 of the MS) states that no non-RCTs were considered relevant and there is no discussion of the results of these two studies in the body of the submission.

a) Please clarify whether any non-RCT evidence was included in the review of dimethyl fumarate, either providing appropriate details of the two included studies or a justification for excluding those identified.

b) Only one of the two non-RCTs in Appendix 7 is included in the reference pack (Schimrigk, 2006). Please provide a copy of the other non-RCT (Macmanus, 2011).

Biogen Idec response:
Two non-RCTs were identified by the systematic review; however, on closer inspection these were not deemed relevant to the submission. One study was a post-hoc analysis of a Phase II RCT (MacManus 2011) while the second included the intervention of interest only as part of a combined treatment with other fumaric esters (Schimrigk 2006). This should have been clarified in the text. We apologise for the error. We have included MacManus 2011 with this response so the ERG can inspect the reference.

Other

A13. The draft European Public Assessment Report (EPAR) includes some limited interim data from study 109MS303 up to August 2011. Please provide the results of any more recent analyses available from this study for annualised relapse rate (ARR), Expanded Disability Status Score (EDSS) progression sustained at three months, and occurrence of adverse events.

Biogen Idec response:
STUDY 109MS303 (ENDORSE) is the 5 year open-label extension study for DEFINE and CONFIRM, with 1,733 patients. The most recent safety analysis was presented at the 65th Annual Meeting of the American Academy of Neurology in San Diego, March 2013. This data is cited on page 156 of our original submission (Reference 96).

Section B: Clarification of the cost-effectiveness data

Search strategy

B1. Section 7 (and Appendix 10, page 316 of the MS) suggests that a number of conference proceedings were searched to identify cost effectiveness studies. Please state the date ranges for conference searching. Please confirm how each conference was searched? Please clarify whether they were searched using a website – (if so, what search terms were used), or hand searched as paper copies (if so, what volumes were used).

Biogen Idec response:
Please see response to question A4. An additional search was carried out for ISPOR in the Value in Health website on 31st Jan 2013 using the search strings 'rrms' and 'relapsing-remitting multiple sclerosis' from 2010–2012.

B2. Section 7.4.5 (and Appendix 12, page 336 of the MS) suggests that a number of conference proceedings were searched to obtain measurement and valuation of health effects data. Please state the date ranges for conference searching. Please confirm how each conference was searched? Please clarify whether they were searched using a website – (if so, what search terms were used), or hand searched as paper copies (if so, what volumes were used).

Biogen Idec response:
Please see responses to questions A4 and B1

Economic model assumptions

B3. Please clarify if the risk at 2 years of '3 months sustained disability progression', 'adverse events' and 'discontinuation', have been assumed to apply at 1 year in the model.

Biogen Idec response:
All risks were annualised by assuming a constant rate of the event over time. The risk at 1 year used in the model was the same as the other years (i.e. an annualised constant probability was used in all years of the model). The annualised risk was computed in the following way:

The risk was transformed into a 1-year rate, using the formula reported by (Briggs 2006; Fleurence 2007)

–

Where:
t= unit of time
r= rate
p=probability.

This method assumes a constant rate of the event (e.g. discontinuation, adverse event) over time.

The 1-year rate was then transformed back into a probability to give an annualised probability to use in the model, using the following formula:

Where:
p= probability
r= rate
t= unit of time

Discontinuation and adverse events:
Where appropriate, this calculation was performed across the different durations of clinical trials and then weighted by the sample size of each study to provide an annualised weighted average risk, which was used in all years in the model (including year 1).

Disability progression:
The MSM package in R was used to derive annual transition probabilities for disability progression. These were used in all years in the model (including year 1).

B4. Please justify the selection of Pokorski et al 1997 to provide the mortality multipliers stated on page 179 of the MS.

Biogen Idec response:
Mortality rates were required to estimate the number of patients who die over the time horizon considered in the model. Mortality rates in patients with multiple sclerosis have been shown to be significantly higher than the general population, including suicide as a significant cause of death (Sumelahti 2002; Pokorski 1997; Sadovnick 1992; Bronnum-Hansen 2004).

Age- and sex-specific all-cause mortality rates for the general population were sourced from interim life tables from England and Wales produced by the Government Actuary's Department (Office for national statistics 2011). These mortality rates were then adjusted using the relative risk of death in an MS population, as compared to the general population. An important consequence of applying this mortality factor to multiple sclerosis patients is the resulting redundancy of Expanded Disability Status Scale (EDSS) 10 to avoid double-counting multiple sclerosis -related mortality.

It is expected that the risk of multiple sclerosis related mortality will increase as EDSS score increases. Therefore, treatments that delay disease progression will also influence the mortality rate of the target population, acting to avoid deaths and lower the overall mortality rate. To capture this effect in the model, the relative measure of multiple sclerosis mortality per EDSS state compared to a general population was required.

Literature search:
A targeted literature search was conducted in Embase on 15 November 2011 to identify any updated sources of the relative measures of mortality in a multiple sclerosis population, compared to the general population. The search strategy used is detailed in Table 40. The search yielded 607 results, of which 30 were included at first screening, based on a review of the abstracts. Two papers were further excluded as repetitions, and the remaining 28 papers were assessed based on their abstracts and full text (where available). Of these, 14 papers were considered relevant to the multiple sclerosis mortality inputs of the model.

Table 40: Search strategy for the mortality data search

Search terms	
Disease facet	Event facet
Multiple sclerosis	Survival
MS	
Search strategy	
(("Multiple Sclerosis") OR MS) AND (survival)	

Abbreviations: MS; multiple sclerosis

Studies were reviewed based on the following criteria:

- Reports mortality multipliers by EDSS state preferred
- UK-applicable population preferred
- Recent study preferred

The relevant data provided by the 14 papers are summarised in Table 41, along with the studies strengths and limitations. Only two studies reported mortality multipliers by EDSS state. A third study was of interest as it reported mortality multipliers in a population based in South Wales.

Table 41: Critical appraisal of mortality data sources

Source	Data available	Strengths	Limitations
Reshef 2012 (poster - NARCOMS)	SMR	Large sample, recent study	Mortality adjustment not reported by EDSS
(Reshef 2011)	No direct data available	--	--
(Kingwell 2010)	SMR for men and women with RRMS at onset	Large sample, recent study	
(Reshef 2010)	No direct data available	--	--
(Ragonese 2010)	Adjusted HR	Recent study	Small sample, Italian population, mortality adjustment not reported by EDSS
(Smestad 2009)	SMR	Reported for RRMS patients specifically	Norway, not report by disability level
(Grytten Torkildsen 2008)	SMR, RMR	Reported for RRMS patients specifically	Norway, mortality adjustment not reported by disability level
(Hirst 2008)	SMR	Population in South Wales in 1985	Doesn't report mortality adjustment by sex or EDSS, prospective study
(Leray 2007)	SMR	Reports mortality adjustment by disability level	French population, doesn't report by sex, no distinction between different types of MS reported in figures by EDSS state
(Bronnum-Hansen 2006)	SMR	Large data set	Danish population, mortality adjustment not reported by EDSS state or sex
(Bronnum-Hansen 2004)	SMRs for men and women	Large sample, SMRs by sex	Danish population, SMRs not reported by EDSS
(Sumelahti 2002)	Crude RR	Reported for RRMS patients specifically (no significant different on mortality found)	Population in Finland, only reports a crude risk ratio
(Pokorski 1997)	SMR for mild, moderate and severe MS levels	Large sample, Reports adjustment by EDSS ranges	Danish population, doesn't report mortality adjustment by sex
(Sadovnick 1992)	SMR for different EDSS levels	Reports adjustment for different EDSS states	No distinction between types of MS, old study
(Phadke 1987)	Mortality in MS cohort in Scotland for ~1970	Scottish population	Doesn't report SMR , old study

Abbreviations: SMR: Standardised mortality ratio, RMR: Relative mortality ratio, MS: Multiple Sclerosis, EDSS: Expanded disability status scale, HR: Hazard ratio, RR: Risk ratio

Selection of data source for use in the model:
The multipliers reported by Pokorski et al were used as the primary source in the model, and applied to the standard mortality probabilities by age to estimate the multiple sclerosis mortality probability for each EDSS score used in the model. Only two studies were found that reported mortality multipliers by EDSS state: Pokorski et al and Leray et al. Pokorski was selected as it provided mortality multipliers that were conservative and more uniformly distributed compared to Leray et al, who report a very high mortality multiplier in EDSS 9 (Table 41).

Another alternative source identified was Hirst and colleagues, which was a population-based study starting in 1985 in South Wales (Table 42). However, this study was not used in the final model as it did not report mortality multipliers by different EDSS states, and had a shorter follow-up period and smaller sample size than the Pokorski study).

Table 42: Reported mortality multipliers

Source	Population	Mortality multiplier
1. (Pokorski 1997)	Patients in EDSS 0 – 3.5	1.6
	Patients in EDSS 4 – 7	1.84
	Patients in EDSS 7.5 +	4.44
1. (Leray 2007)	Patients in EDSS 1 – 3	0.3
	Patients in EDSS 8	6.4
	Patients in EDSS 9	24.3
2. (Hirst 2008)	Men	2.26
	Women	3.14

Abbreviations: EDSS, Expanded Disability Status Scale

Healthcare resource use

B5. Priority Question: Please provide the model code and the model output for the seemingly unrelated regressions (SUR) used to derive the EDSS and relapse state costs.

Biogen Idec response:
R-code and output (Table 43) are provided below.

R-code

```
# Get data

attach(data)

# Define regression equations - remove dmdXedss for now in nhs and gov -

###### QCd - are eqn_gov and eqn_soc supposed to be the same?

eqn_nhspssru <- cost_nhspssru ~  edss+type+relapse+dmd+dmdXedss

eqn_gov <- cost_gov ~ edss+type+relapse+sex+age

eqn_soc <- cost_soc ~ edss+type+relapse+sex+age

system <- list(eqn_nhspssru, eqn_gov, eqn_soc)

labels <- list("NHS & PSSRU", "Govt", "Societal")
```

```
# system <- list(eqn_nhspssru)
# labels <- list("NHS & PSSRU")
# Fit the models - QCd
lin1 <- lm(formula=eqn_nhspssru, data=data[!is.na(sex),])
lin2 <- lm(formula=eqn_gov, data=data[!is.na(sex),])
lin3 <- lm(formula=eqn_soc, data=data[!is.na(sex),])
sur <- systemfit(system, method="SUR", data=data[!is.na(sex),])
summary(sur)
# Variance-covariance matrix - QCd
vcov(sur)
```

Table 43: Model output for the seemingly unrelated regression

NHS perspective	Estimate	Std. Error	t value	Pr(>|t|)	2.50%	97.50%
eq1_(Intercept)	792.054287	4980.13955	0.159043	0.8736513	-8974.72	10558.83
eq1_edss1	96.4420253	5346.60866	0.018038	0.9856103	-10389	10581.91
eq1_edss2	42.7851246	5309.41991	0.008058	0.9935712	-10369.8	10455.32
eq1_edss3	2970.13106	5905.8262	0.502915	0.6150788	-8612.05	14552.31
eq1_edss4	1165.87831	5472.73875	0.213034	0.8313222	-9566.95	11898.71
eq1_edss5	2286.2311	5393.25787	0.423905	0.6716801	-8290.73	12863.19
eq1_edss6	3202.8388	5426.07193	0.590268	0.555077	-7438.47	13844.15
eq1_edss7	10278.7305	5406.46103	1.901194	0.0574194	-324.12	20881.58
eq1_edss8	27350.5208	5661.97691	4.83056	1.46E-06	16246.57	38454.47
eq1_edss9	21192.9628	8349.51626	2.538226	0.0112165	4818.356	37567.57
eq1_typeSPMS	221.530493	1838.19786	0.120515	0.9040872	-3383.44	3826.502
eq1_typePPMS	-3201.5406	2102.57229	-1.52268	0.1279965	-7324.99	921.9072
eq1_relapseYes	1632.53512	1410.1793	1.157679	0.2471325	-1133.03	4398.1
eq1_dmd1 Copax	6808.94856	5445.9069	1.250287	0.2113401	-3871.26	17489.16
eq1_dmd2 BI	8613.39681	3320.2958	2.594165	0.0095509	2101.818	15124.98
eq1_dmdXedssBI >6	3429.13484	5380.96427	0.637271	0.5240206	-7123.71	13981.98
eq1_dmdXedssBI 3-6	221.257939	3911.72412	0.056563	0.9548991	-7450.2	7892.714
eq1_dmdXedssCopax >6	-5736.8058	9631.51855	-0.59563	0.5514905	-24625.6	13151.99
eq1_dmdXedssCopax 3-6	-1230.8726	6756.47059	-0.18218	0.8554623	-14481.3	12019.54
Governmental						
eq2_(Intercept)	1466.16954	552.004521	2.656082	0.0079678	383.6103	2548.729
eq2_edss1	317.904999	528.940653	0.601022	0.5478929	-719.423	1355.233
eq2_edss2	1438.59576	525.28858	2.738677	0.006223	408.4303	2468.761
eq2_edss3	1934.899	574.526177	3.367817	0.0007719	808.1716	3061.626
eq2_edss4	903.492702	527.305266	1.713415	0.0867901	-130.628	1937.613
eq2_edss5	2759.76701	521.841294	5.288518	1.37E-07	1736.362	3783.172
eq2_edss6	3139.72923	525.015432	5.980261	2.63E-09	2110.099	4169.359

NHS perspective	Estimate	Std. Error	t value	Pr(>|t|)	2.50%	97.50%
eq2_edss7	4083.73209	526.283472	7.759567	1.35E-14	3051.615	5115.849
eq2_edss8	5768.35284	553.436435	10.42279	0	4682.985	6853.72
eq2_edss9	5933.7259	821.017361	7.227284	6.96E-13	4323.594	7543.858
eq2_typeSPMS	626.192686	178.313682	3.511748	0.000455	276.4942	975.8911
eq2_typePPMS	139.304569	204.331587	0.681757	0.4954707	-261.419	540.0278
eq2_relapseYes	436.901972	139.6287	3.129027	0.001779	163.0703	710.7337
eq2_sexMale	232.602153	134.572763	1.728449	0.084061	-31.3141	496.5184
eq2_age	-35.592635	6.18132403	-5.75809	9.81E-09	-47.7151	-23.4702
Societal						
eq3_(Intercept)	26609.1714	4392.88363	6.057336	1.65E-09	17994.1	35224.24
eq3_edss1	2598.96441	4209.33789	0.617428	0.537022	-5656.14	10854.07
eq3_edss2	13263.8672	4180.27451	3.172966	0.0015316	5065.755	21461.98
eq3_edss3	19899.261	4572.10992	4.352315	1.41E-05	10932.7	28865.82
eq3_edss4	9814.83716	4196.32341	2.338913	0.0194372	1585.251	18044.42
eq3_edss5	24343.9684	4152.84086	5.862004	5.33E-09	16199.66	32488.28
eq3_edss6	26230.5361	4178.10081	6.2781	4.19E-10	18036.69	34424.38
eq3_edss7	31201.6035	4188.19198	7.449898	1.38E-13	22987.96	39415.24
eq3_edss8	37229.4852	4404.2767	8.45303	0	28592.07	45866.9
eq3_edss9	38227.9273	6533.69994	5.850885	5.69E-09	25414.41	51041.44
eq3_typeSPMS	5027.71588	1419.02986	3.543066	0.0004045	2244.797	7810.635
eq3_typePPMS	201.918667	1626.08199	0.124175	0.9011891	-2987.06	3390.896
eq3_relapseYes	2370.46466	1111.17265	2.1333	0.0330206	191.2973	4549.632
eq3_sexMale	3455.24168	1070.93978	3.226364	0.0012738	1354.977	5555.507
eq3_age	-557.81163	49.1914169	-11.3396	0	-654.283	-461.34

B6. Priority Question: Sections 7.5.3, (page 203 of the MS) and 7.5.6, (pages 206 to 211 of the MS): state that resource use was estimated using the UK MS Survey:

i. Please clarify whether the reference (reference number 128) provided for the MS survey in section 9 of the MS is correct, as the reference refers to utility. If this is the incorrect reference, please highlight the publication that contains the 115 different resources included in the costs in the economic model.

Biogen Idec response:
This has been mis-referenced. The correct reference is the Tysabri submission to NICE as these are unpublished data (1).

ii. Please provide the number of patients used in the UK MS Survey to derive the resource estimates, including the proportion of patients in tertiary care, and the period over which data were collected for those patients.

Biogen Idec response:
These data are available in the Tysabri submission (1). Data were collected by postal survey in February 2005, with 2,048 responses returned which included evaluable information. Characteristics of these patients are summarised in Table 44. No data on the proportion of patients in tertiary care were available, but the proportion of patients with EDSS 7–9.5 may provide some indication of this.

Table 44: Characteristics of patients in the UK MS survey

Characteristic	Proportion or mean (N=2048)
Gender	
Male	24.7%
Female	74.5%
Missing	0.8%
Age	
Mean	51.4 years
18–29	1.4%
30–39	13.8%
40–49	27.0%
50–59	35.3%
60–69	18.0%
70–79	4.2%
80+	0.3%
Mean age at diagnosis	38.8 years
Form of MS	
RRMS	35.5%
SPMS	37.2%
PPMS	27.3%
EDSS score	
0–3	21.3%
4–6.5	59.6%
7–9.5	19.1%
Relapses in previous 3 months	
Yes	28.9%
No	71.1%

B7. **Priority Question:** Please state how the costs were adjusted to be consistent with a 12 month cycle (Section 7.5.6, page 206 of the MS).

Biogen Idec response:
Resources that were collected for less than a year were adjusted assuming consistent resource use throughout the year. For example, if resource use was collected for 3 months only, then the resource use over 3 months was multiplied by four to get the predicted resource use over 12 months. This was applied for "MS drugs", "other prescription drugs", and "health visitor home visits" (see Table 69 in the submission document, pages 207-211). The approach was the same as that used by Tyas et al (Tyas 2007). The 12-month resource use was then multiplied by the appropriate unit cost in order to give an annual cost estimate (see Table 69 in the submission document, pages 207-211).

Results

B8. Priority Question: Please present mean incremental cost-effectiveness ratios (ICERs) from the probabilistic sensitivity analysis (PSA) using 10,000 iterations and explain any significant differences between the PSA and the deterministic results.

Biogen Idec response:
The mean incremental costs, incremental QALYs, and ICERs from the probabilistic sensitivity analyses (PSA) using 10,000 iterations are shown in Table 45. The percentage difference (% error) between the mean probabilistic ICER and the deterministic ICER is shown in Table 46.

Table 45: Results of the probabilistic sensitivity analysis for 10,000 iterations (vs. Avonex, PAS price)

Incremental cost range			Incremental QALY range		
-	Mean	SD	-	Mean	SD
Absolute	Min	Max	Absolute	Min	Max
95% CI	Lower	Upper	95% CI	Lower	Upper

Table 46: Mean probabilistic results from 10,000 iterations of the PSA (vs. Avonex, PAS price)

Incremental (dimethyl fumarate vs. comparator)					
Comparator	Mean probabilistic Costs (£)	Mean probabilistic QALYs	Mean probabilistic ICER	Deterministic ICER	Percentage error
IM IFNβ-1a 30 µg (Avonex®)					

The mean ICERs from the PSA differ from the deterministic results by 18%. It should be noted that PSA results were not consistent between different analysis runs even when using 10,000 iterations for each separate analysis (i.e. the mean probabilistic results from a PSA run of 10,000 iterations was not necessarily close to the mean probabilistic results from another PSA run of 10,000 iterations with the same parameter settings) – see Table 45 and Table 47. This is an indication that the PSA has not converged to a stable value at 10,000 runs, which may be a result of small changes in key parameters having a relatively large influence on the results. The difference between probabilistic and deterministic results could also be explained by small variations in transition probabilities in the natural history matrix, as small variations were allowed in all transitions between EDSS states (prior assumption) even if the transition probability was zero in the deterministic setting (see section 7.6.3 in the submission document).

Probabilistic sensitivity analysis

B9. Priority Question: Distributions need to be specified for the PSA. Section 7.6.3, (page 216 of the MS) states that relative risks and relapse rates were varied using the confidence intervals (CIs). Please confirm what distributional assumptions were made? Were they uniform? If so, please explain that choice.

Biogen Idec response:
The efficacy parameters used for disability progression in the model are hazard ratios, not relative risks. Hence, we refer to hazard ratios instead of relative risks in our response.
The hazard ratio on disability progression and the relative relapse rates were varied using lognormal distributions, based on the confidence intervals from the MTC. The lognormal distribution is bounded between 0 and infinity (the same scale as hazard ratios/relative rates), and skewed towards 0. The stochastic value is sampled from a normal distribution using a log-scale standard error, and then exponentiated before being entered into the model (Briggs 2006).

B10. Please explain the rationale for assuming a 10% standard error (SE) for the beta distribution for the utility data rather than using the variance data available from the DEFINE and CONFIRM trials.

Biogen Idec response:
A standard error of 10% was assumed for utility values to allow the user to evaluate different utility sources without the need to update the uncertainty estimates in the PSA.

Moreover, this assumption does not influence the model results. Updating the model so that the uncertainty in the base case is driven by the standard errors from DEFINE and CONFIRM clinical trials, and running the PSA for 10,000 iterations, the PSA results and probability of being cost-effectiveness at a willingness to pay of £20,000 (Table 47, Figure 20, and Figure 21) are similar to the unaltered model (Table 30, Figure 11- 14 above)

Table 47: Probabilistic results from 10,000 iterations of the PSA (vs. Avonex, PAS price) with utility uncertainty from clinical trials

Incremental cost range			Incremental QALY range		
	Mean	**SD**		**Mean**	**SD**
Absolute	**Min**	**Max**	Absolute	**Min**	**Max**
95% CI	**Lower**	**Upper**	95% CI	**Lower**	**Upper**

Figure 20: Cost-effectiveness plane from 10,000 iterations of the PSA (vs. Avonex, PAS price) with utility uncertainty from clinical trials

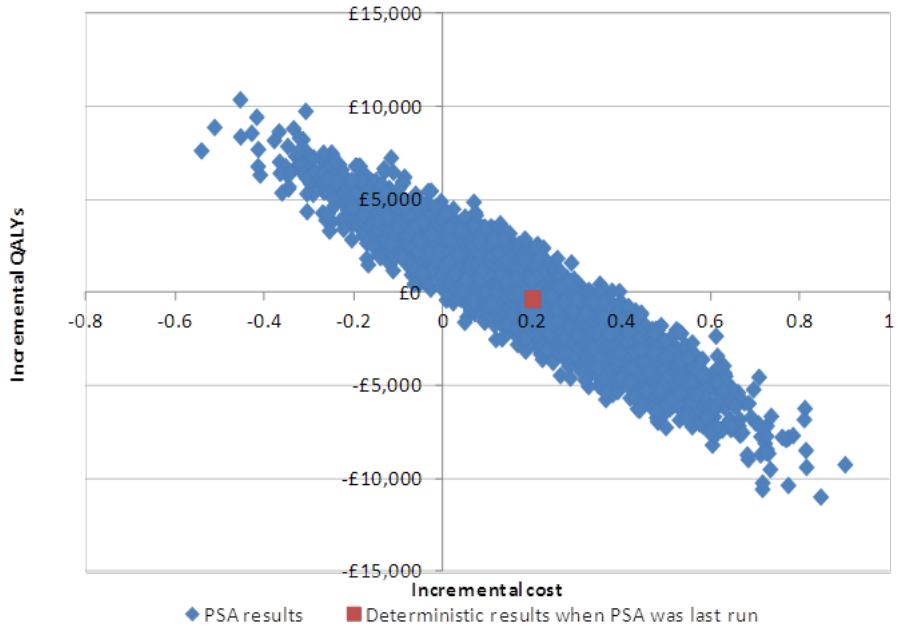


Figure 21: Cost-effectiveness acceptability curve from 10,000 iterations of the PSA (vs. Avonex, PAS price) with utility uncertainty from clinical trials

B11. Please provide the rationale for assuming a 10% SE for the natural history relapse rates and for the risk of discontinuation rather than of using the variance data available from the MTC.

Biogen Idec response:

Risk of discontinuation:

The risk of discontinuation for the placebo arm was sourced from a number of studies identified in the systematic review and it was not feasible to estimate a traditional SE for this parameter due to the differing follow-up periods used in the studies. The relative risks of discontinuation from the MTC were applied onto this placebo value.

However, we agree that the uncertainty inherent in the MTC estimates should also be considered. Updating the model so that the risk of discontinuation for placebo has an assumed SE of 10%, and the discontinuation values vs. placebo have uncertainty taken from the MTC, and running the PSA for 10,000 iterations, the PSA results and probability of being cost-effectiveness at a willingness to pay of £20,000 (Table 48, Figure 22, and Figure 23) are similar to the unaltered model (Table 30, Figure 11 - 14 above), although slightly more variation is seen.

Table 48: Probabilistic results from 10,000 iterations of the PSA (vs. Avonex, PAS price) with discontinuation uncertainty from MTC

Incremental cost range			Incremental QALY range		
	Mean	SD		Mean	SD
Absolute	Min	Max	Absolute	Min	Max
95% CI	Lower	Upper	95% CI	Lower	Upper

Figure 22: Cost-effectiveness plane from 10,000 iterations of the PSA (vs. Avonex, PAS price) with discontinuation uncertainty from MTC

Figure 23: Cost-effectiveness acceptability curve from 10,000 iterations of the PSA (vs. Avonex, PAS price) with discontinuation uncertainty from MTC

Natural history relapse rates:

Natural history relapse rates were calculated using pooled data from the DEFINE and CONFIRM clinical trials (EDSS 0 - 5), and relative increases using the UK MS survey (EDSS 6 - 9). Using this approach, direct estimates of uncertainty were not available for the higher EDSS states. To avoid a scenario where different uncertainty assumptions/approaches were made for relapse rates in different EDSS states, an assumption of 10% was applied consistently to relapse rates across all EDSS states.

Updating the model so that the uncertainty associated with relapse rates for EDSS 0 - 5 are based on sample sizes from the DEFINE and CONFIRM trials, and the uncertainty associated with relapse rates for EDSS 6 - 9 are based on 10% SE, and running the PSA for 10,000 iterations, the PSA results and probability of being cost-effectiveness at a willingness to pay of £20,000 (Table 49, Figure 24, and Figure 25) are similar to the unaltered model (Table 30, Figure 11 - 14 above).

Table 49: Probabilistic results from 10,000 iterations of the PSA (vs. Avonex, PAS price) with relapse uncertainty from clinical trials

Incremental cost range	Incremental QALY range

Incremental cost range			Incremental QALY range		
	Mean	SD		Mean	SD
Absolute	Min	Max	Absolute	Min	Max
95% CI	Lower	Upper	95% CI	Lower	Upper

Figure 24: Cost-effectiveness plane from 10,000 iterations of the PSA (vs. Avonex, PAS price) with relapse uncertainty from clinical trials

Figure 25: Cost-effectiveness acceptability curve from 10,000 iterations of the PSA (vs. Avonex, PAS price) with relapse uncertainty from clinical trials

Section C: Implementation

C1. Please provide the rationale for the assumption (Section 8.2, page 276 of the MS) that 100% of the population eligible to receive treatment would receive interferon or glatiramer acetate treatment, given that fingolimod and/or natalizumab are treatment options for people whose disease meets the criteria specified in NICE technology appraisals 127 and 245 , and that a minority of people may refuse treatment with disease modifying therapy (DMT) or it may be considered an inappropriate treatment.

Biogen Idec response:

Fingolimod and natalizumab were not included as these treatments are generally reserved for patients with high disease activity despite treatment or rapidly evolving severe disease, respectively. These subgroups are likely to be a relatively small proportion of the overall MS population, and the effect of dimethyl fumarate introduction in these groups is therefore also likely to be small. We felt that interferons and glatiramer acetate were the most likely treatments to be displaced by dimethyl fumarate, and these were consequently used in estimating the budget impact. This is a conservative assumption, as fingolimod and natalizumab are both more expensive than interferons and glatiramer acetate. Assuming that dimethyl fumarate would also replace a proportion of the fingolimod and natalizumab market share, this would consequently result in a smaller budget impact.

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